Singapore Med J 2012; 53(8) : 508

CME ARTICLE

The unwelcome visitor

Gim Gee Teng[1], MBBS, ABIM (Rheumatology), *Chung Yan Tong*[2], BSc (Hon), *Choon How How*[3], MMed, FCFP, *Lay Hoon Goh*[3], MMed, FCFP

Mr Alex, a 40-year-old taxi driver with a history of gout presented to you with increasing frequency of attacks involving his left big toe and more recently, his right knee as well. His last attack was barely three weeks ago, and the pain, swelling, warmth and redness began two days ago in his left forefoot. He had had more than five attacks over the past year, with closer intervals between attacks. Although he used to respond to intramuscular injections given by various general practitioners, he noticed that the attacks had been lasting longer. He quit alcohol drinking many years ago and had tried to adhere to a low purine diet for the past year. He was getting frustrated with his condition.

INTRODUCTION

This article provides a guide to the diagnosis, prevention and management of gout for doctors in family medicine, with up-to-date dietary recommendations and emphasis on urate-lowering therapy, in the hope of improving the holistic management of gout.

HOW RELEVANT IS GOUT TO FAMILY MEDICINE PRACTICE?

Gout is a chronic disease resulting from the deposition of monosodium urate (MSU) crystals caused by the overproduction or underexecretion of urate. Despite gout being a disease of antiquity and the most common inflammatory arthritis affecting men, its management has been suboptimal. The challenge in management boils down to a failure to regard gout as a chronic disease of hyperuricaemia with an emphasis on treating only the acute symptoms, at both the physician's and patient's levels. Although the case above illustrates a common and seemingly straightforward scenario of acute arthritis in day to day practice, we highlight areas of potential pitfalls and current paradigm shifts in the treatment of gout. Clinical diagnosis of gout is unequivocal in this scenario with careful history and physical examination. We summarise the pertinent features for diagnosis of acute gout in Table I.

Table I. Diagnosis of gout.

High-risk patients	• Men • Postmenopausal women • Metabolic syndrome, hypertension, obesity, hyperlipidaemia • Chronic kidney disease • Alcohol ingestion • Drugs: aspirin, initiation or increase dose of diuretics, anti-tuberculous medications
Clinical manifestations	• Acute intermittent mono-oligoarthritis lasting 3–7 days, initially involving lower limb joints (first metatarsophalangeal joint, ankle, tarsus, knee) with maximal intensity within a day and complete resolution in-between attacks • Tendinitis, bursitis • A history or finding of podagra and tophi increases the likelihood of gout diagnosis
Diagnostic tests	• Negatively birefringent crystals in synovial fluid aspirate • It is not necessary to measure serum urate level during an attack, as it may be low or normal during an attack
Differential diagnoses	• Cellulitis • Gonococcal arthritis • Septic arthritis • Reactive arthritis
Physical examination	• Swelling, erythema and exquisite tenderness of the affected joint with restricted range of motion; post-inflammatory hyperpigmentation and desquamation may appear during resolution • Tophaceous deposits • Blood pressure, body mass index, waist circumference
Complications of gout	• Disabling pain and physical impairment, reduced work productivity • Chronic destructive arthropathy, tendinopathies, nerve entrapment • Premature mortality due to cardiovascular disease

WHEN AND HOW TO MANAGE GOUT LONG TERM?

In contrast to the traditional textbook or lecture approach, we choose to discuss chronic management first to fortify your fundamental understanding of gout. Physicians need to appreciate that gout is a chronic disease that leads to chronic arthropathy and increased mortality (predominantly from cardiovascular

[1]University Medicine Cluster, Division of Rheumatology, [2]Department of Dietetics, National University Health System, Singapore, [3]SingHealth Polyclinics – Sengkang, Singapore

Correspondence: Dr Teng Gim Gee, Consultant, University Medicine Cluster, Division of Rheumatology, National University Health System, NUHS Tower Block, 1E Kent Ridge Road, Singapore 119228. gim_gee_teng@nuhs.edu.sg

Table II. Management of chronic gout.

Indications to start urate-lowering therapy	• Attacks ≥ 2 times a year • Arthropathy or radiographic erosions • Tophaceous gout • Nephrolithiasis
Treatment targets	• sUA < 360 µmol/L (or 6 mg/dL) • Reduce the number of flares • Reduce tophi size • Improve joint function and quality of life
Urate-lowering drugs	• Start at 100 mg/day, with increments of 100 mg every 2–3 months till target sUA is achieved
Allopurinol	• Dose of allopurinol can be titrated up to 600 mg/day • Allopurinol can be used with caution in renal impairment
Probenecid	• Probenecid is ineffective in creatinine clearance < 30–40 ml/min and is contraindicated in nephrolithiasis; requires divided dosing and plenty of oral fluid
Duration of urate-lowering therapy	• Generally life-long
Laboratory tests*	• sUA, creatinine, ALT, AST, glucose, lipid profile, BMI
Refer to specialist	• When gout is refractory due to drug inefficacy or adverse effects, or gout in advanced CKD

*For monitoring of response, side effects and screening of comorbidities.
sUA: serum urate; ALT: alanine transferase; AST: aspartate transferase; BMI: body mass index; CKD: chronic kidney disease

deaths)[1] Similar to the treatment of any chronic diseases, the window of opportunity arises when the patient experiences the symptoms or complications of the disease, i.e. during or soon after a flare.

The crux of the matter is the initiation and escalation of urate-lowering therapy (Table II – this is probably the most important take-home table). Recent guidelines on gout management[2,3] have not been disseminated to the majority of care provider treating gout, i.e. family medicine doctors. To date, the options for urate-lowering therapy remain few and they are often under-dosed and under-utilised (Table II). Due to the over-publicised concerns for allopurinol hypersensitivity syndrome, many physicians have shied away from initiating this cost-effective drug, even when indicated. Allopurinol can be used in patients with chronic kidney disease.[4] Taking time to document and educate the patient regarding the benefit over risk, as well as immediate withdrawal upon development of rash, is crucial, as Stevens Johnson syndrome and toxic dermal necrolysis can be life-threatening. Early and frequent reviews of the patient will allay anxieties on both sides. Uricosuric agents, such as probenecid, are ineffective in creatinine clearance < 30–40 ml/min, and are contraindicated in nephrolithiasis. Otherwise, probenecid is a good alternative in case of allopurinol allergy. Febuxostat, a nonpurine analogue xanthine oxidase inhibitor, is approved for treatment of gout in the United States and Europe, and is now available in Singapore on a named-patient basis.

Table III. Strategies for achieving the target of urate-lowering therapy (sUA < 360 µmol/L).

Patient education	• Emphasise that it will take months to reach target • Expect flares initially ("no pain, no gain") • Empower with rescue therapy for flares • Patient to track his own sUA levels
Colchicine prophylaxis	• 500 mcg daily until flares are infrequent and manageable, or sUA significantly lowered • Dose reduced to 500 mcg 2–3 times a week in renal impairment
Urate-lowering therapy	• "Start low and go slow" reduce gout flares, e.g. start allopurinol 100 mg daily, with increments of 100 mg every 2–3 months until target sUA achieved is favoured over a fixed dose regimen • Alternatively, start probenecid 250 mg bd, and titrate up to 3 g daily in divided doses
sUA	• Check sUA every 2–3 months while titrating urate-lowering therapy

sUA: serum urate

It should be emphasised that we should target serum urate (sUA) < 360 µmol/L (or 6 mg/dL) with gradual escalation of urate-lowering therapy. This subsaturating concentration of sUA is associated with a significant reduction in the number of flares and tophi size, as well as an improved quality of life, as microcrystals of MSU start to dissolve. Table III provides some guidelines for successful urate-lowering with colchicine prophylaxis, a useful strategy to keep the unwelcome visitor at bay. Holistic care of gout encompasses patient education on simple disease pathogenesis, with emphasis on the chronic derangement of urate metabolism. Screening and treatment of common gout-associated comorbidities, such as hypertension, diabetes mellitus, hyperlipidaemia and obesity, are essential in reducing the overall cardiovascular risk.

WHAT IS THE EVIDENCE-BASED DIETARY ADVICE FOR GOUT?

Recent literature[4] has shown that different sources of dietary purines may have varying effects on sUA levels and the development of gout. Red meat and seafood (including fish) increase the risk of gout, whereas dairy products appear to reduce the risk.[4] Dieticians often advise patients with gout to reduce the frequency of consumption of red meat, offal and seafood, but there is no need for total restriction. However, abstinence from alcohol, particularly beer, is important in reducing sUA and gout flares.[5,6] Sugar-sweetened soft drinks also appear to increase the risk of gout.[7,8]

In Singapore, some health professionals, gout patients and laymen may be misinformed about the association of gout with consumption of plant purines. Western studies have shown that vegetables (even those with high purine content) do not increase the risk of gout.[4] Population-based studies in Taiwan[9] and Shanghai[10] have indicated that vegetable purines have no effect

on hyperuricaemia and that soy products actually lower sUA levels. Unless the rare patient adamantly reports a clear temporal relationship of gout attack after eating certain foods, it is unnecessary to avoid nuts, soy beans (including tofu and soybean products), green beans or bean sprouts (which are low in purine content). In contrast, food sources that are rich in dietary fibre as well as vitamin C,[11] found in fruit and vegetables, protect against gout and should therefore be encouraged.[12] During dietetic counselling, apart from conducting a dietary assessment, the likely precipitants of the patient's gout attacks should be elicited. Non-dietary factors such as dehydration and vigorous exercises are some common triggers. It is also important to dispel myths that sour foods increase 'acidity' in the body and drinking 'alkaline' water helps with reducing 'acidity'.

In summary, dietary recommendations should address patients' misbeliefs and aim to minimise dietary triggers of gout attacks. However, we need to be sensitive to the individual patient's tolerance for change. Purine restriction alone is often insufficient to reduce sUA significantly, as a purine-free diet only reduces sUA by approximately 60 μmol/L (1 mg/dL). As patients with gout are also at risk for cardiovascular disease, the general advice is to adhere to a healthy diet and a healthy lifestyle with regular exercise (Table IV).

Table IV. Dietary and lifestyle advice to gout patients.

• Healthy diet according to the Healthy Diet Pyramid[13]
• Abstain from alcohol, particularly beer
• Reduce consumption of animal purines, e.g. red meat, offal, seafood
• Increase intake of fresh vegetables and fruits; no need to avoid vegetable purines
• Reduce consumption of sugar-sweetened soft drinks and fructose-rich beverages
• Avoid binge eating due to special occasions (e.g. wedding dinner, buffet) and high consumption of animal protein
• Avoid dehydration; drink plenty of water before exercise
• Graduated weight loss, if overweight, but avoid crash diet or rapid weight loss

WHAT ARE THE TREATMENT OPTIONS FOR ACUTE GOUT?

Most primary care physicians are comfortable with the prescription of acute therapy for gout. Acutely inflamed joint should be rested. Anti-inflammatory drugs should be used quickly, preferably within 24 hours of flare onset and at optimal doses. Simple analgesics are usually ineffective. As our population ages, we need to be cognisant of the multiple comorbidities and drug interactions that contraindicate the use of common drugs.[14] Patients should be followed up soon after the acute flare to assess their need for urate-lowering therapy (Table V).

Table V. Management of acute gout.

Pharmacotherapy	Concerns and pitfalls
Oral colchicine 500 mcg tds for 3–4 days in normal renal function (hourly colchicine until diarrhoea develops is discouraged)	• Use with caution in patients with renal impairment and those aged ≥ 70 years. • Drug interactions with cyclosporine, statins and macrolides; long-term use (especially with concomitant use of statin) may cause myopathy
NSAIDs (non-selective or COX-2 inhibitors)	• Contraindicated in renal dysfunction, heart failure and recent GI bleed; consider COX-2 inhibitors if there is a history of gastritis or PUD • Check creatinine level if there is a history of recurrent use
Judicious use of oral steroids (this may be the only option in renal impairment)	• Worsening of glycaemic control in diabetics; parenteral route if unable to take orally

NSAIDs: non-steroidal anti-inflammatory drugs, GI: gastrointestinal; PUD: peptic ulcer disease; COX: cyclooxygenase

Mr Alex realised that he did not need to totally avoid meat and his favourite bean sprouts or tofu. He also realised that his indulgence in a seafood-rich diet in recent months and his habit of drinking minimal water for long hours while driving may have worsened his gout. In view of the frequency of attacks, you started him on allopurinol 100 mg daily and gradually escalated the dose. He had had only one minor attack in the last six months.

CONCLUSION

As Singapore faces the challenges of a rapidly ageing society and rising affluence, the increasing prevalence of gout will have significant impact on public health. We hope that this refresher course on gout management would enable medical practitioners to translate this new knowledge into practice so as to treat gout holistically and optimally. With the above strategies, the unwelcome visitor can be swiftly chased away and effectively prevented from returning.

TAKE HOME MESSAGES

1. Gout should be regarded as a chronic, progressive disease.
2. Risk of gout is increased with alcohol intake (especially beer), higher consumption of meat and seafood, but not vegetable purines.
3. Urate-lowering drugs should be initiated when gout attacks occur more than twice a year, in the presence of tophi, nephrolithiasis and radiographic arthropathy.
4. Long-term, consistent and optimal dosing of urate-lowering drugs to target sUA level < 360 μmol/L is associated with elimination of flares, tophi reduction and improved quality of life.

ABSTRACT Gout is a chronic, progressive inflammatory disease with intermittent arthritic flares, which should not be regarded as a minor inconvenience or nuisance. It can be effectively controlled when the patient's serum urate level is reduced to less than 360 μmol/l (6 mg/dL) by consistent use of urate-lowering pharmacotherapy. Colchicine prophylaxis for gouty flares during titration of urate-lowering therapy has been underused. Holistic long-term management of gout must encompass patient education, evidence-based dietary advice, screening and aggressive treatment of comorbidities such as hypertension, diabetes mellitus, dyslipidaemia and renal impairment. Acute therapies for recurrent attacks with non-steroidal anti-inflammatory drugs, colchicine and/or corticosteroids should be used judiciously, especially in the elderly, due to the risk of toxicities. With appreciation of the underlying pathogenesis and artful use of the limited drug options, control of gout can be effectively achieved, bringing tremendous satisfaction to the patient and doctor.

Keywords: allopurinol, diet, gout, tophaceous, urate-lowering
Singapore Med J 2012; 53(8): 508–512

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SINGAPORE MEDICAL COUNCIL CATEGORY 3B CME PROGRAMME

(Code SMJ 201208A)

	True	False
1. Gout is a chronic disease due to urate cystal deposition caused by overproduction or underexcretion of urate.	☐	☐
2. Patients at high risk for gout include those with chronic kidney disease, metabolic syndrome and obesity.	☐	☐
3. Gout is an acute condition and warrants management for its acute symptoms only.	☐	☐
4. The target serum urate (sUA) level to reduce the number of acute flares and tophi size is 360 μmol/L.	☐	☐
5. sUA level needs to be monitored every six months during titration of urate-lowering therapy.	☐	☐
6. Food products that increase the risk of gout include tofu, offal and alcohol.	☐	☐
7. Milk decreases the risk of gout.	☐	☐
8. A healthy diet according to the Healthy Diet Pyramid can be advised for a patient with gout.	☐	☐
9. Binge eating will not precipitate a gouty attack as long as the patient drinks plenty of water after the meal.	☐	☐
10. There is no pharmacotherapy to prevent a gouty attack.	☐	☐
11. Rapid titration of allopurinol dose over four weeks is required to lower the sUA level in patients with gouty tophi.	☐	☐
12. As long as the patients' acute gouty attacks are quickly aborted, there is no need to ask how many attacks they have in one year.	☐	☐
13. There is no other contraindication to start probenecid for patients with gout, other than for known allergy to the medication.	☐	☐
14. Allopurinol is contraindicated in patients with renal impairment.	☐	☐
15. Allopurinol is generally given as a life-long therapy for most patients with gout.	☐	☐
16. Doctors should monitor their patients for complications of gout, such as renal stones, tophi, chronic destructive arthropathy and premature mortality due to cardiovascular disease.	☐	☐
17. The differential diagnoses to consider in a patient with acute gout are infective arthropathies.	☐	☐
18. There is no medical ground to give prednisolone to relieve acute gout in any patient.	☐	☐
19. The maximum dose of allopurinol that can be given is 300 mg/day.	☐	☐
20. Doctors should screen patients with gout for other comorbidities such as diabetes mellitus, hyperlipidaemia, hypertension and obesity.	☐	☐

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Deadline for submission: (August 2012 SMJ 3B CME programme): 12 noon, 24 September 2012.