Managing gout involves alleviating the pain of an attack and preventing episode recurrence and complications

Gout
managing gout and hyperuricaemia

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Gout is a common condition that has been increasing in incidence over the past few decades. Its management has not changed greatly over this period. The three goals for the management of gout are to:

- Ease the pain associated with the acute attack
- Reduce further recurrences by controlling hyperuricaemia
- Prevent or reverse long-term complications associated with gout, such as joint and kidney damage

An algorithm for treating patients with gout is set out in Figure 1 (p80).

Asymptomatic hyperuricaemia

Although raised uric acid levels are associated with gout flares, treatment of elevated levels is not required routinely if the patient does not show symptoms of gout. Prolonged hyperuricaemia can increase a person's risk of developing gout or kidney stones, and underlying causes of hyperuricaemia should be investigated and addressed. Medical management of asymptomatic hyperuricaemia should be restricted to specific circumstances, such as for patients with a history of kidney stones. Hyperuricaemia can also occur in patients undergoing chemotherapy or radiotherapy for treatment of high-turnover tumours, such as lymphomas or leukaemias. Tumour lysis can result in large amounts of uric acid being released and depositing in the renal tubules (prophylaxis with allopurinol, hydration and urine alkalinisation is recommended).

Acute gout

The early and prompt treatment of an acute gout flare is essential for rapid control of symptoms. The initial choice of therapy should be based on patient characteristics and comorbidities. Considerations for the management of acute gout for patients with chronic kidney disease (CKD) are set out in Box 1 (p81). Patients should also be offered advice about lifestyle factors that can contribute to gout (see Box 2, p82).

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs), with the exception of aspirin, are the preferred treatment for acute gout attacks and the best outcomes occur when they are started early. Attacks resolve within five to eight days of starting treatment in 90% of cases. The NSAID should be given at the full recommended dose (if appropriate), continued for 24 hours after the flare resolves and then titrated down over two to three days. All NSAIDs are equally effective when given in optimum doses. NSAID therapy is associated with increased risk of gastrointestinal bleeding and can have adverse cardiovascular and renal effects. Accordingly, NSAIDs should be used with caution in patients with peptic ulcer disease, renal impairment, liver disease and congestive heart failure, as well as patients receiving concurrent anticoagulation therapy. Elderly patients should be monitored closely (eg, renal function checks).

Colchicine

Colchicine, an antimitotic drug derived from the roots of the herb Colchicum autumnale, is one of the oldest treatments for gout. The medicine is most effective when started in the first 24 to 48 hours of an acute flare. Response to colchicine reduces once a flare has persisted beyond a few days. The traditional high-dose colchicine therapy (1mg initially, followed by 50µg every two to three hours until symptoms resolve) is seldom used due to a high risk of toxicity. Some 50–80% of patients treated

### SUMMARY

The three main goals of gout management are to: alleviate pain associated with an acute attack, reduce the likelihood of future episodes and prevent long-term complications caused by the condition, such as chronic kidney disease.

Acute attacks of gout should be treated promptly. Non-steroidal anti-inflammatory drugs are recommended first line, unless contraindicated. Other options include colchicine or corticosteroids. Urate-lowering therapy is recommended for people who have more than one attack per year. First-line treatment is with allopurinol. Uricosuric medicines are also used.
with high-dose colchicine develop diarrhoea, nausea or vomiting.

A 2010 randomised controlled trial (AGREE) demonstrated similar pain reduction at 24 hours with a high-dose colchicine regimen (1.2mg initially, followed by 600µg every hour for six hours) compared with low-dose therapy (1.2mg initially plus a single dose of 600µg six hours later). This study showed high-dose colchicine was associated with more frequent adverse events (77%), particularly diarrhoea and vomiting, than low-dose colchicine or placebo (37% and 27%, respectively). The study findings were limited by a failure to look at outcomes after 24 hours and the duration of flares. Despite the limited study data, lower doses of colchicine, eg, 500µg three times a day, are used by rheumatologists in practice and are sufficient for most patients with acute gout.

Complications that can occur with long-term use of colchicine include pancytopenia and myopathy, although these adverse effects are rare. Inappropriate dosing and accumulation of the drug in renal or hepatic impairment increases the risk of toxicity.

Additionally, drug interactions have been associated with fatal toxicities. Colchicine is a substrate for P-glycoprotein (Pgp) and is eliminated by this transporter protein. It is also a cytochrome P450 3A4 substrate. Colchicine is contraindicated in patients with renal or hepatic impairment who are taking Pgp inhibitors (eg, ciclosporin, verapamil, quinidine) or strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, itraconazole).

Corticosteroids Patients with confirmed gout flares involving one or two large joints have been shown to be effectively and safely treated with long-acting, intra-articular corticosteroid injections. Oral treatment with prednisolone 10–60mg per day (or an equivalent corticosteroid) can be used to manage acute gout, and has demonstrated similar efficacy to NSAIDs. The dose is often titrated down slowly to prevent recurrence of gout on withdrawal. Adverse effects of corticosteroids are not usually a problem with short-term use. Nevertheless, treatment with oral corticosteroids is usually reserved for those intolerant of NSAIDs and colchicine.

Chronic gout Evidence is lacking on when is the best time to start urate-lowering therapy, but it is encouraged if a patient has two or more acute episodes of gout in one year. Patients with evidence of tophi, joint damage or kidney stones should also be considered for urate-lowering therapy.

Evidence supports the maintenance of SUA below 360µmol/L. One study has shown that 86% of patients with SUA levels maintained below 360µmol/L did not experience any further acute gout flares.

Urate-lowering therapy should be started only once an acute attack has resolved and a patient is stable. Initial treatment can trigger gout flares, so prophylaxis with colchicine 500µg once or twice a day or a low-dose NSAID is recommended for the first three to six months of urate-lowering therapy. Such prophylaxis has been shown to reduce the incidence, frequency and severity of flares. Treatment of patients with chronic gout who have CKD is discussed in Box 1.
Patients with chronic kidney disease (CKD) are more likely to experience gout because of their reduced ability to excrete uric acid. In addition, medicines commonly prescribed for these patients, such as diuretics, ciclosporin and low-dose aspirin, are independent risk factors for hyperuricaemia. Treatment of acute and chronic gout for these patients is also complicated by their reduced drug clearance and increased risk of adverse effects.

**Acute gout**

The use of non-steroidal anti-inflammatory drugs (NSAIDs) is relatively contraindicated for patients with renal dysfunction because of the risk of prostaglandin-mediated pre-renal failure and, less frequently, interstitial nephritis. Sodium and fluid retention caused by NSAIDs can also be problematic in this group. Additionally, concurrent nephrotoxic drugs, such as angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, diuretics, aminoglycosides and calcineurin inhibitors all increase the risk of nephrotoxicity.

For patients with glomerular filtration rate (GFR) <30ml/min, NSAIDs should be started only under the supervision of an experienced clinician, and with close monitoring of renal function. In practice, their use in this population is reserved for patients on long-term renal replacement therapy.

For patients with normal renal function, colchicine is the preferred treatment for patients in whom NSAIDs are unsuitable. However, because of the risk of colchicine accumulation for patients with renal impairment, the dose — or the dose interval — should be adjusted for such patients. The recommended dose for patients with stage 4 or 5 CKD is 500µg once or twice daily. Even with dose reduction, diarrhoea is often a problem for these patients.

Prednisolone remains a useful therapy for the treatment of acute gout in patients with CKD. Low-dose therapy (15–30mg daily), given until a flare resolves, is generally effective. Slow withdrawal is often required to prevent flare recurrence.

**Chronic gout**

Allopurinol is the treatment of choice for managing chronic gout in patients with CKD. Dose reductions are recommended because the active metabolite oxipurinol can accumulate. There is also an increased risk of allopurinol hypersensitivity in this population.

Traditionally, reducing the dose of allopurinol to 100mg every 24–48 hours was recommended for patients with a GFR <20ml/min. However, this dose reduction has been challenged due to concerns that it results in sub-therapeutic treatment. It has been suggested that patients should be started at a reduced dose, and that doses should be titrated by 100mg every two to four weeks to a target serum uric acid level of <360µmol/L. Nevertheless, the long-term safety of increasing the recommended dose of allopurinol for patients with CKD requires further study.

According to its manufacturer, febuxostat should not be used for patients with a GFR <30ml/min because of concerns about accumulation of active metabolites. If GFR is <30ml/min, the maximum concentration of the active metabolites is increased, as is their area under the curve (AUC). Data are lacking about the clinical significance of this and therefore caution should be exercised if febuxostat is prescribed for patients with severe renal impairment.

The uricosuric medicines probenecid and sulfinpyrazone are not used for patients with moderate or severe CKD because they require a GFR >50ml/min to be effective. However, benzbromarone can be used for patients with GFR 30–50ml/min.

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**Box 1: Chronic kidney disease and gout**

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Febuxostat is licensed for the treatment of chronic hyperuricaemia at an initial dose of 80mg daily (increasing to 120mg daily if SUA >360µmol/L at 2–4 weeks). The APEX and FAST trials demonstrated superiority of febuxostat over allopurinol for SUA control. In these trials patients received an allopurinol dose of 300mg/day and no titration of the allopurinol dose to target SUA occurred (a known reason for allopurinol treatment failure). No difference in the incidence of acute gout flares was seen between the febuxostat and allopurinol groups.

A previous trial found a higher rate of cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarction, non-fatal stroke) among patients receiving febuxostat than among those receiving allopurinol. The manufacturer of febuxostat recommends that patients with ischaemic heart disease or congestive heart failure should not be prescribed the drug.

The purine antimetabolite azathioprine (and its active metabolite 6-mercaptopurine) is extensively metabolised by XO. Therefore, allopurinol and febuxostat inhibit the metabolism of both azathioprine and 6-mercaptopurine. Extreme caution is required when prescribing an XO inhibitor to a patient stable on these medicines (and vice versa). The doses of azathioprine and 6-mercaptopurine should be reduced by about two-thirds to three-quarters when given orally with an XO inhibitor. Patients’ full blood counts should also be monitored for signs of bone marrow suppression.

It is worth noting that XO inhibitors do not interact with mycophenolate and, as such, the medicine is often used as an alternative to azathioprine for patients with chronic gout who require immunosuppression.

Uricosuric medicines Uricosuric medicines — benzbromarone, probenecid and sulfinpyrazone — act in the proximal tubule to increase excretion of uric acid. They are effective for patients who underexcrete uric acid (90% of all hyperuricaemic patients), defined as <800mg of uric acid excreted in a 24-hour urine collection.

The use of uricosuric medicines is contraindicated in patients with kidney stones and most are not effective when a patient’s glomerular filtration rate (GFR) is below 50ml/min. Crystallisation of urate in the urine can occur with the use of these medicines and it therefore is important to ensure that patients maintain an adequate urine output, especially in the first few weeks of treatment.

With regard to drug interactions, high doses of aspirin and other salicylates antagonise the effects of uricosuric medicines. Also, the use of aspirin can increase bleeding risk with sulfinpyrazone, since sulfinpyrazone has some antiplatelet activity (it has been used for the treatment of some thrombocytopenic disorders). Sulfinpyrazone can increase the anticoagulant effects of warfarin, reduce ciclosporin levels and increase the clearance of theophylline.

Probenecid (available from “special-order” manufacturers in the UK) reduces excretion of a wide range of other medicines, including NSAIDs and some antimicrobials.

Benzbromarone is not licensed for use in the UK, but is available on named patient basis. However, unlike probenecid and sulfinpyrazone, it is efficacious for patients with GFR of 30–50ml/min. Benzbromarone therapy is associated with a risk of hepatotoxicity and routine monitoring of liver function is necessary. The drug is therefore reserved for specialist clinician use only.

Losartan and fenofibrate have uricosuric properties and, although not recommended for the management of gout, should be considered for patients with gout and comorbidities for which these drugs are indicated.

Rasburicase Rasburicase is a recombinant urate oxidase produced by genetically modified Saccharomyces cerevisiae. Urate oxidase acts as a catalyst in the enzymatic oxidation of uric acid to allantoin, a readily excreted metabolite that is five to 10 times more soluble than uric acid. Rasburicase is licensed for the prophylaxis and treatment of acute hyperuricaemia, before and during chemotherapy, for patients with haematological malignancy and a high tumour burden at risk of a rapid tumour lysis. Although not licensed for the management of gout, a small study (n=5) showed that, for patients with tophaceous gout who were not suitable for allopurinol therapy, monthly treatment with rasburicase reduced average SUA from 612.6 ± 162.4µmol/L at baseline to 341.2 ± 91.8µmol/L after six months (P=0.001). However, because rasburicase is expensive, and evidence for its use for gout is lacking, it is not recommended routinely for the management of chronic gout.

Future treatments Canakinumab is a long-acting human monoclonal antibody that selectively inhibits interleukin-1 beta receptor binding. Its UK license is for some rare inherited auto-inflammatory disorders, but it has shown promise for the treatment of acute gout for patients not responding to
For the management of chronic gout there are three uricosuric medicines in development — RDEA594, MBX-102 and tramistal. Another development for the management of chronic gout is BCX4208, a purine nucleoside phosphorylase inhibitor. It acts upstream of XO in the purine metabolism pathway to reduce the production of uric acid. Its mechanism of action therefore complements that of XO inhibitors.

References

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