

ALLOPURINOL

KEY POINTS

- Allopurinol is moderately effective in reducing uric acid levels and gout recurrence.
- Patients with a gout history who remain hyperuricaemic have a higher risk of an acute gout attack. The risk of recurrent gout is minimised if serum uric acid is maintained below 0.36mmol/L.
- Over half of acute gout relapses occur within the first 3 months after a previous acute attack.
- Gout may be associated with various precipitating factors (diuretic use, acute renal dysfunction, alcohol or dietary indiscretion). When these factors are improved, treatment with allopurinol may become unnecessary.
- Patients with a gout attack in the distant past who have a low risk of relapse can often have their allopurinol deprescribed.

CONTEXT

This guide considers the use of allopurinol as urate lowering therapy to reduce relapses of acute gout.

RECOMMENDED DEPRESCRIBING STRATEGY

- Determine key aspects of the patient's gout history:
 - Presence of factors that contributed to gout attack
 - If the attack was less than or greater than 12 months previously
 - Current uric acid level
 - Dose of allopurinol
- If the patient's gout attack was clearly due to precipitating factors such as acute renal failure, use of diuretics, dietary or alcohol indiscretion, which have since been modified, cessation of allopurinol may be reasonable.
- If the patient's gout attack was more than 12 months previously and the serum uric acid is well in the normal range (<0.36mmol/L) then cessation of low dose (100mg or less) allopurinol may be reasonable (no more than a 50% increase in uric acid may be expected). They can then be considered as a patient with asymptomatic hyperuricaemia.
- If the patient's gout attack was less than 12 months previously and the serum uric acid is high (>0.36mmol/L), then a dose increase or change of drug may be required in an attempt to achieve this target.
- A detailed deprescribing algorithm is shown in **Figure 1** on page 2.

BENEFIT VERSUS HARM

	Favours Continuing Medication	Favours Deprescribing Medication
Main Benefits ➢ Reduced risk of gout relapse	Increased Benefit ➢ Recent gouty arthritis ➢ Presence of tophi ➢ Maintaining Uric Acid levels below 0.36mmol/L	Decreased Benefits ➢ Lower doses of allopurinol ➢ Low risk of gout relapse
Main Harms ➢ Worsening renal dysfunction and serious skin toxicity	Reduced Harms ➢ Appropriate dose adjustment for renal dysfunction	Increased Harms ➢ Renal Dysfunction ➢ Han Chinese, Korean or Thai descent

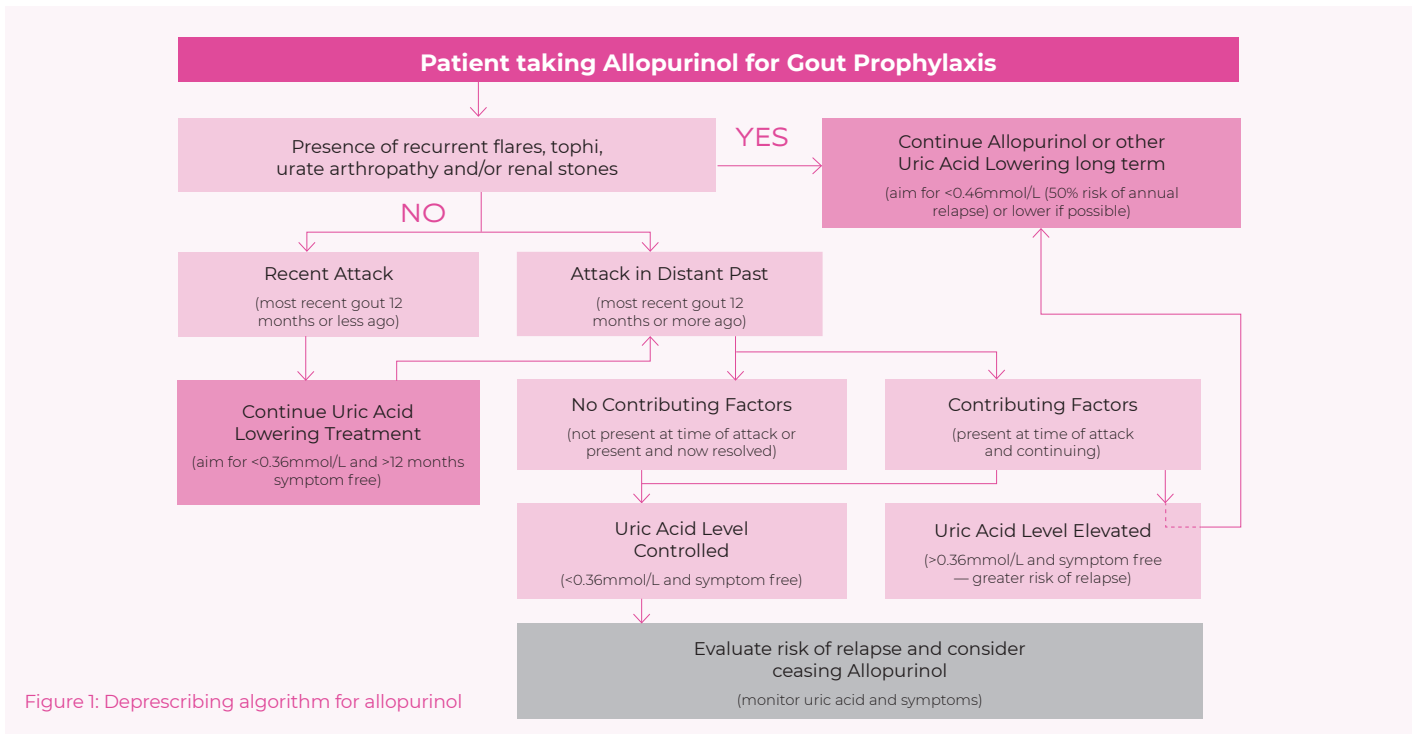


Figure 1: Deprescribing algorithm for allopurinol

BACKGROUND

Gout is a major issue worldwide and is the most common form of inflammatory arthritis. The risk of both an initial gout attack and recurrent gouty arthritis increases with uric acid levels.

Hyperuricaemia, a precondition for gout, is associated with the metabolic syndrome and is an independent risk factor for chronic kidney disease, stroke and possibly ischaemic heart disease.¹ It is associated with multiple adverse health effects including hypertension, cardiovascular disease and is involved as an important aspect of the metabolic syndrome.² In addition, hyperuricaemia is now being considered as a modifiable risk factor for deterioration of renal function.³

The management of gout is complicated by the episodic nature of the disease.

In a population study of 2389 patients in South Australia, the overall prevalence of (self reported) gout was 5.2% (males 8.5%; females 2.1%).⁴ Hyperuricaemia (uric acid $>0.42\text{mmol/L}$ for men and $>0.34\text{mmol/L}$ for women) was present in 17.8% of males and 15.4% of females.

In the Framingham Heart Study, there was an increase in both incidence and relative risk of developing gout with increased serum urate (see **Figure 2**).⁵

The likelihood of recurrent gouty arthritis increases with elevation of the serum uric acid level, with 50% of patients with an average uric acid level of 0.46mmol/L having an attack 12 months or more after an initial attack. An average uric acid level of 0.36mmol/L or less was associated with a risk of relapse of less than 20% (see **Figure 3**).⁶

Reducing the uric acid level below 0.36mmol/L also results in the mobilisation of urate crystals out of joints and soft tissue. The lower the serum urate level, the faster the resolution of the crystal deposition.

The European League Against Rheumatism recommendations for the management of gout suggest lowering of uric acid for people with recurrent flares, tophi, urate arthropathy and/or renal stones.⁷ They recommend treatment be lifelong in such patients (based on a 40% relapse of gout over 5 years after cessation of uric acid lowering therapy).

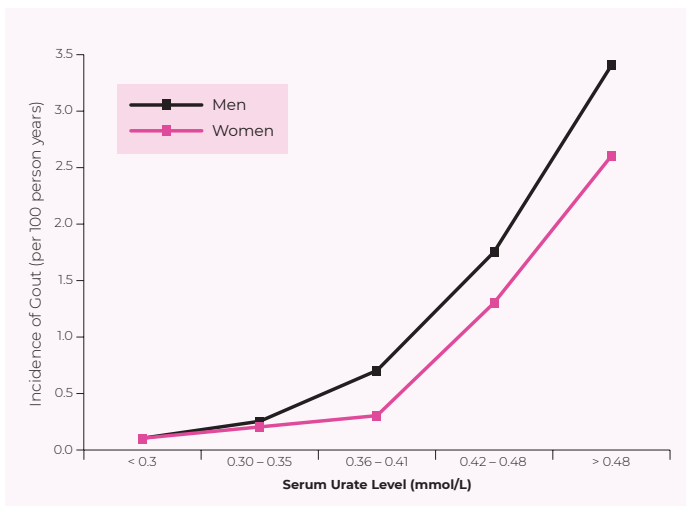


Figure 2: Incidence of initial gout attack based on uric acid level.⁵

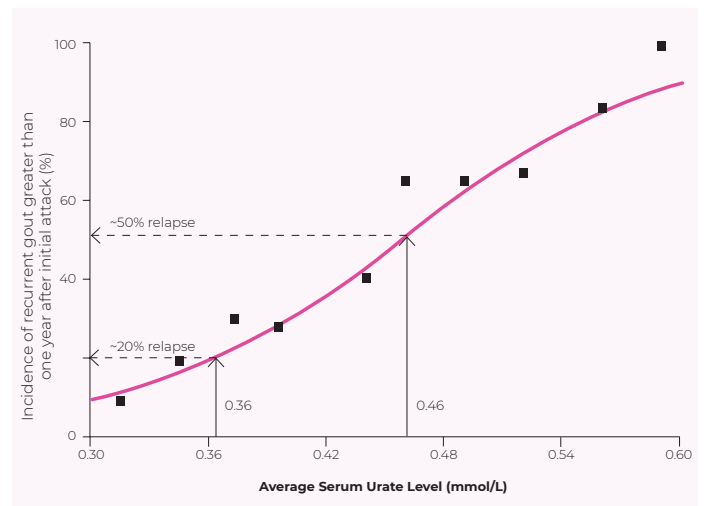


Figure 3: Frequency of recurrent gout according to uric acid level.⁶

EFFICACY

Urate lowering therapy is indicated in patients who have had an acute gout attack and whose uric acid level remains high, increasing the risk of a subsequent attack.

The effect of allopurinol on uric acid level is dose dependent and variable. Graham et al examined blood levels of uric acid in 112 samples from patients taking various doses of allopurinol for at least one month.⁸ As can be seen in **Figure 3**, doses of 300mg or more are required to achieve a 50% or more reduction in uric acid level.

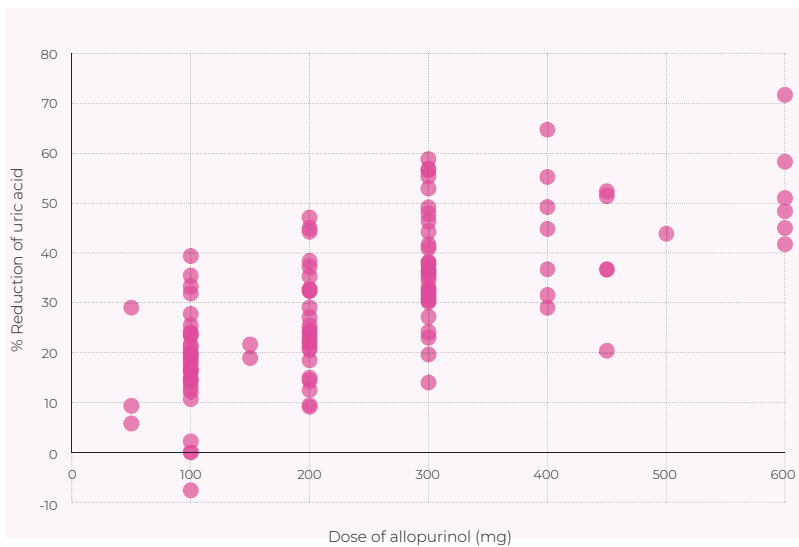


Figure 3: Percent reduction of uric acid level with various doses of allopurinol⁸

It is recommended that the dose of allopurinol be reduced in the presence of renal dysfunction in order to reduce the risk of serious adverse effects from accumulation of oxipurinol, the suspected toxic metabolite. There is little information available about the potential for reduced efficacy in this setting. It would be expected that a lower dose would have lower efficacy. In addition, patients with a degree of renal dysfunction have reduced elimination of uric acid, further limiting the efficacy of xanthine oxidase inhibitors, which reduce production of uric acid, rather than increase elimination.

A study of allopurinol used at an appropriately adjusted dose (based on creatinine clearance) have shown reduction of uric acid to target post-gout range (< 0.36mmol/L) in ~20% of patients at three months and ~40% of patients at 6-12 months.⁹

A review of allopurinol for chronic gout summarised all available literature to January 2014. Acute gout attacks occurred at a rate of 12 per 100 patients over 30 days with placebo, compared to 7.7 per 100 patients with allopurinol [36% relative risk reduction, Absolute Risk Reduction 4% (95%CI -21-12); NNT 25].¹⁰

Over a longer period of time, the percentage of patients who required treatment for gout flares in the first month of treatment with allopurinol (following an attack) was ~11%, compared to ~4% in the sixth month of treatment (**over half of the acute gout treatments were required in the first 3 months after the attack**).¹¹

FACTORS TO CONSIDER

IN FAVOUR OF DEPRESCRIBING

- ✓ Many of the precipitating factors for gout are avoidable or modifiable.
- ✓ It is unclear to what extent pharmacological management of hyperuricaemia in combination with modification of avoidable factors has on the recurrence of gout.
- ✓ Ceasing of allopurinol may be possible in patients who have ceased or reduced diuretics, or whose renal function has improved or whose dietary and alcohol intake have improved.
- ✓ It is unclear whether patients with metabolic syndrome (i.e. glucose intolerance, hypertension, dyslipidaemia and obesity) or chronic kidney disease will gain a benefit from reducing elevated uric acid levels.

AGAINST DEPRESCRIBING

- ✗ Ongoing use of allopurinol is indicated if the person has:
 - recurrent attacks of gout
 - evidence of uric acid nephropathy or urolithiasis
 - presence of tophi.
- ✗ Ongoing treatment may also be indicated if the patient has an underlying condition (e.g. severe renal disease or a myeloproliferative disease) that may be improved by controlling the hyperuricaemia.

RESOURCES

- GENERAL INFORMATION
- ALLOPURINOL
- ANTIHYPERGLYCAEMICS
- ANTIHYPERTENSIVES
- ANTIPSYCHOTICS
- ASPIRIN
- BENZODIAZEPINES
- BISPHOSPHONATES
- CHOLINESTERASE INHIBITORS
- GLAUCOMA EYE DROPS
- NSAIDS
- OPIOIDS
- PROTON PUMP INHIBITORS
- STATINS
- VITAMIN D AND CALCIUM

AUTHORSHIP

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 ADVERSE EFFECTS

Allopurinol is usually well tolerated, with the main adverse effects of concern being dermatological in nature. These include mild to moderate skin rashes which are usually maculopapular and pruritic. More rarely, a purpuric and exfoliative rash can occur as part of a severe and sometimes fatal hypersensitivity syndrome. The presence of the Human Leucocyte Antigen (HLA)-B*5801 allele may be associated with an increased risk of developing Stevens-Johnson syndrome (SJS), syndrome of drug rash with eosinophilia and systemic symptoms (DRESS), or toxic epidermal necrolysis (TEN) during treatment with allopurinol.

The frequency of the HLA-B*5801 allele varies across ethnic groups. It is recommended that screening for the HLA-B*5801 allele be considered in patient groups with a known high frequency of this allele. If genetic testing for HLA-B*5801 is unavailable in patients of Han Chinese, Korean, or Thai descent, the risk-benefit should be considered prior to initiation of allopurinol.^{12,13}

It is the increased likelihood of this potentially life-threatening adverse effect that has brought about the renal function-based dose recommendations for allopurinol.¹⁴ Commencement of allopurinol should therefore be with a low dose, generally no more than 100mg daily. Slow increases may be made at monthly intervals according to response, aiming for a plasma urate concentration <0.36 mmol/L.

Recommended commencement doses based on eGFR are:

- >60mL/minute/1.73m², initially 100mg once daily
- 45–60mL/minute/1.73m², initially 50mg once daily alternating with 100mg once daily
- 30–45mL/minute/1.73m², initially 50mg once daily
- 15–30mL/minute/1.73m², initially 50mg on alternate days
- <15mL/minute/1.73m², initially 50mg twice a week

 DISCONTINUATION SYNDROMES

None described

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