Gout and its management

– the devil is in the detail

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Gout is one of the commonest forms of acute arthritis, particularly in New Zealand among Pacific and Maori, with up to 14% of Maori men and 2% of Maori women having gout. It appears suddenly, often overnight, with severe joint pain and swelling coming on over 12 to 24 hours. This can be accompanied by red and shiny skin over the affected joint. Gout usually affects one or two joints at a time, often in the feet and particularly the base of the big toe (podagra). Without treatment the attack subsides in a week or so and there may be intervals of months or sometimes years before there is a second attack. With time, these tend to get more frequent and more severe, with many joints involved, and increasing difficulty in controlling the inflammation. A state of chronic or continuous joint disease can develop with progressive joint damage, disability and crippling deformities. Gout affects mainly men, and is rare in women until the menopause, after which it is often associated with diuretic therapy.

The diagnosis of gout is usually clinical, though the isolation of urate crystals from the joint, or a tophaceous deposit, contributes to diagnostic certainty. Diagnostic criteria for gout are outlined in Table 1. Almost all patients with gout have hyperuricemia, though uric acid levels can normalise in up to 40% of patients at the time of the acute attack, having been previously raised, so that uric acid estimations between attacks are necessary to determine adequacy of control.

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Hyperuricemia is defined as a uric acid level greater than 0.42 mmol/l, which is the level at which the prevalence of gout rises. At this concentration uric acid becomes a supersaturated solution with crystallisation occurring to trigger the inflammatory response which is responsible for the intense pain, swelling and heat. However, this critical concentration is lower in cooler parts of the body, such as the extremities, so that treatment success is now defined as levels of 0.36mmol/l and below for a sustained period. This is also the level required to reduce the size of tophi, which are the reservoirs of uric acid under the skin and invading joints and bone, which have the potential to maintain hyperuricemia, and trigger further attacks of acute gout.

In 90% of patients increased uric acid levels are due to renal under excretion, with crystallisation of uric acid in the kidneys being aided by a low pH of the urine. As well as the risk of kidney stones this also leads

Table 1. American Rheumatism Association criteria for the diagnosis of gout

1. Urate crystals in either joint fluid or a tophus, and/or
2. Six of the following 12 criteria:
   - (a) Maximum inflammation within the first day
   - (b) More than one attack of acute arthritis
   - (c) Monarticular arthritis
   - (d) Redness observed over joints
   - (e) First metatarsal joint pain attack
   - (f) Unilateral metatarsal joint attack
   - (g) Unilateral tarsal joint attack
   - (h) Suspected tophus
   - (i) Hyperuricemia
   - (j) Asymmetric swelling within a joint on Xray
   - (k) Subcortical cysts with no erosions on Xray
   - (l) Negative bacterial culture of joint fluid

to the likelihood of further renal impairment, to which non-steroidal anti-inflammatory medication can be a contributory factor. This self-perpetuating cycle of increased levels of uric acid and subsequent renal impairment then makes treatment with hypouricemic agents such as allopurinol less likely to achieve normouricemia.

Conditions which are now being identified as being closely linked to hyperuricemia include obesity, hyperlipidemia, hypertension and diabetes, these being associated with the metabolic syndrome, which has been shown to be present in up to 86% of patients with gout. The insulin resistance which is a feature of the metabolic syndrome results in increased insulin levels, which in turn causes an increase in urate reabsorption and hyperuricemia, which provides one explanation for the increased incidence of gout in Maori patients with insulin resistance.

It has been known since 1994 that the baseline level of uric acid is a strong independent predictor of hypertension. With the addition to this of the effects of mild nephrosclerosis, which results from increased insulin levels, there is a compounding of vascular injury to the kidneys. A recent experiment in rats showed that hyperuricemia resulted in hypertensive changes in the kidney which was reversed by the use of allopurinol.

There is also an increasing literature that is suggesting that uric acid is a risk factor for developing cardiovascular events in its own right, not just as an associate of other features of the metabolic syndrome. This includes the onset of ischemic heart disease, cardiovascular disease, and congestive heart failure. Not only is hyperuricemia associated with the increased development of cardiovascular events, but also an increase in overall mortality from ischemic heart disease and congestive heart failure, probably related to increased xanthine oxidase activity. The relative risk for cardiovascular mortality after adjustment for other risk factors is threefold. However before advocating treatment of asymptomatic hyperuricemia, more research is required to determine the extent to which the association between cardiovascular events and hyperuricemia is independent of other risk factors, and the impact on lowering uric acid levels on these potentially fatal outcomes.

Nevertheless, the accumulation of information about the importance of hyperuricemia and gout as risk factors for renal and cardiovascular disease suggests that the earlier introduction of hypouricemic therapy for patients with gout should be strongly considered in all patients, but particularly for those with the risk factors mentioned in Table 2. However, studies in New Zealand reveal marked under-treatment of gout, with approximately half the patients with gout, including those with concomitant diabetes, not having uric acid estimations performed in the previous 12 months and, of those who did, the majority having hyperuricemia which did not result in the prescription of allopurinol, which is the preferred hypouricemic agent for the management of gout.

Guidelines for the introduction of lifelong medication to lower uric acid (Table 2) include the presence of multiple attacks of gout, usually two to three, unless there is a strong commitment to lifestyle modification including weight loss and minimal alcohol. Other environmental modifications which might be implemented include a review of diuretic therapy, recommendations for increased physical activity, and attention to other dietary factors which elevate uric acid levels, such as shellfish, offal meats, beef and pork. Tophaceous gout is an absolute indication for allopurinol, to avoid skin ulceration and infection, and irreversible damage to joints, and to reduce the risk of nephrolithiasis. The young patient, those with a family history, and a uric acid greater than 0.6 mmol/l are also indications. The presence of renal and cardiovascular disease and other features of the metabolic syndrome, such as diabetes, should be a mandatory indication, particularly in light of the evidence outlined above. Diuretic and anti-metabolic treatment also makes gout difficult to control without medication to lower uric acid levels.

In New Zealand the majority of doctors prescribe allopurinol to lower uric acid levels, though probenecid can be used if there are side effects with this drug and if the renal function is normal or only slightly impaired. It is important to wait for the acute attack to subside completely and to introduce allopurinol two to three weeks later, usually in conjunction

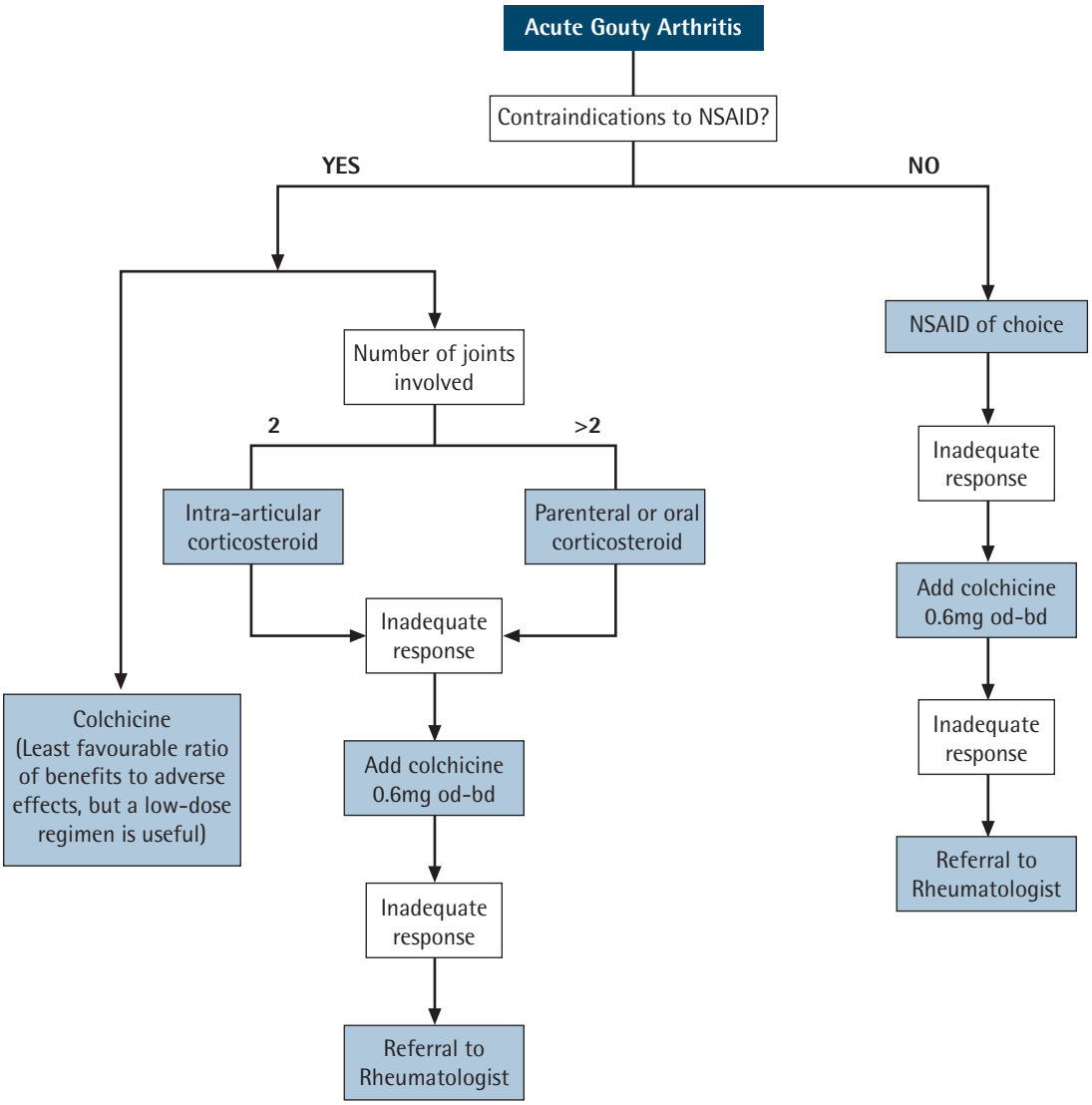
Table 2. Indications for lifelong therapy with Allopurinol

- Multiple attacks
- Tophaceous gout
- Young patient, family history, hyperuricemia >0.6mmol/l
- Concomitant renal or cardiovascular disease (including diabetes)
- Concomitant diuretic or anti-metabolic treatment

Table 3. Use of Allopurinol in chronic gout

- Wait three to four weeks after acute attack of gout before starting allopurinol, unless already stabilised on allopurinol when acute attack occurs, in which case continue allopurinol at same dose and treat acute attack with usual therapeutic options.
- When starting allopurinol, build up dose gradually e.g. by 100mg increments at weekly or fortnightly intervals.
- Monitor dose with regular uric acid estimations e.g. three monthly in the first instance.
- Adjust dose if renal impairment is present.
- Aim to reduce uric acid level to less than 0.36mmol/l.

Figure 1. Treatment algorithm for acute gouty arthritis



with colchicine to prevent the early recurrence of an acute attack (Table 3). This may be necessary for three to six months, or longer if hyperuricemia is unable to be controlled, or tophi are persistent. If an acute attack occurs when a patient has been fully cooperative with therapy, the allopurinol should be continued in the same dose, though many attacks occur just after the previously prescribed hypouricemic medication has run out and has not been renewed promptly, in which case it should not be restarted until the acute attack has been controlled. The initial dose of allopurinol should be low, around 100–150mg, and gradually increased, either from 150mg to 300mg after two weeks, if the patient has normal renal function and is at an early stage of the disease, or from 100mg to 200mg to 300mg at one to two weekly intervals for later disease, with the slower regimen particularly for patients with tophi and renal impairment. Renal impairment requires dose adjustment of allopurinol, and there are calculators which can assist with this. When there is renal impairment it may not be possible to normalise uric acid levels, so long-term colchicine may be necessary, and attention given to concomitant medication and other lifestyle factors, such as gradual and sustained weight loss. Where long-term colchicine is used, care must be taken where there is concurrent renal impairment, since there is an association with neuromuscular complications, such as myopathy and sensory loss.

Although a number of acute attacks occur spontaneously, several factors may precipitate or contribute to an attack, including stress (such as sudden unaccustomed exercise), excessive alcohol consumption, obesity, hypertension, renal disease, infections, red meats, shell fish, surgery and rapid lowering of serum uric acid by either medication or fasting. Acute attacks

may be treated successfully with cold applications for symptomatic relief and the early introduction of effective medication, such as non-steroidal anti-inflammatory drugs, corticosteroids administered orally, parenterally or intra-articularly and low dose colchicine (See Figure 1). The choice of agent depends on the number of joints involved and the patient's other conditions. The presence of significant renal impairment requires a change in approach from the usual initial treatment, which consists of NSAIDs because of their effectiveness (including effectiveness when treatment is delayed) and minimal toxicity. However, when the patients have an active gastric ulcer, are taking anticoagulants, or have hypersensitivity to salicylates, they should be avoided. In addition, they should be used with caution in people over the age of 65 years and in those with congestive heart failure, hypertension, or renal impairment.

Although care is required when the patient with gout has diabetes, prednisone is becoming an increasingly useful agent in the management of gout, especially in view of the increasing toxicity being reported for colchicine when it is used in a two hourly regimen. Colchicine has also fallen out of favour because of its slow onset of action, limited effectiveness if treatment is delayed and narrow therapeutic index. Because of unacceptable levels of toxicity with the use of the two hourly regimen the New Zealand Rheumatology Association has made the following recommendations in a Consensus statement (March 2005).

'In most patients, non steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are the treatment of choice for acute gout. When NSAIDs are contraindicated and corticosteroids are not providing an adequate response colchicine is an option, particularly if taken within the first 24 hours of the onset of pain. The use of large doses of colchicine to treat acute gout is no longer appropriate, especially in older patients, because of the serious adverse effects arising from large doses. The recommended dose for colchicine in the treatment of acute gout is 1.2mg stat, followed by 0.6mg six hourly, up to a maximum dose of 2.4mg per 24 hours. Corticosteroids can be used in combination with NSAIDs or colchicine to provide further relief. Colchicine can also be used prophylactically in the treatment of gout with a dose ranging from 0.6mg every other day to 0.6mg twice daily, just short of that which will induce diarrhoea or soft stool in the patient.'

The use of prophylactic colchicine is particularly useful where normal uric acid is not achieved, either because of renal impairment, hypersensitivity to hypouricemic agents, or lack of ready availability to alternative agents used overseas, such as benzbromarone.

In this article it is hoped that the importance of appropriate treatment of gout and its associated hyperuricemia is recognised not only for the comfort and joint preservation of the patient with gout but also for the morbidity and mortality which can arise as a consequence of the renal and cardiovascular disease which accompanies this. It would be encouraging if funding agencies and decision makers involved in the development of health strategies could provide more attention to this important problem in the future than has been apparent in the past. Medical practitioners and their nursing colleagues also have a critical role in monitoring uric acid levels and instituting appropriate therapy, not only for gout, but for associated features of the metabolic syndrome, including hypertension, diabetes and hyperlipidemia.

Key Points

- Hyperuricemia and gout are associated with an increased incidence of morbidity and mortality from cardiovascular disease.
- Gout is under-treated in New Zealand, with avoidable morbidity as a result.
- Allopurinol treatment is bedevilled by being used too soon after an acute attack, in too high a dose, and without prophylactic treatment.
- The use of the two hourly regimen of colchicine for the treatment of acute gout is toxic, outdated, and should not be used.

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Screening for osteoporosis

'Bone-mineral-density measurements should be obtained routinely in all women over the age of 65 years and in men and younger women who have had a fragility fracture. Compliance with this recommendation alone would be a great advance in comparison with current practice. All patients should be asked about risk factors and secondary causes of osteoporosis and should be advised about the recommended intake of calcium and vitamin D (1200 mg and 400 to 800 IU daily, respectively, for postmenopausal women), weight-bearing physical activity, and the dangers of smoking. The decision to measure bone mineral density in postmenopausal women under the age of 65 should be made on the basis of the presence of risk factors that increase the likelihood of detecting osteoporosis or osteopenia.'

Raisz LG. NEJM 2005; 353: 164-171.