British Society for Rheumatology guideline on gout

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The British Society for Rheumatology published a revised and updated guideline on the management of gout in July 2017, the first in a decade. This article summarises the main recommendations of the new guideline.

This 2017 revision of the 2007 British Society for Rheumatology/British Health Professionals in Rheumatology guideline for the management of gout is overdue. New treatments have become available in the intervening period and the evidence base has increased.

Gout is becoming more common (its prevalence in primary care increased from 1.4% to 2.5% between 1999 and 2012) and, despite the availability of effective treatment, cases are becoming more severe. Perhaps this is because of woeful undertreatment: less than half of patients with gout receive urate-lowering drugs and, of those who do, many do not achieve target reductions in urate levels. A “range of patient and provider barriers” to delivering care is now apparent and “better provision of information and a package of care based on guideline recommendations” can improve outcomes.

The new guideline addresses the need for a patient-focused approach to the management of gout. It is intended for clinicians in primary and secondary care, commissioners and patients. It has four detailed sections: the management of acute attacks; modification of lifestyle and risk factors; optimal use of urate-lowering therapy; and management in patients with renal insufficiency, severe refractory tophaceous gout or in those who are pregnant.

Management of acute attacks
Management includes drug therapy and non-pharmacological interventions. Patients should be educated so that they understand the need to treat an attack as soon as possible – this is founded in common sense as much as clinical experience, the guideline notes. Many patients are not aware that they should continue taking their urate-lowering treatment during the attack, though this is widely supported by clinical opinion. Although there is no trial evidence to substantiate the value of resting, elevating and exposing the affected joints in a cool environment, patient experience and expert opinion show that rest is helpful. Bed-cages and, backed by limited evidence, ice-packs can be effective.

These are summarised in a management algorithm (see Figure 1).

Recommendations for the diagnosis and investigation of gout are not included in the guideline. The European League Against Rheumatism (EULAR) recommendations for the diagnosis of gout are currently being updated.
adjuncts to management, especially when drug therapy is contraindicated.

The drug of choice for relieving pain is an NSAID (at maximum dose) or colchicine (500µg two to four times daily). Which option is preferred depends on patient preference, renal function and co-morbidities. NSAIDs are frequently contraindicated in patients with impaired renal function or a history of gastrointestinal bleeding or ulceration and should, including COX-2 inhibitors, be co-prescribed with a gastro-protective agent.

Colchicine is associated with gastrointestinal intolerance and may increase the risk of myopathy in patients taking a statin. The treatment of choice for patients with co-morbidity and acute monoarticular gout may be joint aspiration and an intra-articular steroid. An alternative for patients unable to take an NSAID or colchicine, and for whom intra-articular injection is not feasible, is a short course of an oral steroid or a single intramuscular steroid injection. Systemic therapy is also appropriate for oligo- or polyarticular attacks of gout. Expert opinion favours combining treatments when monotherapy is insufficient.

The guideline recommends considering an interleukin (IL)-1 inhibitor (eg anakinra, canakinumab) for patients who previously did not respond adequately to standard treatment of acute gout. It acknowledges the absence of support from NICE for this approach – the appraisal of canakinumab was terminated because the manufacturer submitted no evidence and anakinra has not been appraised for gout. A Cochrane review concluded that canakinumab is probably more effective than intramuscular triamcinolone but causes more adverse effects and is more expensive by a factor of 5000.

Modification of lifestyle and risk factors

Diuretics increase the risk of gout (almost 12-fold, according to a 1981 study) but they are an important component of multiple drug therapy to control blood pressure. A recent review failed to find sufficient evidence to support discontinuing diuretics across all indications in patients with gout and the guideline recommends considering an alternative to a diuretic if blood pressure is under control, noting that the risk is confined to loop diuretics and thiazides.

People with gout are victims of the disorder’s reputation as a self-inflicted problem. Many have a poor understanding of the causes and consequences of gout and as a result, adherence to treatment is low, acute attacks are more frequent and quality of life is reduced. Education and tailored lifestyle advice, combined with a urate-lowering drug, can increase adherence and help patients achieve treatment targets. All patients with gout should therefore be given verbal and written information explaining the causes and consequences of gout and hyperuricaemia, management (how to treat acute attacks, the rationale for urate-lowering drugs and target urate levels) and lifestyle advice (covering diet, alcohol consumption and obesity). Management should be individualised, taking account of co-morbidities and other drug therapy. Discussions should also address how the person feels about their illness and what they perceive to be potential barriers to care.

Diet is a major determinant of the risk of gout. Excessive consumption of meat, seafood, alcoholic drinks (especially beer and spirits), sugar-sweetened soft drinks and fructose-containing foods are all significant risk factors. Recurrent gout is associated with episodic excessive consumption of any type of alcohol. By contrast, low-fat dairy intake, folate intake, coffee consumption, fruit intake and a high-fibre diet are associated with a lower risk of incident gout and, in some people, fewer flares. There is little evidence that fortified skimmed milk or vitamin C are helpful but cherries and cherry extract do reduce the risk of attacks. The guideline recommends discussing diet and exercise with patients to encourage avoiding risky foods in favour of a well-balanced diet containing low-risk foods. Patients who are overweight should aim for and maintain a healthy weight.

There is some evidence, albeit of poor quality, that increasing fluid intake can more than halve the risk of recurrent urolithiasis, with further benefit for additional therapy with citrates. Patients with gout and a history of urolithiasis should therefore be encouraged to drink at least two litres of water per day and to avoid dehydration. Adding potassium citrate (60mEq daily) should be considered for patients with recurrent stones.

Recent evidence suggests that gout is an independent risk factor for mortality from coronary heart disease and renal disease. All patients with gout should therefore undergo annual screening for cardiovascular risk factors and co-morbidities; these should include cigarette smoking, hypertension, diabetes mellitus, dyslipidaemia, obesity and renal disease.

Optimal use of urate-lowering therapies

An important part of educating patients is a clear explanation of the value of urate-lowering treatment and the importance of regular and continuous treatment for preventing attacks. This should be discussed when the diagnosis is confirmed as part of the information provided about gout so that patients can be fully involved in deciding when to start treatment. Starting urate-lowering therapy should be delayed until after the acute phase of an attack (unless they are frequent) because this discussion is better held when the patient is not in pain. Patients should be supported during the early weeks of treatment because gout flares may increase as serum uric acid levels are lowered.

It is now evident that gout is already a disease of chronic crystal deposition by the

### Table 1. Allopurinol starting dose in relation to renal function

<table>
<thead>
<tr>
<th>Estimated GFR (ml/min/1.73m²)</th>
<th>Allopurinol starting dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>50mg per week</td>
</tr>
<tr>
<td>5–15</td>
<td>50mg twice weekly</td>
</tr>
<tr>
<td>16–30</td>
<td>50mg every 2 days</td>
</tr>
<tr>
<td>31–45</td>
<td>50mg daily</td>
</tr>
<tr>
<td>46–60</td>
<td>50mg and 100mg on alternate days</td>
</tr>
<tr>
<td>61–90</td>
<td>100mg daily</td>
</tr>
<tr>
<td>91–130</td>
<td>150mg daily</td>
</tr>
<tr>
<td>&gt;130</td>
<td>200mg daily</td>
</tr>
</tbody>
</table>

GFR = glomerular filtration rate

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**Acute attack**
Treat as early as possible
Patient education
NSAID (or coxib) plus PPI or
Colchicine 500µg twice daily – four times daily or
Corticosteroid (ia, oral, im, iv)
Consider adjunctive nonpharmacological treatment (eg topical ice, rest)

**Review at 4–6 weeks**
Assess lifestyle factors (diet, exercise, alcohol, sugary drinks)
Assess cardiovascular risk factors (obesity, hypertension, lipids, diabetes mellitus)
Review prescribed medication (diuretics)
Perform sUA, renal function

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**All patients**
Patient education
Optimise weight (where relevant)
Modify diet (where relevant)
Reduce alcohol intake (where relevant)
Discontinue diuretic (where relevant/possible)
Treat underlying cardiovascular risk factors
Discuss ULT with patient

**Initiating ULT**
First-line ULT: allopurinol
Start at low dose 50–100mg daily
Titrate allopurinol dose in 50–100mg increments every 4 weeks dependent on sUA
Target sUA: <300µmol/L
Maximum dose 900mg daily (dependent on renal function)
Consider prophylaxis (colchicine 500µg once daily – twice daily or NSAID/coxib + PPI)
Do not stop allopurinol during acute attacks

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**Inability to tolerate allopurinol or renal function prevents sufficient dose escalation**
Consider switch to febuxostat 80mg once daily
Increase febuxostat dose to 120mg once daily after 4 weeks if target sUA not reached

**Inability to tolerate febuxostat**
Consider switch to:
Sulfinpyrazone or probenecid or benzbromarone
Titrate dose every 4 weeks dependent on sUA

**Failure to achieve target sUA despite dose escalation**
Consider switch to febuxostat 80mg/120mg once daily or
Consider switch to or addition of:
Sulfinpyrazone or probenecid or benzbromarone
Titrate dose every 4 weeks dependent on sUA

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**Once target sUA (<300µmol/L) and clinical ‘cure’ (tophi resolved, attacks ceased) achieved:**
Consider reducing ULT dose to maintain sUA between 300µmol/L and 360µmol/L
Check ULT annually to ensure target still maintained (otherwise adjust ULT dose)
Continue ULT lifelong unless modifiable risk factors successfully addressed and clinical ‘cure’ achieved

Key: coxib = cyclooxygenase-2 inhibitor; PPI = proton-pump inhibitor; sUA = serum uric acid; ULT = urate-lowering therapy

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Figure 1. Algorithm for the management of gout.1 By permission of The British Society for Rheumatology Guideline for the Management of Gout.
time the first attack occurs. Treatment is not recommended for asymptomatic hyperuricaemia but all patients with gout should be offered urate-lowering therapy and it should be strongly advised in patients with signs and symptoms (recurrent attacks, tophi, chronic gouty arthritis, joint damage) or risk factors (renal impairment \([eGFR<60\text{mL/min}],\) a history of urolithiasis, primary gout with onset at a young age or taking a diuretic). Urate-lowering treatment improves renal function and slows progression in hyperuricaemic patients with chronic kidney disease.

The target serum urate level is \(\leq300\mu\text{mol/L}.\) This prevents further urate crystal formation and dissolves existing crystals. However, some evidence suggests that low serum urate may be associated with an increased risk of neurodegenerative disorders including Parkinson’s disease, dementia, Huntington’s disease and motor nerve disease. Expert opinion therefore favours relaxing the target to \(360\mu\text{mol/L}\) when tophi have resolved and the patient remains free of symptoms after “some years of successful treatment”.

A xanthine oxidase inhibitor is the preferred urate-lowering therapy and allopurinol is preferred over febuxostat. Allopurinol is supported by a large evidence base and is less expensive. Studies suggesting that it is less effective than febuxostat did not take account of the fact that few patients achieve target reductions in serum urate at the widely prescribed dosage of \(300\mu\text{g/day}\) – UK show that the median dosage required is \(400\mu\text{g/day}.\) The guideline therefore recommends starting allopurinol at a low dose (50–100mg daily), increasing in increments of 100mg every four weeks (up to a maximum of 900mg daily) until the target serum urate is achieved.

Allopurinol and its metabolites are mainly excreted renally and a dosage lower than \(100\mu\text{g/day}\) is normally recommended for patients with severe renal impairment. The guideline does not specifically address this but, considering less severely affected patients, it recommends dose increments of 50mg and a lower (unspecified) maximum dose. There has been concern that patients with renal impairment are more likely to develop hypersensitivity reactions but this risk may be reduced by initiating treatment at a dose determined by renal function (see Table 1).

Some ethnic groups have a high prevalence of the HLAB*5801 allele that is associated with a greatly increased risk of severe cutaneous toxicity with allopurinol (6%–12% vs 2% among Caucasians). Screening should be considered for patients of Korean, Han Chinese and Thai descent before prescribing allopurinol.

Febuxostat is an alternative when allopurinol is not tolerated and for patients with mild to moderate renal impairment. It has a simpler dosage regimen (starting at 80mg daily, if necessary increasing to 120mg daily after four weeks) but is not recommended for patients with ischaemic heart disease or congestive heart failure. The risk of severe skin and hypersensitivity reactions in patients who are hypersensitive to allopurinol is currently unclear.

When a xanthine oxidase inhibitor is unsuitable, one option is a uricosuric agent such as sulfinpyrazone or probenecid (for with normal or mildly impaired renal function) or benz bromarone (mild to moderate renal insufficiency). All are contraindicated or should be used with great caution in patients with urolithiasis or severe renal impairment. Probenecid and benz bromarone are available only on prescription.  Allopurinol (6%–12% of severe cutaneous toxicity with allopurinol) is currently unclear.

When a xanthine oxidase inhibitor is unsuitable, one option is a uricosuric agent such as sulfinpyrazone or probenecid (for with normal or mildly impaired renal function) or benz bromarone (mild to moderate renal insufficiency). All are contraindicated or should be used with great caution in patients with urolithiasis or severe renal impairment. Probenecid and benz bromarone are available only on a named-patient basis for the treatment of gout. These agents may also be combined with a xanthine oxidase inhibitor when the target urate level is not achieved with monotherapy. Other options include losartan and fenofibrate: these agents should not be prescribed primarily for their uricosuric effect but, when indicated for hypertension or hyperlipidaemia, this additional property may be taken into account.

Up to six months’ treatment with colchicine may be considered for prophylaxis of acute attacks during the titration phase of urate-lowering therapy. Other options include a low-dose NSAID or COX-2 inhibitor, with gastroprotection.

Special groups of patients

Chronic kidney disease and nephrolithiasis are common among people with gout and are dose-limiting for colchicine and NSAIDs if renal impairment is more than mild; intra-articular or oral steroids may be preferred to treat acute attacks for patients with severely impaired renal function.

Gout is rare during pregnancy except in women with familial juvenile hyperuricaemic nephropathy. Evidence for the safety of drug treatment is therefore lacking but the guideline states that mid-trimester use of NSAIDs is safe, steroids are generally safe, and probenecid was once used extensively during pregnancy without reported fetal toxicity. There is a lack of evidence on allopurinol or febuxostat, and colchicine is contraindicated. Nonpharmacological measures, such as ice for acute attacks, are safe.

Summary

This guideline offers a thorough guide to the non-pharmacological and pharmacological interventions for gout, supported by a readable summary of the evidence relevant to each piece of advice. Importantly, it has its feet firmly planted on the ground, noting that “some secondary care organizations prohibit follow-up of patients with gout, insisting on discharge with a treatment plan to primary care where treatment is known to be suboptimal” and “patients often do not consult for subsequent attacks, so practitioners may not be aware of recurrent attack frequency”. It appears that prescribing is only half the battle.

References


Declaration of interests

None to declare.

Steve Chaplin is a medical writer specialising in therapeutics.