Managing gout in primary care

Part 1 – Talking about gout: time for a re-think

Gout is a treatable form of arthritis that is associated with poor health and reduced life expectancy. Too often, gout management is focused on controlling the patient's symptoms while their risk of irreversible joint damage and negative health outcomes continues to grow. Māori and Pacific peoples are disproportionately affected by gout and often receive sub-optimal care; it is time for a re-think to address this disparity.

KEY PRACTICE POINTS:

- Gout is a serious condition that is often associated with a range of long-term negative health outcomes, e.g. co-morbid cardiovascular disease, renal failure and reduced life expectancy
- The management of gout is sub-optimal in New Zealand, and changes need to be made both in community awareness and in the delivery of healthcare; after making a diagnosis, the emphasis should be placed on providing information to patients about their condition, addressing any misconceptions or concerns and supporting appropriate medicine use
- Gout flares can be treated with a NSAID, prednisone or low dose colchicine, depending on individual clinical circumstances; all are considered to be equally effective
- Discuss urate-lowering treatment with all patients with gout at their first presentation, recommend early initiation and encourage regular and consistent use; lifestyle changes alone are insufficient to prevent future gout flares from occurring
- Allopurinol can be initiated during an acute flare of gout if it is thought that this may improve the likelihood of the patient committing to long term treatment; however, this may not be appropriate for all patients

This is a revision of a previously published article. What's new for this update:

- A general article revision
  - Update of statistics
  - Addition of genetics to the list of risk factors

For further information about initiating and titrating allopurinol, see: "Part 2: Controlling gout with long-term medicines" available from: **bpac.org.nz/2021/gout-part2.aspx**

Gout is controllable with long-term treatment

Gout is the most common form of inflammatory arthritis.[1] It is caused by monosodium urate crystals accumulating in joint fluid, cartilage, bones, tendons and other tissues.[2] Urate is produced via the metabolism of dietary and endogenous purines.[2] When urate levels in the blood reach saturation point, monosodium urate crystals can form.[2] The inflammatory response to these crystals results in gout flares which are characterised by painful, red, hot, swollen joints. Over time, the duration and frequency of these flares may increase, resulting in chronic gouty arthritis and subcutaneous deposits of crystals referred to as tophi, both of which can lead to the destruction of joints.[2]

The risk factors for gout

Long-term hyperuricaemia is the most important risk factor for the development of gout, and in most patients this will be caused by declining renal function.[2] Detecting chronic kidney disease (CKD) early and preserving renal function is therefore an important gout-prevention strategy. Additional factors that contribute to hyperuricaemia and increase the risk of developing gout include:[2–5]

- Older age
- Genetics, e.g. variants of the *SLC2A9* fructose/urate co-transporter genes have been implicated in the greater number of Māori and Pacific peoples living with gout; it is thought that these genetic variants reduce the ability to excrete urate, contributing to hyperuricaemia and therefore the risk of gout
- Male sex
- Hypertension
- Obesity
- Use of certain medicines, e.g. diuretics or low dose aspirin (for more information on the appropriate selection and use of cardiovascular medicines, see: **Part 2: controlling gout with long-term urate-lowering medicines**)
- Excessive consumption of red meat, seafood, beer, spirits, sucrose or fructose-sweetened drinks

The burden of poorly-controlled gout is often over-looked

Gout is much more than an intensely painful condition that prevents people from working, performing daily activities and participating in their communities.[1] People with gout are also more likely than those without gout to die at a younger age due to co-morbid cardiovascular disease and renal complications.[6] In New Zealand, 40% of people with gout have diabetes and/or cardiovascular disease.[7] Despite this, many people consider gout to be a condition that merely requires analgesics to control and are not aware of the potential long-term consequences.[8] Raising community awareness about gout is an important role for health professionals in primary care.

Urate-lowering treatment improves long-term health outcomes

Reducing serum urate levels in patients with gout not only means that flares are less likely, it may also reduce the risk of adverse renal and cardiovascular outcomes. For example, a meta-analysis found that compared to patients who were not taking a urate-lowering medicine (or were taking a placebo), patients with hyperuricaemia and CKD who were taking a urate-lowering medicine:[9]

- Reduced their risk of cardiovascular events or renal failure by more than half
- Had slower rates of decline in renal function
- Reduced their proteinuria

More recently, it was found that people with gout and diabetes who were taking urate-lowering treatment had significantly lower risk of coronary artery disease or stroke.[10]

Māori and Pacific peoples with gout are not receiving adequate care

Gout management in New Zealand needs to change because Māori and Pacific peoples in particular are not receiving the medicines according to their level of need. Furthermore, research suggests that inequities between how gout is managed in Māori and non-Māori is ingrained in the current model of care, with no significant reduction in disparity in recent years.[11]

Gout is more frequent and more severe in Māori and Pacific peoples

The prevalence and burden of gout in New Zealand is higher in Māori and Pacific peoples than in other groups. In 2019, gout was estimated to affect approximately 6% of people in New Zealand aged over 20 years; Māori and Pacific peoples aged 20 to 44 years have a three and seven times greater prevalence of gout than non-Māori and non-Pacific peoples, respectively.[1] The prevalence of gout increases with age; among males aged over 65 years the prevalence is 35% for Māori, 50% for Pacific peoples and 18% for non-Māori and non-Pacific groups.[1] Māori and Pacific peoples with gout are dispensed more prescriptions for NSAIDs each year (41% and 46%, respectively) than other ethnic groups (35%) and are therefore at greater risk of NSAID-related adverse effects, e.g. acute kidney injury and cardiovascular events.[1] Māori and Pacific patients with gout are also five and nine times more likely to be admitted to hospital due to gout than non-Māori, non-Pacific people.[1]

Prescribers often delay initiation of urate-lowering treatment

Numerous studies from New Zealand and overseas show that urate-lowering treatment is often delayed well beyond the point when it is indicated. For example, a small qualitative study of Māori patients with gout found that on average urate-lowering treatment was not prescribed until 18 years after the appearance of symptoms.[13] In 2019, dispensing data showed that Māori and Pacific peoples with gout were more likely to have received urate-lowering treatment (60%), i.e. dispensed medicine at least once in one year, than non-Māori and non-Pacific people with gout (56%). However, Māori and Pacific peoples were less likely to receive regular treatment (39% and 36%, respectively), i.e. dispensed medicine in three or four quarters in one year compared with non-Māori and non-Pacific people (43%).[1]

Once urate-lowering medicines are started, monitoring is also often sub-optimal, meaning that many patients will still have serum urate concentrations above recommended levels for treating gout. A systematic review predominantly of studies from the United States and United Kingdom found only 28 – 38% of patients had their serum urate levels monitored regularly and 23% of patients taking allopurinol had serum urate levels above 0.36 mmol/L.[14]

Identifying the barriers to optimal management

The barriers to the early and optimal use of urate-lowering medicines are multi-factorial. Firstly, there is a lack of clarity in guidelines as to the best time to initiate treatment, and at times there are discrepancies between guidelines. Secondly, there is sometimes a perception among health professionals that gout management is acute, rather than preventative.[8] The limited time that is available in consultations in primary care and the intermittent nature of gout flares also make it difficult for health professionals to focus on the long-term management of gout and promote patient education.[15]

Nurses and pharmacists have an important role in gout management

Most patients with gout are able to achieve serum urate targets if they are provided with effective support. This role is ideal for nurses in primary care; an essential component of gout education is overcoming misconceptions that are barriers to care (see: "Overcoming misconceptions that are barriers to managing gout"). A nurse-led programme in primary care in the United Kingdom found that with education and lifestyle advice, 92% of patients were able to achieve serum urate treatment targets.[8]

Community pharmacists can reduce delays in the diagnosis of gout and the initiation of urate-lowering treatments by asking patients who are purchasing NSAIDs about their symptoms.[8] Patients who may have gout, e.g. those with a history of gout-like flares, can be encouraged to present to general practice for an assessment, and those who know they have gout can be encouraged to discuss the possibility of starting urate-lowering treatment with a general practitioner.

Owning My Gout and Gout Stop are initiatives led by community pharmacists, practice nurses and general practitioners to improve access to medicines for gout and to build on health literacy by educating participants. Further information is available from: **https://www.arthritis.org.nz/wp-content/uploads/2020/07/Gout-programmes-evaluation-report-.FINAL_.-200228.pdf.** Another gout management improvement project was launched by the National Hauora Coalition in collaboration with Papakura Marae Health Clinic, further information is available from: **https://www.nhc.maori.nz/wp-content/uploads/2019/09/HCAnnualReport-Final.pdf**

Overcoming misconceptions that are barriers to managing gout

Perceptions and beliefs about gout can contribute to delays in initiating urate-lowering treatment.[16] Good communication helps to overcome misconceptions that are barriers to care. A structured approach to discussions is therefore recommended:

- Assess the patient's understanding about gout
- Build on their knowledge by validating information that is correct, filling in knowledge gaps and correcting misconceptions
- Check that the patient has understood the information that has been delivered

The goal is to form a loop of communication, with gaps in understanding forming the basis for further discussion.

Further information on effective discussion and communication about gout management with patients is available from: **https://bpac.org.nz/bpj/2014/april/gout.aspx**

Delivering the messages that patients and whānau need to hear

Do not blame yourself because you have gout. Lifestyle factors can trigger gout flares but are not the sole cause of the condition. Biological factors (e.g. chronic kidney disease, certain uric acid renal transporter alleles) and some medicines (e.g. diuretics) contribute significantly to the higher prevalence of gout in Māori and Pacific peoples compared with other ethnic groups.[17] Explaining to patients that they may have a genetic predisposition to gout helps to dispel the perception that the condition is self-inflicted.

Gout is serious, it's not just "a pain in the toe". Patients should understand that gout is associated with an increased risk of co-morbid cardiovascular disease and renal complications. However, by educating patients to actively manage their condition, e.g. regularly taking preventative medicines and making lifestyle changes when appropriate, they can reduce this risk.

Gout is a long-term disease caused by deposits of urate crystals. These crystals are still present in the joint after a flare has settled. The crystals will only dissolve if the urate level in the blood is kept low (< 0.36 mmol/L) by regular use of medicines such as allopurinol.[8]

In the long-term, allopurinol can stop flares from happening. If patients regularly use urate-lowering treatment and serum urate levels are treated to target, flares of gout will be virtually eliminated for many patients within two years.[18]

Allopurinol is a safe and highly effective medicine. Urate-lowering medicines such as allopurinol are associated with an increased risk of flares in the first months of treatment and this may discourage some patients to take them, even if they have collected the prescription from the pharmacist.[2] Patients can be reassured that with prophylactic medicines and appropriate dose titration, the risk of allopurinol causing a flare will be substantially reduced and ongoing use will prevent future flares.

Patient resources for gout, including Samoan and Tongan language versions, are available from: **www.goodfellowunit.org/gout-study-project/gout-study-project**

Diagnose gout, manage the flare and talk about long-term treatment

In primary care, gout is usually diagnosed clinically with supporting evidence provided by elevated serum urate levels; see "Diagnosing gout" for an example of a validated diagnosis tool and alternative diagnoses to consider.[2]

Caution is required when interpreting serum urate levels during a gout flare as up to 40% of patients are reported to have serum urate levels within the normal range;[19] repeat testing for diagnostic purposes may be required once the flare has subsided.[2] Although the gold standard for diagnosing gout is the presence of monosodium urate crystals under polarised microscopy,[2] joint aspiration is usually not necessary unless there is a high suspicion of another cause, e.g. septic arthritis.

Best practice tip: Request a renal function test at the same time as the serum urate to allow for the prompt initiation of urate-lowering treatment, should a diagnosis of gout be confirmed.

Medicines for gout flares are determined by the patient's characteristics

Patients with gout often initially present due to a flare, which will be the treatment priority. Rest and elevation of the affected joint should be encouraged during the gout flare, and some patients may find the use of an ice pack beneficial.[4] Lifestyle changes to avoid obvious triggers, limit purine and fructose/sucrose intake, and reduce weight are important, but alone are insufficient for the management of gout.[2]

Rongoā rākau does not interfere with conventional gout treatments

Rongoā rākau (traditional plant remedies with healing properties) may be used by some Māori patients to treat flares of gout.[13] This may be in the form of a poultice or plant material added to bathwater. Urate-lowering medicines can be used safely in combination with Rongoā rākau and should not be discouraged. Positive discussions about traditional medicines are helpful as they break down barriers with patients and allow prescribers to assess if any interactions with conventional medicines are likely.

Diagnosing gout

Table 1 provides an example of a scoring system to assess the likelihood of gout, which can support a clinical diagnosis. A score of eight or more is associated with a greater than 80% likelihood of gout.[2] A score of four or less rules out gout in almost 100% of patients and an alternative diagnosis should be considered.[2]

Table 1: Clinical score for the diagnosis of gout, adapted from Janssens *et al.* (2010)

Feature	Clinical score
Serum urate > 0.35 mmol/L	3.5
Metatarsophalangeal joint involvement	2.5
Male sex	2
Previous reported flare	2
Hypertension or ≥ 1 cardiovascular disease*	1.5
Joint erythema	1
Onset within one day	0.5
Score	**Maximum 13**

* Angina, myocardial infarction, heart failure, cerebrovascular event, transient ischaemic attack or peripheral vascular disease

Septic arthritis should be considered in patients with monoarticular joint pain, with erythema, warmth and joint immobility; systemic symptoms may also be present.[20] Often the patient will have an underlying condition affecting the joint, e.g. osteoarthritis, and concurrent treatment with an immunosuppressive medicine increases the likelihood of infection.[20] The knee is most often affected by septic arthritis, followed by the hip, shoulder, ankle and wrist.[20] Patients with septic arthritis will often have an elevated serum white blood cell count and C-reactive protein levels may also be raised.[20]

Acute calcium pyrophosphate crystal arthritis, also known as calcium pyrophosphate deposition (CPPD) disease, and previously known as pseudogout, is an arthritis caused by the accumulation of calcium pyrophosphate crystals.[21] Acute calcium pyrophosphate crystal arthritis has a prevalence of 4 – 7% in European populations;[21] the prevalence among Māori and Pacific peoples is unknown. Previous joint damage is a strong risk factor for calcium pyrophosphate crystal arthritis and it becomes more likely if the first onset of symptoms occurs later in life as it is rare in patients aged under 60 years.[21] Patients with calcium pyrophosphate crystal arthritis often have systemic symptoms, including fever and chills, and elevated inflammatory markers, which can make it difficult to distinguish from infection.[21] Where there is clinical uncertainty, calcium pyrophosphate crystal arthritis can be differentiated from gout and septic arthritis by requesting laboratory analysis of aspirated joint fluid.[21] Radiography can also be used to support a diagnosis of acute calcium pyrophosphate crystal arthritis in joints that are unable to be aspirated.[21] Unlike gout, calcium pyrophosphate-lowering medicines do not exist and treatment is focused on symptom relief.

Further information on diagnosing and managing calcium pyrophosphate crystal arthritis is available from: **https://bpac.org.nz/bpj/2013/october/cppd.aspx**

A NSAID, corticosteroids or colchicine may be prescribed to treat gout flares

There are several options that can be used for the acute treatment of gout flares, depending on specific patient characteristics (Table 2). There is insufficient evidence to directly compare the efficacy of medicines for the treatment of gout flares.[3] Medicine selection is therefore based on the patient's preference, renal function, the presence of co-morbidities, e.g. prednisone may be preferred over a NSAID or colchicine in a patient with reduced renal function, and the concurrent use of medicines that may interact with colchicine (see: "Particular care is required with colchicine"). If a patient is experiencing severe flares of gout, e.g. involving multiple joints, it may be appropriate to prescribe combination treatment, e.g. a NSAID with colchicine or corticosteroids with colchicine.[23]

Once treatment for the acute flare has been completed, flare prophylaxis can be started or resumed if appropriate (for further information on flare prophylaxis, see: "Part 2: Controlling gout with long-term medicines" available from: **bpac.org.nz/2021gout-part2.aspx**).

N.B. The initiation of urate-lowering treatment can also be considered during an acute flare in some patients, see: "Talk about urate-lowering treatment before the patient leaves".

Provide a "pill in the pocket" for managing future flares

Patients with gout require ready access to medicines for managing flares until they achieve long-term symptom control with urate-lowering treatment.[2] It is often necessary to prescribe an extra quantity of medicine for this purpose; emphasise to patients that they should stop taking the medicine when the flare has settled, unlike urate-lowering treatment which should be taken every day. Medicines should be stored in a secure and safe location at work and at home. Special care should be taken with colchicine as relatively small overdoses can be fatal. Patients should take medicines promptly for acute flares and those taking colchicine should do so within 12 hours of flare onset.[3]

Talk about urate-lowering treatment before the patient leaves

Urate-lowering treatment should be discussed with all patients with gout once a diagnosis has been established.[3] This includes patients who are currently experiencing a gout flare, as they should be provided with the opportunity to manage their gout immediately, and some may not return for a follow-up consultation once the pain of the flare has resolved. The discussion should also cover the importance of titrating the dose of urate-lowering treatment over time for it to be effective.

Urate lowering medicines are not indicated for the treatment of asymptomatic hyperuricaemia.[4]

Aim to initiate urate-lowering treatment early

Patients with symptomatic hyperuricaemia and any of the following should start urate-lowering treatment:[3, 4, 6]

- Two or more flares per year (this includes any flares the patient did not seek medical evaluation for)
- Tophi or erosions on X-ray
- Renal impairment (eGFR < 60 mL/min/1.73 m^2)

Table 2: Treatment options for an acute gout flare.[22]

Medicine	Dose	Additional notes
Naproxen	750 mg initially, 500 mg eight hours later, then 250 mg every eight hours until the flare has settled	Avoid if eGFR < 30 mL/min/1.73m^2
Prednisone	20 – 40 mg, once daily, for five days	Tapering the dose over 10 – 14 days can reduce the likelihood of a rebound flare, but tapering is not always necessary
Colchicine	Low dose regimen: 1 mg immediately, followed by 500 micrograms after one hour; maximum dose of 1.5 mg over a one-hour period. If eGFR 10 – 50 mL/min/1.73m^2, reduce the initial dose by half (i.e. 500 micrograms); do not exceed 1.5 mg over three days.	Do not repeat acute course within three days. Do not commence prophylaxis (very low dose colchicine) until 12 hours or more after the acute dose is taken. Colchicine should ideally be avoided, or used with caution, in frail patients, those who weigh < 50 kg, or patients with hepatic or renal impairment (eGFR 10 – 50 mL/min/1.73m^2). Colchicine is contraindicated in patients with an eGFR < 10 mL/min/1.73m^2.
Corticosteroid (triamcinolone acetonide)	Intra-articular injection, 2.5 – 40 mg	Dose determined by the size of the affected joint

- Past urolithiasis
- Serum urate level ≥ 0.54 mmol/L

A randomised controlled trial has demonstrated that urate-lowering treatment in patients with early gout (with one or two prior flares) resulted in reduced incidence of gout flares and improved MRI-determined synovitis.[24] Patients who are initiated on urate-lowering treatment are less likely to require treatment for gout flares and are therefore less likely to experience adverse effects from repeated exposure to NSAIDs.

Initiation of urate-lowering treatment can be considered during a flare for some patients, but caution is required

The optimal timing of urate-lowering treatment initiation is still debated.[25] Traditionally, initiation of urate-lowering treatment has been delayed until the pain of a flare has resolved. The rationale being that dispersion of urate crystals during the initiation phase of treatment may make the patient's pain worse. There is now some limited evidence which suggests that initiating a urate-lowering treatment during a flare may have no significant impact on the duration of the flare or on its severity for some patients.[4, 25, 26] As a result, the 2020 American College of Rheumatology (ACR) now conditionally recommend starting treatment during a flare rather than waiting for it to resolve. However, the two randomised controlled trials (RCT) used to justify this recommendation had very small cohorts, alongside strict exclusion criteria and medicine regimens that do not reflect how gout is usually managed in a New Zealand.[25] A third open-label RCT published in 2021 also found that early allopurinol treatment did not significantly worsen or prolong acute flares, however, the study population had considerably different baseline characteristics to people affected by gout in New Zealand.[26] While this strategy may be acceptable for some patients with early stage gout – particularly if they express a preference for starting long-term prevention as early as possible – further evidence is required before it can be conclusively recommended for all patient groups.

Best practice tip: If a decision is made to initiate allopurinol during a flare, start at a low dose and ensure that the patient understands that they need to continue allopurinol after the flare has resolved, even when other medicines for treating the flare are ceased. Medicines used for the treatment of gout flares can be continued at lower doses for flare prophylaxis. In patients for whom urate-lowering treatment is indicated but allopurinol is not immediately initiated, ensure that either a prescription is written for them to pick up once the flare resolves, or that a follow-up appointment is scheduled.

Regular use is the key to long-term management

Explain to patients that the use of urate-lowering medicines needs to be regular and life-long to prevent flares of gout

Particular care is required with colchicine

Colchicine has a narrow therapeutic index meaning that the range between therapeutic and toxic effects is small and can overlap. Serious adverse effects associated with colchicine include paralytic ileus, myopathy, myocardial toxicity and blood dyscrasias. Colchicine is contraindicated in patients with significant gastrointestinal or cardiac conditions or pre-existing blood dyscrasias.[22] The adverse effects of colchicine may also be exacerbated by medicine interactions.[22] Caution is advised when prescribing colchicine to patients who are taking medicines that inhibit the CYP3A4 enzyme and/or P-glycoprotein, e.g. erythromycin, clarithromycin and verapamil.[22] There have also been reports of myopathy and rhabdomyolysis in patients taking colchicine with statins.[22] Colchicine is very toxic in overdose and there is no reversal agent; deaths have occurred with accidental overdose as low as 6 – 7 mg.

Prescribe the lowest effective dose of colchicine for the patient, and provide clear instructions on how and when to take it.[4] Patients should be advised to stop taking colchicine and seek medical attention if they experience nausea, vomiting, diarrhoea or abdominal pain.[22]

If the patient is taking very low dose colchicine for flare prophylaxis, this must be stopped during low dose colchicine treatment for an acute flare.

Further information is available from: **https://bpac.org.nz/bpj/2014/september/safer-prescribing.aspx**

The NZF interactions checker provides details on medicine interactions and their clinical significance, available from: **www.nzf.org.nz**

from returning. If initiation of urate-lowering treatment has been delayed until after a flare has been resolved, ensure that patients know that they should usually continue urate-lowering treatment during any future flares (assuming they have been adherent to allopurinol in the weeks and months leading up to the event). If urate-lowering treatment is stopped, even after years of being symptom-free, most patients will eventually experience a return of flares.[3]

Keep reading: "Part 2: Controlling gout with long-term medicines" available from: **bpac.org.nz/2021gout-part2.aspx**

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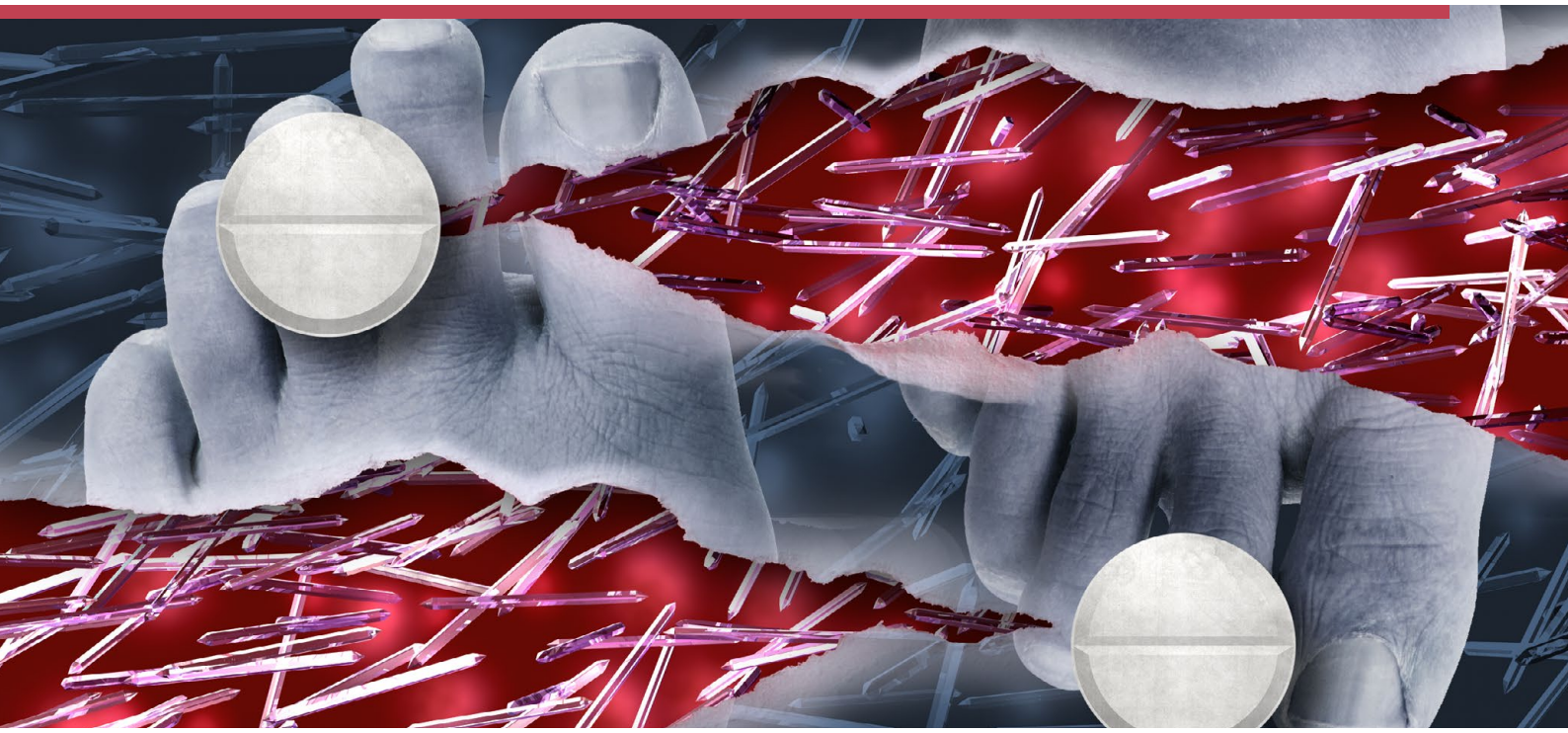

Managing gout in primary care

Part 2 – Controlling gout with long-term urate-lowering treatment

Urate-lowering medicines should be considered and discussed with patients with gout from the first presentation. Doses of urate-lowering medicines need to be titrated to effect so that patients consistently have serum urate levels that are below target. Three urate-lowering medicines are available in New Zealand and patients who are unable to achieve treatment targets with allopurinol alone should be offered an alternative regimen.

KEY PRACTICE POINTS:

- Doses of urate-lowering medicines need to be titrated so that the patient achieves a serum urate level that is below 0.36 mmol/L; a target below 0.30 mmol/L is recommended for those with features of severe disease, e.g. tophi
- Allopurinol is the recommended first-line urate lowering medicine; renal function is used to determine the starting dose
- Probenecid and febuxostat are available for patients who find allopurinol ineffective or intolerable
- Patients with gout require ongoing management of cardiovascular risk and monitoring for associated co-morbidities, e.g. chronic kidney disease and diabetes; they should also be provided with adequate support to ensure regular medicine use

For further information about managing patients with gout, including treating flares, see: "Part 1: Talking about gout: time for a rethink" available from: **bpac.org.nz/2021/gout-part1.aspx**

This is a revision of a previously published article. What's new for this update:

- Changes to urate-lowering medicines: general article revision
  - **Benzbromarone is to be discontinued.** Most people taking benzbromarone will have now switched to a different treatment and no new patients should be started on benzbromarone. Any patients remaining on benzbromarone should be changed to a different urate-lowering medicine as soon as possible.
  - Special Authority criteria has been amended for febuxostat; febuxostat is now funded for people with previous Special Authority approval for benzbromarone

Serum urate levels are treated to target

The goal of urate-lowering treatment is to reduce serum urate levels below saturation point in order to dissolve urate crystals, thereby preventing future gout flares.[1]

The recommended serum urate levels are:[2–4]

- < 0.36 mmol/L for most patients
- < 0.30 mmol/L for patients with severe gout, e.g. those with tophi, chronic gouty arthritis or frequent flares

After several years of symptom-free treatment and resolution of tophi, patients treated to < 0.30 mmol/L can be switched to the less stringent target of < 0.36 mmol/L.[1]

Testing of serum urate levels is recommended prior to dose adjustment, e.g. initially every four weeks, while urate-lowering treatment is being titrated and then every six to 12 months for monitoring.[4] During a flare, serum urate levels should not be tested for the purposes of monitoring the patient's response to treatment as their serum urate levels may be lower than normal.[5, 6]

Blister packs simplify treatment for patients and encourage adherence

Multiple medicines are often required for the initial treatment of gout, including acute flare management and prophylaxis, and increasing doses of allopurinol or another urate-lowering medicine. This requires careful instruction to ensure that the patient takes the right dose of the right medicine at the right time. A potential solution for some patients is to have medicines dispensed in a blister pack. In many cases, pharmacies will charge patients for this service, but some PHOs may fund this – check with your local PHO.

Table 1: Treatment options for flare prophylaxis.[1, 7, 8]

Medicine	Dose	Additional notes
Naproxen	250 mg, twice daily	Consider concurrent use of a proton pump inhibitor Avoid if eGFR < 30 mL/min/1.73m^2
Colchicine (unapproved indication)	Very low dose regimen: 500 micrograms, twice daily Reduce dose if required (see notes)	Reduce dose to 500 micrograms, once daily, or on alternate days, if not tolerated, e.g. diarrhoea develops, chronic kidney disease or concurrent use of CYP3A4/P-glycoprotein inhibitors (e.g. erythromycin, verapamil) Ideally avoid, or use with caution, in frail patients, those who weigh < 50 kg, or patients with hepatic or renal impairment (eGFR 10–50 mL/min/1.73m^2) Contraindicated if eGFR <10 mL/min/1.73m^2
Prednisone	5 mg, once daily	Second-line option if contraindications to NSAIDs or colchicine Taper slowly on withdrawal Monitor for corticosteroid-related adverse effects

Best practice tip: If the patient is receiving treatment for a gout flare with a NSAID or colchicine, continue the same medicine at a lower dose for prophylaxis once the flare has resolved. If a flare occurs during prophylactic treatment, stop the prophylactic dose and change to a regimen for acute treatment of a flare (for further information, see: "Medicines for gout flares are determined by the patient's characteristics" in Part 1 available from: **bpac.org.nz/2021gout-part1.aspx**).

Flare prophylaxis is recommended when initiating urate-lowering treatment

During the first months of urate-lowering treatment the rapid decline in serum urate is thought to disrupt pre-formed monosodium urate crystals making them more likely to provoke a local inflammatory response which can result in an acute flare of gout.[7]

Prophylactic treatment (Table 1) should generally be provided for at least the first six months alongside urate-lowering treatment. However, new guidance suggests that three to six months might be sufficient for some people, e.g. those who are symptom free at their three-month review after initiating urate-lowering treatment and have had a substantial drop in serum urate levels.[2] Prophylactic treatment may be required for longer than six months in people with frequent ongoing flares or tophi, e.g. 12 months or more, but the risks of ongoing treatment (i.e. adverse effects of NSAIDs or colchicine) needs to be weighed up with the potential benefits.[2] Further emphasis on optimising urate-lowering treatment and modifiable factors may be required.

Gradual dose titration also reduces the risk of flares, compared to starting full doses of urate-lowering treatment. The increased risk of flares during initiation of urate-lowering treatment should be discussed with patients and advice given to persist with urate-lowering treatment if a flare does occur.

Allopurinol is the first-line urate-lowering medicine

Allopurinol is a xanthine oxidase inhibitor that decreases the production of urate by inhibiting the metabolism of purines; it is the first-line urate-lowering medicine for patients with gout.[2, 9]

The starting dose of allopurinol is determined by the patient's renal function

Allopurinol is started at a low dose and slowly titrated upwards, to minimise the occurrence of adverse effects, until the patient reaches the target serum urate level (Table 2).[2] Allopurinol can be safely used in patients who have reduced renal function, with a lower starting dose and slower titration. Dose reductions are not routinely required in patients with declining renal function who are already established on allopurinol.

Dose titration is essential to achieve serum urate targets

Once allopurinol has been initiated, regular follow-up with serum urate testing is required while the dose of allopurinol is titrated upwards, until the serum urate target is reached. In patients without renal dysfunction, 30 – 50% will require a dose of allopurinol in excess of 300 mg per day to achieve a serum urate target.[3] Treatment with up to 600 – 800 mg per day of allopurinol can be expected to achieve a serum urate target in 75 – 80% of patients with gout.[3]

Other urate-lowering medicines (see below) are available for patients who are unable to tolerate allopurinol or achieve the serum urate target with allopurinol alone. However, some patients who continue to have serum urate levels slightly above target despite their maximum tolerated dose of allopurinol may choose to persist with allopurinol alone, rather than taking an additional medicine, if flares are controlled.

Community pharmacists may have an increasing role in the titration of allopurinol dosing with the use of standing orders provided by general practitioners, e.g. in the Owning My Gout and Gout Stop initiatives, see: **https://www.arthritis.org.nz/wp-content/uploads/2020/07/Gout-Programmes-Evaluation-Report-April-2020.pdf** for further information.

Table 2: Suggested starting doses and dose titrations for allopurinol determined by renal function.[8]

Estimated glomerular filtration (eGFR) mL/min/1.73m^2	Initial dose of allopurinol	Dose increase
> 60	100 mg, daily	Increase by 100 mg, every four weeks*, if tolerated, until the serum urate target is reached, or to a maximum of 900 mg, daily
30 – 60	50 mg, daily	50 mg, every four weeks, if tolerated, until the serum urate target is reached, or to a maximum of 900 mg, daily†
< 30	50 mg, every second day	

* Some prescribers prefer a more rapid titration, e.g. every two weeks, although this needs to be balanced against the increased risk of adverse effects

† Many people with renal dysfunction will be unable to tolerate the maximum dose of allopurinol; consider referral to or discussion with a rheumatologist if serum urate targets are unable to be achieved and an increase in dose is not tolerated, e.g. over 300 mg allopurinol daily

Adverse effects of allopurinol are relatively uncommon

Allopurinol is generally well-tolerated, although some patients will experience gastrointestinal symptoms.[1, 8] Hypersensitivity reactions caused by allopurinol can occur, e.g. drug rash with eosinophilia and systemic symptoms (DRESS) and Steven-Johnson syndrome. DRESS is a rare, but potentially fatal, condition characterised by an erythematous, desquamating rash, fever, eosinophilia, leukocytosis, hepatitis and renal failure.[4, 8, 10] DRESS is estimated to occur in 0.1% of patients taking allopurinol, most often in the first few weeks to months of initiating treatment.[4, 10] The risk of DRESS can be substantially reduced by introducing allopurinol at a low dose and slowly titrating upwards after tolerance has been established.[10] Patients should stop taking allopurinol and seek medical advice if they develop a rash or itch; an alternative urate-lowering medicine can be trialled. Risk factors for DRESS in patients taking allopurinol include renal impairment, an elevated starting dose of allopurinol relative to renal function, the use of diuretics, and having the *HLA-B*5801* allele which is often present in people of Korean, Thai or Han Chinese descent.[2, 4, 8, 10] Genetic testing for this allele is available; it is recommended to discuss testing with a local laboratory or with Genetic Health Service NZ, **www.geneticehealthservice.org.nz**

Add probenecid if serum urate targets are not achieved with allopurinol alone

Probenecid can be added to allopurinol if despite taking a relatively high dose of allopurinol, e.g. 600 mg daily, the patient is unable to achieve the serum urate target; assess for regular use of allopurinol first.[3] Probenecid can also be prescribed as monotherapy to patients who are intolerant or resistant to allopurinol.[9]

Probenecid dosing is titrated according to the patient's serum urate concentration:[8]

- Initially, 250 mg, twice daily, for one week, then 500 mg, twice daily, with the dose increased by 500 mg every four weeks, to a total of 1 g, twice daily, if required

Probenecid should be avoided in patients with an eGFR < 30 mL/min/1.73m^2.[8] Probenecid is contraindicated in patients with urolithiasis.[2, 9] Patients should be advised to drink plenty of fluids, at least two litres per day, to prevent the formation of uric acid stones and to take the medicine with, or just after, a meal.[8, 9] The most common adverse effects associated with probenecid are nausea and vomiting.[8]

Febuxostat is a further option for urate-lowering

If treatment with allopurinol and/or probenecid is ineffective or cannot be tolerated, febuxostat is a second-line xanthine oxidase inhibitor.[2, 4]

The recommended dose of febuxostat for patients with gout is:[8]

- 80 mg, once daily, increased to 120 mg*, once daily, after two to four weeks if the serum urate is > 0.36 mmol/L

* The maximum daily dose of febuxostat for patients with mild hepatic impairment is 80 mg

Special Authority for febuxostat has changed

The Special Authority criteria for febuxostat has been amended amid plans to discontinue benzbromarone (see: "Benzbromarone to be discontinued"). Febuxostat is now funded with Special Authority approval in New Zealand for patients with gout who:[8]

- Have a serum urate level > 0.36 mmol/L after having been treated with allopurinol at doses of at least 600 mg per day in addition to probenecid at doses up to 2 g per day or to a maximum tolerated dose; or
- Have intolerable adverse effects associated with allopurinol treatment requiring treatment discontinuation and have trialled probenecid at doses up to 2 g per day or to a maximum tolerated dose; or
- Have had treatment with allopurinol optimised, however, renal impairment means that probenecid cannot be added or is that it is likely to be ineffective; or
- Have had previous Special Authority approval for benzbromarone for the treatment of gout

Key prescribing points for febuxostat

Renal impairment. Febuxostat can be used in patients with renal dysfunction as this is not a significant route of elimination, however, caution is advised in patients with an eGFR < 30 mL/min/1.73m^2 due to a lack of safety data; although, as probenecid should be avoided in patients with an eGFR < 30 mL/min/1.73m^2, febuxostat is the recommended choice in this patient group (if allopurinol is not tolerated or adequate).[1, 8]

Hepatic impairment. Febuxostat should be avoided in patients with moderate or severe hepatic impairment as limited dosing information is available. Patients with mild hepatic impairment should not exceed a daily dose of 80 mg.[8] A liver function test is recommended prior to initiating febuxostat to provide a baseline as abnormal liver function tests have been observed in approximately 5% of patients taking febuxostat; liver function tests are recommended periodically thereafter based on clinical judgement.[8]

Cardiovascular disease risk. Caution is advised when considering prescribing febuxostat to patients with a history of CVD, however, this is not a contraindication.[2, 8] Some studies have suggested that febuxostat use is associated with an increased risk of CVD and all-cause mortality compared with

allopurinol.[2] The United States Food and Drug Administration (FDA) therefore updated prescribing information with a boxed warning in 2019, advising that clinicians should discuss the elevated cardiovascular risk with their patients and inform them about important symptoms to look out for, e.g. shortness of breath, chest pain.[11] More recent studies, however, have not found an increase in the risk of all-cause mortality associated with febuxostat compared with allopurinol, and one study even demonstrated a lower risk.[2, 12] Clinicians should ensure patients are aware of the evidence around CVD risk and febuxostat use as part of a shared decision making discussion.[2]

Combination treatment. Probenecid can be added to the treatment regimen if the patient is unable to achieve the target serum urate level with febuxostat alone, however, this combination is associated with a much more rapid decline in serum urate and can trigger flares in some people; prophylactic management with either a NSAID or colchicine is essential when using it for at least the first six months.[1, 7]

The adverse effects of febuxostat

Adverse effects most often associated with febuxostat are diarrhoea, nausea, elevated liver enzymes, oedema, headache and rash.[8] Rarely, hepatotoxicity or severe hypersensitivity reactions can occur in patients taking febuxostat.[8] Hypersensitivity reactions most often occur in the first weeks of treatment, including Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria and anaphylaxis.[8]

There is an increased risk of flares in patients taking febuxostat, compared to allopurinol, therefore flare prophylaxis is particularly important in the first months of treatment.[1]

Benzbromarone to be discontinued

Benzbromarone has not been included as a treatment option for long-term gout prophylaxis in this article as it is set to be delisted from the Pharmaceutical Schedule.*[13] Most people taking benzbromarone will have now switched to a different treatment and no new patients should be started on benzbromarone. Any patients remaining on benzbromarone should be changed to a different urate-lowering medicine as soon as possible.[13] The amendment of the Special Authority for febuxostat now allows patients who were taking benzbromarone to access funded febuxostat treatment.[13]

* As of July, 2021, there is no date set for delisting – for up to date information, visit the **PHARMAC website**

Supporting patients taking urate-lowering medicines[1]

- Acknowledge that taking a medicine every day for gout can be challenging. Regularly ask the patient how they are coping with this process and continue to encourage on-going use of urate-lowering medicines to prevent gout flares.
- Once the patient achieves their serum urate target, continue to measure serum urate levels at least every six to 12 months and make any necessary adjustments to the treatment regimen if the target level is not maintained. Titrating and identifying the optimal dose of a urate lowering medicine can be challenging, and patients need to be supported and reassured throughout this process.
- Re-iterate that although biological factors (e.g. chronic kidney disease, genetic variation) and some medicines (e.g. diuretics) are important causes of gout, other modifiable factors such as diet can trigger flares. By being aware of these triggers, and taking urate-lowering medicines consistently, future flares can be prevented. In some cases, patients will eventually be able to consume small portions of trigger foods, such as kaimoana (seafood), without experiencing a gout flare.
- Use motivational interviewing to encourage lifestyle changes including weight loss and regular exercise which in turn may help to reduce co-morbid cardiovascular and diabetes risk (see: "Part 1: Talking about gout: time for a rethink" available from: **bpac.org.nz/2021gout-part1.aspx**). Other medicines such as statins and antihypertensives may need to be added, if appropriate.
- Track any changes in clinically relevant biomarkers, e.g. at least an annual assessment of blood pressure, HbA_{1c} and renal function

The appropriate selection and use of cardiovascular medicines

For patients with gout and hypertension, losartan or calcium channel blockers are the antihypertensive medicines of choice as they reportedly have mild uricosuric (urate-excreting) properties.[2] Diuretics are known to reduce urate excretion and therefore contribute to the onset or exacerbation of gout. Patients who are taking diuretics for hypertension, for reasons other than heart failure, should be switched to an alternative antihypertensive, if possible.[2] Aspirin is also known to decrease excretion of uric acid, however, patients who are taking low-dose aspirin for the secondary prevention of cardiovascular disease should continue to do so.[2]

Reducing the risk of kidney stones

Kidney stones occur in one in seven patients with gout and patients taking uricosuric medicines, e.g. probenecid, are at increased risk.[1, 4] Increasing water consumption will decrease the risk of uric acid stone formation for all patients with gout (e.g. aim for ≥ 2L water daily). Treatment with a xanthine oxidase inhibitor, e.g. allopurinol, and a reduction in dietary purines (see: "Part 1: Talking about gout: time for a rethink" available from: **bpac.org.nz/2021gout-part1.aspx**) will also decrease the likelihood of uric acid stones forming.[2]

Further information on managing kidney stones and renal colic is available from: **https://bpac.org.nz/bpj/2014/april/colic.aspx**

When to consider referral to a rheumatologist

Patients should be discussed with or referred to a rheumatologist if they have:

- A serum urate level consistently ≥ 0.36 mmol/L, despite adherence to optimal urate-lowering treatment
- Persistent arthritis, despite a serum urate level that is persistently < 0.36 mmol/L
- Significant renal dysfunction and there are concerns about increasing the dose of urate-lowering treatment

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