

Gout

This is one of those satisfying diagnoses you can often make by simply watching the patient walk from the waiting room. But do we still feel confident if we are encouraged to start disease-modifying treatment after just one attack?

Gout is the most common inflammatory arthropathy, affecting 2.5% of adults in the UK.

Thinking is changing and, rather than being 'episodic', it is considered to be a chronic inflammatory arthropathy.

There have been a glut of new guidelines recently focusing on the management of gout. This article summarises the British Society of Rheumatology 2017 guideline (Rheumatology 2017;56:e1), endorsed by NICE. We also answer questions it raises.

The European League Against Rheumatism (EULAR) and the USA have produced similar guidelines, though the USA prefers treat-to-'symptoms' rather than treat-to-target.

These guidelines suggest significant changes to our practice.

Changes to management of gout: headlines

The UK British Society of Rheumatology suggests the following changes to our practice:

- **Explain and discuss the option of urate-lowering treatment with allopurinol to ALL patients after their first attack of gout.**
- Febuxostat is approved by NICE as a second-line choice but see below.
- **Treat-to-target with regular up-titration of doses**, aiming for a serum urate level of:
 - <300 micromol/L (5mg/dl) if tophi present until they resolve.
 - <360 micromol/L (6mg/dl) if no tophi/tophi resolved.
- Higher doses of allopurinol than we have traditionally used in primary care may be needed to achieve this (the UK average required dose is 400-500mg/d).
- **Explain and discuss co-prescribing of colchicine 500mcg once or twice daily for 3–6m** when initiating urate-lowering therapy to reduce the risk of acute attacks. An NSAID + PPI is an alternative if colchicine is not tolerated.
- Start treatment for acute attacks as soon as possible after first symptom.
- Assess and manage cardiovascular risk.

But what is the evidence behind these recommendations? And if we *are* going to start allopurinol after one attack, how can we be more confident in our diagnosis?

Diagnosis

There is an incomplete evidence base for the best way to diagnose gout.

Joint aspiration

The 'gold standard' method to diagnose gout is aspiration of synovial fluid with microscopy for crystals. But aspiration is technically difficult for many of us in primary care. False negative results can be seen if the sample takes too long to reach the lab and this is a real issue in primary care.

Clinical diagnosis

In primary care, we usually make a clinical diagnosis (*a survey of the Red Whale team suggests that none of us do joint aspirations, despite it being the gold standard!*).

- The typical history of gout is sudden-onset acute pain in one joint, peaking within 12-24h and then subsiding in 1–2w.
- 50–75% of the time it affects the 1st MTP joint.
- It can also affect the knee, wrist, fingers, ankles and midfoot.
- The main differentials are acute calcium pyrophosphate crystal arthritis (*what used to be known as pseudogout*) or septic arthritis.

The dilemma we face

A systematic review concluded that synovial fluid analysis should be used where 'clinical judgement indicates a diagnostic test is necessary' – *but what does this mean?* (Ann Int Med 2017;166:52).

For a typical attack, clinical features have a high likelihood ratio of being correct. A scoring system can improve accuracy of diagnosis.

There is a primary care scoring system that does not require aspiration and that performs better than clinical judgement alone (Rheumatology 2015;54:609).

Note that this score includes serum uric acid. If you have historical uric acid measurements, these may be helpful, but we are not advocating testing during the attack because uric acid levels are often falsely LOW at this time. The ideal is to measure it 4–6w AFTER the attack. However, if you **do** measure uric acid during an attack AND it is raised, you have your answer.

Features of presentation		If yes score:
Male sex		2
Previous patient-reported arthritis attack		2
Onset within 1d		0.5
Joint redness		1
1st MTP involvement		2.5
Hypertension or ≥1 cardiac disease (IHD/CHF/Stroke/PVD)		1.5
Serum uric acid >350µmol/L		3.5
Interpretation of scores		
<4 points	Gout unlikely – consider alternative diagnosis	
4–8 points	This group is most likely to benefit from aspiration to establish the diagnosis	
≥8 points	Gout highly likely: start empiric treatment	

- Clinical assessment has a PPV of 64% and an NPV of 87%.
- The tool offers a PPV of 87% and an NPV of 95%.
- Reminder: the PPV (positive predictive value) is the proportion of the people who test positive who actually have the disease; the NPV (negative predictive value) is the proportion of people told they don't have the disease who really don't have it.

Most guidelines suggest aspiration for less typical presentations and for any unexplained inflammatory arthritis

Most patients we treat for gout would score 8 or more points. The ones that can trip us up are first presentations in a knee, ankle or wrist joint. Septic arthritis may be on our differential here, and a secondary care assessment and joint aspiration would be appropriate. Otherwise, if the patient would consider urate-lowering treatment, I may ask the rheumatology on-call team whether ultrasound-guided aspiration was an option – personal correspondence with Professor Doherty (Consultant Rheumatologist) indicates this does not need to be done urgently and can be done after the attack has settled. .

Investigations

Serum urate levels may be falsely low during an attack. **At 4–6w after the acute attack, organise:**

- U&E.
- Lipids.
- HbA1c.
- Urate.

Review results with patient and calculate and act on QRISK.

Now, let's return to the guideline, which is endorsed by NICE.

UK British Society of Rheumatology Gout Management Guideline (Rheumatology 2017;56:e1)

Management of acute attacks

- Offer all patients high-quality written information, e.g. Patient UK, ARUK (see useful resources, below).

<ul style="list-style-type: none"> Start treatment as soon as possible after an acute attack to minimise joint impact (although remember that you need to wait 4w before measuring serum urate as results may be falsely low during an attack). For acute attacks, all treatments are similarly effective: choice will be based on patient preferences and comorbidities. Uric acid levels can be falsely low during an attack, and should NOT be measured until 4w after the acute episode. 	
First-line choices	NSAID + PPI or Colchicine 500mcg 2–4 times daily.
Second-line choices (where contraindications or intolerances exist)	Oral prednisolone, e.g. 35mg once daily for 5d or Intra-articular or intra-muscular steroid.
Non-pharmacological treatments	Rest, elevation, ice, bed cages.
Management of comorbidities	
Gout commonly co-exists with metabolic syndrome. Screen affected individuals annually for: <ul style="list-style-type: none"> Hypertension. Dyslipidaemia. Diabetes. Avoid thiazides and loop diuretics if possible – they increase serum urate levels.	
Dietary advice	
There is a relative absence of evidence for the impact of dietary modification on gout. The following recommendations are made across a range of international guidelines: <ul style="list-style-type: none"> Eat a well-balanced diet, and lose weight if overweight or obese. Avoid excessive consumption of: <ul style="list-style-type: none"> Alcohol. High purine foods, e.g. shellfish and red meat. Sugar-sweetened soft drinks. The role of the DASH diet is discussed below.	
Offer urate-lowering therapy	
<ul style="list-style-type: none"> Discuss starting urate-lowering therapy with all patients at diagnosis with the first attack. Strongly recommend urate-lowering therapy for patients with: <ul style="list-style-type: none"> 2 or more attacks (if they declined treatment after the first attack). Tophi. Impaired renal function (eGFR <60). Initiation of urate-lowering therapy commonly triggers an acute attack of gout (<i>this is a good sign because it suggest that crystals are starting to dissolve!</i>). Consider co-prescribing: <ul style="list-style-type: none"> Colchicine 500mg once or twice daily. Use an NSAID and PPI if intolerant to colchicine. <u>Do not stop urate-lowering therapy</u> during an acute attack. 	
Choice of urate-lowering drug (BNF 2017)	
Allopurinol (first-line choice)	<ul style="list-style-type: none"> Start at 50–100mg daily (in case of hypersensitivity reaction). Increase dose by 50–100mg every 4w until target level of serum uric acid is achieved (see below). The usual dose required is anywhere between 100 and 600mg daily. Doses of more than 300mg should be split so it is given twice daily. The maximum daily dose is 900mg. In those with renal impairment, start at 50mg daily and be cautious about doses >100mg (<i>though the BNF acknowledges that higher doses may be used – we may want to run this by the renal physicians</i>). Co-prescribe colchicine or NSAIDs for at least 3m (or for 1m after uric acid levels have normalised).
Febuxostat (second-line choice)	<p>Febuxostat is a fairly new drug treatment licensed for the prevention of gout. As with allopurinol, it blocks the xanthine oxidase enzyme necessary for the production of uric acid in the body. It is more expensive than allopurinol.</p> <p>In 2008, NICE recommended that we should use febuxostat for patients who:</p> <ul style="list-style-type: none"> Are intolerant of allopurinol. Have renal impairment preventing escalation of doses of allopurinol to effective levels (<i>though the BNF suggests caution in those with eGFR <30 because no studies have been</i>

	<p><i>done in these groups!)</i>.</p> <ul style="list-style-type: none"> • Do NOT use in patients with IHD or CCF. • Febuxostat lowers serum uric acid much more quickly than allopurinol and more commonly triggers acute attacks – always co-prescribe colchicine or NSAIDs for 6m.
Monitoring urate-lowering therapy	
<ul style="list-style-type: none"> • Treat to target, checking approximately every 4w, aiming for a serum uric acid level of: <ul style="list-style-type: none"> ◦ <300µmol/l if tophi present until they resolve. ◦ <360µmol/l if no tophi/tophi resolved. 	

What is the evidence for treating after one attack?

There is a clear causative link between raised serum uric acid and:

- Gout.
- Urate renal stones.

There were five other *associations*: with hypertension, heart failure, diabetes, CKD and death from CHD. The strength of evidence was not sufficient to prove causation (BMJ 2017;357:j2376).

The guidance to offer treatment after one attack is controversial. There is an absence of evidence to support it (DTB 2018;56(1):9).

Joint outcomes

The guideline recommends consideration and discussion of urate-lowering treatment even after one attack. This is a change in practice based on Delphi consensus process (expert and patient opinion). The rationale is:

- Chronic crystal deposition can be seen in multiple peripheral joint and peri-articular sites at the first attack of gout and likely predates symptoms by some years.
- These intra-articular crystals lead to ongoing joint damage and chronic arthritis.

The existing evidence base:

- Strongly supports use of urate-lowering drugs in the presence of 2 or more attacks, tophi or impaired renal function (eGFR <60).
- Based on imperfect studies, a Cochrane review comparing allopurinol (at doses of 100–300mg) with placebo concluded that allopurinol probably does not reduce acute attacks – at best, an absolute risk reduction of 4% is seen. It does reduce serum urate acid. The problem is that the doses of allopurinol were too low to be effective in most patients and follow up was short term.(Cochrane 2014;CD006077).

Cardiovascular outcomes

Patients diagnosed with gout are at increased risk of metabolic syndrome. There is an absence of evidence that urate-lowering treatment alters that risk in a meaningful way (BMJ 2017;357:j2376).

- Meta-analyses have shown that urate-lowering treatment has marginal benefits in improving surrogate markers of cardiovascular disease, e.g. blood pressure, endothelial function and renal function.
- **There have never been any studies that have shown that urate-lowering treatment reduces the risk of important endpoints like heart attack, stroke and mortality.**
- **The available studies in the main are flawed by using doses of allopurinol inadequate to bring urate down into the target range. So the bottom line, we just don't know!**

This means that we should manage the cardiovascular risk as for any other patient, with lifestyle interventions, management of hypertension and lipids, etc. We should also discuss the advantages and disadvantages of long-term urate-lowering treatment and be honest about the current limitations of the evidence.

After a first attack, how likely is a second attack?

The guideline cites evidence which suggests that 62% of patients with gout will have a second attack within 12m.

The risk increases with increased levels of serum urate: at levels of >500 micromol/L, the risk is almost 100%.

What is the evidence for treating-to-target?

A systematic review addressed this and concluded (Ann Int Med 2017;166:37):

- There is a logical appeal in treating-to-target and observational evidence suggests it is beneficial.
- There are no robust RCTs comparing treating-to-target with 'usual care' or 'treating-to-symptom control'.

The authors and editorial conclude that this is an important question to answer; this next study starts to address this issue.

How should we organise gout care?

Nurse-led (or pharmacist-led) clinics. Probably.

Gout is a long-term condition. In keeping with other long-term conditions, a UK-based RCT study demonstrated that nurse-led care can be more clinically-effective and cost-effective than GP-led care (Lancet 2018;392;1403).

More than 500 patients with ongoing gout were assigned to receive nurse-led care or 'usual' GP-led care. The nurses were research nurses who had been trained in the management of gout. They spent more time on patient education and individualising explanations, and in engaging patients in shared decision-making (i.e. recommended best practice). This study had the highest retention rates of any gout trial (at 2yrs, 91% of the nurse-led group), almost certainly reflecting the benefits of full information and positive patient-practitioner relationship and patient engagement. There will be a follow-up study implementing the same protocol for practice nurses.

Patients were followed-up for 2 years.

Outcome measures at 2 years	Nurse-led care (% patients achieving outcome)	Usual care (% patients achieving outcome)
Serum urate <360 micromol/L	95%	30%
Serum urate <300 micromol/L	88%	17%
Taking urate-lowering therapy	96%	56%
Two or more flares	8%	24%
Four or more flares	1%	12%
Presence of tophi	3%	11%
Mean dose of allopurinol	460mg/day	230mg/day
Mean number of contacts over 2 years	9 face-to-face 8 telephone (mostly in the first 6 months)	<1 face-to-face

Note that in the nurse-led group, the number of flares was **greater** in the first 3 months of year 1, but lower than the usual care group after the first 6 months, likely reflecting up-titration of urate-lowering therapy. Allopurinol was successful and well tolerated even in the 20% with CKD stage 3.

Cost-effectiveness analysis suggests that at year 2, it would cost £5066 per QALY gained, modelled to be £286 by year 3 (so a big upfront cost, but well below the NICE threshold of £20 000/QALY), with the potential to save costs by year 5.

Similar, though smaller, benefits have been seen in smaller US studies of pharmacist-led care.

So, nurse-led care led to better patient outcomes and is cost-effective though more expensive for us to administer in primary care. Longer-term follow-up will tell us if this initial investment is offset by later financial savings.

Allopurinol vs. febuxostat for cardiovascular outcomes

A recent pharma-sponsored, non-inferiority, double-blind RCT of more than 6000 patients with gout AND cardiovascular disease compared cardiovascular outcomes in patients on febuxostat with patients on allopurinol (NEJM 2018;378:1200).

The authors pre-specified that febuxostat would be considered 'non-inferior' if it was $\leq 1.3\times$ worse than allopurinol for cardiovascular outcomes (a composite endpoint of CV death and other CV events).

The results show:

- There were high discontinuation and drop-out rates (around 50%) over the course of the trial in both groups.
- The primary event rate (cardiovascular events and cardiovascular deaths) was high in both groups – more than 10.8% in the febuxostat group and 10.4% in the allopurinol group over 5y.

- The authors of the study concluded that febuxostat was ‘non-inferior’; the rate of composite cardiovascular events and deaths was similar and within the non-inferiority margin.

However:

- There was a statistically-significant increase in all-cause and cardiovascular mortality in the febuxostat group compared with allopurinol:
 - Cardiovascular mortality HR 1.34 (CI 1.03–1.73).
 - All-cause mortality HR 1.22 (CI 1.01–1.47).

This supports NICE’s view that allopurinol is the first-line choice for the management of gout, and febuxostat should remain a second-line drug. The UK SPC recommends that febuxostat is not used for patients with ischaemic heart disease or congestive heart failure.

On the basis of this study, in July 2019 the MHRA recommended that we should avoid treatment with febuxostat in patients with pre-existing major cardiovascular disease, e.g. history of MI, angina or stroke, unless no other therapy option is appropriate.

Doses of allopurinol in impaired renal function

A DTB review on the management of gout included a helpful table of recommended starting doses of allopurinol in renal impairment. In these patients, serum uric acid and renal function should be monitored every 3m in the first year, then annually. Advice from renal physicians may be needed for dose escalation (DTB 2018;56(1):9).

eGFR (ml/min/1.73m ²)	Allopurinol starting dose
<5	50mg weekly
5–15	50mg twice weekly
16–30	50mg every 2d
31–45	50mg daily
46–60	50mg and 100mg alternate days
61–90	100mg daily

Antihypertensives and gout

Which is the best antihypertensive for patients with gout?

A UK-based study of over 24 000 patients with gout used the CPRD to answer this question (BMJ 2012;344:d8190). It looked at the relative risk of gout associated with the use of different antihypertensive drugs:

Antihypertensives that lower gout attack risk	Antihypertensives that increase gout attack risk
Calcium channel blockers Losartan	Diuretics Beta-blockers ACE inhibitors Non-losartan ARBs.

Something to consider when you are reviewing your hypertensive patients with gout, particularly if they are having recurrent attacks?

Hyperuricaemia and risk of neurodegenerative diseases

A number of studies have suggested that hyperuricaemia may offer some protection against dementia and Parkinson’s disease (BJGP 2017;67:284). This is an association and was NOT demonstrated in the BMJ umbrella review discussed above.

It is not known whether lowering urate levels in the context of gout increases the risk of these conditions. As a precaution, the guideline suggests that urate levels should not be left significantly below 300 micromol/L once tophi have resolved, but should be maintained between 300-360 micromol/L (BJGP 2017;67:284).

Diet vs. genetics

There is a common perception that gout and raised serum urate are dietary. A recent meta-analysis of five cohort studies including men and women of European ancestry who had never had gout challenges this perception (BMJ 2018;363:k3951).

- It identified an association between some foods (alcohol- and sugar-containing beverages, meat, poultry, potatoes) and elevated serum urate levels.
- None of these foods explained even 1% of variation in urate levels.
- Genetic susceptibility had a **much** larger impact on high serum urate levels than variations in diet.

However, the authors acknowledge that while genetics cannot be changed, diet can. A balanced diet, in terms both of content and quantity, that reduce and maintains overweight/obesity is far more important than individual dietary elements.

The DASH diet

The DASH (Dietary Approach to Stop Hypertension) diet is based on a high intake of fruit, veg, legumes, nuts, low-fat dairy and whole grains, and a low intake of salt, sweetened drinks, and red and processed meats. It has been demonstrated in RCTs to lower serum urate.

A well-designed, prospective cohort study followed more than 40 000 men who had never had gout for 26 years. It looked prospectively at the impact of the DASH diet compared with a typical western diet on the risk of developing gout for the first time (BMJ 2017;357:j1794).

- Individuals who followed a DASH-type diet had a 30% lower risk of developing gout.
- A dose–response effect seen.




Sugary drink consumption

A prospective cohort study of more than 46 000 men looked at the association between fructose-containing sugary drink consumption and the risk of gout (BMJ 2008;336:309).

It found that:

- Gout attacks were more likely in men consuming fructose-containing soft drinks, and that this effect was dose dependent.
- The risk started to accumulate at 5–6 servings per week. If 2 servings per day were consumed, a man had double the risk of gout compared with men who do not consume sugary soft drinks.
- There was no association with diet soft drinks.

It is reasonable to encourage a DASH-type diet, and to ask about fructose consumption and encourage men with gout to reduce this.

	<p>Gout</p> <ul style="list-style-type: none"> • Use a diagnostic tool rather than clinical judgement alone. • Discuss urate-lowering therapy with all patients diagnosed with gout. • If using urate-lowering therapy, treat-to-target – this may need higher doses of allopurinol. • Offer all an annual CV risk assessment and HbA1c. • Use allopurinol first line and febuxostat second line. • If using febuxostat, it is essential to co-prescribe colchicine for 6m.
	<p>Audit your care of gout patients – search for all gout patients on your list.</p> <ul style="list-style-type: none"> • What proportion are on urate-lowering therapy? • Of those on urate-lowering therapy, how many are hitting target levels of uric acid? • How many have an up-to-date cardiovascular risk assessment? • How could you review this and re-audit? • Could you offer standby courses of treatment for management of acute attacks?
	<p>A useful patient information leaflet can be found here: https://www.versusarthritis.org/about-arthritis/conditions/gout/ A PDF of the primary care gout diagnosis tool can be found here: www.mdcalc.com/acute-gout-diagnosis-rule A link to a patient information leaflet about the DASH diet: https://tinyurl.com/GPU-DASH-diet</p>



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