The medical management of GOUT REVISITED

Key concepts:

- NSAIDs are the first-line treatment for an acute attack of gout
- Allopurinol should not be started at the time of an acute attack of gout. However, patients already prescribed allopurinol should continue to take it at the same dose during acute episodes
- A sustained reduction of serum urate to below 0.36 mmol/L is critical for the long-term management of gout (some experts advocate to aim for as low as <0.3 mmol/L)
- Generally, the initial dose of allopurinol should be based upon a patient's estimated glomerular filtration rate (eGFR), thereafter the dose can be gradually increased until the target serum urate is reached
- Lifestyle modifications to prevent recurrence include; eating less high purine foods (e.g. red meat, offal, shellfish), drinking less alcohol and eating more low-fat dairy products and vegetable sources of protein, in combination with a programme of moderate exercise

Kua takoto te mānuka

The leaves of the mānuka tree have been laid down

This is a form of wero, that is preformed in very formal situations on the Marae. It is when you are challenged and you answer that challenge depending on how you pick up the leaves. The wero is to see whether you come in peace or as an enemy. This proverb is used when being challenged, or you have a challenge ahead of you.

THE MEDICAL MANAGEMENT OF GOUT can be classified into three areas:

1. Treatment of an acute attack of gout
2. Long-term urate lowering treatment to prevent recurrent attacks of gout
3. Lifestyle advice for people with gout

For further information see: "Treatment of gout – Hit the target", BPJ 8 (Sep, 2007)

Treating an acute attack of gout

1. Exclude infection

When a patient presents with suspected acute gout, it is important to exclude other causes of inflammation, such as sepsis within the joint, especially if gout has not been previously diagnosed.

The clinical presentation of acute monoarticular gout may be identical to that of an acute septic arthritis and occasionally gout and infection can co-exist. Infection is more likely if the patient is systemically unwell and there is a single, acutely painful, swollen, hot joint (e.g. knee). Gout is the more likely clinical diagnosis if the patient has a history of similar attacks, is of male gender, is systemically well and if there is involvement of the first metatarsal phalangeal joint (MTP). Gout is a more common diagnosis than septic arthritis.[1]

If after clinical review, infection is suspected, aspiration of synovial fluid from the affected joint, for microbiological analysis, is recommended where possible, to confirm or exclude sepsis. N.B. This may also confirm the diagnosis of gout (by the presence of uric acid crystals).

2. Prescribe anti-inflammatory medicine and rest

If gout is the most likely diagnosis, the patient should be advised to rest the affected joint and should be prescribed an anti-inflammatory treatment.

NSAIDs are first-line

First-line treatment is usually an oral, non steroidal anti-inflammatory drug (NSAID), e.g. naproxen 500 mg, twice daily; ibuprofen 200–400 mg, four times daily; or diclofenac 75 mg, twice daily. Medicine should be taken until the attack subsides. Paracetamol can also be used concurrently for pain relief.

Use corticosteroids only if infection is excluded

Corticosteroids may be considered for patients in whom NSAIDs are contraindicated (e.g. peptic ulceration, concurrent anticoagulant treatment), but only if infection has been excluded. A suggested initial dose is 20–40 mg prednisone daily, gradually reduced over 10–14 days. Intra-articular corticosteroids (e.g. triamcinolone acetonide – Kenacort-A – up to 10 mg for small joints, up to 40 mg for large joints) can be especially useful if one or two joints are affected as this reduces the risks of systemic corticosteroids treatment. However, in patients with diabetes, corticosteroids should be used with caution as doses of insulin or anti-diabetic medicines may need to be adjusted.

Consider colchicine if NSAIDs and corticosteroids contraindicated

When NSAIDs or corticosteroids are contraindicated, low dose colchicine remains an appropriate treatment option. Colchicine has a slower onset of action than NSAIDs and serious adverse effects can occur if the dose is too high.[2] Adverse effects include: gastrointestinal disturbance, electrolyte imbalance, haematological effects and multi-organ failure. Colchicine toxicity has also been reported with concomitant use of liver enzyme inhibitors (e.g. erythromycin, ketoconazole, diltiazem), statins, fibrates and digoxin, daily consumption of grapefruit juice and in patients with hepatic or renal impairment.[3]

The recommended dose for colchicine for the treatment of acute gout is 1.0 mg stat, followed by 0.5 mg six hourly, up to a maximum dose of 2.0 mg per 24 hours on the first day and to a maximum of 1.5 mg on subsequent days.[3] Patients should be advised to contact their doctor if gastrointestinal symptoms occur.

N.B. this is a lower dose than suggested in previous guidance.

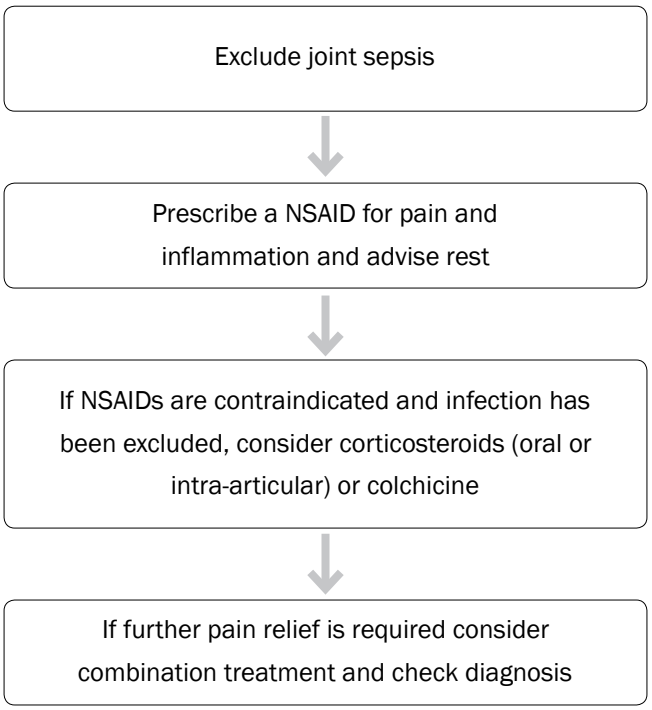
The total dose should not exceed 6 mg over four days. In elderly people who weigh <50kg, or people with renal or hepatic impairment, other treatments should be considered before colchicine but if colchicine is used the maximum cumulative dose should not exceed 3 mg over four days.[4]

Combination treatment may be useful for some people

Corticosteroids can be used in combination with NSAIDs or colchicine to provide further relief during acute gout. Colchicine can be a useful adjunct to NSAIDs in resistant cases, particularly when gouty tophi are present or to prevent flares when starting allopurinol. Weak opioid analgesics, e.g. codeine, can also be prescribed for further pain relief.[2]

If there is no response to treatment, the diagnosis should be reconsidered.

Treatment summary for acute gout



Serum urate levels may not be useful for diagnosis of an acute attack of gout

The diagnosis of gout is often made on clinical grounds, but if possible, should be confirmed by the presence of uric acid crystals on aspiration of the affected joint.

Although serum urate is the most important risk factor for gout, and should be measured in all suspected cases, not all patients with hyperuricaemia will develop gout. Serum urate levels do not confirm or exclude gout during acute attacks, as serum levels may be normal during this time. Serum urate should be measured again once the attack has subsided.

Although x-rays may be useful for the differential diagnosis and may show typical features in chronic gout, they are not useful in confirming the diagnosis of early or acute gout.

Do not start allopurinol during an acute attack of gout

Allopurinol should not be started at the time of an acute attack of gout, however, if a patient is already taking it regularly, then it should be continued at the same dose.

Long-term urate lowering treatment to prevent recurrent attacks of gout

Indications for the initiation of long-term urate lowering treatment in people with gout include:

- Recurrent gout attacks (two or more attacks in a year)
- Tophi
- Chronic gouty arthropathy
- Radiographic changes consistent with gout

Other factors may also influence the decision to initiate urate lowering treatment such as severity of attack, co-morbidities and patient preference.[5]

Allopurinol is the most commonly used medicine for long-term urate lowering treatment and gout prevention as it inhibits the enzyme which is responsible for the production of urate.

It is advisable to wait at least two weeks after an acute attack of gout before starting allopurinol. Starting treatment with allopurinol can often precipitate gout flares. Concurrent administration of low dose NSAIDs (e.g. naproxen 250 mg, twice daily) or colchicine (0.5 mg daily or twice daily) during this two week period, and for the following three to six months (or longer in tophaceous gout), is strongly recommended to help prevent flares. Patients should be monitored for any gastrointestinal adverse effects due to NSAIDs.

Best Practice tip: If the acute gout attack has been severe, consider starting 0.5 mg colchicine daily, three days after the attack has finished, while waiting to start allopurinol. This will help prevent a further gout attack, which would delay the commencement of allopurinol.

"Start low and go slow"

The active metabolite of allopurinol has a plasma half-life which is inversely related to renal clearance, therefore

Calculating creatinine clearance

Most laboratories report eGFR automatically with serum creatinine results, therefore eGFR can be used as a measure of renal clearance. However, eGFR may not be a good estimate of renal function in people at extremes of body size (BMI < 18.5 or > 30 kg/m^2). In this case, an estimate of creatinine clearance is preferable, determined using a hand held or electronic calculating tool or by using the Cockcroft-Gault equation:

Creatinine clearance (mL/min) = (140 – age) x weight (kg) x constant/serum creatinine (µmol/L).

The constant = 1.23 for men, 1.04 for women.

the initial dose is based on the patient's renal function. For patients with an estimated glomerular filtration rate (eGFR)* of at least 30 mL/min/1.73 m^2, a good starting dose is 100 mg allopurinol per day, increasing by 100 mg every four weeks, unless adverse events occur, until target serum urate is reached. An alternative regimen would be 50 mg allopurinol per day, increasing by 50 mg every two weeks.

In practice, patients are often maintained on 300 mg per day as a fixed dose, although maintenance doses as high as 700–900 mg per day are acceptable for severe conditions.[6]

For patients with renal impairment, where the eGFR is less than 30 mL/min/1.73 m^2, it is recommended that the starting dose of allopurinol is reduced to 50 mg per day, or every second day, and then increased by 50 mg every month as guided by the serum urate levels and tolerance.

Historically there has been concern over increasing the dose of allopurinol in patients with renal impairment, however, a recent New Zealand based clinical trial of 90 patients, suggests it is generally safe to do so.[7] It was shown that when the dose of allopurinol was gradually increased, the dose required to reach target serum urate levels ranged from 50–400 mg above the recommended dose based on creatinine clearance. Toxicity was not increased in the patients receiving higher doses of allopurinol, including those with renal impairment.

Adverse effects of allopurinol

The most common adverse effect of allopurinol is a rash (1–2%). A rare, but potentially fatal, adverse effect is "allopurinol hypersensitivity syndrome", characterised by fever, rash, eosinophilia, hepatitis and renal failure.

Probenecid is an option in people who are intolerant to allopurinol

For people with normal renal function who are intolerant, or allergic to allopurinol, probenecid may be used. As with allopurinol treatment, the dose should be slowly increased. The recommended dose of probenecid is 250 mg, twice daily, for the first week, increasing to 500 mg, twice daily, for the second week and then increasing by 500 mg in subsequent months to a maximum of 2000 mg, daily in divided doses. Probenecid is contraindicated in people with a history of renal stones. Patients taking probenecid need to ensure they maintain sufficient fluid intake to prevent the formation of renal stones. As with allopurinol, probenecid should not be administered during the acute phase of a gout attack.

"Treat to target"

The concept of "treat to target" is an important one for both General Practitioners and patients to understand. A target serum urate level of <0.36 mmol/L is thought to be critical for the long-term management of gout, both for suppression of attacks and regression of tophi. The target of 0.36 mmol/L is endorsed by the European League Against Rheumatism (EULAR) in its guidelines for management of gout.[8] However, an even lower target of 0.3 mmol/L is recommended by the British Society of Rheumatology and may be appropriate for patients with large tophi to speed up the removal of these deposits.[2]

Ensure that patients understand that it may take up to 6–12 months, of serum urate levels below 0.36 mmol/L, before acute gout attacks begin to subside. Long-term compliance with treatment is therefore important and also one of the greatest hurdles in treating patients with gout. Strategies that can assist with compliance include:

- Encouraging whānau involvement
- Periodic follow-up on agreed treatment plans
- Regular text reminders

* eGFR may not be a good estimate of renal function in people at extremes of body size (BMI < 18.5 or > 30 kg/m^2. Calculation of creatinine clearance to estimate renal function is preferable in these patients (see sidebar "calculating creatinine clearance").

Summary of treatment to prevent recurrent gout

Treat acute gout attack, wait at least two weeks, then:

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Start allopurinol 100 mg daily (if eGFR or creatinine clearance or at least 30) + prophylactic cover (with low dose NSAID +/- PPI or colchicine) for first three to six months

Or

Start allopurinol 50 mg daily (if creatinine clearance or eGFR less than 30) + prophylactic cover (as above)

Then slow increments in allopurinol to be guided by serum urate concentrations, i.e. "treat to target"

Or

For people who are intolerant to allopurinol give probenecid 250 mg, twice daily for one week, increasing to 500 mg, twice daily. Dose can be increased by 500 mg per month to a maximum of 2000 mg daily in divided doses. Increase fluid intake to prevent renal stone formation.

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There is a risk of precipitating acute attacks for several months – do not stop allopurinol during acute attacks

Gout and diuretics

Use of thiazide and loop diuretics is associated with increased serum urate levels and therefore increased risk of gout. Although low dose thiazides may not exacerbate symptoms, where possible, for patients with gout, use an alternative anti-hypertensive. However, loop diuretics are still recommended for patients with cardiac failure.[9]

In patients with decreased renal function concomitant use of allopurinol with a thiazide diuretic is thought to increase the risk of allopurinol-induced hypersensitivity reactions. This combination should be used with caution.[6]

Lifestyle advice for people with gout

Recommendations for diet, lifestyle modification and non-pharmacological management of gout:[2]

Encourage patients to:	Recommend patients avoid:
Maintain an ideal weight	Avoid (or limit) alcohol, particularly beer
Consume low fat dairy, soy, vegetable sources of protein and foods rich in vitamin C.	Avoid (or limit) high purine foods such as red meat, shellfish, oily fish, liver, kidney, yeast extracts, sucrose and fructose containing soft drinks Avoid high protein, low carbohydrate diets
Drink water > 2 L/day	Avoid dehydration
Exercise moderately Elevate and cool affected joints	Avoid intense exercise and joint trauma

Follow-up for patients with gout

It is recommended that patients with gout should be reviewed at least yearly. The review may be performed by either the General Practitioner or Practice Nurse and should include:

- Enquiring about any gout symptoms in the past year
- Examination, looking for the development of gouty tophi
- Measurement of serum urate level
- If serum urate levels are elevated, consider starting urate lowering treatment, if not already being prescribed
- Discussing compliance with urate lowering therapy (if being prescribed and target not being met)
- Performing CVD risk assessment and providing advice about management of modifiable risk factors due to the potential association between uric acid and higher risk of CVD (see: "Gout: An alarm bell for diabetes and cardiovascular disease" opposite page)

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