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REVIEW

Management of gout in the primary care setting

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Abstract

Gout is a commonly treated inflammatory arthritis that is often managed in the primary care setting. This disease is prevalent among the multi-ethnic Malaysian population. Unfortunately, gout is still frequently managed sub-optimally, even in the hospital and primary care settings. Gout should be considered a major disease since it can potentially lead to multiple disabilities from joint destruction, nephropathy and increased cardiovascular morbidity and mortality. The objectives of this review are to summarise the latest updated information and management of gout in the primary care setting.

Introduction

Gout is an ancient disease first described by Hippocrates in fifth-century BC. Gout is also known as the "Disease of Kings". It remains the commonest type of inflammatory arthritis and is an often disabling but treatable arthritis of adulthood.[1] The commonest cause of gout is a decrease in urate clearance (renal underexcretion), resulting in a raised serum uric acid level.[2] That said, hyperuricemia alone is not adequate for the development of urate crystal disease. Deposition of monosodium urate crystals in the joint interacts with macrophages and subsequently perpetuates the secretion of various cytokines. This cascade amplifies the inflammatory process, leading to a clinical manifestation of painful swollen joints.[2] The incidence of gout is in the rise due to the increasing prevalence of metabolic syndrome.[3] Moreover, the progression from asymptomatic hyperuricemia to chronic tophaceous gout is escalating.[3,4] Gout often occurs earlier in males than females. Women of child-bearing age rarely develop gout, as oestrogen has a uricosuric effect.[1] Notably, a variety of dietary and physical factors, comorbidities, medications, and other factors may predispose an individual to a gouty flare.

Internationally, the *British Journal of General Practice* published a guideline on improving gout management in primary care in 2017.[5] In 2019, the *Australian Journal of General Practice* issued an article on the challenges of managing gout in primary care.[6] In 2020, the American College of Rheumatology released its latest guideline on the management of gout.[1] Malaysia's clinical practice guideline (CPG) on the management of gout was released in 2008, and a newer CPG update is in the pipeline.[7] The authors believed that an updated local gout management guideline for primary care doctors would be timely, considering the many newer drug options, additional data on safety and efficacy of available drugs and new practices to help primary care doctors provide the latest evidence-based medicine.

Disease Burden of Gout Internationally and in Malaysia

In the United States, the prevalence of gout ranges from less than 3 million to 8 million individuals; the latest estimate suggested a prevalence of gout to be around 3% of the adult American population.[8] In general practice in the United Kingdom, the overall prevalence of gout increased from 1.4% in 1999 to 2.49% in 2012.[9] To date, there is still a lack of national prevalence study of gout. In an article on epidemiology and the management of gout in a rheumatology tertiary centre in Perak, Malaysia, Wahinuddin Sulaiman et al. (2019) reported 54 cases of gout under their rheumatology clinic follow-up. The predominant ethnic group affected was Malay, followed by Chinese. The mean age of onset of gout in this study was 53.1 (Standard deviation 13.6) years, with a duration of 7 years.[4]

Teh et al. (2014) reported on a total of 126 patients with acute gout who were admitted from 1 July 2011 to 1 July 2012 at Sarawak General Hospital. Among those admitted, 112 (88.9%) were male.[10] A majority of these patients were from the indigenous population of Sarawak. The mean age was 60 (SD 14.2) years. Most of the patients were overweight (68%), with comorbidities including

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hypertension (78.6%), chronic kidney disease or CKD (48.4%), type II diabetes mellitus (30.2%), dyslipidaemia (27.8%) and ischaemic heart disease (11.9%).[10]

Reasons for Poor Management of Gout[1,9-11]

The management of gout is suboptimal, as:

- Primary care doctors are often unclear about the diagnosis.
- Some patients only present to a doctor when they have an acute gouty attack but do not return for follow-up to initiate urate-lowering therapy (ULT).
- Patients may not be compliant with therapy.
- More than 50% of patients do not reach the targeted serum uric acid.
- Guidelines for the management of gout are often not followed, and the availability of ULTs may be limited.
- There is a lack of alternative xanthine oxidase inhibitors or uricosuric agents.

Diagnosis of Gout

The diagnostic criteria for gout include 2 of the following:

(a) A clear history of at least 2 attacks of painful joint swelling with complete resolution within 2 weeks;
(b) A clear history or observation of podagra, presence of tophus;
(c) A rapid response to colchicine within 48 hours of starting treatment.[1]

Definitive diagnosis: Presence of monosodium urate crystals in the serum, joint fluid or in the tissues.

The diagnosis of gout concentrates on the fundamental pathophysiologic events defining the clinical state: tissue deposition of urate crystals and accompanying inflammatory and potentially destructive consequences. A gout flare involves the presence of monosodium urate (MSU) crystals in synovial fluid obtained from joints or bursas visualised under polarised light microscopy, a technique that is frequently used to identify these crystals. In contrast, plain radiography may not reveal the presence of early disease that may not demonstrate any abnormality, as the joint spaces are usually preserved, and periarticular osteopenia is absent, unlike in the radiographic changes' characteristic of rheumatoid arthritis. Advanced gout typically shows bone erosions characterised by an overhanging edge and sclerotic rim. Ultrasonography can be very useful in early detection and in the case of a diagnostic dilemma. Critical diagnostic features include hyperechoic linear density (double contour sign) overlying the surface of the hyaline cartilage or tophaceous deposits in joints or tendons, described as hyperechoic, in homogenous material surrounded by a small anechoic rim.

The primary care setting employs a clinical diagnostic rule to estimate the likelihood of gout without joint fluid analysis. The model uses seven variables, including male gender (2 points), previous patient-reported arthritis (2 points), onset within one day (0.5 points), joint redness (1 point), first metatarsal phalangeal joint involvement (2.5 points), hypertension or at least one cardiovascular disease (1.5 points), serum urate level >5.88 mg/dL or 350 micromol/L (3.5 points).[12] Based on the total score, patients can be identified as having low (≤4 points), intermediate (>4 or <8 points), or higher (≥8 points) probability of gout. Patients in the intermediate category benefit most from a further evaluation via synovial fluid analysis.[12] This clinical diagnostic rule was validated in a group of 390 Dutch primary care patients with acute monoarthritis, where this diagnostic rule outperformed a physician diagnosis and offered a good outcome in the derivation study.[13]

Primary care doctors should beware that gout flares can occasionally coexist with another type of joint disease, such as septic arthritis or acute calcium pyrophosphate crystal arthritis (pseudogout). A referral to an orthopaedic surgeon or rheumatologist for joint aspiration will help with the analysis of the synovial fluid and subsequently establish the diagnosis.

Three classical stages of gout are currently seen in our daily clinical practice:

(a) Acute gout flare
(b) Inter-critical gout
(c) Chronic gouty arthritis and tophaceous gout

Management of Acute Gout

A gout flare, which frequently occurs in the lower extremities, is commonly monoarticular and intensely inflammatory. Patients often report severe pain, redness, warmth, swelling and disability, with the maximum severity within 12 to 24 hours from onset. Twenty per cent of patients experience a polyarticular gouty flare.[14]

The principles of managing an acute gouty flare include the following:[1,16-17]

(a) In an acute flare, oral colchicine, non-steroidal anti-inflammatory agents (NSAIDs), or glucocorticoids (oral, intra-articular or intramuscular) are appropriate first-line therapy. There is no superiority between NSAIDs versus colchicine in an acute attack, and the decision should be based on the suitability of the patient's profile. For example, in patients with CKD or ischaemic heart disease, NSAIDs should be avoided.[13] The use of NSAIDs should also be avoided in patients with poorly controlled hypertension or known peptic ulcer disease. In patients exhibiting inadequate response to monotherapy, a combination therapy (colchicine plus NSAIDs or glucocorticoids) can be used.[1,15]

(b) **Pill in the pocket**: Treat as early as possible. Oral colchicine 1 mg stat and 0.5 mg 1 hour later during an acute attack, followed with colchicine 0.5 mg bd to tds subsequently. Patients should be taught how to self-monitor and watch for warning signs of an impending gouty attack.[1,16-17]

(c) Adjunctive (s)[16-19]:
Adequate fluid intake of 2-3 L per day.
Ural sachets, 1 sachet 3 times a day.
Oral vitamin C 500 mg daily.
Elevate leg, ice and rest.

(d) ULT[1,18]
During an acute attack, do not stop allopurinol. Conventionally, ULT is not started during an acute gouty flare based on observations that it may worsen or prolong an existing flare.[18] However, two small, randomised control trials and one observatory study on initiating ULT during a flare showed no differences between the 2 arms in mean pain scores, the frequency of additional gout flares, or in levels of acute phase reactants.[21] Hence, some experts have suggested that ULT can be initiated for a selected group of patients with very difficult to manage or continuous flares, along with anti-inflammatory therapy. In 2020, the American Society of Rheumatology conditionally recommended this new approach of initiating ULT during a flare based on patient factors or preferences using a case-by-case technique[1,20]

Colchicine

Table 1: Colchicine dose in acute gout management.[21-23]

Colchicine dose	
eGFR (ml/min/1.73 m^2)	Dosage
>50	0.5 mg tds
10-50	0.5mg od to 0.5 mg bd
<10	Contraindicated

Colchicine can be given both during an acute gout flare or as prophylaxis. The prophylactic dose of colchicine is 0.5 mg once to twice daily for up to 6 months.[22] The potential side effects of colchicine include diarrhoea, nausea and vomiting, bone marrow suppression, myopathy and rhabdomyolysis. Colchicine should not be given to patients who are receiving CYP 3A4 inhibitors such as clarithromycin.[23] The dose adjustment for colchicine should be in accordance with the creatinine clearance (**Table 1**).

Steroid

Table 2: Steroid dose in acute gout management.[24-25]

	Steroid dosages
Polyarticular gout	Oral prednisolone 30-35 mg daily for 5 days. Intra-muscular triamcinolone acetate up to 1 mg/kg.
Monoarticular gout or polyarticular involvement with effusion	Ultrasound-guided intra-articular steroid injection. 40 mg into large joints or 10-20 mg into small- to medium-sized joints. In monoarticular joint involvement, intra-articular steroid injection is an option.

Steroids are highly effective as rapid-acting anti-inflammatory agents in an acute flare. The route of administration of steroids will depend on several factors, including the number of affected joints, patient preference, availability of joint injection services, clinician experience and patient preferences.[24] Clinicians should exercise caution when using steroids in patients with heart failure, poorly controlled hypertension, uncontrolled diabetes or moderate to severe renal insufficiency. A rebound flare is common when steroids are withdrawn, especially in patients not on anti-inflammatory flare prophylaxis. Thus, clinical follow-up is required to ensure an adequate treatment response is achieved.[25,26]

NSAIDs

Table 3: Choice of NSAIDs in acute gout management.[27-28]

Choice of NSAIDs			
Non-selective NSAIDs		**Selective COX-2 inhibitors**	
Indomethacin	25-50 mg tds	Etoricoxib	90 mg od 120 mg od
Meloxicam	15 mg od	Celecoxib	200 mg bd
Naproxen	500 mg bd		
Mefenamic acid	500 mg tds		
Diclofenac sodium	50 mg bd to tds		

NSAIDs are most effective when initiated within 48 hours of symptom onset. NSAIDs can be discontinued 2 to 3 days after clinical signs have completely resolved.[29] A typical duration of NSAIDs in gout flare is 5 to 7 days (**Table 3**). Patients should not be treated concurrently with more than one NSAID, and a detailed review of medication history should be conducted to avoid any potential over-the-counter therapies that may include NSAIDs.[30] Caution should be taken in the use of NSAIDs in patients with known cardiovascular disease. Aspirin should not be used to treat gout flare, as it has a paradoxical effect on serum uric acid.[28] However, low-dose aspirin, such as the doses taken by many patients as cardiovascular prophylaxis, does not need to be discontinued during a gout flare.[18,28]

ULT

During the initial initiation phase of ULT, concomitant anti-inflammatory prophylaxis with colchicine for 3-6 months should be given to reduce the risk of a flare.[20,31] Before initiation of ULT, patients should be educated on the indications of ULT, modes of action, dosing regime, monitoring and uric acid targets, compliance, possible side effects, gout flares and risk hypersensitivity reaction, especially to allopurinol.[1,20] Shared decision-making with the patient is essential for the best outcome.

Allopurinol

Allopurinol remains the first line ULT for all patients, including those with stage 3 and above CKD. This substance is a purine analogue xanthine oxidase inhibitor (XOI). Often there is an underdosing issue among gout patients, as most of them receive a dose of 300 mg daily instead of the maximum 900 mg daily dose.[1] The serum urate levels are not commonly measured after initiation of allopurinol; consequently, serum urate targets are not achieved. The authors recommend an initial dose of 50 mg daily for allopurinol and subsequent up-titration every 4 weeks until the target uric acid level is achieved. That said, a lower starting dose of allopurinol could reduce the risk of allopurinol acute hypersensitivity syndrome.[28,32]

The starting dose of allopurinol should be adjusted according to the eGFR (**Table 4**). In addition, primary care providers should aim for dose reduction of allopurinol in CKD patients and monitor their serum creatinine trend. It is well known that allopurinol is associated with severe cutaneous adverse drug reactions in patients who carry the genotype HLA-B*58:01 or 73, which is common among African Americans, Koreans, and Han-Chinese.[28,33] Patients should be counselled to stop allopurinol immediately and seek medical attention if they experience any coryzal symptoms, fever, mucosal ulcers, or rashes.[20]

Table 4: Allopurinol initiation dose according to eGFR level.[1,20]

eGFR (ml/min/1.73m²)	Allopurinol initiation dose
Less than 5	50 mg per week
5-15	50 mg twice a week
16-30	50 mg every 2 days
31-45	50 mg/day
46-60	50 mg alternate 100 mg od
61-90	100 mg per day
91-130	150 mg per day
More than 130	200 mg per day

Historically, allopurinol is commenced 2 weeks after the complete resolution of an acute gout attack.[34] However, some studies have shown that starting allopurinol during an acute gout flare does not prolong the flare, provided the acute episode is being treated adequately.[1,21] Whenever allopurinol regimen is newly initiated, regular oral colchicine prophylaxis should be prescribed to be taken along with allopurinol for at least 2 weeks and can be continued up to 6 months to avoid an acute gout flare.[1,20-21]

Febuxostat

Another ULT is febuxostat, a non-purine analogue XOI. Febuxostat is a second line ULT when allopurinol is not tolerated or contraindicated and should be used in patients with a history of hypersensitivity reactions to allopurinol. Note that the manufacturer recommends periodic liver function test monitoring.[32] The doses of febuxostat are 40, 80 and up to 120 mg daily. There is no dose adjustment required if eGFR is above 30 ml/min/1.73m^2 (**Table 5**).[35] There is strong evidence in favour of febuxostat in flare reduction, tophi resolution, and safety, especially in the mild to moderate renal impairment group (more than 30 ml/min/1.73m^2).[20,32] Unlike allopurinol, febuxostat is rarely associated with hypersensitivity reactions. However, there is a cardiovascular safety concern with febuxostat in patients with an increased cardiovascular risk, as seen in a previous trial of around 6200 patients with gout and coexisting cardiovascular conditions[28] The Febuxostat versus Allopurinol Streamlined Trial (FAST) results released in November 2020 showed that among 6100 patients enrolled, there was a non-significantly lower risk of composite cardiovascular safety outcome among the febuxostat group with a median follow-up of 4 years.[33] The European Medicines Agency, which recommended the FAST study, has not yet released a new position regarding its warnings. Until more cardiovascular safety data are available, we continue to prefer allopurinol over febuxostat, particularly in patients at higher cardiovascular risk.[20]

Table 5: Initiation dose of febuxostat in renal impairment patients.[32-33]

Creatinine clearance (CrCl) (ml/min/1.73m^2)	Febuxostat dose
30-89	No dosage adjustment. Initiation dose is 40 mg daily; may increase up to 80 mg, then 120 mg daily if target serum uric acid is not achieved.
<30	Maximum 40 mg daily.
Dialysis	No data.

Uricosurics

Uricosurics, another group of drugs used in urate lowering, work by enhancing uric acid renal excretions.[34] These drugs can be used in patients who are resistant or intolerant to xanthine oxidase inhibitors. Uricosurics can also be used in combination with xanthine oxidase inhibitors. Examples of uricosurics are probenecid 500-2000 mg daily, benzbromarone 50-200 mg daily or sulfinpyrazone 200-800 mg daily.[20,34] Uricosurics are contraindicated in patients with renal impairment with creatinine clearance of less than 30 ml/min, patients with high urine uric acid excretions, urolithiasis or nephrocalcinosis.[20,36] Benzbromarone can be used in patients with moderate renal impairment, but there is a risk of liver toxicity.[34-35]

(a) Probenecid

Probenecid is a potent uricosuric agent with a starting dose of 500 mg once or twice daily, with dose titration up to 2000 mg daily.34 Allopurinol in combination with probenecid is an option for patients who have failed to achieve their target serum uric acid level and have a high cardiovascular disease risk. Probenecid has a diminished urate-lowering efficacy in patients with moderate to severe CKD (creatinine clearance less than 45 mL/minute).[35, 37]

Treat to target

Primary care providers should educate gout patients who have been started on ULT and should provide an individual uric acid target. All gout patients on ULT should aim to achieve a serum uric acid of less than 360 µmol/L (6 mg/dL) for flare prevention, as well as reduction of gout attack and tophi formation. In contrast, in patients who have tophaceous gout, the target for serum uric acid should be below 300 µmol/L or 5 mg/dL. Gout flares have almost been eliminated after one year of treatment by targeting a serum uric acid level below 6 mg/dL. A lower serum uric acid can decrease tophus size faster. However, a serum uric acid level below 180 µmol/L is not recommended, as some studies have suggested that uric acid may be protective against neurodegenerative diseases such as Alzheimer's, Parkinson's, or amyotrophic lateral sclerosis.

Lifestyle modification

Regular exercise, weight loss and a low-purine diet should be advised to all patients with gout. Such a diet includes avoiding organ meat with

a high purine content, such as kidney, liver, or brain. Patients should also abstain from food or drinks containing high-fructose corn syrup and avoid alcohol overuse.[36] Additionally, medical professionals should encourage patients with gout to limit their seafood intake, such as sardine and shellfish, which are high in purine. Instead, a balanced diet consisting of high-fibre fruits and vegetables, along with low-fat or non-dairy products, should be encouraged. Avoidance of alcohol, especially beer products, should be emphasised.[37]

Management of gout in CKD and end-stage kidney failure patients

Gout has been closely associated with kidney disease and is a risk factor for the development of CKD. Uric acid is the final product of xanthine/hypoxanthine, which is catalysed by xanthine oxidase in endogenous urate biosynthesis. Renal excretion of uric acid follows 4 pathways: filtration, reabsorption, secretion, and post-secretory reabsorption.[28,37] Acute uric acid nephropathy develops due to oligo-anuric renal failure caused by renal tubular obstruction by urate and uric acid crystals. This is commonly observed in the setting of malignancy such as leukaemia, lymphoma, small cell lung cancer and germ cell tumour, in which a rapid cell turnover or cell lysis occur, especially post chemotherapy. Chronic urate nephropathy features long-standing micro-tophi formation in the renal medullary interstitium. Uric acid nephrolithiasis due to uric acid precipitation in the collecting system represents 5 to10% of all renal calculi in the United States population.[39] Gout is a risk factor for incident CKD stage ≥ 3 CKD, which can then progress to end-stage kidney failure. The associations between hyperuricemia, gout and CKD are bidirectional.[1,36]

Table 6: Management of gout in renal impairment patients.[36-37]

	CKD	End-stage kidney failure
Acute gout	Colchicine is contraindicated if eGFR <10 ml/min/1.73 m^2 (**Table 1**). Oral or intravenous steroids (**Table 2**). Monoarticular involvement: Intraarticular steroids. NSAIDs are contraindicated if creatinine clearance is less than 60 mL/minute per 1.73 m^2.	Oral or intravenous steroids (**Table 2**). Monoarticular involvement: Intraarticular steroids. In patients with no residual kidney function, NSAIDs should be avoided. Avoid colchicine in haemodialysis patients, as it is not removed by dialysis and there is a risk of colchicine toxicity.
Chronic gout	Allopurinol is recommended, with a lower allopurinol starting dose (**Table 4**). In mild to moderate renal impairment, febuxostat is an option (**Table 5**).	Allopurinol is recommended with a lower allopurinol starting dose (**Table 4**). No data are available on febuxostat use in end-stage kidney failure patients.

Referral to a rheumatologist

The following are indications for referral of gout patients to rheumatologists:[38-39]

(a) Unclear aetiology
(b) Refractory disease
(c) Recurrent gouty attacks
(d) Difficulty in achieving target serum urate level
(e) Renal impairment
(f) Adverse effects of ULT or intolerance
(g) Chronic tophaceous or/and erosive gouty arthritis

Conclusion

Gout is an easily treatable disease and may be curable. The aim of management in an acute flare is the rapid resolution of pain with early introduction of treatment and disability prevention. ULTs are readily available and effective, and allopurinol remains the first-line treatment.[39] Primary care providers should be familiar with the indications for initiating ULT and setting serum uric acid targets with patients, as well as being competent in handling possible side effects of ULTs and educate patients about lifestyle and dietary modifications.[38] Because gout is frequently part of the metabolic phenomenon, testing for hypertension, diabetes, and hypercholesterolemia and monitoring weight is pivotal, not only through diet and lifestyle modification but also treatment when necessary.[39]

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Conflicts of interest

The authors declare that they have no competing interests in the publication of this article.

How does this paper make a difference to general practice?

- The increasing prevalence and consequences of poorly treated gout mandate a greater focus for practitioners to improve and ensure a better outcome for patients.
- As gout is the most prevalent type of inflammatory arthritis, this is the first local paper written that summarises a wide range of aspects related to better gout management.

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