**Gout**

Achieving the management goal

**Key messages**

1. Provide lifestyle management to all patients with gout.
2. Do not delay urate-lowering therapy (ULT) for patients with gout who meet ULT treatment criteria.
3. “Start low, go slow” with ULT.

**Managing gout as a chronic condition**

Gout is a form of arthritis and is due to deposition of monosodium urate (MSU) crystals—a result of chronic serum urate elevation. Although gout is a chronic condition, it usually presents episodically as painful acute flares.

Without appropriate long-term management, acute flares may increase in frequency or severity. Crystal build-up may form tophi that could lead to joint damage or functional impairment. In addition, renal complications, such as urate nephrolithiasis or chronic nephropathy may develop. As renal impairment is also a known risk factor for gout, the relationship between the two is bidirectional.

Besides renal impairment, patients with gout often have multiple comorbidities, including obesity, metabolic syndrome, type 2 diabetes mellitus, and cardiovascular disease.

The increasing prevalence of gout, related complications, and comorbidities call for improved long-term management of gout—as a chronic condition with ongoing management, as opposed to management of acute flares only. When lifestyle management is insufficient, urate-lowering therapy (ULT) is the mainstay of the long-term management approach to gout.¹ ²
The management goal for gout

Gout is the clinical manifestation of MSU crystal deposition from chronic serum urate elevation. In contrast, asymptomatic hyperuricaemia refers to elevated serum urate without symptoms or signs. Unlike in gout management, evidence on using ULT to treat asymptomatic hyperuricaemia is not established, and advice on lifestyle could be given to patients with persistent asymptomatic hyperuricaemia.

Although gout stems from chronic serum urate elevation, serum urate naturally fluctuates, and therefore serum urate may not always correspond to clinical features of gout.

Ensuring long-term management

Comorbidities, risk factors, and lifestyle

Manage gout long-term as it is a chronic condition. Patient education on gout pathophysiology and management approach can improve adherence. Review and manage comorbidities and risk factors associated with gout. As part of lifestyle management, provide advice on healthy lifestyle, including diet, to reduce the risk of acute flares (see Patient education aid 1).

Lifestyle management may be insufficient to achieve the management goal. Discuss with patients the benefits and risks of ULT, including adverse effect monitoring.

Do not delay ULT for patients with gout who meet ULT treatment criteria (see Table 1 below).

Using ULT to achieve the management goal

Consider starting patients on ULT, particularly when they meet ULT treatment criteria (see Table 1). The management goal can be achieved with ULT through lowering serum urate. Generally, the effects of ULT on decreasing acute flare frequency, tophi number or size are greater when serum urate is reduced and maintained long-term:

- Below 360 μmol/L (6 mg/dL) in non-tophaceous gout, or
- Below 300 μmol/L (5 mg/dL) in tophaceous gout

When using ULT, consider starting with allopurinol. Allopurinol, a xanthine oxidase inhibitor (XOI), is effective, generally well tolerated, and commonly used. Initiate allopurinol at a low dose, typically 100 mg/day. Slowly titrate upwards in 50 to 100 mg increments every two to eight weeks, informed by serum urate and clinical features (“start low, go slow”). Allopurinol doses of more than 300 mg/day may be needed to achieve the management goal. Doses could be increased up to a maximum of 900 mg/day in patients with normal renal function.*

Febuxostat is a newer XOI and generics are not currently available. Compared to a potentially suboptimal dose of allopurinol 300 mg/day, febuxostat has been found to result in a higher proportion of patients reaching serum urate target, but no difference in acute flares or tophi reduction. While recent research suggests a higher risk of death with febuxostat than with allopurinol in patients with gout and major cardiovascular disease, evidence is still developing to further examine cardiovascular risk with febuxostat.

Uricosuric agents are another class of ULT and include probenecid and benz bromarone. Uricosuric agents promote urate excretion through the kidneys, and hence are less effective in patients with renal impairment (see Table 2 on page 3). An uricosuric agent could be used alone. It could also be used in combination with an XOI (usually allopurinol) for enhanced effectiveness, if there is inadequate response to an XOI alone. Benz bromarone is not commonly used locally.

“Start low, go slow” with ULT, informed by serum urate and clinical features.
Addressing clinical precautions of using ULT

A summary of clinical precautions when using ULT is presented in Table 2. Main considerations for specialist referral and key points for patient education can be found in Figure 1.

Table 2. Key clinical precautions with ULT†

<table>
<thead>
<tr>
<th>Xanthine oxidase inhibitors</th>
<th>Uricosuric agents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allopurinol</strong>§</td>
<td><strong>Febuxostat</strong></td>
</tr>
<tr>
<td>• Risk of SCAR (see section “Understanding SCAR in ULT” below)</td>
<td>• Risk of SCAR, although the risk is lower than with allopurinol (see section “Understanding SCAR in ULT” below)</td>
</tr>
<tr>
<td>• Contraindicated in patients with previous hypersensitivity to allopurinol (including SCAR)</td>
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</tr>
</tbody>
</table>

| • May precipitate acute flares during initial period of ULT (see section “Prophylaxis against acute flares during initial period of ULT” on page 4) |

CrCl, creatinine clearance; G6PD, glucose-6-phosphate dehydrogenase; SCAR, severe cutaneous adverse reactions; ULT, urate-lowering therapy

† Information sourced from package inserts and UpToDate (www.uptodate.com). Please refer accordingly for full details on these medications.

‡ Available on government subsidy list.

§ For more information on allopurinol-induced SCAR, please refer to the summary of Ministry of Health (MOH)-Health Sciences Authority (HSA) Drug Safety Information No. 59 published on 21 September 2016:

Allopurinol-induced SCAR are uncommon and include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS). SCAR may result in long-term complications and even be life-threatening. Most of SCAR occur within the first few weeks to months after therapy initiation. Monitoring for SCAR in patients starting on allopurinol is important to ensure early detection and prompt management.

Key factors that increase the risk of allopurinol-induced SCAR\(^8\) can be easily remembered with the acronym RASHES:

- **R**enal impairment
- **A**gent concomitant use of therapeutic agents, such as diuretics
- **S**tarting **d**ose high allopurinol starting dose
- **H**LA-B*5801 presence of this allele
- **E**scalation rapid escalation of allopurinol dose
- **S**eniority older age

Legend: Genetic factor Non-genetic factor

Assess the RASHES factors in all patients starting on allopurinol. Mitigate the risk of developing SCAR by addressing the RASHES factors where possible, for example by starting allopurinol at a low dose and slowly titrating upwards. Monitoring for SCAR is important in all patients starting on allopurinol.

While the HLA-B*5801 allele is a known risk factor for allopurinol-induced SCAR, reactions may still develop without the allele as there are non-genetic factors that increase the risk. The positive predictive value (PPV) of HLA-B*5801 for allopurinol-induced SCAR is estimated at around 2% (around 2 out of 100 patients with the allele starting on allopurinol may develop SCAR).\(^3\) The low PPV, coupled with a lack of alternative cost-effective ULT options, limit the overall value of routine genotyping in the Singapore population before initiation of allopurinol. Testing for the allele may be more useful in informing treatment decision-making if the patient is assessed to already be at higher risk of allopurinol-induced SCAR with renal impairment or older age.\(^3\)

SCAR have also been reported with febuxostat, although the risk is lower than with allopurinol. Some of the patients who developed SCAR with febuxostat had renal impairment or a history of hypersensitivity to allopurinol.\(^13\)

“Start low, go slow” with ULT to minimise the risk of adverse effects. Inform patients of SCAR risk and provide counselling on SCAR monitoring (see Patient education aid 2).
Paradoxically, initiating ULT may precipitate acute flares, as reduction of serum urate mobilises MSU crystals from tissue deposits. Mitigate the risk of acute flares by starting ULT at a low dose before slowly titrating upwards, and by providing prophylaxis with colchicine, typically 0.5 mg once daily. Prophylaxis with colchicine is generally recommended for up to six months. However, prophylaxis duration could be tailored depending on the occurrence of acute flares.

For patients who cannot use colchicine, consider a low-dose oral nonsteroidal anti-inflammatory drug (NSAID), including a cyclooxygenase-2 (COX-2) inhibitor. Alternatively, a low-dose oral corticosteroid could be considered for patients who cannot use colchicine, and who are unsuitable for prophylaxis with NSAIDs (such as patients with renal impairment). Optimal prophylaxis duration with these non-colchicine medications is not established.

Medications for prophylaxis are also used to treat acute flares (see section “Managing acute flares” below). If an acute flare occurs during prophylaxis and the same medication for prophylaxis is chosen to treat the acute flare, use the higher acute flare treatment dose instead of the prophylactic dose. Reinitiate the prophylactic dose after the acute flare resolves. If a different medication is chosen to treat the acute flare, exercise more caution with the combination of an oral NSAID plus an oral corticosteroid due to the increased risk of gastrointestinal ulcer or bleeding.

Colchicine adverse effects and interactions

Nausea, vomiting, and diarrhoea are the most common adverse effects of colchicine. The frequency of adverse effects increases with higher doses or longer duration of use.

Colchicine has the potential for many drug-drug (such as macrolide antibiotics, azole antifungals, statins, verapamil, or diltiazem) and drug-food interactions. Patients with renal or hepatic impairment are at increased risk of toxicity, including myopathy, neuropathy, and pancytopenia.

Anti-inflammatory medications in renal impairment

Renal impairment affects treatment options both in prophylaxis and treatment of acute flares:

- As renal impairment increases the risk of colchicine toxicity, consider reducing colchicine dose or increasing dosing interval.
- Use of oral NSAIDs, including COX-2 inhibitors, requires more caution in patients with renal impairment, and is not suitable for patients with CrCl less than 30 ml/min or for prolonged duration (such as for prophylaxis).

Managing acute flares

Acute flares should be treated as soon as possible. Anti-inflammatory medications for treatment of acute flares include:

- Colchicine
- Oral NSAIDs, including COX-2 inhibitors
- Oral corticosteroids
- Intra-articular or intramuscular corticosteroids

A combination of medications could also be used. However, exercise more caution with the combination of an oral NSAID plus an oral corticosteroid.

Considerations informing choice of treatment include comorbidities, concomitant medications, patient preferences, and patient characteristics, such as renal function.

Advise patients to rest affected joint(s) and apply ice packs.

For patients who are on ULT, continue ULT during an acute flare. Review the long-term management plan, including the ULT dose. As serum urate naturally fluctuates, serum urate may be normal or low during an acute flare. ULT could be initiated during an acute flare provided that the acute flare is adequately treated, followed by prophylaxis. However, delaying the initiation until after the acute flare subsides is also an option.

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**Please refer to package insert or drug information references for full details on colchicine.

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Low-dose colchicine for acute flares

Use one of the following low-dose colchicine regimens for acute flare treatment:

- One-off treatment with 1 mg loading dose, followed by one dose of 0.5 mg one hour later
- 0.5 mg two to three times per day until the acute flare resolves.

Historically, acute flares were treated with a higher dose of colchicine, starting with 1 mg loading dose, followed by 0.5 mg every four hours until acute pain improved, patient felt sick or had diarrhoea. However, there is a greater likelihood of gastrointestinal adverse effects with doses higher than 1.5 mg/day, without added benefits.

†† Information sourced from package insert.
**Management of comorbidities**
- Review and manage comorbidities and risk factors, including:
  - Renal impairment
  - Obesity
  - T2DM
  - Hypertension
  - Hyperlipidaemia

**Lifestyle management**
- As part of lifestyle management, provide advice on healthy lifestyle, including diet (see Patient education aid 1)

**ULT**
- Consider starting patients on ULT, particularly when ULT treatment criteria are met (any of the following):
  - Frequent acute gout flares (two or more per year)
  - Presence of any tophus
  - Clinical or imaging findings of gouty arthropathy
  - History of urolithiasis

**Specialist referral**
- Specialist referral could be made at any point. Main considerations for referral include:
  - Severe or refractory gout
  - Severe renal impairment
  - Difficulty in achieving the management goal, particularly with renal impairment
  - Serious adverse effects from ULT

**Patient education**
- Include the following key points as part of patient education, as appropriate:
  - Gout pathophysiology (see Patient education aid 1)
  - Lifestyle advice (see Patient education aid 1)
  - Benefits and risks of ULT, including adverse effect monitoring, particularly SCAR (see Patient education aid 2)
  - Benefits and risks of medications for prophylaxis
  - Acute flares should be treated as soon as possible after symptom onset
  - Benefits and risks of medications for acute flare treatment
  - Advice on resting affected joint(s) and applying ice packs during an acute flare

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COX-2, cyclooxygenase-2; CrCl, creatinine clearance; NSAIDs, nonsteroidal anti-inflammatory drugs; SCAR, severe cutaneous adverse reactions; T2DM, type 2 diabetes mellitus; ULT, urate-lowering therapy; XOI, xanthine oxidase inhibitor
About the Agency

The Agency for Care Effectiveness (ACE) is the national health technology assessment agency in Singapore residing within the Ministry of Health (MOH). ACE develops evidence-based “Appropriate Care Guides” or ACGs to guide a specific area of clinical practice. ACGs are aimed at complementing MOH Clinical Practice Guidelines when these are available, by providing additions and updates as reflected in the evidence at the time of development, and incorporating cost-effectiveness considerations where relevant. The ACGs are not exhaustive of the subject matter. When using the ACGs, the responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional. This ACG will be reviewed 3 years after publication, or earlier, if new evidence emerges that requires substantive changes to the recommendations.

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Driving better decision-making in healthcare

References

Gout causes pain and swelling in joints. This form of arthritis is due to high levels of uric acid, a substance in the body.

**A healthy lifestyle is important:**
- Maintain a healthy weight (including weight loss if overweight)
- Exercise regularly, but rest affected joints during a gout attack
- Avoid smoking
- Maintain a healthy diet

**The following diet can help to prevent gout attacks:**

**Avoid**
- Excessive alcohol (especially beer and spirits)
- Sugary drinks
- Excessive high-purine foods, such as seafood or meat, including organ meats (the body converts purine into uric acid)

**Include more of**
- Low-fat dairy products
- Vegetables
- Fluids
  - Drink plenty of fluids (at least 2 litres a day), unless under fluid restriction

Your doctor may add urate-lowering therapy (ULT) medications to a healthy lifestyle.
Urate-lowering therapy (ULT) is an effective treatment for gout. However, severe cutaneous adverse reactions (SCAR) may develop with allopurinol (the most common ULT) or febuxostat (another ULT).

**SCAR are serious and generally affect skin, eyes, or mouth**
- SCAR are uncommon
- Around 3 out of 1,000 people taking allopurinol may develop SCAR (even less with febuxostat)
- Some people are at higher risk of SCAR. However, it is not possible to know who will develop SCAR

People starting on allopurinol or febuxostat need to look out for early symptoms of SCAR, which include:

- Flu-like symptoms, such as fever, body aches or feeling unwell
- Mouth ulcers or sore throat
- Red or sore eyes
- Rash

These symptoms may not happen together and they are not the only ones.

Monitor for SCAR symptoms, especially in the **first 3 months** after starting the medication (but they can also happen after 3 months).

Seek advice from your doctor if you experience **any** SCAR symptoms or if you are unsure about your symptoms.

Remember to:
- **Stop the medication completely** and see your doctor right away
- **Photograph** the rash if possible
- **Inform the doctor** that you have recently started taking a new medication for gout

For more information, please refer to the Health Sciences Authority (HSA) consumer guide on the safe use of allopurinol.