Chronic gout: Barriers to effective management

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Background
Gout is one of the most common inflammatory arthropathies, and the pathogenesis is well understood. In Australia, most patients with chronic tophaceous gout (CTG) are treated by general practitioners (GPs). Urate-lowering therapy, if adhered to continuously, can suppress the disease, reduce the likelihood of flares and prevent long-term complications such as disfiguring tophi and joint damage. Many rheumatology societies recommend a treat-to-target (T2T) approach, lowering serum urate to 0.35 mmol/L or below with urate-lowering therapy.

Objectives
The aim of this article is to discuss inconsistencies in treatment guidelines, identify patient and physician barriers to optimal gout care, explain why a T2T approach is appropriate and make a series of recommendations that are practical for GPs.

Discussion
Despite an in-depth understanding of this controllable disease and the availability of simple, safe treatments, chronic gout remains poorly managed. The development of Australian gout guidelines that are easily implemented by GPs is vital and overdue.

THE PREVALENCE OF medically diagnosed gout in adult Australians may be as high as 5.2%. The pathogenesis of gout is clearly understood. Risk factors include increasing age, genetic factors, purine-rich foods, alcohol, diabetes and diuretic use. Gout often recurs and, when inadequately treated, may progress to chronic tophaceous gout (CTG) and joint damage. Gout is associated with metabolic syndrome, nephrolithiasis, cardiovascular disease and chronic renal impairment. Hyperuricaemia and gout have been associated with increased risk of cardiovascular events in a variety of populations; urate-lowering therapy either has no increase in risk, or may lower risk, of cardiovascular events.

Treatments indicated in the management of chronic gout include education, diet and lifestyle changes, pharmacotherapy for acute flares and long-term urate-lowering therapy for repeated episodes and CTG.

Urate-lowering therapy optimally reduces serum uric acid levels below the solubility constant for urate (48 µmol/L or 6.8 mg/dL) and, with long-term adherence, may place the patient in remission from gout and resolve tophi.

Therapy is effective when adhered to; however, adherence in chronic gout is the lowest among seven chronic diseases.

Practice guidelines
Major guideline inconsistencies are presented in Table 1. Gaps exist in relation to the definition of ‘severe’ gout when considering the presence or absence of tophi, frequency of attacks, number of affected joints and the balancing of comorbidities in treatment decisions. The varying levels of evidential strength in existing guidelines led to the proposition in the ACP guidelines that the absence of high-quality evidence supporting a treat-to-target (T2T) approach means a ‘treat-to-avoid-symptoms’ (TTS) approach is more supportable. This major discrepancy between a generalist versus a
sub-specialty perspective implies that the absence of (strong) evidence indicates lack of efficacy; this does not reflect clinical practice realities.

**Physician barriers to care**

Although 50% of patients with gout may see a rheumatologist, GPs are mostly responsible for ongoing care. Treatment regimens are often insufficient to control attacks of gout or prevent complications; less than 30% of patients undergo serum uric acid monitoring and of those, only 33% achieve the target serum uric acid. Typically, patients remain on the starting dose of allopurinol without titration to achieve the target serum uric acid. To achieve target serum uric acid, the allopurinol dosage can be increased to 600 mg daily (very rarely higher), or a uricosuric agent can be added. Before doing so, it must be ascertained that the patient is adherent; if not adherent to the medication regimen, this approach is futile.

Qualitative studies reveal that clinicians believe they have the knowledge and skills to educate patients with gout; however, many patients report uncertainty regarding its causes and treatment.

**Patient barriers to care**

Up to 57% of patients with chronic gout are non-adherent to the medication regimen; 70% have interrupted therapy; and long-term adherence is lowest in younger males of lower socioeconomic status without comorbidities and with fewer acute flares. Most non-adherence is ‘purposeful’, due to clinical/financial factors rather than forgetfulness.

Patients cite concerns regarding side effects and medication interactions; acute attacks and pain are the main drivers for adherence. Patients may believe that without acute flares, urate-lowering therapy drugs need not be taken continuously. Patients may also report that potential complications of gout have not been explained, and have a poor understanding that gout is an arthritis. Patients typically believe that gout is a self-inflicted consequence of ageing and are reluctant to seek medical advice. Qualitative evidence suggests that some men hesitate to seek help despite intense pain.

**Discussion**

Most guidelines concur with a serum urate-defined T2T approach to eventually suppress gout; the target serum uric acid is defined, yet variable units of measurement add complexity to the implementation of guidelines. Most guidelines endorse a lower target serum uric acid for severe gout without a consensus definition of severity encompassing frequency of attacks, number of joints involved, presence of tophi or comorbidities. Hence, the ACP characterises T2T as unproven/inappropriate/impractical, contentious and not evidence-based.

The ACP suggests a TTS approach for acute flares, without urate-lowering therapy, to correct hyperuricaemia, and fails to acknowledge the potential long-term morbidity of chronic gout, including the potential for tophus development, joint damage and patient suffering. Implementing the ACP guidelines may worsen already suboptimal care.

The costs of allopurinol and serum uric acid monitoring are minimal, compared with the potential downstream costs for CTG, without evidence of an unfavourable risk-benefit ratio for T2T.

Guidelines agree that allopurinol is a first-line urate-lowering therapy, easy to administer, well tolerated, widely available and economical. However, ACP and ACR guidelines also endorse optional first-line febuxostat, which, compared with allopurinol, is significantly more expensive, with less long-term tolerability and cardiovascular safety data. Febuxostat should not be used in Australia as first-line therapy; it is available on Pharmaceutical Benefits Scheme authority when allopurinol is contraindicated, imposing increased taxpayer costs.

Lack of clinician education is a significant barrier to optimal gout care. Compared with other arthritides, gout receives less attention in non-rheumatological training.
The lack of direct GP involvement in guideline development, and limited dissemination, contribute to poor accessibility and use. Many patients receive suboptimal allopurinol dosages if tight serum uric acid control is not correlated with treatment success.33

Gout recommendations issued by the Australian Therapeutic Guidelines20 are accessible online and may be used more readily by GPs. However, further discordance exists between these guidelines and those already discussed. The Therapeutic Guidelines advise urate-lowering therapy for all patients with diagnosed gout, while most evidence-based recommendations agree that urate-lowering therapy should be reserved for those with recurrent flares or those experiencing more than two attacks per year. Historically, a lower maximal dose of allopurinol was recommended in patients with impaired renal function because of the fear of allopurinol hypersensitivity syndrome (AHS); its incidence is only 0.1–0.4%, and it is most frequent in Asian peoples and those with HLA-B*5801 mutations.34 Overestimation of the frequency of AHS may result in suboptimal urate-lowering therapy. Using higher starting doses of allopurinol increases the risk of AHS.35

‘Gouty nephropathy’ is evident post-mortem in almost 40% of patients clinically diagnosed with gout.36 For treating chronic kidney disease, some authors note that control of hyperuricaemia (without incident gout) may slow progression of renal disease.37 Gout is usually asymptomatic between attacks, so patient-initiated discontinuations are common. Gout must be understood to be a chronic and potentially disabling arthropathy. Patients’ perceptions of the meaning of the illness are intrinsically related to their resultant behaviour and adherence, and stigma surrounding gout stems from historical portrayals of gout as a disease of affluence, from men overconsuming ‘rich’ food and excess alcohol, and somehow ‘comical’.

**Table 1. Comparison of published gout guidelines**

<table>
<thead>
<tr>
<th>SUA target</th>
<th>ACP</th>
<th>EULAR</th>
<th>Aust &amp; NZ</th>
<th>3e Initiative</th>
<th>ACR</th>
<th>BSR</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>-</td>
<td>&lt;6 mg/dL (0.36 mmol/L)</td>
<td>&lt;0.36 mmol/L</td>
<td>&lt;0.36 mmol/L (6 mg/dL)</td>
<td>&lt;6 mg/dL</td>
<td>&lt;300 µmol/L</td>
</tr>
<tr>
<td>Specified</td>
<td>-</td>
<td>&lt;5 mg/dL (0.30 mmol/L) severe gout</td>
<td>&lt;0.30 mmol/L tophaceous gout</td>
<td>&lt;0.30 mmol/L (5 mg/dL) tophaceous gout</td>
<td>&lt;5 mg/dL severe gout</td>
<td>-</td>
</tr>
</tbody>
</table>

**ULT indications**

<table>
<thead>
<tr>
<th></th>
<th>ACP</th>
<th>EULAR</th>
<th>Aust &amp; NZ</th>
<th>3e Initiative</th>
<th>ACR</th>
<th>BSR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tophi</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Attacks ≥2/year</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Arthropathy</td>
<td>-</td>
<td>✓</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Radiographic evidence</td>
<td>-</td>
<td>✓</td>
<td>-</td>
<td>-</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>✓</td>
<td>✓</td>
<td>-</td>
<td>-</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>ULT initiation</td>
<td>-</td>
<td>Near time of diagnosis</td>
<td>-</td>
<td>-</td>
<td>During attack</td>
<td>1–2 weeks after attack</td>
</tr>
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</table>

**First-line ULT**

<table>
<thead>
<tr>
<th></th>
<th>ACP</th>
<th>EULAR</th>
<th>Aust &amp; NZ</th>
<th>3e Initiative</th>
<th>ACR</th>
<th>BSR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose (mg/day)</td>
<td>-</td>
<td>100</td>
<td>-</td>
<td>50–100</td>
<td>100</td>
<td>50–100</td>
</tr>
<tr>
<td>Titrination to target SUA</td>
<td>-</td>
<td>100 mg every 2–4 weeks Gradual increases</td>
<td>Slow increases</td>
<td>Every 2–5 weeks Every 2–5 weeks 50–100 mg every few weeks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Programs and is viewed academically as unimportant.30

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**Recommendations**

**Australian guideline development**

Broadly disseminated Australian GP-focused, evidence-based guidelines
are required. Online or other auditable disease management tools could reinforce guideline usage.

**Practitioners**

Gout should be appreciated as a risk for significant comorbidities. Online education models incorporating gout guidelines and case-based scenarios may increase awareness, pragmatism and confidence in treating gout. A practical T2T CTG treatment approach is outlined in Box 1.

**Patients**

Patient education may be the most effective means of improving adherence to treatment. Ideally, provision of education by nurse specialists will achieve target serum uric acid levels in more than 90% of patients.³⁸

Raising public awareness of gout and its consequences may correct misperceptions and stigma regarding gout and improve health-seeking behaviour.

**Conclusion**

Multiple barriers to effective management of CTG, a common and arguably ‘curable’ inflammatory arthritis, still exist. There remains considerable disunity in published guidelines, which are typically not disseminated to GPs. Patient non-adherence is frequent and attributable to lack of knowledge of the disease and cognitive biases towards its causes.

Neither physicians nor patients alone are responsible for the suboptimal management of gout. Clear, universally accessible Australian evidence-based guidelines agreed upon through collaboration between GP and specialty groups are necessary to overcome barriers and achieve consensus around the indications for CTG therapy.

**Key points**

**Target serum uric acid**

Although <6 mg/dL (360 µmol/L = 0.36 mmol/L) is the most common target serum uric acid, levels differ in value and unit measurement. Some guidelines

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**Box 1. Suggested treatment approach for patients with episodic gout**

**General approaches**

Measure SUA out of context of an acute attack.

Do not commence allopurinol (or other ULT) in the context of an acute attack.

When commencing allopurinol (or other ULT), ensure the patient is taking prophylactic therapy:

- colchicine, NSAIDs or corticosteroids are appropriate.

If diarrhoea occurs, consider:

- NSAIDs, COX-II inhibitor, or very low-dose corticosteroids, contextualised to patient’s overall health.

Inform the patient of the objectives of treatment.¹

Consider dietary advice – generally, low-urate diets are not complied with. Diets compatible with optimal glycaemic control and primary cardiovascular prevention are usually acceptable.¹

Always assess patients for the presence of manageable comorbidities: hypertension, obesity, type 2 diabetes/metabolic syndrome, cardiovascular disease and renal calculi/renal disease.

**Allopurinol for ULT**

Explain that allopurinol is a preventative strategy, not a treatment for an acute attack; the analogy of relievers and preventers in asthma is well understood.

- Commence with allopurinol 100 mg daily (maximum), or 50 mg daily if eGFR ≤50 ml/min.

**Consider:** HLA-B*5801 mutation genotyping for people of Asian origin.

**Titrate:** increase the dose of allopurinol by 50–100 mg every 3–4 weeks, monitoring for rash/itch.

**Target SUA:** increase allopurinol to a maintenance dose sufficient to reduce the SUA to <0.35 mmol/L in non-topaceous disease, or 0.25–0.30 mmol/L in tophaceous disease.

**Prophylactic therapy:** continue for up to three months after a stable dose of ULT sufficient to reach target SUA, or three months after an acute attack has occurred, whichever is longer.

**Acute attack:** if an attack of gout occurs, do not stop allopurinol; treat the acute attack as appropriate.

**Monitor:** monitor SUA when other blood tests are taken, preferably six-monthly for two years after last attack.

**Continue:** do not cease allopurinol (or other ULT) even if the patient has been free of attacks (for years).¹

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¹Includes patients with gout that affects quality of life, results in excess time off work, or whose concurrent health conditions pose contraindications to agents used for acute treatment (eg prior upper gastrointestinal tract ulceration/bleeding, anticoagulation, impaired renal function, cardiovascular disease or diabetes).

²The objectives of treatment are:

- elimination of attacks – which may take months or even years on occasion to achieve. Many patients do not achieve target SUA on allopurinol 300 mg daily; the dose may be increased or a uricosuric agent may be added. Always check for medication adherence prior to increasing/adding medications, as this with have no effect in a non-adherent patient

- shrinkage of tophi – which can be achieved over years and may require combination therapy with the addition of a primary uricosuric agent to a xanthine oxidase inhibitor in certain cases.

³Explain that though some dietary modifications, such as increased consumption of milk/dairy and cherries, may be helpful, diet alone or the removal or addition of some foodstuffs will almost never be sufficient to control gout. The ‘Mediterranean diet’ is now mainstream and accepted by many. There are numerous ‘urban myths’ based on folklore and mistakenly felt to be factual that can be addressed by a dietitian. Patients equate high-protein foods with foods high in purine generally. Avoid idiosyncratic dietary advice.

⁴Never commence allopurinol in a person treated with azathioprine or 6-mercaptopurine, which is the pharmacologically effective first metabolite of azathioprine; these agents may cause hyperuricaemia, but the addition of allopurinol will increase the serum level of 6-mercaptopurine threefold to fourfold, often resulting in myelotoxicity. Other first-line options include probenecid (not discussed in this paper) if renal function is sufficient.

⁵When ULT is ceased, the serum urate will simply increase and eventually this may result in recurrence of attacks. Patients often understand the analogy of long-term treatment for hypertension or cholesterol to reduce cardiovascular risks.

eGFR, estimated glomerular filtration rate; NSAIDs, non-steroidal anti-inflammatory drugs; SUA, serum uric acid; ULT, urate-lowering therapy
suggest a lower target serum uric acid for tophaceous or ‘severe’ gout.

Indications for urate-lowering therapy

The presence of tophi is the most common indicator for urate-lowering therapy, although this is not universal. Frequency of attacks varies from more than two per year to recurrent flares. The BSR recommends diuretic use as an indicator of the need for treatment;11 most other guidelines recommend avoiding diuretics in chronic gout.

When to initiate urate-lowering therapy

The ACP recommends against urate-lowering therapy after a first gout attack or in those with infrequent attacks.3 EULAR guidelines suggest initiating urate-lowering therapy close to the time of diagnosis,4 and the BSR specifies initiating 1–2 weeks after an acute attack.5 The ACR guidelines state that urate-lowering therapy can be initiated during an attack, if combined with anti-inflammatory management.10

Choice of urate-lowering therapy

All guidelines establish allopurinol as a first-line urate-lowering therapy. ACP and ACR guidelines recommend febuxostat as a comparable first-line agent. Starting doses of urate-lowering therapy vary, or are in some cases not specified, and techniques for titrating doses to target serum uric acid lack detail.

References


