Best Practice Message

March 2023

Gout Prophylaxis

Practice changing moments:

- Start urate lowering therapy early. In high-risk populations treatment should be considered at the first flare and highly recommended at the second presentation of gout.
- Allopurinol can be initiated during an acute flare and should be continued if a flare occurs during treatment.
- Consider prophylactic cover while titrating dose of allopurinol AND for at least a month after reaching target to reduce the risk of gout flare during titration.
- The starting dose of allopurinol is dictated by renal function, however if renal function declines, allopurinol dose does not need to be adjusted.
- Consider referring to the Mate Taihā programme to support tāne Māori (Māori men) with gout.

Introduction

The key risk factors for gout are genetics and ethnicity (diet only plays a minor role). Māori and Pacific peoples are, respectively, two and three times more likely than non-Māori, non-Pacific peoples to get gout[2]. Māori and Pacific patients with gout experience early onset, poorly controlled serum urate concentrations and severe disease with frequent flares[3]. Māori are also 6.9 times more likely to be hospitalised with gout when compared to non-Māori and non-Pacific people[4]. Gout carries a large medical and economic burden;

- Gout is frequently associated with co-morbidities such as, diabetes, chronic kidney disease, hypertension and cardiovascular disease[5].
- People with gout are more likely than those without gout to die at a younger age due to cardiovascular disease and renal complications[5].
- When untreated, acute attacks can become more frequent and persist longer while involving more joints.
- In 2019 the average cost of a hospital admission with a primary diagnosis for gout was $4301[1]. In Hawke's Bay there were 62 such admissions last year.
- For patients, time off work during flares and cost associated with receiving treatment.

Many people manage gout by only treating acute flares, often with NSAIDs. Māori and Pacific peoples are significantly more likely than European patients to be hospitalised with serious complications, including acute kidney injury, after being dispensed NSAIDs[6]. The treat to target approach, using urate lowering therapy is the most effective medical strategy for gout management and is recommended by all rheumatology bodies. Māori and Pacific peoples are less likely to receive regular urate lowering therapy, due to a complex combination of issues[2]. Long-term medication adherence is influenced by:

- Patient understanding of the condition and of the different roles of their medications.
- Medication cost.
- Patient age and co-morbidities. Younger patients and those who do not take other regular medicines are less likely to take regular urate-lowering therapy[1].

Initiate Urate Lowering Therapy (ULT) early

Well managed ULT reduces the need for acute medicines therapy. The benefit of ULT also goes beyond gout. People with gout who take urate-lowering treatment also have significantly lower risk of coronary artery disease or stroke[7].

ULT, should be discussed at the first gout flare and strongly recommended at the second in the high-risk populations of Māori and Pacific peoples, even in patients presenting at a young age (<40 years).

Allopurinol

Allopurinol is still the first-line urate-lowering medicine. Allopurinol inhibits xanthine oxidase, the enzyme that catalyses the conversion of purine to xanthine before it is converted to uric acid, reducing levels, supressing gout flare, and facilitating dissolution of tophi[8]. Allopurinol can be initiated during an acute flare[9] and does not need to be stopped if a flare occurs during treatment.

Initiating allopurinol

Sudden changes in serum urate are likely to precipitate a gout flare. To reduce the risk of triggering a flare:

- Start at a low dose and increase gradually.
- Allopurinol should be titrated to a target serum urate less than 0.36mmol/L or 0.30mmol/L for tophaceous gout. (On average patients with normal renal function require a dose of 400mg to achieve uric acid target of 0.36mmol/L[10].)
- Monitor serum urate 1 to 3 monthly until target is achieved, then continue 6 to 12 monthly to ensure maintenance of target[11,12].
- Prescribe in combination with a prophylactic dose of colchicine, naproxen, or prednisone. With prophylaxis the risk of a flare is reduced to 20-30% compared to 77% of patients without cover, within the first 6 months of allopurinol therapy[13].

See Appendix 1 for suggested allopurinol initiation and prophylactic cover treatment regimen.

Allopurinol and renal function

Renal function results dictate the starting dose and titration of allopurinol. A safe starting dose of 1.5mg/ml/min of eGFR with 4 weekly increments of dose titration is recommended to minimise the risk of AHS and gout flares (See Appendix 1). Once the dose of allopurinol required to produce a urate level target of less than 0.36mmol/L is reached, there is no need to reduce the dose if renal function declines.

Allopurinol Hypersensitivity Syndrome (AHS)

AHS is the most concerning adverse effect of allopurinol. It is estimated to occur in 0.1 %, with mortality of 27%. The risk is greatest during the first few months of therapy. AHS presents as a rash (Stevens-Johnson syndrome, toxic epidermal necrolysis), eosinophilia, leucocytosis, fever, hepatitis and renal failure[14]. Starting at a high dose, or titrating too quickly, and HLA-B*5801 allele (predominantly in Han Chinese or Thai ancestry) can increase the risk AHS[14].

Although there are non-AHS rashes, the risk of AHS means that patients should be told to report any rash immediately.

Other ULT options

Probenecid

Probenecid is a uricosuric and renal tubular blocking agent, which increases uric acid excretion. Probenecid should not be used in patients with a history of kidney stones. Patients need to drink at least 2 litres of water per day to reduce their risk of developing uric acid stones. See NZF for further prescribing advice[15].

Febuxostat

Febuxostat can be used in patients who do not tolerate or respond to allopurinol or probenecid. It should be avoided in patients with major cardiovascular disease[16]. Febuxostat lowers serum uric acid much more quickly than allopurinol and more commonly triggers acute attacks, always co-prescribe colchicine or NSAID for 6 months. See NZF for further prescribing advice and special authority links[16].

Losartan

Consider losartan as a first line option for treating hypertension when the patient also has gout. It is thought that losartan inhibits the renal urate transporter URAT1 decreasing reuptake from the urine, and it has been proven to reduce serum urate by 20 to 25%.[17]

Introducing Mate Taihā

The Mate Taihā pilot programme is a Māori centric, culturally responsive programme to support tāne Māori who experience inequitable gout outcomes. The Te Whatu Ora, Te Matau a Māui led initiative is based on the successful Counties Manukau community pharmacy gout management service. The service also has similarities to the Community Pharmacy Anticoagulation Management Programme (CPAMs) provided by many Hawke's Bay pharmacies.

The point of difference with the Hawke's Bay programme is that it is led by a team of kaitakawaenga, who will be working closely with tāne Māori to educate and support.

Contracted and trained community pharmacists will be able to do point of care uric acid testing and escalate allopurinol doses under a standing order to reach uric acid targets. Any changes made to dosing will be communicated to General Practitioners via HL7 messaging to inboxes (similar to INR monitoring with CPAMs).

In the initial phase of the programme the standing order will be signed by a Rheumatologist, while work is underway to contract general practices.

The intention is that this will be a collaborative programme between kaitakawaenga, general practices, and community pharmacies to offer a whānau centred service.

Tools available:

- Epic dashboard: Gout
- NZF interaction checker
- Medsafe: Medicines for gout patient information
- HQSC. Atlas of Healthcare Variation: Gout
- He Ako Hiringa: Gout resources
- SafeRx colchicine
- Let's talk gout – Health literacy model

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Appendix 1: Treatment of acute flare, initiation of allopurinol and prophylactic cover

1. Treat acute gout flare with colchicine, naproxen or prednisone (depending on co-morbidities) short term as directed.
2. Initiate allopurinol and titrate to target. This can be done during an acute flare, as long as the flare is treated appropriately. Continue lifelong.
3. After treating acute flare, initiate prophylactic cover with colchicine, naproxen or prednisone. Continue for 3 to 6 months.

Treatment options for acute gout flare			
Consider renal function:			**Consider cautions and contraindications:**
eGFR ≥60ml/min	**eGFR ≥30 to <60ml/min**	**eGFR <30ml/min**	
Colchicine			
1 mg immediately, followed by 0.5mg after one hour; maximum dose of 1.5mg within 3 days.	0.5mg immediately, followed by 0.5mg after one hour; maximum dose of 1.5mg over 3 days.	0.5mg immediately, followed by 0.5mg after one hour; maximum dose of 1.5mg over 3 days. **Contraindicated if eGFR <10ml/min**.	Contraindicated in: • Severe liver impairment (Child-Pugh C). • Blood disorders. Use in caution: • Concurrent strong CYP3A4 inhibitors or P-glycoprotein inhibitors (eg macrolides, verapamil). • Concurrent medicines that can cause blood dyscrasias or bone marrow suppression. • Gastrointestinal disease. Do not start prophylactic colchicine until 12 hours or more after acute dose.
Naproxen			
500mg BD for 5 days (or less if symptoms resolve).	250mg BD for 5 days (or less if symptoms resolve).	Avoid.	Contraindicated in: • Cardiovascular disease HF, HTN. • Active duodenal or gastric ulcer. Use in caution: • Concurrent thiazide, ACEi or ARB. • Risk of peptic ulceration or gastro-intestinal bleeding (consider a PPI).
Prednisone			
20- 40mg once daily for 5 to 10 days.	20- 40mg once daily for 5 to 10 days.	20- 40mg once daily for 5 to 10 days.	Use in caution: ▪ Diabetes; prednisone may cause a short term rise in blood glucose.

Allopurinol initiation and titration

Consider renal function:			**Consider cautions and contraindications:**
eGFR ≥60ml/min	**eGFR ≥30 to <60ml/min**	**eGFR <30ml/min**	
Initiation:			Consider drug interactions, such as: • Azathioprine and mercaptopurine. • Warfarin.
100mg PO daily for 1 month.	50mg PO daily for 1 month.	50mg PO alternate days for 1 month.	
Titration until uric acid target reached:			
Titrate by 100mg each month.	Titrate by 50mg each month.	Titrate by 50mg every month.	

Treatment options for prophylactic cover

Consider renal function:			**Consider cautions and contraindications:**
eGFR ≥60ml/min	**eGFR ≥30 to <60ml/min**	**eGFR <30ml/min**	
Colchicine			
0.5mg PO od.	0.5mg PO od.	0.5mg PO od. **<u>Contraindicated if eGFR <10ml/min.</u>**	Contraindicated in: • Severe liver impairment. • Blood disorders. Use in caution: • Concurrent strong CYP3A4 inhibitors or P-glycoprotein inhibitors. • Concurrent medicines that can cause blood dyscrasias/bone marrow suppression. • Gastrointestinal disease. *Off license indication
Naproxen			
250mg PO bd.	250mg PO bd.	Avoid.	Contraindicated in: • Cardiovascular disease HF, HTN. • Active duodenal or gastric ulcer. Use in caution: • Concurrent thiazide, ACEi or ARB. • Risk of peptic ulceration or gastro-intestinal bleeding (consider a PPI).
Prednisone (3rd line)			
5mg od.	5mg od.	5mg od.	Use in caution: • Diabetes; prednisone may cause a short term rise in blood glucose . Consider only if colchicine and NSAIDs are contraindicated.

Adapted from the LASSO Medication plan, provided by Professor Nicola Dalbeth (Consultant Rheumatologist), University of Auckland, with input from Rachael McNeill and Dr Hamish Gibbs

Appendix 2: Key points to raise with gout patients:

Adapted from Health Navigator New Zealand

- Gout is a long-term disease caused by deposits of urate crystals:
  - Gout is the most common form of inflammatory arthritis. It's caused by a build-up of uric acid in joints which is often very painful.
  - Most Māori and Pasifika have genes that stop their kidneys getting rid of uric acid in their urine.
  - If your kidneys can't get rid of uric acid, it turns into crystals in your joints which cause a painful gout attack. Once the pain goes away the crystals remain in the joints.
  - If you don't treat your high levels of uric acid, the crystals can cause permanent damage to your joints and harm to your kidneys.

- In the long-term, allopurinol (or other long-term urate lowering treatments) can stop flares from happening.
  - The only way to help your body get rid of uric acid and dissolve the crystals in your joints is to take long-term urate lowering treatment.
  - Daily, life-long treatment can be challenging and hard to accept, however long-term urate lowering treatment will reduce and potentially stop gout attacks and harm with overuse of anti-inflammatories.
  - Allopurinol is a safe and highly effective medicine.

- 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.
  - Gout is serious, it's not just "a pain in the toe".
  - If gout isn't treated, it can cause permanent damage to your joints and harm your kidneys.
  - Long-term uric acid medicines can reduce the risk.

- Raise awareness of genetic predisposition to gout in Māori and Pacific peoples; this can reduce whakamā and encourage treatment programme participation:
  - What you eat and drink only makes a small difference to your uric acid levels.
  - Gout is not your fault. There is no shame in having gout, and no need to blame yourself. Remember it's your genes that stop your kidneys getting rid of uric acid.

- Discuss the purpose and benefits as well as potential side effects of prophylaxis treatment.