



Therapeutic brief

21



Revisiting gout management in your veteran patients

In 2008, 27,357 Australian veterans were dispensed medicines for gout¹, the most common form of inflammatory arthritis. Gout is a chronic condition that can also cause uric acid calculi in the renal tract. Tophaceous deposits can result in joint damage and sometimes nerve compression and chronic skin ulcers. There is a clear association between serum uric acid levels and future risk of gout.

Men with gout have a higher risk of death from all causes but especially coronary artery disease.² Both hyperuricaemia and gout are strongly associated with hypertension, obesity, diabetes, hyperlipidaemia, atherosclerosis and alcohol abuse. The median number of co-morbidities among Australian veterans with gout is 7.¹ The limited evidence available suggests prophylactic treatment is not required after only one episode of acute gout or for asymptomatic hyperuricaemia. Other studies indicate drug doses are not always adjusted in older people or those with renal impairment despite the risk of toxicity.^{3,4}

This module aims to assist GPs in tailoring their veteran's gout treatment by considering the co-morbidities which impact on the choice of gout medications.

Key points

- ✓ Do not treat asymptomatic hyperuricaemia
- ✓ Remember half of those with acute gout will have a normal serum uric acid level
- ✓ Review need for and dose of allopurinol; 100-150mg/ daily will be sufficient for most elderly veterans
- ✓ Reduce dose of allopurinol in renal impairment
- ✓ Avoid long term use of colchicine
- ✓ Reduce dose of short term colchicine in renal impairment

Inside

- Gout and the veteran population p1
- Is it gout? p1
- Management of acute gout p2
- Prevention of recurrent gout p3
- Addressing risk factors for gout p4
- Advise your patients to p4

www.veteransmates.net.au

Gout and the veteran population

The prevalence of gout has doubled over the last two decades and may be related to increased longevity, obesity, renal disease, use of diuretics and low dose aspirin, hypertension and metabolic syndrome.⁵ Analysis of the UK General Practice database showed prevalence rates for gout peaked in men between the ages of 75 and 84 yrs while in women disease prevalence continued to rise beyond 85 years of age.⁶ When it occurs in the elderly, gout tends to have a polyarticular presentation, fewer acute gouty episodes, an indolent clinical course and an increased incidence of tophi.^{7,8}

Within the ageing veteran population gout will become an increasingly recognised source of morbidity.

Is it gout?

Deposition of uric acid crystals causes the inflammation associated with gout, however half of all patients with acute gout will have a normal serum uric acid level. Joint aspiration and synovial fluid microscopy is the gold standard for diagnosis. Other diagnoses to consider when assessing monoarticular 'arthritis' include septic arthritis, haemarthrosis, osteoarthritis, psoriatic arthritis, bursitis and pseudogout. Pseudogout (calcium pyrophosphate deposition disease) also presents as episodic monoarthritis but takes longer to reach maximal inflammation and resolves more slowly than gout.⁷



② Management of acute gout

Acute gout is an intensely painful condition so the goal of initial therapy is prompt and safe relief of pain and inflammation. Several drugs have traditionally been used despite a lack of high quality randomised placebo-controlled trials. These include;

NSAIDs (including COX-2 inhibitors)

Usually considered first line therapy for most patients with acute gout. Resolution of symptoms usually occurs within 7 to 10 days. There is comparable efficacy between the various NSAIDs and COX-2 inhibitors. Side effects are well known and include GI ulceration, renal impairment, worsening of heart failure and hypertension, making them potentially unsuitable for many veterans with gout. The dose of NSAID/COX-2 inhibitor should be reduced to half as soon as improvement is noted and then gradually withdrawn over no less than one week.⁹

Corticosteroids

Can be given orally or injected into the affected joint. Intraarticular corticosteroids are a reasonable option for those with only one or two affected joints and either methylprednisolone or triamcinolone can be used. Infection must be excluded before joint injection is considered.

Systemic corticosteroids are usually administered orally and the dose typically used is prednisone 20–50mg once daily for 3 to 5 days, tapering over 7 to 10 days.^{9,10} Side effects from short-term systemic corticosteroids can include fluid retention, mood or sleep disturbance and hyperglycaemia.

Colchicine

Reduces the inflammatory reaction to urate crystals and has been used for decades although the published doses for gout are based on little evidence. Colchicine may be slower to work than NSAIDs and at traditional doses the majority of patients will experience adverse effects - nausea, vomiting or diarrhoea - within 24 hours, making it unsuitable for many elderly patients with gout. Dose reduction is also required in those with renal or hepatic impairment.^{9,11}

The United States Food and Drug Administration has recently clarified safety concerns associated with the use of colchicine and advised the use of much lower doses.¹² This recommendation followed a multicentre, randomised, double-blind trial which demonstrated that a significantly lower dose of colchicine was as effective in acute gout as traditional higher doses, with fewer adverse events (See Table 1).

To address some of these safety concerns, a smaller pack size of 30 tablets will be available in early 2010 in Australia. Current recommended dose is 0.5 mg orally given 6 to 8 hourly until the attack has abated.¹³ The United States Food and Drug Administration advise that the total dose of colchicine used in acute gout should ideally not exceed 2mg.¹² In the elderly veteran population (average age of 80 years with 7 co-morbidities) it would seem prudent to use this lower colchicine dose and avoid exposing veterans to increased risk of gastrointestinal side effects for no gain in pain management.

Cases of fatal colchicine toxicity have occurred with concomitant administration of clarithromycin in particular, but also erythromycin, verapamil, diltiazem and ketoconazole.

A recent Cochrane Review determined colchicine should be used as second line therapy in acute gout when NSAIDs/COX-2 inhibitors or corticosteroids are contraindicated or ineffective.¹⁴

Table 1. Results of US clinical trial evaluating safety and efficacy of lower dose colchicine in acute gout

Colchicine dose*	High 4.8mg total (N=52)	Low 1.8mg total (N=74)	Nil Placebo (N=59)
Patients achieving 50% reduction in pain	33%	38%	16%
Patients experiencing gastrointestinal side effects	77%	26%	20%

*600mcg tablets available in the USA.

Prevention of recurrent gout

Intervals between gout flare ups vary but most untreated patients will experience a second episode within 2 years.¹⁵ The main indications to start preventive therapy in patients with a history of gout are;

- Frequent and disabling attacks (generally defined as more than 2 or 3 annually)
- Chronic gouty joint disease
- Tophaceous gout
- Recurrent nephrolithiasis

Treatment to lower urate levels is initiated once the acute inflammatory phase has resolved as initiation during an acute attack can worsen the arthritis. Medications which lower serum urate levels do so by reducing production of uric acid (xanthine oxidase inhibitors) or enhancing its renal excretion (uricosuric drugs).

Allopurinol

Allopurinol, a xanthine oxidase inhibitor, is the drug most commonly used for prevention of recurrent gout. It has a renally excreted active metabolite, oxypurinol, so caution is required when the patient has renal impairment. The degree of renal impairment can be estimated using the Cockcroft-Gault formula (Fig 1) and the dose of allopurinol adjusted as necessary (Table 2).

Fig.1 Cockcroft-Gault formula* for creatinine clearance estimation⁹

Males:

$$\text{Creatinine Clearance (ml/minute)} = \frac{(140 - \text{age}) \times (\text{weight in kg})}{0.815 \times \text{serum creatinine (micromol/L)}}$$

Females:

as above then multiply result by 0.85

*The Cockcroft-Gault formula produces a less reliable result with extremes of body weight or where the serum creatinine is rapidly changing.

The Cockcroft-Gault formula is preferred for adjusting drug doses in elderly people and can be found in general practice prescribing software. Estimated glomerular filtration rate (eGFR) has not yet been validated for this purpose and is used to identify asymptomatic kidney dysfunction.^{16,17}

Uric acid levels generally begin to fall within 2 days of starting allopurinol. Aim to check serum uric acid level after 4 weeks and adjust dose to achieve uric acid concentration less than 0.36mmol/l.

Treatment with allopurinol should be limited to patients with appropriate indications and used only at the minimum dose necessary.

Table 2. Suggested allopurinol dosage in renal impairment⁹

Renal function	Initiation dose	Maintenance dose
CrCl > 50ml/min	100mg daily, increase by 100mg daily each month to achieve serum uric acid < 0.36mmol/l	100-300mg daily
CrCl 25-50ml/min	50mg daily	100-200mg daily
CrCl 10-25ml/min	50mg daily	100mg daily
CrCl < 10ml/min	50mg on alternate days	100mg on alternate days

NOTE: Further work is needed to clarify the safety and efficacy of allopurinol dose escalation, particularly in those with renal impairment. Current allopurinol dosing guidelines may result in suboptimal control of hyperuricaemia.

Whilst the effectiveness of allopurinol is well known, serious side effects and adverse reactions include;

- Precipitation of acute gout - this can be minimised by starting with low doses of allopurinol and by using low dose NSAIDs or colchicine (500 micrograms daily) for prophylaxis for 1-3 months only.
 - On-going use of colchicine for prevention of gout is not recommended as there is no evidence of benefit and it increases the risk of rare but severe side effects such as bone marrow suppression, hepatotoxicity and peripheral neuropathy.^{9,18}
 - Allopurinol should not be discontinued if an acute attack of gout occurs.
- Rash, leukopaenia or thrombocytopenia and diarrhoea occur in 3-5% of patients on allopurinol.⁹
- Allopurinol hypersensitivity syndrome (toxic epidermolysis, fever, hepatitis and acute renal failure) occurs in less than 0.1% of patients but has a mortality rate of close to 25%. It is more likely to occur in patients with renal impairment treated with standard doses of allopurinol and a diuretic. Maximum risk is at about 1 month after commencing allopurinol.
- A potentially fatal interaction between allopurinol and azathioprine.

Uricosuric drugs such as Probenecid are unlikely to be of benefit to elderly veterans because of co-morbid conditions, especially renal impairment.



④ Addressing risk factors for gout

Obesity

A BMI of between 30 and 35 more than triples the risk of developing gout.⁵ Central obesity, even with a relatively normal BMI, also increases the risk.⁸

Diet

People with gout have typically been advised to avoid food rich in purines such as meat and seafood, however, dietary manipulation may be impractical in an elderly population and there is little evidence of benefit. Dairy intake has been inversely correlated with the risk of gout but this protective effect is only seen with low fat dairy products. Studies have also suggested a significant uricosuric effect of Vitamin C, however, its role in prevention and management of gout has not been established.⁵

Alcohol

The risk of gout increases with increasing intake of alcohol - the greatest association being with beer (including light beer), followed by spirits. Moderate wine drinkers appear to have a lower serum uric acid level.⁵

Hypertension and diuretics

Both essential hypertension alone and diuretic use are associated with hyperuricaemia and gout. Thiazide and loop diuretics confer similar risks, however, the degree of uric acid retention is dose-dependant. Hydrochlorothiazide 12.5mg or equivalent will lower blood pressure as effectively as 50mg but will not induce hyperuricaemia.¹⁹ In patients with hypertension, the use of an ACE inhibitor or angiotensin 2 receptor blocker can minimise the diuretic-induced rise in plasma urate concentration.

Advise your patients to;

- Always report any other medications being taken including over-the-counter and those from other health care providers
- Lose excess weight
- Keep alcohol intake to a minimum, especially beer and spirits
- Maintain sufficient fluid intake to avoid dehydration
- Opt for low fat dairy products to help reduce the risk of recurrent gout
- Be aware of the difference between medications for acute gout and preventive treatment
- Consider a Home Medicines Review

Suggested further reading

For information on changes to colchicine dosing,

http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022351lbl.pdf

References

1. Veteran's Datamart, University of South Australia, QUMPRC. Accessed June 2009
2. Choi KH and Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. *Circulation* 2007; 116:894-900
3. Singh JA, Hodges JS and Asch SM. Opportunities for improving medication use and monitoring in gout. *Ann Rheum Dis*; 68: 1265-1270
4. Smith P, Karlson N and Nair BR. Quality use of Allopurinol in the elderly. *J Qual Clin Practice* (2000) 20, 42-43
5. Lee S et al. Recent developments in diet and gout. *Curr Opin Rheumatol* 2006; 18(2):193-198
6. Mikuls TR, Farrar JT, Bilker WB, Fernandes S, Schumacher HR and Saag KG. Gout epidemiology: results from the UK General Practice Research Database, 1990 – 1999. *Ann Rheum Dis* 2005; 64: 267-272
7. Singh H and Torralba K. Therapeutic challenges in the management of gout in the elderly. *Geriatrics* 2008;63(7): 13-20
8. Jordan KM, Cameron JS and Snaith M et al. British Society for Rheumatology and British Health Professionals in Rheumatology Guideline for the management of Gout. *Rheumatology* 2007; 1-17
9. Australian Medicines Handbook, Adelaide: Australian Medicines Handbook Pty Ltd 2009
10. Becker MA. Treatment of acute gout. Literature Review Jan 2009. www.uptodate.com Viewed June 22 2009
11. MIMS Prescribing Information for Colchicine. www.mims.com.au Viewed Aug 12 2009
12. Information for Healthcare Professionals: New safety information for Colchicine. www.fda.gov Viewed 3 August 2009
13. eTG complete [CD-ROM]. Melbourne: Therapeutic Guidelines Limited; 2009 July.
14. Schlesinger N et al. Colchicine for acute gout. *Cochrane Database of Systematic Reviews* 2006, Issue 4
15. Becker M et al. Prevention of recurrent gout. Literature Review Jan 2009. www.uptodate.com Viewed June 22 2009
16. Martin J, Fay M and Ungerer J. eGFR – use beyond the evidence. *MJA* 2009; 190: 197-199
17. Mathew T, Johnston D and Jones G on behalf of the Australasian Creatinine Consensus Working Group. Position Statement: Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: revised recommendations. *MJA* 2007; 187 (8):459-463
18. Colchicine: Drug information. www.uptodate.com Viewed 31 July 2009
19. Rose B. Diuretic-induced hyperuricaemia and gout. Literature Review Dec 2007. www.uptodate.com Viewed 29 June 2009