REVIEW

Diagnosis and management of gout: a rational approach

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Gout is one of the best understood among the rheumatological disorders and one of the most satisfying to treat. Even non-specialists should be able to diagnose and treat most patients provided some important principles are appreciated. Management of a minority of patients, including those with renal impairment is difficult and often unsatisfactory, because of restricted treatment options. In this paper, the basic principles underlying the diagnosis and management of gout are discussed first, followed by practical approaches.

Gout is derived from *gutta* (Latin for drop), as it was believed in the 13th century that poison falling in drops into the affected joint caused gout. We now know that gout results from inflammatory responses to deposition of microcrystals of monosodium urate (MSU) derived from body fluids saturated with urate. There are three pre-requisites for development of gout[1]:

(1) Development of hyperuricaemia leading to urate saturation
(2) Formation of MSU crystals and
(3) Interactions between MSU crystals and leucocytes.

Recurrent episodes of acute gouty arthritis occur in patients who progress through these steps. Some patients with recurrent acute gout, especially those with uncontrolled hyperuricaemia, develop chronic tophaceous gout characterised by tophi (macroscopic aggregates of MSU) in soft tissues.

DEVELOPMENT OF HYPERURICAEMIA

Hyperuricaemia is based upon the solubility limit of urate in serum. A concentration of >416 μmol/l (in both sexes) is taken to denote hyperuricaemia, the concentration above which urate saturation occurs. Risk of gout increases progressively beyond this value, and a serum concentration of >535 μmol/l corresponds to an annual incidence of about 5%.[2] Serum urate concentrations rise sharply at the time of puberty in men, and after the menopause in women. About 95% of pre-menopausal women have serum urate concentrations of <357 μmol/l, well below the solubility limit, as oestrogens increase urate clearance.[3] Thus, gout is uncommon in pre-menopausal women, and its prevalence is higher at all ages in men.[4]

Hyperuricaemia results from insufficient renal excretion or urate overproduction from purines, or both. Most patients with hyperuricaemia have primary impairment of renal urate clearance,[5] possibly mediated through genetic predisposition.[6–8] However, renal underexcretion in itself is not sufficient to cause gout, and other factors are required including rich food, excess alcohol consumption, obesity, and insulin resistance[9] (insulin increases renal tubular reabsorption of urate[10]). For centuries, gout was a disease of the upper social class (''Gout *n* – A physician's name for the rheumatism of a rich patient'' in *Devil's Dictionary*, 1911) but this trend seems to have reversed,[11] possibly because of widespread availability of cheap fast foods, increased alcohol consumption, and decline in physical activity. This would also explain the results of recent surveys in USA and UK that have found an overall prevalence of gout of about 1% of the total population—more than three times higher than previous estimates.[4 12]

Secondary causes of hyperuricaemia include chronic renal failure and ingestion of drugs that compete with urate for renal excretion including loop or thiazide diuretics,[13] low dose aspirin,[14] or cyclosporin.[15] Myeloproliferative and lymphoproliferative disorders lead to hyperuricaemia through increased cell turnover. Certain rare enzyme defects[16] (hypoxanthine guanine phosphoribosyl transferase deficiency, phosphoribosyl pyrophosphate synthetase overactivity, glucose-6-phosphatase deficiency, and fructose-1-phosphate aldolase deficiency) can result in persistent hyperuricaemia and should be suspected in patients with early onset gout (before the age of 30).

Hyperuricaemia is often associated with cardiovascular disease and with the metabolic syndrome (hypertension, diabetes mellitus, hypertriglyceridaemia, and obesity)[17–28] probably mediated by insulin resistance,[9] and increased serum leptin concentration.[29] It is still uncertain whether hyperuricaemia is an independent risk factor for cardiovascular disease but a diagnosis of hyperuricaemia or gout should prompt a search for cardiovascular risk factors.[17 18]

FORMATION OF MSU CRYSTALS

Formation of MSU crystals from body fluids that are saturated with urate is favoured by a combination of various factors such as increased urate concentrations, reduced local temperature, acidosis, and imbalance between promoters and inhibitors of urate crystal formation.[30] Most patients with persistent hyperuricaemia remain asymptomatic as the risk of gout depends on the person's propensity for forming crystals. Crystallisation is slow and requires many years. This may explain why the peak incidence of gout occurs in men after the age of 35 years, and in

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women after the age of 65 years, several years after the time when urate surges occur. Additionally, increasing degenerative changes may make aging joints vulnerable, with cartilage fragments acting as seeds for crystal formation.[31] Thus gout most commonly affects the first MTP joint as degenerative changes are most common in this joint[32] and crystallisation is possibly encouraged by low temperature in the foot.[33]

INTERACTIONS BETWEEN MSU CRYSTALS AND LEUCOCYTES

Because microtophi have been found in synovial biopsy in acute gout,[34] it was thought that intermittently released MSU crystals initiated acute episodes[35] but MSU crystals are present in asymptomatic and previously affected joints of patients not receiving hypouricaemic therapy.[36 37] Higher percentages of polymorphonuclear leucocytes are present in synovial fluids with crystals, suggesting that chronic low grade inflammation is maintained in joints with MSU crystals.[38] Acute episodes are then superimposed upon this background inflammation. Initiating mechanisms are elusive. It is believed that shedding of their apolipoprotein coat enables urate crystals to be phagocytosed by macrophages, mast cells, and fibroblasts. This is followed by release of inflammatory mediators such as IL1 and TNFα and influx of neutrophils. Phagocytosis of urate crystals by neutrophils then elicits lysosomal fusion, rupture of phagolysosomes, and further release of inflammatory mediators. The mechanisms behind resolution of an acute episode are also obscure, and may be caused by binding of apolipoprotein to urate crystals, neutrophil apoptosis, and phagocytosis of urate crystals by well differentiated macrophages leading to downregulation of joint inflammation.[39]

CLINICAL DIAGNOSIS OF GOUT

Acute gout

Most patients know when an acute episode is imminent, describing itching (possibly caused by prodromal mast cell degranulation and release of histamine[40]). Acute episodes often begin at night—hence the suggestion ''suspect gout when acute arthritis begins between 2 and 7 a.m.''[41] The episode builds to a peak over several hours with intense pain and increased sensitivity of overlying skin such that even pressure of bed covers cannot be tolerated (''Screw up the vice as tightly as possible- you have rheumatism; give it another turn, and that is gout!''). The reason for extreme pain in acute gout is unknown. Gout affects the first MTP joint in >70% of cases but other joints such as tarsal joints, ankles, knees, and wrists can also be affected. Central joints such as hips, shoulders, and spine are seldom affected, possibly because higher temperatures in these joints are not conducive to crystallisation. It is unclear why only one or two joints are affected at a time, but occasionally episodes can be polyarticular especially later in the course of the disease. Fever is common and more likely with polyarticular episodes (in about 50%).[42] Gout can also cause bursitis and tenosynovitis. Resolution is usual within a week even without treatment. As acute gout tends to be recurrent, a history of previous self limiting episodes is a helpful (or deceptive) pointer. A positive family history can be obtained from some patients.

Infection, trauma, surgery, crash dieting, total parenteral nutrition, and the start of hypouricaemic therapy may all precipitate an acute episode.[39 43 44] Possible reasons include lactic acidosis (with infection), ketoacidosis (with fasting), increased tissue breakdown (with trauma or surgery), intra-articular flaking of urate crystals (with trauma), or sudden lowering of urate levels by hypouricaemic therapy[39] to below saturation levels around microcrystalline deposits, which allows more crystals to be released from the edges of the deposit.

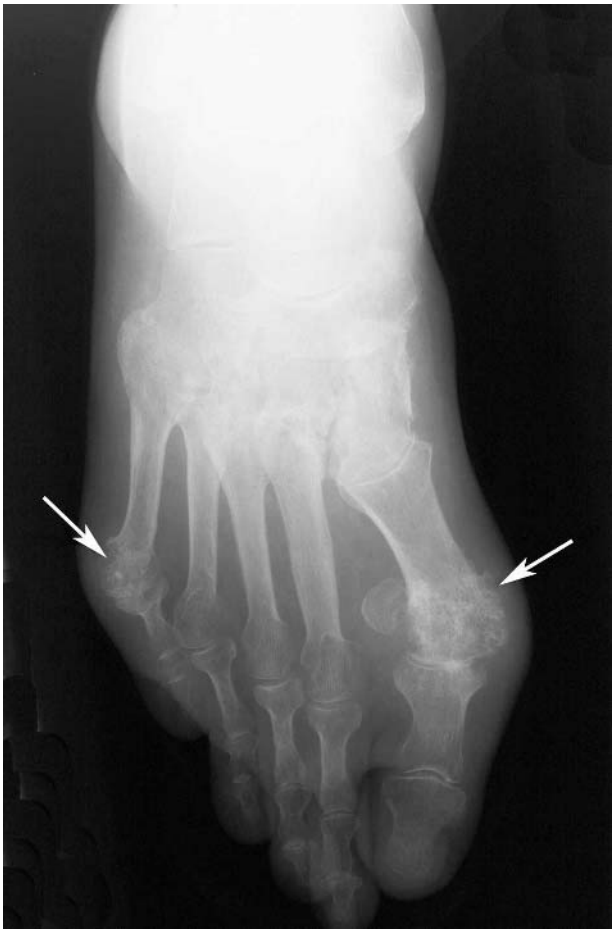

Figure 1 Plain radiograph of foot from a patient with chronic tophaceous gout showing asymmetrical soft tissue swellings consistent with tophi, and punched out ''erosive'' changes around the first and fifth metatarsophalangeal joints (arrows) that are situated away from the joint margin.

Physical findings

Physical findings in the affected joint are those of acute inflammation (redness, swelling, heat, tenderness, and global loss of movement).

Differential diagnosis

Septic arthritis is the important differential diagnosis, as the consequences of not treating it can be disastrous. The clinical features of acute gout and septic arthritis are often indistinguishable (especially when joints other than first MTP joint are affected) and sometimes coexist.[45] If in doubt, the patient should be treated for septic arthritis pending investigations. Other conditions that can cause acute onset arthritis include reactive arthritis, pseudogout (characterised by elderly onset, predilection for knees or wrists, radiological chondrocalcinosis, and synovial fluid pyrophosphate crystals) and rheumatoid arthritis (with polyarticular presentation).

Chronic tophaceous gout

The symptom free interval between acute episodes may last a few days to several years. In some patients, asymptomatic periods progressively shorten and, about 10 years from the first episode, the chronic tophaceous phase develops (*topus*, Latin for porous friable stone). Chronic tophaceous gout refers to clinically apparent tophi and inapparent tophi

probably form several years earlier.[46] Tophi are occasionally detected before the first episode, especially in elderly women with risk factors such as renal impairment and diuretic therapy.[47] Tophi usually form within joints previously affected by acute gout, over Heberden's nodes (encouraged by degenerative changes and low temperatures), in comparatively avascular areas such as the pinnae or over pressure points such as the olecranon. The rarity of tophus formation over other cooler areas such as the nose is unexplained.

The clinical effects of a tophus depend on where they form. Those that form in the pinnae and over Heberden's nodes do not result in an inflammatory response (as pinnae are comparatively avascular and DIP joints are not subjected to the same stresses as first MTP joints). Tophi that form adjacent to bones can result in destructive osseous lesions and ''erosions''. Chronic tophaceous gout has become a rarity since the availability of effective long term prophylactic therapy.

HELPFUL (AND UNHELPFUL) INVESTIGATIONS

The aim of investigations is to confirm or suggest gout, exclude alternative diagnoses (particularly septic arthritis), guide long term treatment, or identify associated conditions.

To confirm or suggest diagnosis of gout

Joint aspiration with synovial fluid analysis should be considered if septic arthritis is a possibility or if a diagnosis of gout has not been confirmed before. If aspiration is thought necessary but is unsuccessful, ultrasound guided aspiration should be considered. Urate crystals are needle shaped and are negatively birefringent on polarising microscopy. The presence of crystals does not prove that gout is acute.[37] In patients with tophi, detection of MSU crystals in the toothpaste-like material aspirated from the lump is diagnostic for gout.

Serum urate concentrations are often (49% in one series) normal during acute gout[48] and many patients with hyperuricaemia never develop acute gout. Thus, a raised serum urate concentration favours gout, but is not diagnostic. Plain radiographs are unhelpful in patients with acute gout and might show only soft tissue swelling. In patients with recurrent episodes, there is likely to be evidence of osseous destruction or erosive changes in the joint (fig 1).

To exclude alternative diagnoses

MSU crystals in synovial fluid do not exclude coincidental septic arthritis[45] and synovial fluid leucocyte counts (predominantly polymorphs) are raised in both gout and septic arthritis. Worse, peripheral blood leucocytosis, neutrophilia, raised erythrocyte sedimentation rate (ESR), and C reactive protein (CRP) are encountered in both and there is no absolute differentiating cut off level.[49] Synovial fluid and blood cultures are mandatory in patients with suspected septic arthritis, as synovial fluid Gram stain would reveal an organism in only 60% of patients with septic arthritis.[50] If septic arthritis is suspected, the patient should be treated with antibiotics until negative cultures are reported.

Plain radiographs are helpful to differentiate chronic tophaceous gout from rheumatoid arthritis. Erosions in gout are characteristically punched out with overhanging sclerotic margins and are situated away from joint margins, sometimes outside the joint capsule (fig 1). Rheumatoid arthritis causes marginal erosions, always within the limits of the joint capsule. The absence of periarticular osteopenia and preservation of joint space in gout also help to differentiate the two conditions.

To guide long term treatment

Serum urate concentrations can help to monitor long term prophylactic therapy.

Box 1 Key learning points in diagnosis of gout

- Diagnosis of hyperuricaemia or gout should prompt a search for cardiovascular risk factors.
- Diuretic therapy and alcoholism are important risk factors for development of gout.
- The clinical and laboratory features of acute gout and septic arthritis are often indistinguishable.
- The sine qua non for diagnosis of gout is demonstration of urate crystals in synovial fluid, but this would not exclude septic arthritis.
- Serum urate concentrations and plain radiographs are unhelpful in making a diagnosis of acute gout.

To identify associated conditions

If there is renal impairment, gout is more likely and renal impairment complicates management. Finally, it is worth screening the patient for cardiovascular risk factors (fasting lipids and glucose).

MANAGEMENT OF ACUTE GOUT

Acute gout is a self limiting condition typically lasting 7 to 10 days, but treatment ensures pain relief and speeds recovery. Drugs that treat an acute episode of gout act at step 3 (see above) to suppress acute inflammation. The sooner drug treatment is started, the quicker the response. As gout is likely to recur (see below), giving patients a supply of NSAID or colchicine to start at the onset of the next episode may be appropriate.

Therapeutic options are:

- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Colchicine
- Intra-articular corticosteroids
- Systemic corticosteroids (oral or intramuscular)

The drug of choice in most patients would be a NSAID provided there were no contraindications (renal impairment, active peptic ulcer disease, congestive cardiac failure, known hypersensitivity, or anticoagulant therapy). There are no important differences in efficacy between different NSAIDs.[51–53] Although selective COX II and non-selective agents are equally efficacious,[54 55] COX II selective agents are best avoided in patients with established ischaemic heart disease or cerebrovascular disease in view of recent concerns over cardiovascular safety.[56] For all other patients, the choice of NSAID (COX II selective or non-selective) depends on an individual assessment of cardiovascular and gastrointestinal risk factors. The NSAID is usually continued for at least five to seven days[57] (the duration for which patients are likely to have pain if they receive no treatment[58]) or longer if pain takes longer to resolve. To reduce gastrointestinal toxicity, the dose of NSAID should be gradually tapered as soon as improvement occurs. Parenteral preparations or suppositories are available for patients who cannot swallow tablets.

The drug of second choice is colchicine, ''old fashioned but effective''.[59] It works by inhibiting urate crystal phagocytosis by neutrophils.[60] Colchicine is most effective when started shortly after the onset of acute episodes, before phagocytosis establishes itself.[61] Colchicine is not the drug of first choice because of its narrow therapeutic index. Most patients develop diarrhoea, which often occurs before symptomatic relief is achieved (''patients on colchicine have to run before they can walk!''). The *British National Formulary* recommends a dose of 1 mg initially followed by 500 μg every two to three

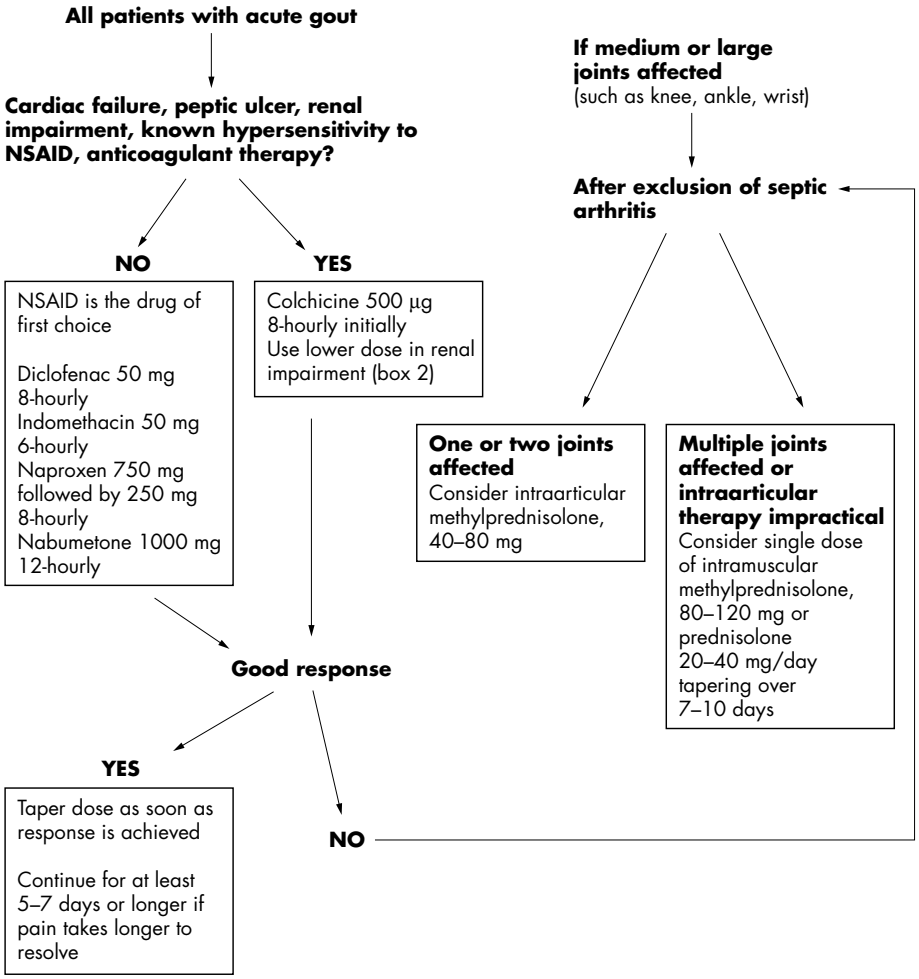

Figure 2 Flow chart for the treatment of acute gout.

hours until pain relief is obtained or vomiting or diarrhoea occurs, but a dose of 500 μg given three times a day is effective.[62] The dose should be gradually tapered when improvement occurs (to reduce diarrhoea), and then stopped after pain completely resolves. Colchicine should be used in lower doses in patients with renal impairment (box 2).

In gout affecting medium or large sized joints and in the certain absence of septic arthritis, intra-articular corticosteroids[63] are useful, especially if patients cannot take NSAIDs or colchicine. Methylprednisolone is the preparation most commonly used. The dose is typically 80 mg for large joints (knees or ankles) and 40 mg for medium joints (wrists or elbows). Pain relief can be expected within 24–48 hours.

In patients with polyarticular gout in whom other treatments are difficult, systemic corticosteroids are an option.[64] Corticotrophin (ACTH) is effective in acute gout,[65] but offers no special advantage over corticosteroids. Intramuscular corticosteroids are as effective as ACTH and NSAIDs.[65 66] A single dose of 80–120 mg of methylprednisolone is effective. Oral prednisolone (20–40 mg/day initially with gradual taper over a week to 10 days to prevent rebound flare) is also effective.[64] Even short courses of systemic corticosteroids may affect blood pressure or glucose control, but such large doses are required because gout episodes are

Table 1 Reduction in allopurinol dose related to creatinine clearance concentrations

Creatinine clearance (ml/min)	Dose
⩾100	300 mg/day
60	200 mg/day
40	150 mg/day
20	100 mg/day
10	100 mg on alternate days
<10	100 mg thrice weekly

Box 2 Dose reduction in patients with renal impairment

Treatment of an acute episode

- Colchicine should be used in a lower dose of 500 μg once or twice daily in patients with creatinine clearance between 10–20 ml/min or serum creatinine between 300–700 mmol/l. Avoid if creatinine clearance <10 ml/min or serum creatinine >700 mmol/l.
- NSAIDs should be avoided

Prophylaxis against recurrent episodes

- Dose of allopurinol should be reduced (see table 1).[78]
- Probeneceid and sulphinpyrazone might be ineffective in patients with creatinine clearance <50 ml/min, while benzbromarone might be ineffective if creatinine clearance <25 ml/min.

known to occur in renal transplant patients receiving 7.5 mg of prednisolone/day.[67]

Figure 2 summarises the management of acute gout.

PROPHYLAXIS AGAINST RECURRENT EPISODES

Acute gout is likely to recur sooner or later (see below) and prophylaxis may be indicated.

General measures

Patient education

The main reason for treatment failure is poor compliance, and patient education improves compliance. Patient education leaflets are produced by the UK Gout Society (http://www.ukgoutsociety.org) and by the Arthritis Research Campaign (http://www.arc.org.uk). For the enthusiastic patient, *Gout—the at your fingertips guide* (a short book by Rodney Grahame *et al*) offers a wealth of information.

Patients should understand differences between short term symptomatic treatment and long term prophylactic therapy. Wortmann suggested a simple analogy that is useful for patients and medical students (see box 3).[68]

Diet, drinking, and diuretics (correctable risk factors)

In a large prospective study, an increased risk of gout was found with increased meat consumption (particularly beef, pork, or lamb) or seafood but not with consumption of purine rich vegetables or protein. A low incidence of gout was found in those with a high consumption of low fat dairy products.[69] A rigid purine free diet is however unpalatable, impractical, and can rarely be sustained.[9] Serum urate concentrations and frequency of episodes can be reduced by weight reduction through calorie restriction, decreased intake of carbohydrates, and increased proportional intake of protein and unsaturated fat.[70] Such a diet would also decrease plasma glucose, insulin, and triglyceride concentrations and improve insulin sensitivity, thereby reducing cardiovascular morbidity and mortality. Crash dieting and fasting should be avoided as they can precipitate acute episodes.

An association between alcohol and gout was also prospectively confirmed in the same cohort.[71] Excess consumption of any alcoholic beverage should be discouraged, as increasing alcohol intake is associated with increasing risk of gout. Beer conferred a larger risk than spirits, and moderate wine drinking did not increase the risk of gout.

Alternatives to diuretic therapy should be considered, if feasible.

Pharmacological prophylaxis

Sixty two per cent of patients experience a second episode within one year, 78% within two years, while 7% have no further episodes for 10 years or more even without antihyperuricaemic drugs.[72] Hence, prophylactic treatment is reasonable only for patients with frequent episodes, chronic tophaceous gout, radiological erosions, or urate calculi. Prophylaxis with hypouricaemic drugs is also appropriate for asymptomatic patients with urinary urate excretion of >1100 mg/24 hours (there is a 50% chance of developing renal calculi)[73] or those with persistently raised serum urate (>773 μmol/l in men and 595 μmol/l in women) as there is a risk of urate nephropathy.

Box 3 Simple analogy to teach patients and medical students[68]

"Gout is caused by the body's response to uric acid crystals and uric acid crystals are like matches. Over time these matches accumulate in and around the joints, and when they catch on fire, one gets a gout attack. The NSAID (or colchicine) will put out the fire, and it will do so more effectively if taken right away. If one does not take the medication right away, the fire will continue to burn igniting more and more matches causing a more severe attack, one that will require much more medication to control. After the fire is put out, the matches are still there and can light again. Further measures must be taken to eliminate them from the body so that they will no longer get acute attacks".

Drugs that are used to prevent recurrent episodes act at step 1 (see above), aiming to reduce serum urate to below the solubility limit. The lower the serum urate concentrations, the less the likelihood of recurrent episodes.[74] Maintaining serum urate below 360 μmol/l is necessary to prevent recurrence and assist resolution of tophi. Prophylaxis is a long term commitment and patients who have had just one or two acute episodes are unlikely to be complaint.[75] Recurrences are probable if treatment is intermittent[76] or if withdrawn after apparent good control.[77]

More than 90% of patients with gout underexcrete and less than 10% overproduce urate.[5] Two types of drugs are used in practice: xanthine oxidase inhibitors (allopurinol) reduce uric acid production through competitive inhibition of xanthine oxidase, which converts xanthine and hypoxanthine to uric acid. Uricosurics (probenecid, sulphinpyrazone, and benzbromarone) increase urinary uric acid excretion by inhibiting tubular urate reabsorption. Allopurinol, rather than a uricosuric, is almost always used initially because it reduces urate concentrations in all patients, can be conveniently given once daily, is comparatively safe unless the dose is exceeded in renal impairment,[78] is appropriate in patients with renal impairment, and is not contraindicated in patients with urate calculi.

Acute episodes are more likely during the months after the start of hypouricaemic therapy. Thus:

- Prophylactic treatment should not be started for at least three to four weeks after an acute episode to avoid prolonging the acute episode.
- Allopurinol or uricosuric drugs should be started in low doses and increased over several weeks, aiming to lower urate concentrations slowly to minimise risk of acute episodes. There is also a risk of crystallisation of urate in the urinary tract with uricosuric drugs.
- Either colchicine in a dose of 500 μg twice daily or a low dose NSAID should be prescribed at the same time as prophylaxis and continued for at least a month after serum urate concentrations have been normalised (usually for three months, or until resolution of tophi). Colchicine is usually favoured,[79] but there is a possibility of myopathy with long term use[80] (especially in patients with renal impairment). If patients develop an acute episode, the dose of allopurinol should remain unchanged and the acute episode should be treated in the usual way.

Allopurinol is usually started in a single daily dose of 100 mg and gradually increased every three to four weeks until serum urate concentrations are normalised. Most patients require 200–300 mg/day, although some may need up to 600–900 mg/day. Compliance should always be checked before increasing doses. About 2% of patients develop hypersensitivity reactions, which in most cases are mild[81] with erythematous rashes and pruritus. Occasionally, hypersensitivity reactions are severe with fever, toxic epidermal necrolysis, hepatitis, and renal failure. Mortality can be up to 20%.[78] Severe reactions are more likely to occur in patients with renal impairment in whom the dose of allopurinol had not been appropriately reduced (table 1) or in those receiving

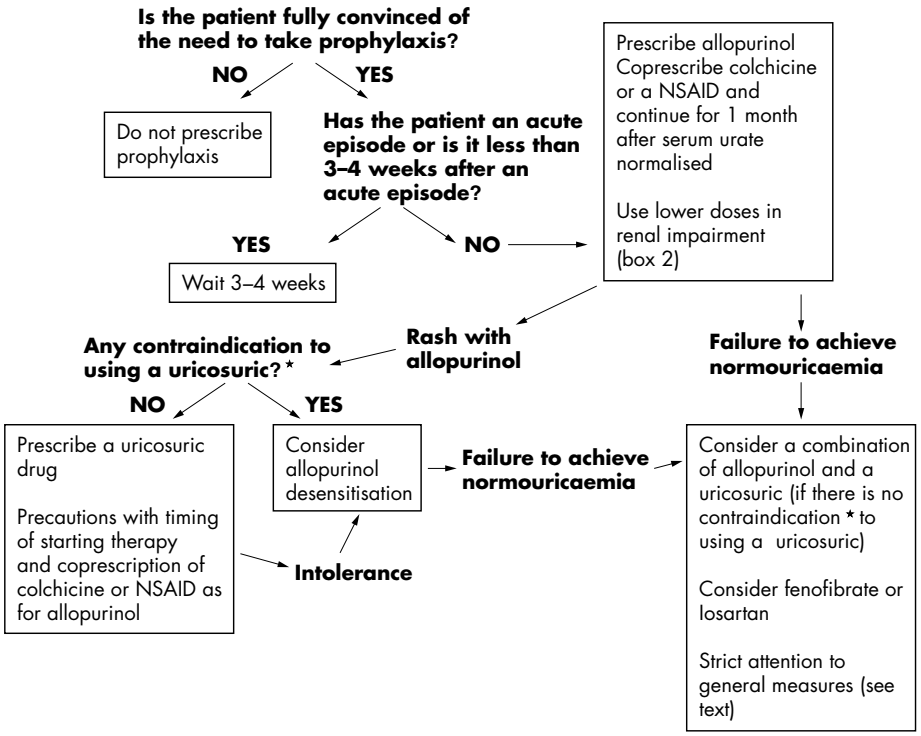

Figure 3 Pharmacological prophylaxis in patients with recurrent gout, clinical tophi, or radiological erosiosns. * Contraindications to uricosuric drugs include: known urate calculi, renal impairment (creatinine clearance <50 ml/min), 24 hour urinary urate > 800 mg, or previous intolerance.

thiazide diuretics.[82] If azathioprine and allopurinol are used together (for example, after renal transplantation), azathioprine doses should be reduced by 75% as both drugs are metabolised by xanthine oxidase.[83]

If uricosuric drugs are contraindicated and the reaction was mild, then it is possible to desensitise the patient by giving an initial oral dose of 25–50 µg of allopurinol, progressively increasing every third to seventh day to reach a dose sufficient to normalise serum urate.[84] Twenty five of 32 patients (78%) who underwent desensitisation continued to take allopurinol after a mean of about 33 months in one study.[85]

For patients who are unable to tolerate allopurinol, a uricosuric drug should be tried after obtaining a 24 hour urine collection to ensure that urate excretion is already not in excess.[86] Uricosuric drugs are risky if urinary urate excretion is already >800 mg/24 hours while on a normal diet, and contraindicated in those with urate calculi. Uricosurics are ineffective in renal impairment (creatinine clearance below 50 ml/min) but benzbromarone can be tried in patients with a creatinine clearance as low as 25 ml/min.[87] Probenecid (not available in UK) is used in a dose of 500 mg/day gradually increased to 2 g/day, while sulphinpyrazone is used in a dose of 100 mg/day gradually increased to 600 mg/day and benzbromarone (not licensed in UK) in a dose of 100–200 mg/day. All three uricosuric drugs can cause gastrointestinal upset and allergic rashes. Benzbromarone can rarely cause fulminant hepatic failure.[88] It is important to ensure adequate urine output to reduce risks of urate stone formation. Giving sodium bicarbonate in a dose of one gram three to four times daily minimises crystallisation, which is likely in acid urine.[57]

If allopurinol and uricosuric drugs separately fail to control hyperuricaemia and reduce further episodes, then a combination should be tried.[89] There is limited evidence for agents such as fenofibrate[90 91] and losartan,[90] which could be tried in patients with hyperlipidaemia and hypertension respectively. Both fenofibrate and losartan reduce serum urate concentrations by increasing renal urate clearance. The only option in some resistant patients might be to treat each acute episode and pay strict attention to general measures.

Figure 3 summarises the pharmacological prophylaxis of gout.

Box 4 Key learning points in the management of gout

- The sooner drug started is started in acute gout, the quicker and better the response.
- The main reason for failure of prophylactic treatment is poor patient compliance.
- Prophylactic treatment should never be started during or soon after an acute episode of gout.
- Either colchicine or a non-steroidal anti-inflammatory drug should be coprescribed during the initial months after the start of prophylactic treatment, as acute episodes are more likely.
- The dose of allopurinol should remain unchanged during an acute episode of gout.
- Allopurinol hypersensitivity is more likely in patients with renal impairment in whom the dose of allopurinol has not been appropriately reduced.

CONCLUSION

Most patients with gout can be satisfactorily treated. Patients with renal impairment, renal transplant patients receiving cyclosporine, and allopurinol hypersensitive patients pose therapeutic challenges because of restricted treatment options. Fortunately, the development of new xanthine oxidase inhibitors such as febuxostat[92] and Y-700,[93] and of uricase[94] is likely to result in an expansion of the therapeutic armamentarium in the near future. Both febuxostat and

Y-700 are more potent than allopurinol, and may be safe in patients with renal failure. Uricase catalyses the conversion of urate to more soluble allantoin, but it is highly antigenic. PEGylation of uricase (formulation of uricase with poly ethylene glycol) reduces antigenicity and prolongs half life. Febuxostat and PEGyltaed uricase are currently undergoing phase 3 trials. Recent advances in understanding of the molecular mechanisms of renal urate handling should in addition pave the way for development of better uricosuric drugs.[95] Finally, whether or not hyperuricaemia is an independent risk factor for cardiovascular disease remains controversial. Should data supporting treatment of hyperuricaemia to prevent cardiovascular disease become available in future, it will significantly change the way we treat gout.

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