

## Clinical Review: Management of gout

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Gout is the most common inflammatory arthritis, affecting 1-2% of the population. 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 management of acute and chronic gout.

### 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.<sup>1</sup> 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.<sup>2-4</sup> 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.<sup>5-6</sup> Indometacin was associated with more gastrointestinal adverse events, however, and is best avoided.<sup>5</sup>

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.<sup>7-8</sup> 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).<sup>9</sup> 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.<sup>10</sup> 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.<sup>11</sup> 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.<sup>7</sup> Several drugs can increase the risk of colchicine toxicity.

Corticosteroids provide a further treatment option. Although there are no RCTs,<sup>12</sup> expert consensus agrees that joint aspiration and intra-articular injection of corticosteroids is a rapid and highly effective treatment for acute gout.<sup>1,7</sup> 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.<sup>1,8</sup> Two high quality RCTs found that oral prednisolone at doses of 30-35 mg daily for five days are as effective as NSAIDs.<sup>5-6</sup>

Rest and cooling of the joint are also effective for acute gout. A small RCT found that the application of topical ice in combination with oral prednisolone and colchicine reduces pain more effectively than combined prednisolone and colchicine alone.<sup>13</sup>

### 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).<sup>1,7</sup> 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.<sup>14-15</sup>

### 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.<sup>1,7</sup> 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. 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.<sup>16</sup> 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.<sup>17</sup> 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  $\mu\text{mol/L}$ . 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.<sup>18-19</sup> Some expert consensus groups recommend reducing uric acid further, to below 300  $\mu\text{mol/L}$ ,<sup>7</sup> at least for the first one to two years of treatment, because this speeds up the rate of crystal elimination and tophus reduction.<sup>20</sup>

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.<sup>17</sup> 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.<sup>21-22</sup> Clinical risk factors for allopurinol hypersensitivity syndrome include renal failure, diuretic use, and higher allopurinol dose at initiation.<sup>21-22</sup>

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  $\mu\text{g}$  twice daily.<sup>23</sup> Allopurinol should not be discontinued if an acute attack occurs. The main alternative to allopurinol is the specific non-purine xanthine oxidase inhibitor, febuxostat. Urate lowering therapy in patients who cannot tolerate or have contraindications to allopurinol (or alternatives) 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.

### Footnotes

**Contributors:** All authors conceived and designed the article, drafted the manuscript, and approved the final version. JB is guarantor.

**Competing interests:** We have read and understood the BMJ policy on declaration of interests and declare the following: DF is funded by a NIH clinician scientist award; SN receives no specific funding; JB has received fees from Jenka Pharmaceuticals for consultancies and being an advisory board member.

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