*South African Family Practice* 2015; 57(4):267–272
http://dx.doi.org/10.1080/20786190.2015.1047148



S Afr Fam Pract
ISSN 2078-6190 EISSN 2078-6204

RESEARCH

# Update on hyperuricaemia and gout with evidence based management guidelines

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Gout is now the leading cause of inflammatory arthritis, affecting 1–2% of the population. The metabolic syndrome, cardiovascular risk factors, cardiovascular events and mortality are more common with gout. However, the role of uric acid as an independent risk factor is inconclusive. The identification of urate transporters has improved our understanding of urate homeostasis and identified targets for the development of newer drugs. Experience with ultrasound and dual energy computed tomography led to the detection of urate crystals in patients with asymptomatic hyperuricaemia. Several evidence-based management guidelines are now available. The dietary and lifestyle recommendations focus on general health and management of comorbidities. A low dose colchicine regimen is effective and better tolerated than the traditional use of higher doses in acute gout. Alternative measures for acute gout include non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. Allopurinol is the most widely used initial therapy; treatment is started with 100 mg or less per day, and titrated upwards to achieve a target level of 0.36 mmol/l (in patients with tophi, a lower target of 0.30 mmol/l is recommended). A new non-purine more potent xanthine oxidase inhibitor, febuxostat, is available (currently not registered in South Africa). Probenecid is the most widely used uricosuric agent. Prophylactic therapy with colchicine, NSAIDs or corticosteroids is used when urate lowering therapy is initiated. Although the cause of gout is known and effective treatment is available, gout is poorly managed worldwide with failure to achieve the target urate level.

**Keywords:** African blacks, evidence based, gout, guidelines, hyperuricaemia, review

## Introduction

Although the cause of gout is known and effective treatments are available, studies around the world show that the majority of patients with gout are not taking urate lowering therapy (ULT). Large studies in Taiwan and the United Kingdom show that only 20–33% of patients with gout are taking ULT.[1–3] A number of evidence based recommendations or guidelines have been published recently. The 2006 European League Against Rheumatism (EULAR) recommendations for gout were followed by the British guidelines in 2007.[4–6] In 2012 the American College of Rheumatology (ACR) published its first guidelines on gout [7,8] and the multinational 3e initiative (evidence, expertise, exchange) recommendations were published in 2014.[9] There have also been major recent advances in our understanding of the epidemiology, pathogenesis, co-morbidities, role of imaging and management of hyperuricaemia (HU) and gout.

The aim of this review is to highlight some of the recent observations on HU and gout, and their relevance to primary care. In addition, the evidence for the recommendations was analysed, and measures that can be implemented in primary care are the focus of the summarised guidelines. The widespread dissemination of current practice recommendations will hopefully result in more patients receiving ULT and achieving target levels of uric acid.

## Recent observations in hyperuricaemia and gout

### *Epidemiology of gout*

Gout is currently the leading cause of inflammatory arthritis and the overall prevalence is 1–2% in men in the Western world.[10] The major contributory factors are longevity of the population and changes in diet and lifestyle. In the USA, the self-reported prevalence of gout was 3.9% of adults.[11] The prevalence of gout in the UK General Practice Research Database (GPRD) of 4 634 974 persons was 2.49% (3.7% in men and 1.5% in women).[12] The prevalence increased to nearly 10% in men over 70 years. An analysis of the National Health Insurance Research Database of over 23 million people in Taiwan showed a prevalence of gout of 6.24%.[1] A rise in the prevalence has also been reported in the developing world. In 1980 gout was rare in Eastern China but recent surveys show that the prevalence has risen to 1.14%.[13]

In South Africa epidemiological studies by Beighton *et al*. in the 1970s showed that there was a rise in the level of the serum uric acid in urban Africans ($n$ = 424) when compared with a rural Tswana ($n$ = 370) and Xhosa population ($n$ = 479).[14–16] However, gout was uncommon as they did not identify any patient with gout in these studies. A report of 19 African blacks with gout, seen over a five-year period in Durban, was followed by another report of 106 patients a decade later.[17,18] A Johannesburg study of 90 African blacks with gout showed that the risk factors in men were a 'white collar' occupation, obesity, hypertension and alcohol intake, and alcohol intake alone in females.[19] A 2008 study of 448 African black volunteers from the Transition and Health during Urbanisation in South Africa (THUSA) study showed a significant increase in the prevalence of HU in the urban population compared with the semi-urban and rural population.[20] The THUSA study also found that patients with HU were 3.5 times more likely to develop the metabolic syndrome.[20] There have not been any recent epidemiological studies in South Africa and research is needed to document the transition in the prevalence of HU and the burden of gout.

In the 1980s, data from general practice studies in the UK and the Framingham study in the USA reported a peak incidence of gout in the age band around 50 years.[21,22] More recent analyses of

large databases showed a rise in the peak age incidence to 65–84 years in the UK and 70–85 years in Taiwan.[1,2,12]

### *Increased mortality and co-morbidities in patients with hyperuricaemia and gout*

The association of HU with the metabolic syndrome has been shown in several studies.[23–25] The serum uric acid was found to increase with the number of components of the metabolic syndrome, e.g. the mean serum urate of 0.27 mmol/l with no components to 0.35 mmol/l in patients with three components.[24] The Third National Health and Nutrition Examination Survey (NHANES III) showed that metabolic syndrome features occurred in 18.9% of patients with serum urate level < 0.36 mmol/l to 70.7% in those with urate level > 0.60 mmol/l.[25]

Although there are no data to show an increased risk of coronary heart disease or strokes with HU, many large long term studies in patients with gout have shown an increased prevalence of cardiovascular events and mortality.[26–29] Patients who were treated with allopurinol had a lower mortality and lower risk of cardiovascular events.[30,31] In the NHANES survey the prevalence of the metabolic syndrome was 62.8% in patients with gout compared with 25.4% of patients without gout.[25] Patients with gout also had a significant increase in the prevalence of abdominal obesity, low HDL-cholesterol, hypertriglyceridaemia, hypertension and hyperglycaemia. The UK GPRD showed a significant association between gout and coronary heart disease, hypertension, diabetes and chronic renal failure.[2] However, despite these strong associations, at present there is inconclusive evidence to confirm a direct causal role for uric acid in cardiovascular disease as there are contradictory reports.[32,33]

### *Urate homeostasis and the role of urate transporters*

A number of urate transporters play a role in the renal handling of uric acid. The main transporters are urate anion transporter 1 (URAT1) and glucose transporter 9 (GLUT9). Genetic studies have shown that polymorphisms or mutations of the URAT1 gene, and polymorphisms around the GLUT9 gene are associated with HU and gout.[34,35]

The reabsorption of urate by URAT1 and GLUT9 is inhibited by uricosuric agents such as probenecid and benbromarone, and drugs such as losartan, which have a uricosuric effect.[34,36]

An understanding of the physiological effects of urate transporters has led to the development of several drugs that inhibit URAT1. One of them, Lesinurad, is currently in phase 3 clinical trials.[34] Lesinurad has specificity for URAT1 and does not inhibit any other transporters. Therefore drug interactions, which are seen with other uricosuric drugs, do not occur. It is being evaluated on its own and in combination with xanthine oxidase inhibitors.[37] Arhalofenate was being evaluated in the management of type II diabetes. It was found to inhibit URAT1 and lowered the serum uric acid. It has the potential to have a dual effect of controlling blood sugar and lowering uric acid.[37]

### *Role of imaging in patients with asymptomatic hyperuricaemia*

In patients with gout, ultrasound may show the presence of uric acid deposits, tophi and bony erosions.[38,39] Ultrasound may detect uric acid deposits in patients with asymptomatic HU, and inflammation may be detected with power Doppler studies. Dual-energy computed tomography (DECT) can accurately identify monosodium urate deposits in the soft tissues and joints.[40,41] DECT is of value in cases of diagnostic uncertainty or where joint aspiration is difficult. Screening is not recommended in asymptomatic HU as the risk benefit of treating these patients is unknown.

The detection of uric acid crystals in patients with asymptomatic HU led to a review of the stages in the evolution of gout: namely, from asymptomatic HU, to asymptomatic HU with uric acid deposits, acute gout and then chronic tophaceous gout.[42]

### *Practice points*

- Gout is now the commonest cause of inflammatory arthritis with a marked increase in the elderly.
- Epidemiological studies are required to determine the prevalence of HU and the burden of gout in South Africa.
- A study among South African black volunteers found that patients with HU were 3.5 times more likely to develop the metabolic syndrome.
- All patients with gout should be screened for hypertension, diabetes mellitus, hyperlipidaemia and other cardiovascular risk factors — early detection and aggressive management will improve patient outcome.
- Ultrasound imaging can detect uric acid crystals in cases of diagnostic uncertainty or where joint aspiration is not possible

## Management of asymptomatic hyperuricaemia

The concept of HU as a benign condition is being challenged in view of its association with other cardiovascular risk factors.

The ACR guidelines did not address the management of asymptomatic HU. The 3e initiative noted that there is an absence of evidence to support the use of ULT in asymptomatic HU.[43] They recommended advice on lifestyle measures including diet, weight and exercise, assessment of renal function, and screening and management of cardiovascular risk factors.[43]

The EULAR guidelines noted that appropriate treatment of co-morbidities could lower the serum uric acid, e.g. the use of losartan and fenofibrate to treat hypertension and hyperlipidaemia respectively.[4]

## Evidence based recommendations for the management of gout

The ACR evaluated the evidence for the management of gout and reported the level of evidence available to support its recommendations. The level of evidence was categorised as A, B or C (Level A: supported by multiple (more than 1) randomised clinical trials or meta-analyses; Level B: derived from a single randomised trial or non-randomised studies and Level C: consensus opinion of experts, case studies or standards of care).[7,8] The findings were proposed as 'recommendations' to ensure the non-prescriptive nature of decision making in individual patients.

It is important for the management to be individualised depending on the presence of co-morbidities, a history of adverse effects of the medication and possible drug interactions with concomitant medication. Education of the patients is critical to improve adherence to ULT and achievement of the target levels of uric acid.

Newer drugs such as interleukin-1 inhibitors and uricosuric agents are currently undergoing clinical trials and they are also briefly discussed.

### *General recommendations for patients with gout*

The proposed general measures (level C evidence) include (i) weight loss for obese patients, (ii) a healthy diet which also takes into consideration other co-morbidities such as the metabolic syndrome, diabetes, hypertension and hyperlipidaemia, (iii) exercise to achieve physical fitness, (iv) cessation of smoking and (v) maintaining adequate hydration.[7]

The specific dietary recommendations for gout include limiting alcohol intake in all patients and avoidance in patients with poorly controlled gout (B). Meat with high purine content (sweetbreads, liver and kidney) and high fructose containing drinks should be avoided (B). The intake of seafood with a high purine content (sardines, shellfish), beef, lamb (B) etc. and naturally sweetened fruit juices (C) should be limited. The intake of vegetables (C) and low fat/non-fat dairy products (B) should be encouraged.

In view of the high prevalence of co-morbidities, as discussed above, all patients should be screened for hypertension, diabetes, hyperlipidaemia, renal function and other cardiovascular risk factors. The early detection and management of these co-morbidities will improve outcome. There are no guidelines to suggest that all patients with cardiovascular disease should be screened for uric acid.

Losartan has a uricosuric action and reduces serum uric acid levels by 20–25% in healthy volunteers, hypertensive patients and renal transplant recipients.[23,44] Thus it is recommended for the control of hypertension in patients with asymptomatic HU and gout.[4] Calcium channel blockers, amlodipine and nifedipine, were also associated with a reduction in the serum uric acid and a 21% and 13% reduced risk of gout.[23] Fenofibrates, which are effective in the management of hyperlipidaemia, also have a uricosuric effect and lower the serum uric acid.[24] They have also been shown to enhance the effect of allopurinol in patients with HU and gout.[45] Diuretics are associated with a rise in the uric acid and alternative treatment should be considered where possible.

**Table 1:** Treatment of the acute attack of gout (level of evidence in parentheses)[8]

| | |
|---|---|
| NSAIDs | • Should be used in high doses, if appropriate, and continued until the acute attack resolves (C)<br>• Indomethacin, naproxen and etoricoxib (A), high dose (800 mg/day) celecoxib (B) and other NSAIDs (C) |
| Colchicine | • Use alternate treatment if already on prophylaxis for preceding 14 days<br>• Dose of 1.0 mg stat, then 0.5 mg 1 hour later, then maximum of 0.5 mg tds until attack resolves (lower dose with chronic kidney disease or drug interactions) (A) |
| Corticosteroids (CS) | • Oral CS 0.5 mg/kg/day — full dose for 5–10 days and then stop (A) 0.5 mg/kg/day — for 2–5 days, taper 7–10 days, then stop (C)<br>• Intra-articular Used if 1–2 large joints ± oral CS or other modalities (C)<br>• Intramuscular Followed by oral CS (C) |
| Topical ice | • Used as supplementary therapy as required (B) |

### *Management of acute gout*

The treatment of the acute attack requires pharmacological therapy with colchicine, non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids as shown in Table 1. Optimum benefit is obtained if treatment is started within 24 hours of the onset of the attack (C). If patients are already receiving ULT, it should be continued during the acute attack (C). The use of the traditional high dose regimen of colchicine is no longer recommended as the low dose regimen is safer and effective. Monotherapy is recommended if a few small joints or 1–2 large joints are involved while combination therapy is used if the attack is polyarticular or multiple large joints are involved (C). The combined use of NSAIDs and corticosteroids is not recommended because of concerns about gastrointestinal toxicity.

### *Urate lowering therapy*

The choice of ULT and considerations for its use are shown in Table 2. The target level for uric acid in most patients is < 0.36 mmol/l (A). However, if tophi are present, then aim for a level of < 0.30 mmol/l (B).

*Allopurinol* is the first choice ULT in most patients. The usual initial dose is 100 mg/day, with a gradual increase to achieve the target level of serum urate. A lower starting dose of 50 mg/day or less is

**Table 2:** Use of urate lowering therapy in patients with gout (level of evidence in brackets)[7]

| | |
|---|---|
| Allopurinol | • First-line therapy (A) — start with 100 mg/day per day or lower dose of 50 mg/day with CKD stage 4 or worse (B)<br>• Dose is increased every 2–5 weeks to achieve target uric acid (C)<br>• Dose may be gradually increased to more than 300 mg if necessary, with adequate patient education and careful monitoring for toxicity (B)<br>• Can be combined with probenecid to achieve target uric acid level (B) |
| Uricosuric agents | • Alternate first-line therapy if allopurinol is contraindicated or not tolerated (B)<br>• Probenecid is the first choice among uricosuric agents (B)<br>• Uricosuric agents are contraindicated in patients with elevated urinary uric acid excretion or urolithiasis; also not recommended if creatinine clearance is < 50 ml/min (C)<br>• Urinary uric acid excretion should be measured before starting uricosuric agents and it should be monitored during therapy (C)<br>• Ensure adequate fluid intake, alkalinise the urine and monitor urinary pH to reduce the risk of urolithiasis (C) |
| Febuxostat | • Used for patients who are refractory or intolerant to allopurinol or in whom uricosuric agents are contra-indicated (it is considerably more expensive than allopurinol)<br>• Used in a dose of 40 mg/day for 2 weeks; may then be increased to 80 mg/day if necessary<br>• Dose adjustment is not necessary if creatinine clearance > 30 ml/min (no long-term data for patients with CKD stage 4 or worse) |
| Peggloticase | • Used if gout is refractory or if intolerant to above therapy (A) |

used in patients with impaired renal function. The adverse effects include a pruritic rash, liver abnormalities or gastrointestinal intolerance. The major adverse effect is the allopurinol hypersensitivity syndrome (AHS), which occurs in about 0.1% of patients and is associated with a severe morbidity and mortality rate of 20–25%.[7] It occurs within a few weeks of starting therapy and within the first six months in 90%. The manifestations include a severe skin reaction such as the Stevens-Johnson syndrome or toxic epidermal necrolysis, liver or kidney injury, fever, vasculitis, eosinophilia or leucocytosis. A strong association between HLA-B*5801 and the risk of developing the AHS has been noted in certain populations and routine screening is recommended in patients of Korean, Han Chinese and Thai descent.[7]

*Febuxostat*, a new non-purine xanthine oxidase inhibitor, is primarily metabolised in the liver and is more effective than allopurinol in achieving target uric acid levels of < 0.36 µmol/L. The daily dose is 40 mg/day for two weeks and can be increased to 80 mg/day, if target levels are not achieved. Dose adjustment is not necessary with creatinine clearance > 30 ml/min. Long-term data are not available for patients with chronic kidney disease (CKD) stage 4 or worse. The most common side effects are skin rashes, liver abnormalities and arthralgia. Febuxostat is considerably more expensive than allopurinol. It is not registered for use in South Africa but may be obtained with permission from the Medicines Control Council.

*Pegloticase* is a recombinant mammalian urate oxidase (uricase), which is modified by polyethylene glycol. It converts urate to allantoin, and is excreted by the kidney. It is administered by infusion every two weeks. Infusion reactions are common and anaphylaxis may occur. It is very expensive and is used only in chronic refractory gout. Pegloticase is not available in South Africa.

### *Interleukin 1 inhibitors* e.g. anakinra, canakinumab and rilonacept

Interleukin-1 (IL-1) plays an important role in the pathogenesis of acute gout and IL-1 inhibitors have been studied in acute gout. Sivera *et al*. reviewed 3 studies comprising 654 patients who were treated with canakinumab compared with 40 mg intramuscular triamcinolone.[46] They noted moderate quality of superior efficacy and probable increased risk of adverse events. There are no comparative studies with the more commonly prescribed first-line therapies such as NSAIDs and colchicine. Terkeltraub *et al*. found that rilonacept alone, or in combination with indomethacin, was not superior to indomethacin alone. Thus, in view of their very high costs they will have a limited role in acute gout.[47]

### *Prophylactic therapy for the prevention of acute gout in patients on urate lowering therapy*

There is an increased risk of acute attacks during the early stages of ULT because lowering of the uric acid results in remodelling of the urate crystal deposits during their dissolution. The occurrence of acute attacks after staring ULT contributes to non-adherence to treatment. The treatment options are shown in Table 3 and include colchicine, NSAIDs and corticosteroids, either singly or in combinations.

The IL-1 inhibitor rilonacept is effective as prophylactic therapy in preventing gout flares when ULT is initiated or continued.[12,48,49] It is administered subcutaneously in a weekly dose of 80 mg or 160 mg weekly for 16 weeks. Rilonacept was well tolerated and was associated with 70.3% fewer gout flares in a multinational phase III study of 1 315 patients.[50] In view of the cost, it will have a limited role only when conventional prophylactic therapy is contraindicated or ineffective. It is currently not available for use in South Africa.

**Table 3:** Prophylactic therapy for acute attacks of gout (level of evidence in parentheses)[8]

| | |
|---|---|
| Colchicine (A) | • Use 0.5 mg once or twice a day<br>• Reduce dose with chronic kidney disease or drug–drug interactions |
| NSAIDs(C) | • Used in low doses<br>• Combined with a proton-pump inhibitor where indicated |
| Prednisone (< 10 mg/day) (C) | • Used when there is intolerance, lack of response or contraindications to NSAIDs<br>• Avoid prolonged use |
| IL-1 inhibitors (e.g. rilonacept) | • Weekly subcutaneous injections for 16 weeks when initiating or continuing ULT<br>• Associated with 70.3% fewer gout flares per patient<br>• Consider only in patients with contraindications or lack of response to above treatment |
| Duration of prophylaxis | • At least 6 months (A)<br>• 3 months after target urate achieved with no tophi on physical examination (B)<br>• 6 months after target achieved if one or more tophi on physical examination (C) |

### *Practice points*

- Large epidemiological studies show that only 20–33% of patients with gout are taking ULT — thus better patient education is required to improve adherence to therapy.
- Dietary measures should not only focus on purine restriction but also address co-morbidities such as obesity, hypertension, diabetes and hyperlipidaemia.
- The goal of management is to is to achieve a target uric acid level (< 0.36 mmol/l) and prevent gout flares; aim for < 0.30 mmol/l in patients with tophi.
- Allopurinol is the first-choice ULT and the starting dose should not exceed 100 mg/day (lower doses with chronic kidney disease).
- Some patients may require allopurinol in a dose greater than 300 mg per day to achieve their target level of uric acid; careful monitoring is required with gradual upward titration of the dose as necessary.
- Patients who are on established ULT should not interrupt their treatment during an acute attack.
- A low-dose colchicine regimen is safer and more effect in acute gout than the traditional high-dose regimen.
- Losartan and fenofibrates have uricosuric effects — their use should be considered for management of co-morbidities such as hypertension and hyperlipidaemia.

In conclusion, we face challenging and exciting times in the management of HU and gout in the future. Although the prevalence of gout is rising, epidemiological studies are providing greater insight into the associated co-morbidities and outcomes. Our improved understanding of the pathophysiology of urate metabolism and pathogenesis of gout has led to the development of newer targeted therapies, which will improve outcomes in future. The use of imaging will improve our ability to diagnose gout in selected patients. In the interim, our challenge is to make an early diagnosis, screen for and manage co-morbidities, improve patient education to increase adherence to ULT and

make optimal use of the available drugs to improve outcomes for our patients. The research agenda includes the need for local epidemiological data and critical evaluation of our clinical practice as more than 50% of the recommendations in the guidelines are based on level C evidence (opinions of experts, case studies or standards of care).

*Funding* – The Department of Rheumatology received financial support from the Aaron Beare Family Chair of Rheumatology Endowment Fund.

*Conflict of interest* – Professor GM Mody served as a member of the Vimovo advisory Board for AstraZeneca (South Africa) and is a member of the Global Advisory Board for GSK Consumer Healthcare's Pain Franchise.

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**Received: 06-10-2014 Accepted: 23-04-2015**