Management of gout: Primary care approach

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Keywords: gout; management; primary care; anti-inflammatory agents

Abstract

Great strides have been made in understanding gout as a disease over the centuries. Despite these advances, reports suggest that the management of gout is relatively suboptimal at the primary care level. This article reviews important considerations in the management of gout and provides an evidence-based approach for the management of acute and chronic gouty arthritis at the primary care level. Recurrent monoarticular pain and swelling should raise the suspicion of gout and the demonstration of urate crystals in synovial fluid during a clinical episode confirms the diagnosis. Acute gouty attacks should be managed with appropriate doses of non-steroidal anti-inflammatory drugs (NSAIDs) or colchicines or steroids. Recurrent attacks of gout, presence of tophi and urate stones necessitate urate-lowering drugs. Prophylactic anti-inflammatory agents for up to six months should be added at initiation of urate-lowering therapy to reduce flares of acute attacks. Gout management requires lifelong commitment and adherence to lifestyle modification and treatment improves clinical outcomes.

Ⓟ **Peer reviewed. (Submitted:2009-10-03, Accepted:2009-12-09). © Medpharm** **SA Fam Pract 2009;51(6):471-477**

Introduction

Most reports suggest that gout affects at least 1% of the adult male population and it is the commonest form of inflammatory disease of the joints in men over the age of 40 years.[1] It occurs more in males than in females, in whom it is rare in the pre-menopausal period. Furthermore, it is rarer among the Black population compared to other racial sub groups in South Africa.[2] But the current health transition in South Africa, which results from a change in diet and lifestyle among the Black population may increase the prevalence of gout among them in the future.[2]

Gout is a disorder of urate metabolism where an excess of serum uric acid leads to the formation of monosodium urate crystals in various tissues of the body and presents with acute inflammatory joint disease, urate nephropathy, and/or tophi deposits.[3] The excess uric acid results from urate under-excretion (90%), overproduction (approx 10%) and enzyme defect (1%). A small proportion results from myeloproliferative diseases, renal insufficiency, drug therapy, etc.[4] An important cause of hyperuricaemia and gout is the use of the drug, cyclosporin, which augments the post-secretory re-absorption of uric acid in renal transplant patients.[5] The management of gout has evolved over the centuries, underpinned by the progressive understanding of its pathogenesis, development of anti-inflammatory and uric acid-lowering agents. The association of hyperuricaemia with adverse cardiovascular outcomes has also increased interest in the disease, given the increasing global burden of cardiovascular diseases.[6]

In a USA study, increased primary care visits were found to be associated with better adherence to quality indicators for gout treatment.[7] Family physicians are first-contact physicians who provide continuous care, and this role places them in a good position to manage both acute flares and chronic follow-up of gouty patients. This article reviews current considerations in the management of acute and chronic gout, and provides primary care physicians with an approach in managing gout patients at the primary care level.

The problem of poor management of gout

Despite the advances reported in the understanding of the pathogenesis of gout and the significant health impact associated with gout, reports suggest that the management of gout may be suboptimal.[8] Areas of low management performance identified include[7,9]:

- The appropriate use of NSAID and other anti-inflammatory agents
- The correct use of urate-lowering agents especially the dosing of allopurinol in renal impairment; concomitant use of azathioprine or 6-mercaptopurine with allopurinol; use of allopurinol in asymptomatic hyperuricaemia
- Six-monthly monitoring of urate levels, blood count levels, and creatine kinase levels where there is prolonged use of colchicines

Poor patient compliance like in most other chronic diseases is another factor that contributes to poor gout management. This may be a reflection of poor patient education and the general difficulty experienced by patients when challenged to modify their lifestyle. The lack of consensus on the management of gout has not helped the situation as it constitutes a barrier to the study of the quality of care rendered to gout sufferers. Attempts at addressing this lack of consensus led Mikuls et al[10] to develop a list of quality indicators for aspects of care. These indicators include criteria such as "the use of urate-lowering therapy", "behavioural/lifestyle modifications" and "the use of anti-inflammatory agents".

Confirming the diagnosis

Acute gouty arthritis presents with agonising pain, swelling and tenderness of the affected joint(s).[7] A recurrent monoarticular arthritis, usually of the lower limb should trigger the suspicion of gout but more joints could be affected. A guide to diagnosis provided by the American Rheumatism Association is shown in Table I.[11]

Table I: American Rheumatism Association criteria for the diagnosis of gout[7]

Criteria for the diagnosis of gout
• Urate crystals in either joint fluid or a tophus, and/or
• Six of the following 12 criteria: – maximum inflammation within the first day – more than one attack of acute arthritis – monoarticular arthritis – redness observed over joints – first metatarsal joint pain attack – unilateral metatarsal joint attack – unilateral tarsal joint attack – suspected tophus – hyperuricaemia – asymmetric swelling within a joint on X-ray – subcortical cysts with no erosions on X-ray – negative bacterial culture of joint fluid

Many physicians do not aspirate the joint (for crystal microscopy) when making the diagnosis of gout.[12] However the presence of urate crystals in the joint during a clinical episode confirms gout.[13] Joint aspiration when undertaken must be done under sterile conditions by clinicians who are skilled and understand the anatomy of the joint. Limitations imposed by lack of equipment and clinical skills may therefore limit the performance of joint aspirations in primary health care settings. It is important to note that urate crystals can be demonstrated in synovial fluid in-between attacks; when there are no signs of joint inflammation.[13]

Hyperuricaemia is a hallmark of gout but many patients with raised serum urate levels do not manifest clinically with gout. Conversely, those who have the clinical disease may have normal serum urate levels during attacks. The serum urate level is therefore not a reliable criterion for diagnosing acute attacks of gout.

In addition, there are no specific changes on plain joint radiographic films during acute attacks but joint destruction characterised by erosion and sclerotic edges, and the presence of tophi are features of long-standing gout (see Figure 1).[14]

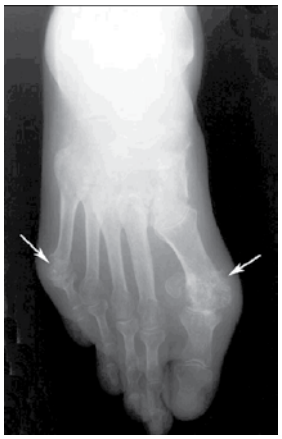

Figure 1: Erosion of 1st and 5th metatarsals, asymmetric swellings and tophi (Courtesy: Suresh E, 2005)[14]

Full blood count may show leucocytosis, raised C-reactive protein (CRP), electrolytes and urea (to check renal function), and other tests dictated by the clinical encounter may assist in establishing the diagnosis. Other causes of acute joint swelling such as rheumatoid arthritis, septic arthritis and pseudogout should be excluded as part of the management of acute gout.

Management of gout

There are effective inter-ventions for the management of gout. These focus on health education, behavioural modification, and pharmacotherapy for acute and chronic gout. Clinical considerations in the management of gout should be evidence-based and the levels of such evidence are as shown in Table II.[13]

a. Behavioural modification and commitment to management

Adherence to gout treatment has been shown to be poor.[15] Success of lifelong treatment is therefore dependent on the patient's commitment to treatment, which is a function of the patient's understanding of the illness and treatment. Lifestyle changes and drug management need to be explained to the patient and efforts made to ascertain the level of patient understanding. Commitment to treatment and adherence should then be monitored and appropriate interventions developed to address any gaps.

Table II: The levels of evidence of clinical considerations (Adapted from Eggebeen A, 2007)[13]

Clinical considerations	Levels of evidence
• Serum uric acid measurements are useful in the evaluation of gout; however, they should not be used alone to confirm or exclude the diagnosis.	[C]
• Nonsteroidal anti-inflammatory drugs, corticosteroids and colchicine are effective treatments for acute gout.	[B]
• In patients with gout, modifiable risk factors such as obesity, diuretic use, high-purine diet and alcohol intake should be addressed.	[B]
• Urate-lowering therapy is recommended for patients with recurrent gout attacks, tophi or ongoing arthropathy with joint damage seen on a radiograph.	[C]
• When initiating urate-lowering therapy, prophylaxis with low-dose colchicine for three to six months may reduce the risk of flare-ups.	[B]
• During urate-lowering therapy, target serum uric acid level below 0.3 mmol/L.	[B]
• Allopurinol is the recommended first-line agent for urate-lowering therapy.	[C]

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series

The influence of lifestyle changes on gout, including dietary components has been studied and the effects are summarised in Table III.[16,17] Obesity, diets containing high purine content, and alcohol intake should be addressed as these are risk factors associated with gout, metabolic syndrome and adverse cardiovascular outcomes.[15] A diagnosis of gout should raise the possibility of concurrent cardiovascular risk and should trigger review of the patient's lifestyle, followed by the development of appropriate interventions.[18] Adequate hydration should be ensured as dehydration may precipitate acute attacks and urate stones, especially in patients on probenecid. Drugs such as thiazide diuretics, low dose aspirin, ethambutol and pyrazinamide increase serum urate levels and should be avoided, except where there are compelling indications.

Table III: Food type and effect on serum urate level[16,17]

Increase serum urate levels	Decrease serum uric acid level	No impact
Animal purines • Red meat • Sea food	**Low-fat dairy products** • Low-fat yogurt	**Vegetable purines**
Drinks Beer (high guanasine content) Spirits (moderate increases)	**Decreased weight** (more studies needed)	**Red wines** (possibly due to the antioxidant – resveratrol)
Fructose-containing drinks		

Though coffee has a diuretic effect and may likely raise serum urate levels, a large prospective study of 45 869 participants over 12 years on coffee consumption suggests that long-term coffee consumption of

four cups or more per day may lower the risk of gout. This protection increases with an increase in the number of cups of coffee consumed per day, irrespective of the caffeine content [RR for > or = 6 cups/day = 0.41; 95% CI (0.19–0.88)].[19] A similar relationship between coffee consumption and serum urate levels was found in the third National Health and Nutrition Examination survey involving 14 758 nationally representative sample of US adults.[20] The observations noted with coffee, (including decaffeinated coffee) in these studies were not observed with tea consumption and may suggest that components other than caffeine may be responsible for this effect.

b. Anti-inflammatory agents during acute attacks

Acute gout is marked by inflammatory response in affected joint(s) triggered by the deposit of urate crystals and associated with release of cytokines and chemokines.[4,21] Therefore anti-inflammatory agents remain the cornerstone of the management of acute gout attack. Non-steroidal anti-inflammatory drugs (NSAIDs) are effective in controlling pain and inflammation at adequate doses. Although gastrointestinal side-effects and renal impairment (especially in the elderly and those with compromised renal allografts), may limit their use, the short duration of treatment reduces the risks of developing these side-effects. These risks need to be borne in mind and NSAIDs used with caution in these subgroups. Evidence from randomised controlled trials (RCTs) is not available to support one NSAID over another in aborting pain and inflammation. However, differences in the incidence of gastrointestinal side-effects and adverse cardiovascular events (for COX 2 inhibitors) should be considered in making choices for individual patients.[1,22] Although high-dose aspirin (> 3 g/day) has uricosuric effects, urate retention at doses less than 3 g/day contraindicates its use in normal dosages for the treatment of acute gout. At low doses such as 75 mg/day (used for antiplatelet activity), a 15% decrease in the rate of urate excretion has been reported. In this study, the reduction in urate excretion was more pronounced in the elderly, particularly those with pre-existing hypoalbuminaemia.[23] Low-dose aspirin prophylaxis should, however, be continued when there are indications, such as in high risk cardiovascular patients.

Colchicines are no longer recommended for the treatment of acute gout but in conditions where NSAIDs are not desirable, oral colchicine is an effective alternative but gastrointestinal side-effects limit its use. Lower doses (0.5–0.6 mg given six to eight hourly) are associated with less gastrointestinal side-effects but few evaluative studies have been done to confirm its effectiveness. Slow intravenous infusion (over at least 10 minutes) is rarely used when oral intake is impossible, and in this case, total daily dose should never exceed 4 mg because of life-threatening colchicine toxicity and sudden death.[24] Colchicine may cause a reversible myoneuropathy and in suspected colchicine toxicity, a rising serum troponin level has been suggested as a predictor of cardiovascular collapse and calls for more intense management of toxicity.[25] Despite the high mortality associated with colchicine toxicity, good outcomes were reported in a severe case which was managed with intravenous colchicine-specific Fab fragment.[26]

Oral steroids may be used for acute attacks when there is polyarticular involvement. Intra-articular injection may also be used when one or two joints are involved. Evidence of joint infection must, however, be excluded, as the use of steroids in the presence of septic arthritis will aggravate the infection.

Where polyarticular acute gout is refractory to conventional treatment, the patient should be referred to a rheumatologist for further management. Further management by the rheumatologist may include intramuscular injection of adrenocorticotrophic hormone (ACTH), 40–80 IU which has been shown to be effective in the treatment of acute gout.[24] However, ACTH is not readily available in South Africa and not routinely used by local rheumatologists.

c. Urate-lowering agents in chronic gout

While anti-inflammatory agents are the mainstay of treatment in acute gout, patients with recurrent attacks (> 2 per annum), presence of tophi, joint erosion and urate calculi should be offered urate-lowering drugs. Urate-lowering agents should not be started during acute attacks but after an acute attack has subsided. However, it is not advisable to discontinue urate-lowering drugs in patients already on them during an acute gouty attack. Lowering the serum uric acid level should be a long-term goal of gout management and both patients and clinicians must commit to achieving this goal. Continuous lowering of urate levels (compared to intermittent attempts) has been shown to result in fewer gout flares, reduction in the sizes of tophi and amount of crystals in the joint.[27] Urate-lowering drugs should be commenced well before tophi develop and before radiological evidence of gout becomes evident.[27]

To minimise the chances of precipitating an acute gout attack due to fluctuations in serum urate levels, anti-inflammatory agents such as colchicines (0.5 mg once or twice daily) or NSAID should be used in addition to urate-lowering agents in the initial phase of urate-lowering therapy until the urate level normalises; up to six months depending on the body store of urate. [24, 28]

Allopurinol is the drug of choice for long-term lowering of serum urate levels. It is a xanthine-oxidase inhibitor that blocks urate production from purines. Reports indicate that inappropriate prescription and wrong use of allopurinol abound.[2] Important clinical considerations from the South African Essential Drugs List for primary health care which clinicians should be aware of when prescribing allopurinol include: [27,28,29]

- Starting at 100 mg daily and increasing to 300 mg daily over several weeks; the maximum recommended daily dose is 400 mg/day
- Reducing doses in renal impairment
- Adjusting doses in cases of drug interactions (e.g. azathioprine)
- Target serum urate is < 0.3 mmol/L. Note that this is not always easily achieved and a high dose of allopurinol may be necessary
- Rare but potentially fatal hypersensitivity syndrome may develop

Other agents which promote urinary urate excretion, such as probenecid, are known as *uricosuric* agents. These drugs are useful when the patient is an under-excretor, has good renal function, is not a urate over-producer and is committed to adequate water intake of at least 1500 ml/day.[18] Ensuring that these conditions are met is important to reduce the chances of precipitating urate stones.

Newer drugs available in the lowering of serum urate

Febuxostat, a non-purine xanthine-oxidase inhibitor has been reported to reduce serum urate level compared to placebo and allopurinol.[30,31] However, more acute flares of gouty attacks were reported among patients on febuxostat than others, even when colchicine was added as an adjunct anti-inflammatory.

Fenofibrate, a fibric acid derivative lipid-lowering drug has been shown to reduce serum urate levels. This effect is explained by an increased renal clearance of uric acid and is reversed when fenofibrate is withdrawn.[32] The combined lipid and urate-lowering effects of fenofibrate makes the possibility of its use exciting, given the association between gout and increased risks for adverse cardiovascular outcomes.[33]

In a randomised controlled study on ascorbic acid (vitamin C) supplementation at a daily dose of 500 mg, the latter was shown to lower serum urate levels, possibly through a uricosuric effect as shown

by increases in glomerular filtration rates of urate.[34] How vitamin C supplementation will interact with other urate-lowering drugs and the extent to which the decreased urate levels translate into clinical benefits are questions for further studies.

Humans cannot convert urate to a more soluble allantoin due to natural enzyme defect in the urate-oxidase pathway. However, reports of a phase 1 trial suggest that administration of exogenous recombinant uricase is effective in lowering serum urate levels. This has implications for the future management of gout.[35] Other interventions which show future prospects include the induction of a near iron-deficiency state which was shown to induce a state of gout remission. The underlying mechanism for this effect, is however, not clear.[36]

Losartan (angiotensin-receptor blocker) and amlodipine (calcium-channel blocker) are reported to have mild uricosuric effects.[24]

Urate crystals have been shown to trigger interleukin 1L release through interactions with inflamasomes and IL-1 inhibitors have been shown to abate the inflammatory process and pain associated with acute gout. IL-1 inhibitors therefore provide hope for the future treatment of acute gout, especially in patients who are intolerant to NSAIDs and steroids or have treatment-resistant gout.[21,37,38,39]

Summary of drug treatment of gout

In line with available evidence, the rational approach to gout treatment is summarised in the principles listed by the EULAR report[17] and by Wortmann RL (2006)[40] which are:

- For typical presentations of gout (such as recurrent podagra with hyperuricaemia), a clinical diagnosis alone is reasonably accurate but not definitive without urate crystal confirmation.
- Identification of urate crystals in synovial fluid or tissue aspirates establishes the diagnosis of gout.
- Acute gout attacks can be terminated with the use of a non-steroidal anti-inflammatory drug (NSAID), colchicines, corticosteroids, or corticotrophin.
- High doses of colchicines lead to increased side-effects, but low doses (0.5 mg three times daily) may be sufficient for some patients with acute gout with fewer side-effects.
- When recurrent attacks occur, a urate-lowering agent should be prescribed and should be life long.
- Low-dose colchicine (0.5 mg once or twice daily) or NSAID should be prescribed in a prophylactic manner prior to initiating urate-lowering therapy and continued for some time thereafter.
- Uricosuric agents such as probenecid and sulphinpyrazone can be used as an alternative to allopurinol in patients with normal renal function but are relatively contraindicated in patients with urolithiasis. Benzbromarone can be used in patients with mild to moderate renal insufficiency on specific patient basis but carries a small risk of hepatotoxicity.
- Risk factors for gout and associated co-morbidity should be assessed, including features of the metabolic syndrome (obesity, hyperglycaemia, hyperlipidaemia, hypertension).
- When gout is associated with diuretic therapy, stop the diuretic if possible. For hypertension and hyperlipidaemia, consider use of losartan and fenofibrate, respectively (both have modest uricosuric effects).

Conclusion

Recurrent monoarticular pain, swelling and erythema should raise the suspicion of gout and prompt synovial fluid aspiration for crystals where possible. Acute gouty attacks should be managed by appropriate doses of NSAIDs or colchicines or steroids. Recurrent attacks of gout necessitate urate-lowering drugs; accompanied by the concurrent use of prophylactic anti-inflammatory agents for up to six months. Adherence to quality indicators such as developed by Mikuls et al [10] can improve the clinical outcomes of gout management. Lifestyle changes and pharmacotherapy are critical for good clinical outcomes and gout management requires lifelong commitment from both the patient and clinician,

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