Abstract and Introduction

Abstract
There have been recent advances in the understanding of underlying mechanisms and treatment of gout and chronic hyperuricemia, making this an important time to review the current state of the disease. The goal of this article is to provide a practical review of the current standard of care as well as discuss some new developments in the management. There is an increasing prevalence of gout and hyperuricemia worldwide. Gout confers a significant individual and societal burden and is often under-treated. Appropriate diagnosis and treatment of acute gout should be followed by aggressive and goal-oriented treatment of hyperuricemia and other risk factors. Allopurinol remains as a first-line treatment for chronic hyperuricemia, but uricosuric agents may also be considered in some patients. Febuxostat, a non-purine xanthine-oxidase inhibitor, is a new agent approved for the treatment of hyperuricemia in patients with gout, which may be used when allopurinol is contraindicated.

Gout and hyperuricemia appear to be independent risk factors for incident hypertension, renal disease and cardiovascular disease. Physicians should consider cardiovascular risk factors in patients with gout and treat them appropriately and aggressively.

Introduction
The recent approval of febuxostat, the first new agent for gout in 40 years for use in the treatment of chronic hyperuricemia associated with gout, lead the editors of the IJOP to request this review to address current guidelines for the diagnosis and management of gout, some new developments for consideration by the treating physician and the epidemiology of this increasing international health concern. The goal of this review is to provide the practicing physician with a practical overview of the state of gout worldwide with specific attention to management strategies, both current and novel.

Epidemiology
Gout is the most common form of inflammatory arthritis in men > 40 years of age, often presenting initially in the form of podagra (acute onset of pain, erythema and swelling of the first metatarsophalangeal joint). Women may develop gout later in life, and in women it is more likely to involve the upper extremities. The lifetime prevalence of gout in the United States has been estimated at 6.1 million, and studies in the UK have reported a prevalence approaching 7%.[1,2] Hyperuricemia is significantly more prevalent. For example, it is now present in as many as 25% of people in China (defined for that study as serum urate > 420/> 360 µmol/l in men and women, respectively).[3] The prevalence of gout and hyperuricemia has been increasing over the past few decades in response to a number of factors.

An elevated serum uric acid level (SUA) is perhaps the most highly correlated laboratory value with the metabolic syndrome,[4] which is a concern with global westernisation of diet, increasing access to high caloric foods and greater prevalence of obesity.[5] Increasing life expectancy and use of predisposing medications, such as diuretics, may also contribute to this trend. Recent evidence suggests that the intake of fructose in beverages and foods, which has also increased worldwide, may increase the risk of both metabolic syndrome and gout.[6,7]

As a result of this global trend, it will be important to establish the wide use of safe, inexpensive and effective approaches to prevent and treat gout worldwide. Close attention to risk factors for gout such as high-purine diet, alcohol use, obesity, diabetes and kidney disease will be important in preventing and controlling an epidemic of hyperuricemia and gout, but it is unlikely to be sufficient.

The Burden of Gout
Patients with acute gout experience significant pain and swelling, which can severely impair quality of life (QOL). Long-term complications from gout can also impair QOL, as patients may develop chronic debilitating arthritis and loss of function. Using a variety of distinct validated measures, patients with gout have been shown to experience a significant overall reduction in QOL.\[8\]

Gout is also associated with health care and economic costs.\[9\] It has been estimated that the direct burden of illness for new cases of acute gout may be as high as $27 million in the United States.\[10\] Care of chronic gout represents approximately 6% of a patient's all-cause yearly healthcare costs.\[11\] A diagnosis of gout is independently associated with higher medical and arthritic comorbidity as well as higher utilisation of health care.\[12\] Gout is also associated with significant costs to employers. Patients with gout use more absence days and are less productive.\[13\] This observation again underscores the need for inexpensive, yet effective means of prevention and treatment.

**Diagnosis**

One important key to the early and effective management of gout is an accurate diagnosis. EULAR recommendations have been made regarding the sensitivity and specificity of certain clinical features and their use in establishing a diagnosis of gout.\[14\] The history of episodic self-limited joint pain, swelling and erythema is highly sensitive for clinical gout, but not specific for gout. More specific, but still not diagnostic, features for gout include a history of podagra and the presence of a suspected tophus. There is the reasonable specificity of about 80–90% for these clinical markers in making a provisional diagnosis.\[15\] If however, the course and response to appropriate treatment is not as anticipated, it is recommended that undiagnosed inflamed joints be examined by an experienced laboratory for monosodium urate (MSU) crystals as this permits a definite diagnosis.\[15\] Identification of MSU crystals in synovial fluid from asymptomatic joints may also allow definite diagnosis.\[14,16\]

Serum uric acid levels, although elevated at some time in all patients with gout and helpful in diagnosis, should not be relied upon solely in the diagnosis of gout as they may be normal during an acute flare, and hyperuricemia can be present in asymptomatic individuals.\[17\] Radiographs are not typically useful early in the diagnosis of acute gout although they may help to rule out other causes of joint pain and swelling.

Even with visualisation of crystals, other coexisting causes of joint pain and swelling should be considered, such as trauma and infection. Septic arthritis and gout have been described together, although the occurrence is rare.\[18,19\]

In patients diagnosed with gout, care should be taken to assess for underlying risk factors for the development of hyperuricemia and gout, such as features of the metabolic syndrome, chronic kidney disease and diuretic use. In patients with the onset of gout under the age of 25, with a family history of young-onset gout, or with a history of renal calculi, renal uric acid excretion should be determined to assess for urate overproduction.

**Treatment of Acute Gout**

Current published guidelines, including those of EULAR, suggest the use of oral colchicine or non-steroidal anti-inflammatory drugs (NSAIDs) as the first-line systemic treatment for acute gout\[20\] (Table 1). The use of oral prednisolone (35 mg daily) has recently been shown to be comparably effective to Naproxen 500 mg twice daily in a randomised trial\[21\] and is often preferred for polyarticular gout. As patients frequently have comorbidities associated with hyperuricemia and gout, risks and benefits of these systemic treatments should be considered in the individual patient. For instance, uncontrolled diabetes and active infection are often contraindications for systemic corticosteroids, while NSAIDs should be avoided in patients with chronic kidney disease. High doses and hourly use of colchicine should be avoided, if possible, because of high frequency of toxicity. However, use of this medication at low doses (0.6 mg 2–3 times daily) is widely accepted and may be sufficient for some patients, although the efficacy of this approach has not been demonstrated in controlled trials.

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<th>Drug class</th>
<th>Examples and dosing</th>
<th>Relative contraindications</th>
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**Table 1. Medications for use in acute gout**
An alternative to systemic treatment is intra-articular injection, which is considered safe and effective. This modality has not been well studied, but in one uncontrolled trial, all 19 patients receiving intra-articular depot corticosteroid injections improved within 48 h.[22] This approach is less favoured when multiple joints are involved, or a site is involved that is not easily amenable to aspiration. Systemic and intra-articular steroids should be avoided if septic arthritis is suspected.

Physicians should also include patient education regarding lifestyle in the plan for prevention of subsequent flares. Patients should be encouraged to lose weight and counselled to avoid excessive consumption of animal purines, high-fructose sweeteners and alcohol. In a minority of patients, these interventions may be enough to lower SUA levels and to prevent further attacks of gout.

Pharmacotherapy for Chronic Hyperuricemia in Gout

Treatment with agents to lower SUA is recommended for patients with recurrent attacks, polyarticular attacks, tophaceous gout, radiographical joint damage and/or severe hyperuricemia (Table 2). It is not recommended to treat asymptomatic hyperuricemia without one of these features of gout as the risks and benefits of such an intervention have not been clarified. Although the possible need for lowering of uric acid levels should be mentioned at the time of diagnosis, urate-lowering therapy should, in most cases, be initiated after resolution of an acute gouty attack. However, there is no specific evidence to support the widely accepted belief that acute flares of gout may worsen with immediate initiation of treatment, and this can be considered along with anti-inflammatory therapy in some patients.

Table 2. Medications for use in chronic hyperuricemia and gout

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<th>Drug class</th>
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| Xanthine-oxidase inhibitors | Allopurinol 100–800 mg daily  
 Febuxostat 40–80 mg daily | Previous hypersensitivity  
 Abnormal liver function  
 Severe renal disease |
| Uricosuric agents     | Probenecid 250–1000 mg 2× daily  
 Benzbromarone 25–100 mg 2× daily | Kidney stones, excessive uric acid excretion, liver disease |

The current guidelines suggest treating to a SUA goal below the saturation point for MSU of approximately 6.8 mg/dl, to achieve a level < 6 mg/dl (< 360 umol/l). Patients will over time note a reduction in clinical flares when maintained at this concentration, as urate stores are depleted. Achieving this goal requires frequent adjustment of doses of allopurinol or other urate-lowering agents with close attention to SUA levels. Allopurinol should be started at low dose (100 mg) and increased every 2–4 weeks to as much as 800 mg/day as required to reach the above goal. Prophylactic daily use of 0.5 mg once or twice a day colchicine or low dose NSAIDs is appropriate during the first 6 months of urate-lowering therapy or until resolution of tophi. Acute flares can occur during urate lowering and may interfere with patient adherence. Patients with tophi should be aware that resolution is slow and may take several years in some cases after SUA levels have met their treatment goal. Tophi that are complicated by infection or deformity and are difficult to treat with medication may require surgical excision or debridement.

Allopurinol is the first-line therapy for most patients. The side effects of allopurinol are largely limited to rash and fever, however, the allopurinol hypersensitivity syndrome (AHS) can be life threatening, occurring in an estimated 0.1% of those
Chronic kidney disease has been proposed as a risk factor for the development of AHS, and there have been guidelines for dosing of allopurinol in renal insufficiency. These were suggested by Hande et al. in 1984, who reported that most patients who developed AHS at their institution had pre-existing renal impairment and were on full treatment doses of allopurinol (> 300 daily). Unfortunately, these recommendations for dose adjustment of allopurinol may limit the number of patients who attain an optimal SUA level. A study by Dalbeth et al. found that target SUA concentrations were reached in only 28% of their patients on such recommended doses of allopurinol, whereas 60% reached that goal safely when on higher doses. More recent data would also challenge the current dosing recommendations. Two recent large case-control studies found no difference in the dosing of allopurinol between patients who had developed AHS and those who were tolerant to allopurinol. In addition, there are no prospective data to suggest that dose-adjustment results in a decreased risk of AHS. Understanding these uncertainties, the gradual escalation to more aggressive dosing regimens for many patients may be appropriate to avoid under-treatment.

Probenecid and other uricosuric agents may also be used in patients who are under-excreters of uric acid with otherwise normal renal function and are likely to comply with increased oral fluid intake needed to decrease the risk of stone formation. Benzbromarone is another, probably more potent uricosuric that is available in only a few countries but seems more effective, even in patients with mild renal disease. Both medications act on the recently defined URAT1 transporter to decrease urate reabsorption from the renal proximal tubule. Medications that may increase SUA such as thiazide diuretics should be discontinued if possible.

Under-treating hyperuricemia may have significant consequences to patients including increased number and frequency of gout flares, resultant decreased QOL and productivity, and increased use of NSAIDs and systemic steroids. Other possible risks of under-treated hyperuricemia include worsening of endothelial dysfunction, hypertension, renal disease, systemic inflammation and increased cardiovascular risk. These considerations will be discussed in greater detail. Further study is needed to determine if intervention with allopurinol or other methods to lower SUA ameliorates these risks.

**New Therapies**

**Acute Gout**

The recent interest in the role of the NALP (NACHT, LRR and pyrin domain-containing protein) inflammasome, which generates interleuking (IL)-1β has suggested that this cytokine may be a target for therapy for inflammation associated with gout. An uncontrolled trial of IL-1 inhibition with anakinra was effective in the treatment of acute gout in 10 patients and may also have a role in treatment-resistant inflammation associated with tophaceous gout. Another IL-1 inhibitory agent, rilonacept, has also been shown to be effective at suppressing flares of gouty arthritis and C-reactive protein (CRP) levels. There are insufficient data to recommend the routine use of these expensive IL-1 inhibitory systemic therapies, although they may be considered in some refractory cases.

**Chronic Hyperuricemia**

Febuxostat, an oral non-purine selective inhibitor of xanthine oxidase, has recently been approved in the United States for the treatment of hyperuricemia in gout. The pharmacodynamics of febuxostat is not altered by moderate renal impairment and it has appeared safe in initial studies in those with mild to moderate renal impairment.

Febuxostat, at a dose of 80–240 mg, was superior to standard dose allopurinol in reaching a SUA goal of < 6 mg/dl with similar rates of adverse events in patients with serum Cr < 2 mg/dl. This medication is approved at dosing of 40–80 mg, however, a greater percentage of patients were able to meet their goal SUA with doses as high as 240 mg without increased rates of adverse events. The safety of febuxostat has not yet been assessed in those with severe renal impairment. With this caution, this medication is likely to be a useful adjunct to current therapies, especially in those who are unable to tolerate allopurinol.

Other agents that may lower the SUA level are under investigation. Pegylated recombinant mammalian uricase (PEG-uricase) has been shown to be effective in a phase two trials at lowering SUA and preventing subsequent flares of gout. This advance may play a role in the management of some patients with difficult to manage tophaceous gout.

Losartan, fenofibrate, statins, vitamin C and increased coffee intake have all been shown to modestly increase urine uric acid...
There are currently no data in regard to the clinical utility of these interventions alone in the treatment of hyperuricemia and gout. However, consideration of hyperuricemia when choosing between blood pressure and cholesterol treatments may be appropriate and helpful in many patients. Similarly, increasing coffee (> 4 cups daily) and vitamin C consumption in the diet might be recommended for those patients with the modest hyperuricemia who are resistant to medication, however, the benefits of these interventions are likely to be small compared with other pharmacological interventions.

Other Considerations

Cardiovascular Risk

Acute flares of gouty arthritis are associated with increases in inflammatory markers such as CRP. Elevated CRP is an independent risk factor for cardiovascular disease. A history of gouty arthritis appears also to be an independent risk factor for acute myocardial infarction, perhaps through this increase in systemic inflammation. Large population based studies have shown that a diagnosis of gout is associated with increased cardiovascular and overall mortality independent of other risk factors.

As previously mentioned, hyperuricemia is associated with a number of cardiovascular risk factors including obesity, hypertension and dyslipidemia. Studies suggest that uric acid has harmful cardiovascular effects independent of these associations. SUA levels are associated with carotid atherosclerosis independent of hypertension and other risk factors. Gout and hyperuricemia are independent risk factors for the development of acute myocardial infarction, stroke and peripheral arterial disease. Emerging data also suggest that hyperuricemia is an independent predictor of cardiovascular morbidity and mortality.

The effect of hyperuricemia on cardiovascular outcomes is likely to be the modest when compared with other risk factors. There have been no studies to suggest a benefit of uric acid-lowering therapy on cardiovascular outcomes in either asymptomatic hyperuricemia or hyperuricemic patients with gout.

Endothelial Dysfunction and Hypertension

Serum uric acid levels have been associated with endothelial dysfunction. Induction of elevated uric acid levels in rats with a uricase inhibitor has been shown to decrease nitric oxide production by endothelial cells and increase blood pressure; a finding that was reversible with allopurinol. Soluble uric acid activates the renin-angiotensin system and has been shown to have proinflammatory and proliferative effects on vascular smooth muscle cells.

The association between hyperuricemia and hypertension is well known. Large epidemiological studies, including a subset of the Framingham Heart Study, have also revealed that hyperuricemia predicts incident hypertension. Several small studies have demonstrated some improvement in blood pressure in patients treated with allopurinol. It is not yet clear if hypertensive patients with gout will receive blood pressure reduction upon initiation of uric acid-lowering therapy.

Progression of Kidney Disease

Hyperuricemia has also been shown to predict the development of chronic kidney disease in a number of studies. It is unclear from these studies if an elevated SUA has a causal role in the incidence and progression of renal disease or if it is simply a sensitive marker of nephron loss. In patients with stage 3–4 chronic kidney disease, hyperuricemia is also an independent risk factor for all-cause mortality.

One uncontrolled study has suggested that withdrawal of chronic allopurinol therapy may result in worsening hypertension and accelerated loss of renal function. A controlled clinical trial of allopurinol in 54 patients with hyperuricemia and mild-moderate chronic kidney disease resulted in decreased progression of disease at 12 months of therapy. This evidence would support aggressive, goal-oriented treatment of hyperuricemia in patients with renal disease and gout.

Conclusions

Gout is a common, burdensome and often challenging disease. Clinical diagnosis although easy in classical attacks can be
challenging in some patients. Anti-inflammatory agents are critical for treatment of acute flares and for prophylaxis when initiating urate-lowering therapy. The importance of appropriate and aggressive urate-lowering pharmacotherapy is often under-recognised. This should be undertaken in a goal-oriented approach to reach a SUA level of < 6.0 mg/dl. Patients with gout and hyperuricemia should be considered at increased risk for hypertension, cardiovascular disease and kidney disease.

Sidebar

Review Criteria

Relevant papers were identified through a literature search and reviewed in a narrative manner to help discuss the clinical questions.

Message for the Clinic

Gout is often under-treated or inadequately treated. An aggressive approach to diagnosis and goal-oriented management with both existing and emerging tools can limit the individual and societal burden associated with gout. Patients with gout and hyperuricemia should be considered at increased risk for hypertension, cardiovascular disease and kidney disease.

References

Update on Gout and Hyperuricemia (printer-friendly)


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