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CLINICAL REVIEW

Gout

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Gout is the most common inflammatory arthritis, affecting 1-2% of the population. Acute gout is one of the most painful forms of arthritis and is characterised by the abrupt onset of severe joint pain (classically the first metatarsophalangeal joint), swelling, and erythema. The major risk factor is a raised serum urate concentration (hyperuricaemia), which results in the deposition of monosodium urate crystals in and around joints. Untreated, continuing crystal deposition can result in irreversible joint damage. Although effective treatments are available for acute and chronic gout, uptake is poor, and many patients experience repeated acute attacks and reduced quality of life. This clinical review summarises current evidence for the diagnosis and management of acute and chronic gout.

What is gout?

The pathogenesis of gout is well understood. If serum urate concentrations persistently exceed the physiological saturation threshold of urate (around 380 μmol/L; 1 μmol/L=0.02 mg/dL), monosodium urate crystals form and deposit, particularly in cartilage, bone, and periarticular tissues of peripheral joints. Continuing crystal deposition is clinically silent, with about 10% of people with hyperuricaemia developing clinical gout.[1]

The first acute attack of gout occurs when crystals are shed from the articular cartilage into the joint space. It is usually monoarticular and typically affects the lower limb. Involvement of the first metatarsophalangeal joint ("podagra") is common and occurs in 56-78% of first attacks.[2] The mid-foot, ankle, knee, finger joints, wrist, and elbow are also commonly affected.[2] The shoulder, hips, and spine are rarely affected. Acute attacks are characterised by sudden onset, severe joint pain—which reaches peak intensity within 12-24 hours and is associated with swelling and erythema—and then complete resolution within one to two weeks.[3]

The time between acute attacks is termed the intercritical period. If untreated, a second acute attack often occurs within two years. Recurrent attacks may become more frequent and affect different joints or more than one joint. Chronic tophaceous gout can be a consequence of untreated gout and is associated with progressive joint damage, chronic pain and disability, and clinically evident subcutaneous tophi (hard, impacted monosodium urate crystals (fig 1⇓). Tophi mainly occur on the fingers, olecranon processes, toes, Achilles' tendons, knees, and occasionally the helix of the ears.

Who gets gout?

Gout usually affects men aged 40 years and over and women over 65 years.[4] It increases with age, affecting 7% of men aged over 75 in the United Kingdom.[4] The incidence and prevalence of gout are rising because of an ageing population, increasing prevalence of the metabolic syndrome, and possibly dietary changes.

Uric acid is the relatively insoluble endproduct of purine metabolism. Around 70% of uric acid derives from the breakdown of endogenous purines, with the remaining 30% from dietary purines. Most uric acid (around 70%) is excreted through the kidney, the remainder through the gut.[5] Hyperuricaemia is caused by reduced renal elimination (most commonly) or increased production (or both). Epidemiological studies show that the metabolic syndrome and its components (insulin resistance, obesity, hyperlipidaemia, and hypertension) are strongly associated with gout (box 1).[4 6 7] A large cross-sectional study found a 62.8% prevalence of the metabolic syndrome in people with gout compared with 25.4% in those without gout (adjusted odds ratio 3.05, 95% confidence interval 2.0 to 4.6).[8]

Although associations between gout and dietary factors—including alcoholic drinks and purine-rich foods—have been recognised for centuries, these have only recently been examined in high quality prospective studies (box 1).[9 10] The risk of developing gout is directly related to alcohol consumption (multivariate relative risk 1.17 per 10 g alcohol intake/day, 95% confidence interval 1.11 to 1.22).[9] The risk is high for beer (2.51, 1.77 to 3.55) and spirit consumption (1.60, 1.19 to 2.16), but not for wine (1.05). Compared with the lowest fifth of consumption, the relative risk of developing gout in the highest fifth was 1.41 (1.07 to 1.86) for red meat and 1.51 (1.17 to 1.95) for seafood.[10] Dairy products are protective (0.54, 0.42 to 0.74). Sugar sweetened soft drinks, especially those with fructose (1.85, 1.08 to 3.16) increase the risk of gout, whereas

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Summary points

- Gout is associated with serious comorbidity and increased risk of cardiovascular disease
- The definitive diagnosis of gout requires microscopic identification of monosodium urate crystals
- A clinical diagnosis can be made when typical features of inflammation affect the first metatarsophalangeal joint; serum urate values have limited diagnostic value
- First line medical treatment options for acute gout are a non-steroidal anti-inflammatory drug or low dose colchicine
- Long term management requires full patient education, dealing with any modifiable risk factors (such as overweight or obesity, chronic diuretic intake), and urate lowering drugs
- Start allopurinol at a low dose (such as 100 mg daily) and increase gradually with the aim of lowering then maintaining serum urate below 360 µmol/L

Sources and selection criteria

We searched Medline, Embase, PubMed, Cochrane Controlled Trials Register, ISI Web of Science, and AMED (Allied and Complementary Medicine Database) using the search terms "gouty arthritis", "podagra", "tophus", "monosodium urate crystals" and "hyperuricaemia". We also used personal archived references. Priority was given to systematic reviews, meta-analyses, randomised controlled trials, and prospective epidemiological studies where possible.

Box 1 Clinically important risk factors for gout

- Male sex
- Older age
- Genetic factors (mainly reduced excretion of urate)
- Metabolic syndrome
- Obesity (reduced excretion of urate)
- Hypertension (reduced excretion of urate)
- Hyperlipidaemia (reduced excretion of urate)
- Loop and thiazide diuretics (reduced excretion of urate)
- Chronic kidney disease (reduced excretion of urate)
- Osteoarthritis (enhanced crystal formation)
- Dietary factors (increased production of uric acid):
  - Excess purine-rich foods, fructose, sugar sweetened soft drinks
  - Excess alcohol consumption, particularly beer

consumption of caffeinated and decaffeinated coffee (0.41, 0.19 to 0.88) is thought to be protective.[11 12]

Gout often runs in families, and this is possibly related to lifestyle and genetic factors. Patients may inherit a genetic predisposition to gout, with several rare enzymatic defects known to be a cause. A twin study estimated the hereditability of renal clearance and fractional excretion of urate to be 60% and 87%, respectively.[13] Putative mutations affecting several genes involved in renal urate transport have been proposed to influence developing hyperuricaemia and gout including *SLC22A12*, *SLC2A9* (*GLUT9*), *ABCG2*, and *SLC17A3*, although work is ongoing.[14]

Drugs are often implicated in the pathogenesis of gout (box 1). A recent systematic review including 13 original studies found a trend towards a higher risk for acute gout in patients taking loop and thiazide diuretics, although the magnitude of risk and independence were not consistent.[15] Although no randomised controlled trials (RCTs) have tested cessation of chronic diuretic use in people with gout, consider cessation or reduction when the indication is hypertension rather than cardiac or renal failure.[16 17] Low dose aspirin (75-150 mg/day) has well recognised urate retaining properties, but this is thought to be clinically insignificant, and low dose aspirin should continue if needed for cardiovascular prophylaxis.

Is gout associated with any other diseases?

Gout is increasingly being viewed as more than just a joint disease. Comorbidity including hypertension (74%), hyperlipidaemia, chronic kidney disease (20%), osteoarthritis, obesity (53%), diabetes (26%), congestive heart failure (11%), and ischaemic heart disease (14%) is common and often unrecognised and undertreated.[6-8 18] Comorbidity may adversely affect diagnosis, limit management options, and contribute to long term adverse clinical outcomes.

How is gout diagnosed and assessed?

For patients presenting with classic symptoms (rapid onset, podagra, swelling, erythema) a clinical diagnosis is usually accurate.[3] Figure 2⇓ shows likelihood ratios for different clinical features. Podagra has high sensitivity (0.96, 0.91 to 1.01) and specificity (0.97, 0.96 to 0.98), performing better than pain, swelling, and erythema. A definitive diagnosis requires confirmation of the presence of monosodium urate crystals in synovial fluid or tophi. Although joint aspiration is not needed when the presentation is classic, aspiration and examination of synovial fluid for crystals can be useful when presentation is atypical or involves other joints, during either the acute attack or the intercritical period. It also allows differentiation from the main differential diagnoses of acute calcium pyrophosphate crystal arthritis (pseudogout) and septic arthritis.[3] A systematic review highlights the high degree of interobserver reliability (κ

A patient's perspective

During my early 50s I suddenly woke up one night with severe pain in one of my big toes. My doctor sent me up to the hospital where they said I had gout, but I wasn't prescribed any treatment. I'd heard of gout, although I didn't know much about it or know that it was a form of arthritis. I thought that possibly it was seen in older men who liked drinking alcohol.

Because I hate taking tablets I wanted to avoid long term medication. I asked my GP if I could try to control my gout by watching what I ate. He allowed me to do what I was comfortable with. I was later prescribed naproxen to deal with the attacks as and when they occurred.

Watching my diet worked reasonably well for a while. It didn't stop me getting gout, but at least I felt I was a bit in control of it. That was basically the case for 10 years or so, but the flare-ups started to become more frequent.

Gout is extremely painful—I can't possibly describe what the pain is like. I can only say it is excruciating. When I get a flare-up, I often can't walk or drive the car, and I occasionally wasn't able to go to work. It is exhausting because you can't sleep and you can't move or have the bedclothes on the affected joint because of the pain. I enjoy competing in agility competitions with my dogs, but when I had a flare-up of gout I couldn't do this. As the years went by, I got better at recognising when I was going to have a flare-up and starting my anti-inflammatory drugs quickly, but I decided that I needed to do something more than just managing my diet and dealing with episodes when they occurred.

I went to see my doctor last year and agreed to start on a low dose of allopurinol. Because I was still getting attacks, my GP increased the dose from 200 mg to 300 mg. I had a blood test six weeks later and was told that my uric acid concentration (281 µmol/L) was now within the target range and lower than before I started taking the allopurinol (555 µmol/L). Touch wood, I haven't had an attack since.

I feel positive about the future. Gout doesn't cause me lots of worry any more. Maybe I should have bitten the bullet long ago and gone straight on to allopurinol. If I could turn the clocks back, yes, I probably would have taken allopurinol sooner.

0.35-0.63) for identifying monosodium urate crystals in synovial fluid, emphasising the need for training and quality control.[19]

Serum uric acid concentrations, although important when "treating to target," are less useful in the diagnosis of gout. Two large population based cohorts found that, although the risk of clinical gout increases with increasing concentrations of serum urate, not all people with hyperuricaemia develop gout.[20 21] There is no evidence to support drug treatment of people with asymptomatic hyperuricaemia. Patients with confirmed gout may have normal serum urate concentrations, especially during an acute attack, when concentrations are often reduced because renal urate excretion increases during the acute phase.[22]

It is also useful to screen for comorbidity by requesting urea and electrolytes, estimated glomerular filtration rate, glucose, and lipids. Measuring and dealing with problems of blood pressure, body mass index, smoking, alcohol use, and cardiovascular risk should form part of a comprehensive gout assessment.

Imaging is not usually needed to diagnose gout. Plain radiographs are often normal, although radiographic evidence of asymmetrical swelling and subcortical cysts without erosion may be useful to diagnose chronic gout.[3] A systematic review concluded that ultrasound is a promising diagnostic tool, but further research is needed to assess the responsiveness, reliability, and feasibility of using this modality routinely.[23] The "double contour" sign—hyperechoic enhancement of the superficial margin of the articular cartilage—is an ultrasound finding thought to be specific to gout (sensitivity 44%, specificity 99%) that is also seen in 25% of patients with asymptomatic hyperuricaemia.[23-25]

How are acute attacks of gout treated?

Treatment of acute gout aims to provide rapid relief of joint pain and swelling. First line oral drugs are usually non-steroidal anti-inflammatory drugs (NSAIDs) or colchicine.[16] There is no evidence that any one NSAID is more effective than another. A systematic review commented on the poor quality of existing NSAID trials in acute gout, with the exception of two moderately sized RCTs, which found an equivalent effect of indometacin 50 mg three times daily and etoricoxib 120 mg daily on pain.[26-28] More recently, two well conducted trials have found indometacin (50 mg three times daily for two days, then 25 mg three times daily for three days) and naproxen 500 mg twice daily to be as effective as oral prednisolone.[29 30] Indometacin was associated with more gastrointestinal adverse events, however, and is best avoided.[29]

British Society for Rheumatology and American College of Rheumatology guidelines suggest using a fast acting NSAID, such as naproxen, at full dose. Caution is needed, however, in people with heart failure, ischaemic heart disease, renal insufficiency, or a history of gastrointestinal ulcers, bleeds, or perforations.[17 31] Continue treatment until the attack has resolved (typically a few days to two weeks).

Colchicine is a naturally occurring alkaloid that inhibits leucocytic phagocytosis of monosodium urate crystals, the inflammasome, and cell mediated immune responses. It has traditionally been used in high doses (1 mg initially, followed by 500 µg every two to three hours until pain relief is obtained). Although a small trial showed the effectiveness of high dose regimens over placebo, all participants randomised to receive colchicine developed diarrhoea or vomiting (or both).[32] Lower doses of colchicine are as effective and better tolerated than high dose regimens.

A recent well conducted moderately sized RCT found at least a 50% reduction in pain within 24 hours in 33% of participants treated with high dose colchicine (1.2 mg initially and then 600 µg hourly for six hours). There was also a 38% reduction in those treated with low dose colchicine (1.2 mg initially, followed by 600 µg after one hour) and a 16% reduction in those receiving placebo.[33] Diarrhoea affected 77% of the high dose group, 23% of the low dose group, and 14% receiving placebo. The *British National Formulary* recommends 500 µg two to four times daily.[34] Although no head to head comparison between colchicine and a NSAID exists, oral NSAIDs are generally considered to be the first line treatment for acute gout, with colchicine reserved for those with contraindications to, or intolerance of, NSAIDs.[17] Several drugs can increase the risk of colchicine toxicity (box 2).

Corticosteroids provide a further treatment option. Although there are no RCTs,[35] expert consensus agrees that joint aspiration and intra-articular injection of corticosteroids is a rapid and highly effective treatment for acute gout.[16 17] The diagnosis can be confirmed by microscopy of aspirated fluid, and such treatment is probably best practice in a hospital setting. However, the necessary skills to perform aspiration and injection might not be present in all settings, particularly primary care. Intramuscular or oral corticosteroids provide a useful option, particularly when there are contraindications to NSAIDs and colchicine and more than one joint is affected or joint injection is not possible.[16 31] Two high quality RCTs found that oral prednisolone at doses of 30-35 mg daily for five days are as effective as NSAIDs.[29 30]

Rest and cooling of the joint are also effective for acute gout. A small RCT found that the application of topical ice in

Box 2 Drugs that might increase the risk of colchicine toxicity

- Amiodarone
- Ciclosporin
- Digoxin
- Diltiazem
- Fibrates
- Antifungals (itraconazole, ketoconazole)
- Macrolide antibiotics
- Protease inhibitors
- Statins
- Verapamil

combination with oral prednisolone and colchicine reduces pain more effectively than combined prednisolone and colchicine alone.[36]

How is gout managed in the long term?

Long term management of gout aims to prevent formation of new monosodium urate crystals and cause existing crystals to dissolve by lowering serum urate below the physiological saturation threshold. This will cause acute attacks to cease and tophi to resolve, as well as prevent long term joint damage. Urate lowering is best achieved by combining non-drug based and drug based interventions. Individualised patient education is a fundamental component of management and should focus on the causes and consequences of hyperuricaemia and gout,[37] the importance of urate lowering, and how this can be achieved.

What does non-drug based management of gout consist of?

Non-drug based management consists of risk factor modification, including lifestyle factors. Dietary modification comprises restriction of, but not total abstinence from, purine-rich foods (including red meat and seafood) and alcohol (particularly beer).[16 17] Weight loss is recommended if appropriate. Uncontrolled intervention studies have confirmed modest effects of weight loss and low purine diet on urate lowering and frequency of attacks.[38 39] Although there is currently insufficient evidence to support modification of other dietary factors—such as consumption of cherries, dairy products, vitamin C, and coffee, and restriction of fructose and sugar sweetened soft drinks—patients are often aware of the preliminary evidence for each of these. Patients should therefore be advised that although these factors may influence the risk of developing gout, the effectiveness of modifying these factors is unclear.

How and when should urate lowering drugs be used?

There is debate about the indications for urate lowering therapy. Expert consensus advocates offering such drugs to patients with recurrent acute gout, tophi, radiographic damage, renal insufficiency, or uric acid urolithiasis.[16 17] The precise threshold at which recurrence of acute attacks warrants treatment is controversial. Opinions vary from starting these drugs after the first attack, when the crystal load is small and substantial joint damage has not yet occurred, to waiting until two or more attacks have occurred over 12 months. Because most patients experience recurrent attacks, it is best to discuss treatment options early on. Urate lowering therapy is usually started two to four weeks after resolution of an acute attack to reduce the risk of the drug exacerbating the attack. However, one RCT of 51 patients found no difference in pain between those started on allopurinol during an attack and those given placebo.[40] Delaying initiation of allopurinol also allows a rational discussion about treatment when the patient is no longer in pain. When fully informed about urate lowering therapy, most people wish to receive it, and subsequent adherence can be excellent.[37]

The most commonly used drug is allopurinol—a purine, non-specific xanthine oxidase inhibitor. Allopurinol should be started at low dose (usually 100 mg daily) and increased in 100 mg increments monthly until serum uric acid is below 360 µmol/L. Two small observational studies reported that the effect on cessation of acute attacks, resolution of tophi, and reduction of crystal load is greatest if uric acid is reduced below this value.[41 42] Some expert consensus groups recommend reducing uric acid further, to below 300 µmol/L,[17] at least for the first one to two years of treatment, because this speeds up the rate of crystal elimination and tophus reduction.[43]

The maximum permitted dose of allopurinol in the UK is 900 mg per day. Although such doses are rarely needed, many patients need doses of 400-500 mg daily to reduce uric acid.[37] During the dose escalation phase, measure full blood count, renal function, liver function, and serum uric acid monthly. The active metabolite of allopurinol (oxypurinol) is excreted through the kidney, so lower doses and more cautious upward titration are recommended in people with renal failure because of the risk of the rare but potentially life threatening allopurinol hypersensitivity syndrome, which involves severe skin reactions and hepatic and renal dysfunction.[44 45] Clinical risk factors for allopurinol hypersensitivity syndrome include renal failure, diuretic use, and higher allopurinol dose at initiation.[44 45]

Ninety per cent of people tolerate allopurinol without problems. As with all urate lowering drugs, patients may experience an acute attack of gout when they start allopurinol because it encourages crystal shedding through partial crystal dissolution. Although the likelihood of this is reduced by gradual dose escalation, prophylactic low dose colchicine or an NSAID can be coprescribed for up to six months until a stable dose is reached. One small placebo controlled RCT showed fewer gout flares when allopurinol was coprescribed with colchicine 600 µg twice daily.[46] Allopurinol should not be discontinued if an acute attack occurs.

The main alternative to allopurinol is the specific non-purine xanthine oxidase inhibitor, febuxostat. A recent systematic review found that target serum urate values are more often achieved with febuxostat at either of its licensed doses (80 mg or 120 mg daily) than with allopurinol.[47] However, allopurinol was used at a fixed dose of 300 mg daily rather than best practice dose escalation. Only 70% of participants taking 120 mg febuxostat achieved the therapeutic target. Febuxostat is largely metabolised by the liver, does not require dose reduction in

mild-moderate renal impairment, and does not interact with warfarin. In England and Wales, the National Institute for Health and Care Excellence (NICE) has approved febuxostat as an option for the management of chronic hyperuricaemia in gout for people who are intolerant of allopurinol or for whom allopurinol is contraindicated.[48] It is not recommended in people with ischaemic heart disease, congestive cardiac failure, organ transplant recipients, or, like allopurinol, those taking azathioprine.[49]

Urate lowering therapy in patients who cannot tolerate or have contraindications to allopurinol and febuxostat is challenging. Options include uricosuric drugs such as sulfinpyrazone, probenecid, and benzbromarone, but these have limited availability. Such patients are best referred to a rheumatologist for specialist care.

Treatment is life long. Once a stable target serum urate concentration has been achieved, measurements must be repeated about every six months to ensure the therapeutic target is being maintained. Once the patient is considered crystal free and "cured" (no attacks, resolution of tophi—usually achieved after two years of treatment), the dose may be adjusted to maintain uric acid concentrations of 300-360 μmol/L and monitored every one to two years. Treating to target is a new concept, but when combined with appropriate patient education it can result in "cure" and considerable improvements in patient centred outcomes.

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Questions for future research

Are cardiovascular and renal risk reduced by lowering serum urate in people with gout?

Which is the most effective and safest treatment for acute gout—a non-steroidal anti-inflammatory drug or low dose colchicine?

How effective are dietary modification and weight loss at lowering serum urate and treating gout?

How effective is cessation of diuretics at lowering serum urate and treating gout?

When starting a urate lowering drug such as allopurinol that can be slowly uptitrated from a low dose, is prophylaxis against acute attacks (with colchicine or a non-steroidal anti-inflammatory drug) needed?

When starting urate lowering therapy, what is the optimum target to which serum urate levels should be lowered?

Tips for non-specialists

The diagnosis of typical gout can usually be made clinically

When assessing patients with gout, screen for common comorbidities including hypertension, diabetes, renal disease, and hyperlipidaemia

Urate lowering therapy is safe and effective yet underused in primary care. Treating to target can reduce and eventually eliminate acute attacks and prevent longer term joint damage

Don't forget about non-drug based approaches when managing chronic gout, including dietary modification and weight loss if relevant

Additional educational resources

Resources for healthcare professionals

Jordan KM, Cameron JS, Snaith M, Zhang W, Doherty M, Seckl J, et al. British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout. *Rheumatol (Oxford)* 2007;46:1372-4.

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Zhang W, Doherty M, Bardin T, Pascual E, Barskova V, Conaghan P, et al. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2006;65:1312-24

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Khanna D, Khanna PP, Fitzgerald JD, Singh MK, Bae S, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. *Arthritis Care Res* 2012;64:1447-61

Resources for patients

Arthritis Research UK (www.arthritisresearchuk.org/arthritis-information/conditions/gout.aspx)—Booklet with information on what gout is, what causes it, how it presents, and how it is diagnosed and treated

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Figures

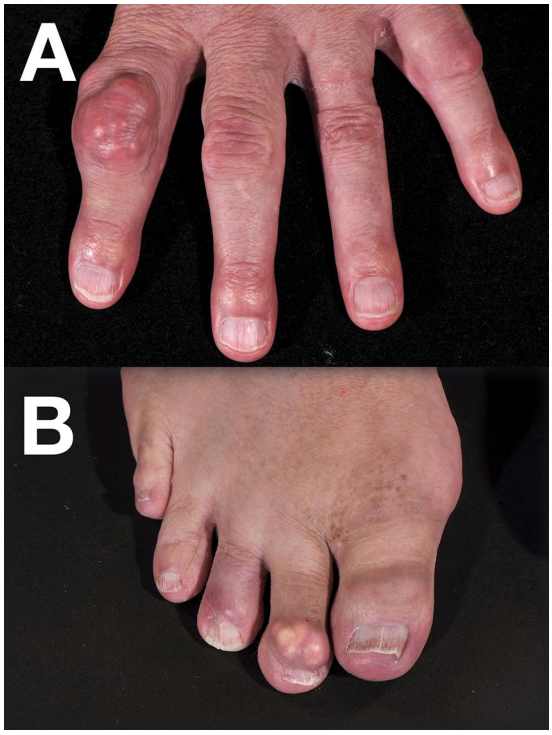

Fig 1 Tophi affecting the interphalangeal joints of the left hand (A) and right second toe (B). Note asymmetry of swelling and yellow-white discoloration

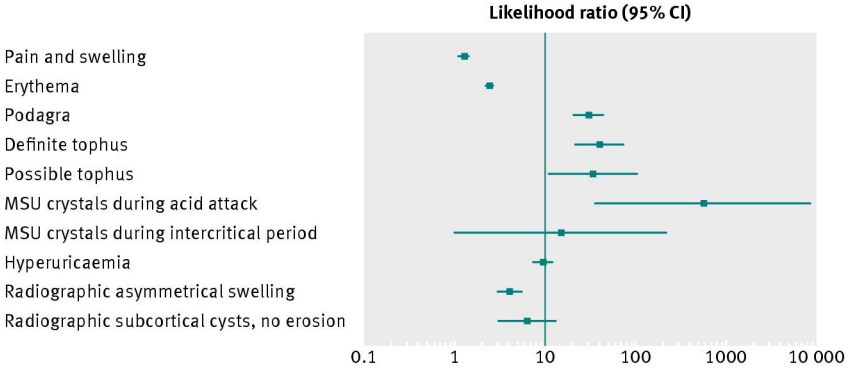

Fig 2 Likelihood ratio and 95% confidence interval (CI) for various features in the diagnosis of gout. MSU=monosodium urate. Reproduced, with permission, from the *Annals of the Rheumatic Diseases*[3]