UNIT NO. 2

AN UPDATE ON THE DIAGNOSIS AND MANAGEMENT OF GOUT

Dr Anindita Santosa

ABSTRACT

Gout is characterised by monosodium urate crystal deposition in synovial fluid, articular surfaces, and other tissues, which occurs after the chronic elevation of uric acid levels above the saturation point of 360mmol/L (6mg/dL). Amongst all inflammatory arthropathies, gout is the most common. Given the rising prevalence of gout, it is imperative to keep up with the recent advances in the understanding of the pathophysiology, diagnostic modalities, and therapies of gout. It is important to understand that gout is not as harmless a condition as perceived in the past and is, in fact, associated with significant morbidity and even mortality if left untreated. This article seeks to provide a useful review of the current standard of care and to discuss new developments in the management of gout applicable in any family medicine practice setting.

Keywords: Gout; Uric Acid; Urate-lowering Therapy; Treat-to-target; Treatment;

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INTRODUCTION

While a deeper understanding of the pathophysiology of gout has been evolving for the past 10 to 15 years, a resurgence of interest in the management of gout has only picked up significantly with the recent approval of febuxostat. This review aims to provide family physicians who are, more often than not, the first point of contact for patients afflicted with gout, with an overview of the management strategies of gout.

EPIDEMIOLOGY

Incidence and Prevalence

Globally, gout is the most common inflammatory arthritis. Data from some national surveys, hospital registries, and the Community Oriented Program for Control of Rheumatic Diseases (COPCORD) — though incomplete and differing in method of data collection — demonstrate an almost universal trend of increasing prevalence of hyperuricaemia and gout.[1] The estimated prevalence of gout in Singapore was 4.1 percent in 2012.[2] In the US and the UK, the incidence of gout varies from 0.3 per 1000 person-years in the 1970s to 2.68 per 1000 person-years in the 2000s.[1] No recent data is available on the incidence of gout in Singapore.

Men in their fourth decade are more often affected. While premenopausal women hardly ever present with gout, the incidence of gout in women increases with ageing due to declining levels of oestrogen, which possesses uricosuric effects in post-menopausal women.[3]

ANINDITA SANTOSA
Department of Medicine (Rheumatology)
Changi General Hospital

Comorbid Disorders

Gout and asymptomatic elevated serum uric acid levels are correlated with metabolic syndrome.[4] Commonly associated conditions are hypertension, chronic kidney disease (stage 2 or greater), obesity, diabetes mellitus, ischaemic heart disease and stroke.[5] It has also been associated with increased mortality, especially due to cardiovascular disease.[6] It is thus imperative to remember to control modifiable cardiovascular risk factors in patients with gout. Gout patients appear to have a reduced risk of neurological disorders, such as Parkinson's disease,[7] Alzheimer's disease,[8] and both vascular and non-vascular dementia.[9] The mechanism of this protective effect is, however, unclear and again a cause-effect relationship has not been established.

Risk Factors

There are both genetic and non-genetic risk factors for gout. The former will not be discussed as it is beyond the scope of his paper. It is important to recognise that hyperuricaemia is the primary risk factor for the development of gout,[10] and hence unsurprisingly, most risk factors identified for gout are also risk factors for increased urate concentrations (see Table 1).

Table 1: Risk factors for development of gout.

Non-modifiable risk factors
- Male sex
- Increasing age
- Family history
- Ethnicity
- Genes
- Menopause

Modifiable risk factors

Drugs
- Diuretics
- Calcineurin inhibitors: Cyclosporine, tacrolimus
- Angiotensin-converting enzyme inhibitors
- Angiotensin II receptor blockers (except losartan)
- β blockers
- Pyrazinamide
- Ritonavir

Dietary
- Red meat
- Seafood
- Beer
- Spirits
- Sugar-sweetened beverages, especially those with high fructose content

Comorbidities
- Chronic kidney disease
- Obesity
- Hypertension
- Hyperlipidaemia
- Hypertriglyceridaemia
- Congestive cardiac failure
- Obstructive sleep apnoea
- Psoriasis
- Sickle cell anaemia
- Haematologicalmalignancy

The Burden of Gout

Patients with acute gout often experience pain and swelling, which are significant enough to impair their quality of life (QOL) severely. Long-term complications from gout, such as chronic debilitating arthritis, deformities, and loss of function, can also reduce QOL. Studies using validated measures have demonstrated a significant global reduction in QOL.[11]

Gout also poses a significant healthcare and economic burden on the afflicted individual, employers, and society. Gout patients may use more days of absence and may be less productive.[12]

CLINICAL ASSESSMENT AND DIAGNOSIS

Presentation

The typical initial presentation of gout is that of acute arthritis affecting the joints of the foot or ankle.[13] Patients would typically have had an episode of hyperuricaemia preceding this first flare. Acute flares are usually self-limiting within 1–2 weeks, with complete resolution of the signs and symptoms of inflammation during the intercritical period between episodes. With persistent hyperuricaemia, recurrent flares can occur, and these become increasingly frequent and prolonged and become polyarticular (involving the joints of the upper limbs as well). Without initiation of urate-lowering therapy at this stage, individuals may develop chronic gouty arthritis, advanced gout with tophi, or both. Advanced gout is characterised by chronic joint pain, activity limitation, structural joint damage, and frequent flares (sometimes without full resolution of symptoms of inflammation between flares).

It would be best to keep in mind that there may be atypical presentations of gout, such as early presentation (especially in those with genetic predisposition and strong family history) or tophaceous disease without previous acute flares.[14]

Symptoms and Signs

In 2006, the European League Against Rheumatism (EULAR) came up with an evidence-based recommendation for the diagnosis of gout. The clinical markers identified in the recommendation (episodic self-limited joint pain, swelling, and erythema) were considered to be highly sensitive for clinical gout but not specific for gout. A history of podagra and the presence of suspected tophi were seen as more specific (80–90%) but still not diagnostic.[15] The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) developed new classification criteria for gout.[16] Although it is important to remember that this set of criteria was meant for research and not for diagnostic purposes, the characteristic symptoms and signs (Table 2) may be utilised as a guide in the clinical diagnosis of gout.

Table 2: Typical symptoms and signs of gout.

Symptoms

- Prodromal period of mild joint discomfort/tingling
- Acute onset of severe joint pain that peaks within 24 hours (often occurs at night, and patient wakes up with severe joint pain)[17,18]
- Maximum pain of a flare usually measures 7 or above on a 0-10 scale[19]
- Pain is usually of a throbbing or burning nature
- Joints involved: first metatarsophalangeal joint (most frequently affected), other small joints of feet and ankle; in advanced gout, upper limb joints can be affected as well
- Loss of function: inability to walk/weight bear, and perform daily activities.
- Other symptoms of inflammation: swelling, heat, redness
- Often able to identify triggers for flares: acute medical/surgical illness, dehydration, alcohol intake (especially beer), purine-rich foods[20,21]
- If the patient had a previous similar episode – usually self-limiting with resolution of symptoms within 14 days
- May report fever
- Might describe subcutaneous nodules – may or may not be inflamed; could have a history of discharging tophaceous material from these nodules[22]

Signs

- During a flare: synovitis (swollen, tender joints), erythema, swelling, and warmth of affected joints[19]
- Bursitis, tendinitis
- Fever (especially in the presence of polyarticular flare)
- On resolution of flare: skin peeling over affected joints
- Tophus "chalk-like subcutaneous nodule under transparent skin, often with overlying vascularity"[16]
- Tophi most often occur over the first metatarsophalangeal joint, Achilles tendon, peroneal tendon, helix of the ear, olecranon bursa, and finger pad.
- Evidence of comorbid conditions, e.g. central obesity, hypertension, psoriasis

Diagnostic Investigations

The demonstration of monosodium urate crystals by polarising light microscopy of the synovial fluid (of inflamed joints) or tophaceous material remains the gold standard for the diagnosis of gout.[23] The demonstration of monosodium crystals in synovial fluid from asymptomatic joints in a patient who presents with a typical clinical history of gout would also allow making a definite diagnosis of gout.[24]

Serum urate testing is useful to assist with the clinical diagnosis of gout in symptomatic individuals, but hyperuricaemia alone is not sufficient to make a diagnosis of gout if the patient is asymptomatic. Gout is unlikely in a patient with persistently low serum uric acid concentrations (less than 360mmol/L).[19] Conversely, a normal or low serum uric acid level during an acute flare does not exclude the diagnosis of gout as serum urate levels may fall.[25] If the diagnosis of gout is uncertain, serum urate should be retested after the flare has resolved.

Inflammatory markers, such as C-reactive protein, are usually elevated during a flare. Likewise, neutrophil leukocytosis can also be present. These reflect systemic inflammation and are not diagnostic of gout. Other laboratory tests may be useful in the assessment of comorbid disorders in patients with suspected or confirmed gout.

Increasingly, imaging modalities are used to assist with the diagnosis of gout, especially when joint aspiration is not feasible. In the early stages of gout, conventional radiographs are of limited use as they would only show non-specific soft tissue swelling of the affected joint. In advanced gout, bone erosions with sclerotic rim and overhanging edges may be seen.[16] Ultrasonography might demonstrate features of monosodium urate crystal deposition, such as the double contour sign, tophi, and the snowstorm appearance of crystals within synovial fluid.[26,27] Dual-energy CT (DECT) is also recognised as a useful imaging modality in identifying monosodium urate deposits in patients with gout.[28] The radiological changes seen in ultrasonography and DECT are also present in patients with asymptomatic hyperuricaemia and, currently, it remains to be seen whether these individuals are at higher risk of developing symptomatic disease in the future.

Differential Diagnosis

The key differential diagnosis for gout is septic arthritis, especially in the case of a monoarticular flare. It is crucial to remember that septic arthritis can coexist with gout (though rarely so).[29] As such, obtaining a synovial fluid sample for Gram stain and culture is necessary to exclude septic arthritis.

Other forms of inflammatory arthritis can mimic the clinical presentation of gout, including other crystal-induced arthropathies such as acute calcium phosphate crystal arthritis, psoriatic arthritis, palindromic rheumatism, and reactive arthritis.[19] Clinical assessment usually allows rheumatoid arthritis and osteoarthritis to be differentiated from gout.

MANAGEMENT OF GOUT

Principles of Management

It is key that an accurate diagnosis of gout is made, as it allows rapid treatment of acute flares and effective long-term management where indicated. In 2016, EULAR published an updated evidence-based recommendation for the management of gout.[30] The three overarching principles of management stipulated in the guidelines emphasised the following:

1. Patient education on the nature of the disease, available treatment options, comorbidities, management of acute attacks, and need for lifelong lowering of serum uric acid levels below target level.

2. Patient education on lifestyle modifications required to maintain a low-purine diet and healthy lifestyle.

3. Routine and systematic screening of gout patients for associated comorbidities and cardiovascular risk factors.

Treatment of Acute Flares

Acute flares should be treated as early as possible. With adequate education, fully informed patients should be taught to self-medicate on the occurrence of prodromal symptoms of an acute flare. The choice of drug(s) would depend on the following factors: contraindications, patient's previous experience (efficacy, adverse effects) with treatments, time of initiation after flare onset, and the severity of the flare (type and number of joint[s] involved).

The recommended first-line option for an acute flare is colchicine (within 12 hours of onset of symptoms).[31] While the EULAR recommendation advocates a loading dose of 1mg followed 1 hour later by 0.5mg on day one, some patients may not be able to tolerate this dose of colchicine and may develop diarrhoea, which may worsen the gout attack. Other options would be:

1. Non-steroidal anti-inflammatory drugs (NSAIDs), with the addition of a proton pump inhibitor where appropriate.

2. Oral corticosteroids (30–35mg/day of Prednisolone for 3–5 days).[32] Though not supported by randomised controlled trials, the ACR 2012 guidelines recommended Prednisolone at an initial dose of 0.5mg/kg/day for 2–5 days, followed by tapering for 7–10 days, and then discontinuation.[33]

3. Joint arthrocentesis and injection of intra-articular corticosteroids (feasible option if only 1–2 joints are affected).[34] A combination of any two of these options is possible if a suboptimal response is achieved with just one of them.

Significant contraindications and drug interactions to remember:
1. Colchicine and NSAIDs should be avoided in patients with severe renal impairment.
2. Colchicine should not be given to patients receiving strong P-glycoprotein and CYP3A4 inhibitors such as cyclosporine and clarithromycin.
3. Use colchicine with caution in patients on statins and fibrates.
4. Glucocorticoids (both oral and injectable) should be avoided if there are concerns of septic arthritis and in the presence of systemic infections.
5. Glucocorticoids (both oral and injectable) should be used with caution in patients with diabetes mellitus and hypertension.

In patients with frequent flares and contraindications to the aforementioned first-line options for the treatment of acute gout flares, IL-1 blockers should be considered. This may not be an option in family practice/primary health care at present, but being aware of this option may help trigger a referral/early review request with the rheumatologist if the patient's gout is being co-managed by the primary physician and rheumatologist. The main contraindication for IL-1 blockers is a current infection. To date, canakinumab has been shown to be capable of reducing pain in patients with an acute flare.[35] In patients requiring IL-1 blockers for acute gout flares, urate-lowering therapy should be initiated.

Whenever needed, non-pharmacological modalities may be utilised for the purpose of pain relief during acute flares.

Table 3: Therapeutic Options for Acute Gout Flares

Pharmacological	Non-pharmacological
• Colchicine • NSAIDs (with proton pump inhibitor where appropriate) • Prednisolone • Intra-articular injections of corticosteroid • Combination therapy • IL-1 blockers (may be considered if there are contra-indications to all other first-line options, and only if septic arthritis and systemic infections have been excluded)	• Rest • Cold Compress • Adequate hydration

Prophylaxis against Flares

Prophylaxis against flare is recommended during the first 6 months of urate-lowering therapy, as the dispersion of monosodium urate crystals during the initial phase of dissolution of deposits may increase the rate of acute flares that can contribute to poor treatment adherence.[36] It is pivotal, however, that the patient is informed and involved in the decision to initiate prophylaxis as cautious up-titration of urate-lowering therapy may not necessarily increase flare frequencies, and the patient may choose not to take prophylaxis.

The usual options for prophylactic treatment are:
1. Colchicine 0.5–1mg/day (renal dose adjustment as indicated).
2. Low-dose NSAID (Naproxen 250mg BD).

Although not advocated in the recent EULAR guidelines, the ACR 2012 guidelines allowed the use of "low-dose" Prednisolone (10mg/day) as second-line prophylaxis if colchicine and NSAIDs are both not tolerated, contraindicated, or ineffective.[33] However, the managing physician must pay continued attention to the risk-benefit ratio (paying attention to gout activity and adverse side effects of glucocorticoids) when employing this method, as well as ensure continued efforts in optimising urate-lowering therapy.

Urate-lowering Therapy

The initiation of urate-lowering therapy (ULT) should be addressed in every patient with a definite diagnosis of gout, even at first presentation.

As gout has been shown to be potentially debilitating and is associated with cardiovascular morbidity and mortality, early initiation of ULT and a treat-to-target approach has been

Table 4: Indication for initiation of urate-lowering therapy.
• Recurrent flare (≥ 2/year)[36,37]
• Tophi[38]
• Urate nephropathy
• Renal stones
Initiation of ULT is recommended close to the first diagnosis in patients presenting at a young age (<40 years), with very high serum uric acid levels (>480mmol/L), and comorbidities (renal impairment, hypertension, ischaemic heart disease, heart failure).[39,40]

adopted in the management of gout. ULT would allow the resolution of gout features as long as uricaemia is maintained at target level (<360mmol/L). In patients with severe gout, i.e. tophi, chronic arthropathy, frequent attacks, a target level of <300mmol/L is advocated until total crystal dissolution and resolution of gout. After that, the target can be readjusted to <360mmol/L.[30] As uric acid has been postulated to have a protective effect against neurodegenerative diseases, the maintenance of serum uric acid concentrations of <180mmol/L is not recommended in the long term.

Table 5: Urate-Lowering Strategies

Pharmacological	Adjunct therapy	Non-pharmacological

• Xanthine Oxidase Inhibitor
  • Allopurinol
  • Febuxostat
• Uricosuric agents
  • Probenecid
  • Benzbromarone
• Combination of xanthine oxidase inhibitor and uricosuric agent
• Pegloticase (severe chronic tophaceous gout, not responding to the above)
	• Stop diuretics
	• Use losartan
	• Use fenofibrate or statin
		• Dietary modification
		• Weight loss

The first therapeutic option for the long-term management of gout in patients with normal renal function is allopurinol.[41] It should be started at a dose of 100mg/day and increased by 100mg increments every 2–3 weeks if required[42] to reach the target serum uric acid levels. The rationale for an initial low dose is to reduce early gout flares and because high starting doses are associated with an increased risk of serious cutaneous adverse reactions (SCARs).[43]

If the uricaemic target cannot be achieved at a maximum dose of allopurinol, a combination with uricosurics or a switch to either uricosurics or febuxostat is recommended. In the event of allopurinol intolerance, a switch to febuxostat or uricosuric agents is advocated. If these steps still do not yield target urate levels, then Pegloticase should be used instead.[30] Unlike the 2012 ACR recommendation for the management of gout, the 2016 EULAR recommendation allows the use of febuxostat as urate-lowering only if allopurinol fails to achieve the serum uric acid target or if there is an intolerance to allopurinol, taking into account the costs and effectiveness of both drugs at their optimal dosage.

Allopurinol (up to 800mg/day)[59] is a prodrug for the active metabolite, oxypurinol, which is eliminated via the kidneys over 18–30 hours. Accumulation of oxypurinol in patients with renal impairment leads to toxicity and, in susceptible individuals (e.g. those with HLA-B*5801), to hypersensitivity reactions, including SCAR. It is important to educate the patients on the potential adverse effects of allopurinol and the features of hypersensitivity reactions. All patients who have been started on allopurinol should be reviewed within two weeks of initiation and 4–6 weeks of dose adjustment, and assessed for rashes, mucositis, fever, transaminitis, renal impairment, cellular urines, eosinophilia, and leukocytosis, which may suggest drug hypersensitivity. Early recognition of these features and cessation of allopurinol are crucial in reducing the risk of progression to SCARs or chronic complications of drug hypersensitivity, e.g. renal failure or even death.

Febuxostat (40–80mg/day) is a potent non-purine selective xanthine oxidase inhibitor. It is metabolised in the liver, and as the main route of elimination is not renal, the drug can be used in patients with mild-to-moderate renal impairment. Intolerance to allopurinol is not a contraindication for febuxostat use. Prescribers are cautioned to keep a lookout for the occurrence of hypersensitivity reactions regardless of a history of previous allopurinol hypersensitivity. Multiple trials showed that febuxostat (at 80 or 120mg/day) was superior compared to a fixed daily dose of 300mg allopurinol, but no large, good trials have compared the efficacy of febuxostat to higher daily doses of allopurinol.[44,45,46]

Benzbromarone (50–200mg/day) is a potent uricosuric agent. It is associated with a risk of hepatotoxicity and, hence, should not be used in patients with liver pathologies. Given its mode of action, benzbromarone must not be prescribed to patients with renal impairment and previous history of renal stones.[47]

Probenecid (up to 1–2g/day) is another uricosuric which has been shown to be effective in lowering uricaemia to target. Again, the main contraindications are that of renal impairment and a history of urolithiasis.[48]

Pegloticase (8mg every two weeks) is a pegylated uricase

derived from a genetically modified strain of Escherichia coli. It catalyses the oxidation of uric acid into allantoin, a water-soluble end product.[49,50] Allergic reactions and loss of efficacy occur due to the occurrence of antibodies against pegloticase.

Emerging Therapies

Lesinurad, a selective uric acid reabsorption inhibitor, was approved for use in combination with allopurinol or febuxostat for the treatment of hyperuricaemia associated with gout in 2015 by the United States Food and Drug Administration. The use of lesinurad is contraindicated in patients with severe renal impairment (estimated creatinine clearance <30mL/min), tumour lysis syndrome, or Lech-Nyhan syndrome.[60] In the local context, however, it has not been used routinely.

Other drugs in the pipeline are arhalofenate, which is an oral medication which inhibits URAT1 and decreases inflammation by limiting interleukin-1b production. It is meant to be used in fixed-dose combination with febuxostat, and two more URAT1 inhibitors under development, RDEA3170[(60)] and URC102.

Challenges in the Management of Gout

The management of gout remains poor despite the increased understanding of the pathophysiology of the condition, as well as the increasing number of therapeutic options available to treat it. This trend of suboptimal control of gout holds true in both primary[51,53] and specialist care settings.[52] The factors identified for the suboptimal control of gout are as outlined in Table 6.

To overcome these barriers to optimal treatment of gout, both patient and physician (both primary physicians and specialist) education and empowerment is central. Changes in prescribing practices and a multidisciplinary approach have been shown to be effective in improving gout control.[52]

Table 6: Factors resulting in a suboptimal gout management.

Physician factors	Patient factors
• Poor understanding of natural history of disease, i.e. gout is a chronic condition despite the intermittent nature of flares.[54,58] • Poor awareness of management guidelines and therapeutic options available, and hence, non-adherence to current standard of care.[55,56,57] • Unfamiliarity with options of urate-lowering drugs and the potential complications and drug interactions of these drugs; wariness over hypersensitivity reactions[59] — e.g. resulting in underdosing of allopurinol. • Infrequent use of adjunctive therapy, such as losartan, fenofibrate, and oral vitamin C, which have uricosuric effects. • Poor education on the use of prophylaxis against acute flares during initiation of urate-lowering therapy.[61] • Inadequate screening and control of comorbidities.	• Poor understanding of the disease and the potential complications if it remains untreated.[58] • Stigma of gout being associated with a decadent lifestyle may lead to embarrassment and reluctance to seek treatment. • Poor adherence to pharmacotherapy (Various reasons were given: fear of side effects, pill burden, and incorrect belief that they have been cured).[54]

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LEARNING POINTS

- **Gout is a chronic condition and requires long-term treatment to maintain serum uric acid levels at a target of <360 mmol/L (or <300 mmol/L in chronic tophaceous gout or patients with frequent gout attacks).**
- **Physician and patient education on the natural history, pathophysiology, comorbidities, available treatment options, and the role of prophylaxis in the initiation of urate-lowering therapy is key in empowering both parties in the management of gout.**
- **Lifestyle changes and dietary modification are important in the management of gout.**
- **Given its association with metabolic syndrome and cardiovascular morbidity and mortality, it is important that systematic screening is performed.**