

Topical Reviews

An overview of current research and practice in rheumatic disease



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AN UPDATE ON GOUT

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- **Gout and pseudogout are commonly occurring clinical problems, predominantly dealt with in primary care**
- **An accurate diagnosis of gout should be made prior to committing the patient to lifelong urate-lowering treatments**
- **Asymptomatic hyperuricaemia may be a marker for cardiovascular disease and other conditions**
- **When a patient presents with a recurrent attack of crystal arthritis, the possibility of septic arthritis or pseudogout must always be borne in mind – these conditions may co-exist**
- **Renal disease accompanying hyperuricaemia is most often related to inadequately treated hypertension**

INTRODUCTION

In 1848, Sir Alfred Garrod linked gout with hyperuricaemia. Articular crystal deposition and its association with arthritis was established by McCarty and Hollander in 1961 when they identified monosodium urate (MSU) crystals in the synovial fluid (SF) of patients with acute gout.¹ This was followed by the identification of calcium pyrophosphate crystals in association with acute calcium pyrophosphate dihydrate crystal deposition disease (pseudogout) in 1962.²

Gout and pseudogout are common forms of arthritis, seen in both primary and secondary care. A study of the management of gout in England revealed that only 9% of patients diagnosed with gout were referred to a rheumatology department and that investigation and treatment varied enormously in primary care.³ Furthermore, a retrospective review of 67 hospitalised adults showed that 25% of patients with crystal arthritis treated by generalists were misdiagnosed or mismanaged, resulting in an overall increase in morbidity and a 4-day delay in appropriate in-patient care.⁴

DEFINITION

Gout is a disorder manifest by MSU crystal deposition in articular tissues. Hyperuricaemia predisposes to gout. Hyperuricaemia is defined as a serum uric acid level of more than 0.42 mmol/l (>7.0 mg/dl) in men or more than 0.36 mmol/l (>6.0 mg/dl) in women. Gout is a heterogeneous disorder that can progress through four clinical phases if untreated: asymptomatic hyperuricaemia, acute gout, intercritical gout, and chronic tophaceous gout.

'Screw up the vice as tightly as possible – you have rheumatism; give it another turn, and that is gout.'

Anonymous

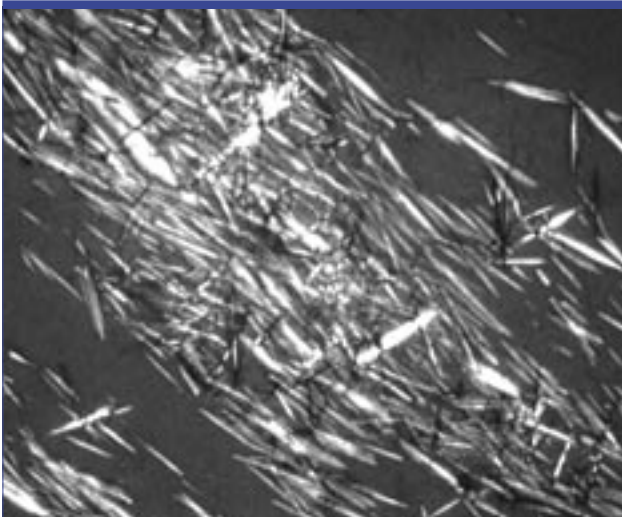


FIGURE 1. Monosodium urate crystals.

BIOCHEMISTRY

Purines are derived from two sources, diet and *de novo* synthesis. Uric acid is the end product of purine biosynthesis. Its biochemical role in man remains unknown.

MSU forms crystals in tissue and joint fluid that are needle- or rod-shaped (Figure 1). Both uric acid and MSU crystals are negatively birefringent under compensated polarised light microscopy. This permits identification from SF or tissue deposits and therefore is an important diagnostic aid.⁵

EPIDEMIOLOGY

Gout is the most common cause of inflammatory arthritis in men aged >40 years. It is a rare finding in children and premenopausal women. The peak age of onset in men is 40–50 years; in women it is later, partly due to the uricosuric effects of oestrogens. In older age groups it may be precipitated by commencement of diuretic therapy.

Incidence and prevalence

The cumulative incidence of gout in a population of Caucasian US men was 8.6% over a 29-year period; that of gout without history of diuretic use was 5.9%.⁶ In the UK, the Royal College of General Practitioners (RCGP) National Morbidity Survey of 1981/2 reported that a mean of 2.7/1000 patients visited their GP with an episode of gout; first-time episodes had an incidence of 1.4/1000.⁷

In the National Health Interview Survey (NHIS) of 1996, the overall prevalence of reported gout was 4.6% in men and 2% in women.

There is evidence from the Rochester Epidemiology Project to suggest the incidence of gout is rising.⁸ In

1977/8 the annual incidence of gout was 45/100,000, representing 39 new cases. For the interval 1995/6, 81 new cases were diagnosed with an increased incidence of 62.3/100,000. The male to female ratio remained the same at 3.3:1 but, compared to the 1977/8 cohort, gout was diagnosed at a younger age in the 1995/6 cohort. Also, there was a greater than 2-fold increase in primary gout (no diuretic exposure) over the two time periods, although diuretic-induced gout did not increase over time. These findings are echoed by a survey in England which found a 3-fold increase in gout prevalence from the 1970s to 1993,⁹ and also by a New Zealand survey which demonstrated an increase in both gout and hyperuricaemia in Maoris and Europeans, particularly men, from 1978 to the 1990s.¹⁰

The increased rate may have occurred for several reasons – increasing longevity, changes in diet and lifestyle, increased use of low-dose aspirin, or increasing physician awareness. There is also a higher prevalence among younger patients and those who have had renal transplants (2–12%).¹¹

Geography

Environmental and genetic differences may influence the well-documented different prevalence of gout in varying geographic regions. Due to varying study design and outcome measures, comparability between studies is limited. Both level of hyperuricaemia and gouty attacks are often investigated. In New Zealand, both hyperuricaemia and gout are significantly more prevalent in Maori than in Europeans.¹⁰ Tokelauan migrants to New Zealand also had a greater prevalence of gout than non-migrants.¹² Areas of Taiwan report a high prevalence of hyperuricaemia and gout, with onset at a younger age,^{13,14} as does a study from Kinmen, an island located close to Southern China.¹⁵ Low rates of gout are found in Australian Aborigines and in rural Western Maharashtra, India.

Risk factors

Hyperuricaemia is the major risk factor for gout, although most subjects with hyperuricaemia will not develop gout and acute attacks of gout can occur when serum urate levels are in the normal range. It is thought that to develop the disease two things are required: first, a high enough uric acid level to allow MSU crystal formation, and second, a relative lack of inhibition of crystal formation in the connective tissues. Renal underexcretion of uric acid is the main mechanism for the development of primary hyperuricaemia. Patients with gout have been shown to excrete less urate than normal people for any given plasma urate concentration, mainly due to decreased proximal tubule secretion,¹⁶ so it would seem they have ‘built-

TABLE 1. Risk factors for gout.

- Ageing
- Male sex
- Hyperuricaemia
- Family history
- Genetic predisposition
- Hypertension
- Central obesity
- Alcohol consumption
- Renal insufficiency
- Trauma

in' renal handling anomalies. The Normative Aging Study¹⁷ demonstrated that subjects with urate levels <7.0 mg/dl had a 0.1% annual incidence of gout but subjects with urate levels ≥9.0 mg/dl had a 4.9% annual incidence. A screening programme in Kinmen identified a cohort of men with asymptomatic hyperuricaemia;¹⁸ over 5 years, the cumulative incidence of gout for that group was 19%, and the only predictor for developing gout was baseline urate level.

Hypertension also increases the risk of developing gout,⁶ with a relative risk of 2.7. This is partially explained by hypertension-induced renal insufficiency, which can reduce urate clearance.

In addition to those already mentioned, there are many other risk factors for gout (Table 1).

CLINICAL PRESENTATION

Asymptomatic hyperuricaemia

Hyperuricaemia can be due to underexcretion or overproduction of urate or both (Table 2). The majority of patients with primary gout are underexcreters. Those who have elevated levels of urate and do not have gout or renal tract stones are classified as having asymptomatic hyperuricaemia. Almost 10% of adults are documented to have hyperuricaemia at least once in their lifetime and this in itself does not constitute a disease entity. However, hyperuricaemia may be a risk factor

for acute coronary syndromes and is associated with type II diabetes mellitus, lipid abnormalities, hypertension, stroke, pre-eclampsia, human immunodeficiency syndrome (HIV) and secondary amyloid.^{19–23}

It remains controversial as to whether lowering serum urate in asymptomatic hyperuricaemia can affect these co-morbid conditions.

Acute gout

Classically, gout presents in the early hours of the morning as an acute monoarthritis affecting the lower extremity, often the 1st metatarsophalangeal joint (70% of attacks are in this joint), instep, ankle or knee. The affected joint is warm, tender and swollen, and in most cases the overlying skin is erythematous. Low-grade fever, general malaise and anorexia may accompany the symptoms. Occasionally, the attack is preceded by twinges of pain (petit attacks) in the affected joint. Left untreated, the attack will usually subside within 7–10 days. With resolution, the patient becomes asymptomatic and enters the intercritical period (period between gouty attacks).

The first attack usually occurs between the fourth and sixth decades. Onset in younger individuals should alert the physician that this might be an unusual form of gout requiring further investigation, for instance first presentation of a myeloproliferative disease.

Although most attacks present as a monoarthritis, 3–14% present as polyarthritis. Multiple small joints may be involved in a symmetric or asymmetric fashion. Elderly women may have more finger involvement, particularly occurring in Heberden's nodes.²⁴ Older patients presenting with gout are more likely to have polyarticular disease, be female, have small joint involvement, develop tophi early (often in atypical locations), and have a greater use of diuretics and renal disease.²⁵ 25% of women first present with hand involvement and polyarticular disease.²⁶

TABLE 2. Causes of hyperuricaemia.

Urate underexcretion	Urate overproduction
Primary hyperuricaemia Secondary hyperuricaemia <ul style="list-style-type: none"> • Renal impairment • Hypertension • Drugs <ul style="list-style-type: none"> – Low dose aspirin – Diuretics – Ciclosporin – Ethanol • Lead nephropathy • Hypothyroidism 	Primary hyperuricaemia (<10%) HPRT deficiency (Lesch–Nyhan syndrome) <ul style="list-style-type: none"> • Increased PRPP synthetase • Glycogen storage disease Secondary hyperuricaemia <ul style="list-style-type: none"> • Excessive dietary purine intake • Lympho-/myeloproliferative disorders • Psoriasis Drugs <ul style="list-style-type: none"> • Cytotoxics • Ethanol • Vitamin B₁₂

Some patients may never have a second attack. However in one series only 7% had experienced no attacks in 10 years and 62% had recurrence within 1 year.²⁷ The frequency of attacks usually increases with time in untreated patients, with later attacks being less explosive in onset, polyarticular, more severe, and longer-lasting. There appears to be a predilection for previously damaged joints.

The prevalence of patients with acute gout with normal uric acid levels at diagnosis was found to be 12%, but 81% of these patients subsequently developed hyperuricaemia at a median of 1 month after diagnosis.²⁸ Of those who had normal urate levels at diagnosis, their mean age was higher but their urea and creatinine levels were lower compared to those with hyperuricaemia. Interestingly, those who remained normouricemic followed a mild disease course without secondary attack. Uric acid levels taken at diagnosis and then following resolution of an attack of gout may therefore be useful in predicting disease course. However, the main learning point is that serum uric acid levels are not diagnostic of gout.

Chronic tophaceous gout

In the late stages of untreated disease, the patient may enter a period of chronic polyarticular disease with no pain-free intercritical periods. Chronic polyarthritis and/or tophi developing after a first gouty attack ranges from 3–42 years, with an average of 11.6 years.²⁹ Tophi have been reported to occur in 12% of patients after 5 years and 55% after 20 years of untreated disease.³⁰

Tophi are chalky deposits of urate embedded in a matrix of lipid, protein and calcific debris. They are usually subcutaneous, but may occur in bone and other organs including heart valves and the eye. The most common sites are the olecranon bursa, Achilles tendon, and small joints of the hands and feet (Figure 2). Tophaceous deposits correlate directly with both the degree and duration of hyperuricaemia.³¹ Tophi can be seen radiographically as soft tissue swellings



FIGURE 2. Chronic tophaceous gout affecting the small joints of the hand.

(occasionally with associated calcification) and can contribute to a destructive arthropathy and secondary osteoarthritis.

Complications

Complications are more likely to occur in those with chronic disease and severe hyperuricaemia, particularly if there are high levels over a sustained period of time, and in those with an underlying secondary cause (Table 3).

TABLE 3. Complications of gout.

Disability
Tophi
Renal disease
<ul style="list-style-type: none"> • Uric acid calculi (10–15%) • Chronic urate nephropathy • Acute uric acid nephropathy (usually secondary to chemotherapy)
Avascular necrosis of the femoral head

DIAGNOSIS AND INVESTIGATION

The classical history of an acute attack of gout allows diagnosis by clinical pattern recognition alone, but many attacks are atypical, making diagnosis difficult in these cases.

Serum uric acid cannot be used as a diagnostic investigation and possibly leads to many diagnoses of ‘non-gout’ in the general population, when in fact patients have an inflamed 1st metatarsophalangeal bursa and also have high serum uric acid levels. Imaging, particularly plain x-ray, is not helpful in the acute setting, but can be characteristic in chronic tophaceous gout (bony erosions appear ‘punched out’ with sclerotic margins and overhanging edges – rat-bite erosions).

Fresh SF identifying the intra- or extracellular typically needle-shaped MSU crystals is the only definitive way of establishing a diagnosis of gout. SF in gout is inflammatory and consequently contains neutrophils (typically 20,000–100,000 leucocytes/mm³) sometimes identical to those seen in sepsis. Conversely, septic SF can also contain MSU crystals. As a result all SF specimens in suspected gout should be sent for culture as well as microscopy, and treatment for sepsis initiated where there is doubt regarding the diagnosis.

Blood investigations may demonstrate an inflammatory response, with elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), a mild neutrophil leucocytosis, and possibly a reactive thrombocytosis.

Once a diagnosis of gout is made, patients should have lifelong monitoring of renal function and an assessment should be made of cardiovascular risk.

TREATMENT

Treatment goals are to terminate an acute attack, prevent recurrent attacks and prevent complications from occurring. These are achieved by combining lifestyle modifications (Table 4) with pharmacological therapy. Control of any underlying disease, for instance diabetes mellitus, hypertension and hyperlipidaemia, should also be undertaken and the likely association with cardiovascular disease considered.

TABLE 4. Conservative treatment/lifestyle measures for patients with gout.

- Weight loss
- Diet (low purine)
- Alcohol reduction/cessation
- Avoiding diuretic therapy
- Local ice therapy

Conservative treatment

Although pharmacological therapy is the cornerstone of treatment in gout, non-pharmacological treatments are also indicated and are useful in their own right.

- Alcohol consumption, weight gain and diuretic use were found to be independent predictors of gout in a community-based epidemiological study and therefore avoidance may lead to a reduction in gout.¹⁵ Dietary intervention using a moderate calorie/carbohydrate restriction reduced serum urate levels by 18% and frequency of gouty attacks by 67%.³²
- Cherries have been reported to help alleviate gouty attacks for many years.³³ This is thought to be due to anthocyanins within cherries having COX inhibition. A recent study demonstrated cherry consumption significantly lowered urate levels.³⁴
- Low purine diets have been used in an attempt to reduce serum uric acid levels in the past, often with limited success.
- Local ice therapy during bouts of acute gouty arthritis in patients treated with prednisolone had a significantly greater reduction in pain compared to those treated with prednisolone alone.³⁵

Although simple and common sense, these measures may help alleviate some of the signs and symptoms of gout when used in conjunction with pharmacological therapy.

Pharmacological treatment

ACUTE GOUT

The affected joint(s) should be rested and drug therapy started as soon as possible to ensure the most rapid and complete response. Treatment options include NSAIDs, colchicine and corticosteroids (systemic or intra-articular). Urate-lowering drugs should be con-

tinued throughout acute episodes if they have been commenced previously but should **not** be commenced during an acute episode.

NSAIDs

Non-salicylate NSAIDs given initially at their highest licensed dose and continued in decreasing doses until all signs of inflammation have resolved are indicated in patients with no contra-indications (a 'decrecendo regime'). Although no comparative studies have been conducted, NSAIDs are generally better tolerated than colchicine and have more predictable effects. Due to the short duration of use of NSAIDs in acute gouty attacks, they confer few serious adverse events. NSAIDs do not alter uric acid levels.

Indometacin^{36,37} has been shown to be effective, as have piroxicam and ibuprofen.^{38,39} Etoricoxib, a COX-2 selective NSAID, at doses of 120 mg daily was comparable to high-dose indometacin (150 mg/day) in treating the signs and symptoms of acute gout within 4 hours;³⁷ this may be useful in patients who cannot take/tolerate conventional NSAIDs. Azapropazone can be used in patients who do not respond to other NSAIDs and in whom alternate treatments are contraindicated or ineffective. It exhibits both anti-inflammatory and hypouricaemic properties, the latter being attributed to a uricosuric effect. Care needs to be taken, however, due to an increased risk of gastrointestinal side-effects.

The use of NSAIDs should be limited in patients with cardiovascular disease and/or renal impairment.

Colchicine

Colchicine is variably used in acute gout cases by rheumatologists. Some feel it is not effective, is likely to cause troublesome diarrhoea in a patient with limited mobility, and should be used for prophylaxis only or as a last resort.

Colchicine has been in therapeutic use since the 1920s. It disrupts the mitotic spindle and inhibits cell division and is excreted in the urine.⁴⁰ It does not affect urate crystals or serum urate levels and needs to be administered **as soon as an acute attack commences** to be optimally effective. It can also be used to prevent acute attacks⁴¹ and it is recommended that low-dose colchicine is initiated before commencing urate-lowering drugs and then continued for up to 1 year after the serum urate has returned to normal.⁴²

When administered orally, a bolus dose of 1 mg is usually given, followed by regular doses of 0.5 mg. Although the BNF recommends dosing every 2 hours until diarrhoea develops or a total of 8 mg has been administered, this is rarely adhered to. Most patients respond within 18 hours and joint inflammation subsides in 75–80% of patients within 48 hours.⁴³

Intravenous colchicine can be used if **no** other therapeutic options can be utilised but, due to its potential serious toxicity, should definitely **not** be used if oral colchicine has been tried and has failed. An initial dose of 2 mg is given slowly intravenously; a maximum of two additional 1 mg doses may be given at 6-hourly intervals.

Adverse reactions include gastrointestinal upset, bone marrow dysfunction, and neuromuscular dysfunction. These are more likely to occur in patients with renal or hepatic impairment and in the elderly. Colchicine constricts blood vessels and has stimulating effects on central vasomotor centres, and therefore care should also be taken in patients with chronic heart failure.⁴⁴ Colchicine-specific Fab (fragment, antigen-binding) can be used effectively for colchicine intoxication.⁴⁵

Corticosteroids

Intra-articular corticosteroid injections are very useful when the use of NSAIDs or colchicine is problematic, for instance in patients with chronic heart failure or renal or hepatic impairment. They are also useful in acute gout limited to a single joint or bursa. However, septic arthritis should be excluded prior to steroid injection.

High-dose oral (30–40 mg) or intramuscular corticosteroid tapered over a 7–10 day period may also be useful in patients who cannot tolerate colchicine or NSAIDs or who have failed on this treatment, and those with polyarticular attacks. They can be problematic in patients with heart failure.

CHRONIC GOUT

Optimal treatment of chronic gout requires long-term reduction of serum urate to the lower half of the normal uric acid range; this must be maintained in order to eliminate acute gouty attacks, reduce tophi volume and prevent on-going damage. Urate-lowering therapy should not be commenced during an acute attack.

Urate-lowering drugs are indicated for:

- patients who have more than 2 attacks of gout per year
- chronic tophaceous gout
- uric acid overproduction (primary and purine enzyme defects)
- chronic gout with associated renal impairment or urate renal calculi
- adjunct to cytotoxic therapy for haematological malignancy.

These drugs can be divided into three categories:

1. **uricostatic** (xanthine oxidase inhibitors), e.g. allopurinol, oxipurinol
2. **uricosuric**, e.g. benzbromarone, sulfinpyrazone, probenecid
3. **uricolytic**, e.g. urate oxidase (Uricozyme).

Uricostatic (xanthine oxidase inhibitors)

Allopurinol is the urate-lowering drug of choice. It is a xanthine oxidase inhibitor and accordingly inhibits the biosynthesis of uric acid. The risk of precipitating an acute episode of gout on initiation is reduced by starting with a small daily dose (50–100 mg), and increasing as necessary. Colchicine or NSAID prophylaxis should be used to avoid an acute episode. Doses of 50–600 mg daily are usually required in order to reduce and maintain urate at a satisfactory level. Normalisation of serum urate is usually seen within 4 weeks and acute gouty attacks cease within 6 months of continuous therapy. Tophi reduction may take years. Occasionally doses of up to 900 mg are required.

There are numerous potential drug interactions, particularly with oral anticoagulants, theophylline and azathioprine. The main side-effects are rash (2%) and hypersensitivity reaction (0.4%; increases to 20% with ampicillin concomitantly prescribed);⁴⁶ these may be exacerbated by thiazide diuretic therapy. Hypersensitivity reaction carries a high mortality. Care also needs to be taken in patients with renal impairment as allopurinol is excreted solely via the kidney and therefore dosage adjustment according to creatinine clearance must be made.

Oxipurinol, the active metabolite of allopurinol, may be used on a compassionate use basis in those sensitive to allopurinol. However, similar adverse reactions have been noted in 40% of these patients.⁴⁷ Desensitisation with allopurinol may be necessary in certain individuals and appears to be effective.⁴⁸

Febuxostat is a novel, oral, xanthine oxidase inhibitor currently being developed. It has been shown to be more potent in lowering urate than allopurinol in animals,⁴⁹ and in a phase II human study in 115 patients with gout lowered serum urate by 44%; when used with prophylactic colchicine this was enhanced to 59%.⁵⁰ The drug is mainly metabolised by the liver and therefore mild–moderate renal impairment does not appear to impede its effect.

Uricosuric

Uricosuric drugs increase the renal excretion of urate by inhibiting reabsorption in the proximal tubule. Due to their mechanism of action they may precipitate renal and urinary calculi. In order to minimise this risk they should be initiated at low dose and increased slowly, and adequate hydration must be maintained. They should not be used in conditions where there is urate overproduction or known renal nephrolithiasis. They appear to be useful in diuretic-induced hyperuricaemia.

Probenecid is no longer available and sulfinpyrazone

is currently in limited supply. Neither of these agents should be used in patients with renal impairment.

Benzbromarone has been investigated as an alternative to allopurinol in patients with normal and impaired renal function with good effect. It has been successfully used in patients who have had no improvement when taking allopurinol and in renal transplant patients treated with ciclosporin A.⁵¹⁻⁵⁴ There is concern regarding potential hepatotoxicity, and its usefulness in allopurinol-allergic patients with renal impairment has not been examined. Doses of 25–150 mg/day are given.

Losartan, an angiotensin II converting enzyme inhibitor used for the treatment of hypertension, inhibits renal tubular reabsorption of urate and therefore acts as a uricosuric agent; this does not appear to be a class effect.⁵⁵ Losartan has also been shown to reduce the increase of serum urate caused by thiazide diuretics. The drug may be particularly useful as adjunctive therapy in treating patients with hypertension and gout/hyperuricaemia.⁵⁵

Fenofibrate, a lipid-lowering drug, has also been found to have uricosuric properties; again this is not a class effect. Sustained reduction in serum urate of 20–35% has been seen.⁵⁵ This may be useful in individuals with hyperlipidaemia and gout/hyperuricaemia.

Combination therapy of fenofibrate or losartan with anti-hyperuricaemic agents, which included benzbromarone (50 mg once daily) or allopurinol (200 mg twice a day), significantly reduced serum uric acid concentrations in accordance with increased uric acid excretion.⁵⁶ A combination of fenofibrate or losartan with anti-hyperuricaemic agents is potentially a good option for the treatment of gout patients with hypertriglyceridaemia and/or hypertension, though the additional hypouricaemic effect may be modest.

Uricolytic

Urate oxidase catalyses the conversion of uric acid into allantoin in lower animals. Humans do not possess this enzyme. Administered parenterally, uricase is a more potent and faster acting urate-lowering drug than allopurinol.⁵⁷ Urate oxidase prevents formation of urate and also breaks down pre-existing uric acid, unlike allopurinol.

There are two main preparations, non-recombinant (native) and recombinant. Uricozyme (non-recombinant) was introduced in to Europe in 1974 and used predominantly in patients with malignancy to prevent hyperuricaemia and tumour lysis syndrome.⁵⁷ Recombinant uricases are currently in development and appear to have a potent and rapid urate-lowering effect without significant toxicity.⁵⁸ Long-term uricase therapy has not yet been evaluated, and is limited by

the need for parenteral administration and the development of antiuricase antibodies in about 10% of patients.⁵⁷

SUMMARY

Gout is an increasingly prevalent condition worldwide. Recommended best therapy for both acute attacks and long-term prophylaxis has remained unchanged for many years; however, patients are often still treated inadequately and risk factors for their disease are not explored.

Although well-designed, long-term comparability studies of current treatments and their cost are welcomed to assess burden of disease, educating doctors in optimising the currently available management options would improve current care.

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