

## Review

## Gout and its comorbidities: implications for therapy

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## Abstract

Gout is a common form of arthritis. It is associated with a number of comorbidities, including hypertension, cardiovascular disease, renal impairment, diabetes, obesity, hyperlipidaemia and frequently in a combination known as the metabolic syndrome. These comorbidities and their treatment may have an effect on the development of gout and on the choice of therapeutic agent. Treatment of acute gout with short-term corticosteroids may be a safer option than either NSAIDs or colchicine in patients with significant renal and/or cardiac impairment. Sustained reduction of serum urate <0.36 mmol/l is required for long-term management of gout. The optimal dosing regimen for patients with renal impairment is the subject of on-going investigation. There is less experience with newer urate-lowering therapies. This review will consider the relationship between comorbidities and gout with a particular focus on the treatment of gout and the potential interactions between drugs used for gout and those for comorbid conditions.

**Key words:** gout, serum urate, renal impairment, cardiac disease, allopurinol.

## Introduction

Patients with gout frequently have multiple comorbidities, including hypertension, cardiovascular disease (CVD), renal impairment, diabetes, obesity, hyperlipidaemia and in combination known as the metabolic syndrome. These comorbidities and their treatment may have an effect on the development of gout and on the choice of therapeutic agent. Likewise, hyperuricaemia and gout may have an important role in the pathogenesis of the comorbidity. This review discusses the relationships between these comorbidities and gout and the therapeutic options for patients with gout and comorbidities.

## Interactions between hyperuricaemia, gout and its common comorbidities

## Hypertension

Hyperuricaemia is common in patients with hypertension. Twenty-five per cent of patients with untreated hypertension, 50% of patients on diuretics and >75% of patients with malignant hypertension have hyperuricaemia [1]. Conversely, among patients with gout, ~40% have hypertension [2, 3]. Hyperuricaemia may have a pathogenic role

in hypertension [4], and many medications used in the management of hypertension have effects on serum urate (SU) (Table 1). Loop and thiazide diuretics increase SU, whereas the angiotensin II receptor antagonist losartan [5] and the calcium channel blocker amlodipine reduce SU [7, 8]. A nested case-control study of 24 768 people with newly diagnosed gout and 50 000 control subjects examined the risk of incident gout in patients with hypertension. The relative risk of incident gout was 0.87 (95% CI 0.82, 0.93) for calcium channel blockers, 0.81 (95% CI 0.70, 0.94) for losartan, 2.36 (95% CI 2.21, 2.52) for diuretics, 1.48 (95% CI 1.4, 1.57) for  $\beta$ -blockers, 1.24 (95% CI 1.17, 1.32) for ACE inhibitors and 1.29 (95% CI 1.16, 1.43) for non-losartan angiotensin II receptor blockers [17]. Surprisingly, a recent meta-analysis reported that there was a trend toward a higher risk for acute gout in patients on loop and thiazide diuretics, but the magnitude and independence of the association was not consistent. The authors concluded that stopping these drugs in patients who develop gout was not supported [18]. Although there may be no specific literature on the effects of stopping diuretics in those patients who develop gout, their presence may make urate lowering more difficult.

Treatment with the xanthine oxidase (XO) inhibitor allopurinol may contribute to a reduction in blood pressure. In a study of 48 hyperuricaemic patients, treatment with allopurinol 300 mg/day for 3 months resulted in a significant reduction in blood pressure [19]. In another study of 30 adolescents (aged 11–17 years) with essential hypertension, allopurinol 200 mg b.i.d. for 4 weeks resulted in a significant reduction in blood pressure [20]. Similar studies have not been undertaken in patients with gout. Although

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**TABLE 1** Effect of cardiovascular medications on SU concentrations

	Increase SU	No effect on SU	Lower SU	Reference
Anti-hypertensive agents		Lisinopril	Losartan ACE inhibitors (captopril, enalapril, ramipril), calcium channel blockers (e.g. amlodipine, felodipine)	[5–8]
	Beta blockers (propranolol, atenolol, metoprolol, timolol, alprenolol)			[9]
Diuretics	Furosemide, thiazides	Spironolactone		[10, 11]
Lipid-lowering agents		Simvastatin	Atorvastatin, fenofibrate	[12–15]
NSAIDs	Piroxicam	Diclofenac, naproxen	Indomethacin	[10]
Aspirin	Low doses of 60–300 mg/day reduce renal urate excretion and may increase SU	Doses >1 g/day increase renal urate excretion and lower SU		[16]

there are no similar human studies with febuxostat (a newer XO inhibitor), in the clinical studies of febuxostat, changes in blood pressure were not reported. However, a study in rats reported that febuxostat partly reduced blood pressure in rats with oxonic acid-induced hypertension, with no effect on blood pressure in normal rats [21].

### Cardiovascular disease

Gout is associated with an increased risk of CVD and death, particularly in those with a high cardiovascular risk [22–24]. Hyperuricaemia is an independent risk factor for CVD [25]. Associations between hyperuricaemia/gout and stroke [26] and peripheral vascular disease [27] have also been reported. Conversely, many of the drugs used to treat CVD can have an impact on SU (Table 1) and contribute to hyperuricaemia and the development of gout.

A number of studies have examined the effects of XO inhibition on cardiovascular outcomes. In a large retrospective, nested case–controlled study of 25 090 patients with congestive heart failure (CHF), a history of gout and a recent acute episode of gout ( $\leq 60$  days) were associated with an increased risk of re-admission for CHF or death [relative risk (RR) 2.06; 95% CI 1.39, 3.06;  $P < 0.001$ ] [28]. In the subgroup of patients with gout, allopurinol use was associated with a significant reduction in CHF re-admissions or death (RR 0.69; 95% CI 0.60, 0.79) and reduced all-cause mortality (RR 0.74; 95% CI 0.61, 0.90) [28]. In a placebo-controlled trial, the addition of oxypurinol or placebo to standard CHF therapy in 405 patients reported a trend toward improved outcomes in the subgroup of patients with baseline SU  $\geq 9.5$  mg/dl [19]. Allopurinol, through its ability to reduce myocardial oxygen demand, also appears to be beneficial in patients with ischaemic heart disease [30, 31]. These data give weight to the need for urate-lowering therapy (ULT) in patients with gout who are at high risk of CVD. Whether the current target SU of  $< 0.36$  mmol/l is appropriate for preventing cardiovascular events is unknown.

### Renal impairment

There are well-recognized relationships between renal function, SU and gout. Renal impairment is associated with hyperuricaemia, which also contributes to renal impairment. Renal under-excretion of urate is a common cause of hyperuricaemia, and is the dominant mechanism of hyperuricaemia in the majority of patients with gout [32]. Patients with gout are also much more likely to have renal impairment than those with OA [33].

There are a number of inter-related variables that can influence both SU and creatinine, including hypertension, diuretic use, body mass index and increasing age (for a review see [34]). However, creatinine has been shown to correlate with SU independent of these variables and is one of the most important determinants of SU [35–42]. Creatinine clearance (CrCL), which adjusts for some of the variability in creatinine due to age, weight and gender, is a better indicator of renal function and correlates inversely with SU [43–46].

Hyperuricaemia (SU  $> 0.40$  mmol/l) is an independent risk factor for renal impairment in healthy normotensive individuals [47], is a predictor of renal progression in IgA nephropathy [48] and is associated with early glomerular filtration rate (GFR) loss in patients with type 1 diabetes [49]. Hyperuricaemia has also been associated with an increased incidence of end-stage renal disease and has been shown to be an independent predictor of end-stage renal disease in women [50]. Unlike the situation with chronic kidney disease, acute gout is rarely a complication of acute renal failure.

### Effect of urate lowering on renal function

In patients with chronic kidney disease, allopurinol has been shown to slow the progression of renal disease [51, 52]. In patients with gout, effective ULT improves renal function. At least part of this effect may be due to reduced NSAID use when gout is adequately controlled [53]. Specific studies on the effects of febuxostat on renal function have not been undertaken. However, a *post-hoc* analysis of the FOCUS study demonstrated that urate

lowering with febuxostat was associated with an improvement in renal function [54].

### Diabetes

There is a complex relationship between blood glucose and SU, as well as between diabetes and gout. Using data from the Third US National Health and Nutrition Examination Survey, SU increased with increasing haemoglobin A1c (HbA1c) up to 6–6.9% and then decreased with a further increase in HbA1c [55]. The authors suggested that people with pre-diabetes (moderately increased HbA1c) may be at increased risk of hyperuricaemia and gout, whereas those with established diabetes or significantly increased HbA1c may be at lower risk [55]. A subsequent case-controlled nested study from a UK general practice database reported that the RR of incident gout in patients with diabetes was 0.67 (95% CI 0.63, 0.71) compared with patients without diabetes [56]. This inverse relationship was stronger for patients with type 1 diabetes than those with type 2 diabetes and stronger in men compared with women. This lower risk of future gout in patients with diabetes likely relates to the uricosuric effect of glycosuria [57] and the impaired inflammatory responses observed in diabetes.

Despite the aforementioned observations, men with gout and high cardiovascular risk are at risk of developing type 2 diabetes independent of other known risk factors compared with men without gout (RR for incident type 2 diabetes 1.34 (95% CI 1.09, 1.64) [58]. Whether optimal management of gout with ULT reduces the risk of future diabetes is unknown.

## Management of gout in patients with comorbidities

The management of gout includes effective therapy of acute attacks and long-term preventive therapy through adequate urate lowering. There are a number of therapies available, and in all cases, the patients' comorbidities, particularly renal function, need to be considered when choosing the most appropriate therapy. In a study of 575 patients with gout, the majority had more than one contraindication to at least one of the commonly used gout therapies, and a number of patients had contraindications to multiple therapies [59]. Furthermore, patients were frequently prescribed medications for which they had a contraindication.

### Treatment of acute attacks

The aim of treatment of acute gout is rapid resolution of the pain and inflammation induced by monosodium urate (MSU) crystals. There are three therapeutic options: NSAIDs, corticosteroids and colchicine.

#### NSAIDs and COX-2 inhibitors

There is good evidence for the efficacy of NSAIDs in acute gout [60–66], and in individuals with normal renal function and no other comorbidities, they are usually the treatment of choice. NSAIDs exert their anti-inflammatory effect by

inhibiting cyclo-oxygenase (COX), thereby decreasing production of pro-inflammatory eicosanoids (prostaglandin E<sub>2</sub>, prostacyclin and thromboxane A<sub>2</sub>), which have important effects on renal haemodynamics. In patients who are dehydrated, have pre-existing renal or cardiac impairment, inhibition of prostacyclin and prostaglandin E<sub>2</sub> by NSAIDs may lead to renal vasoconstriction, reduced renal blood flow, salt and water retention, hyperkalaemia and hypertension, resulting in acute or worsening renal impairment. Within the kidney, both COX-1 and COX-2 have important and overlapping physiological functions, thus COX-2 inhibitors do not offer any significant advantage over traditional NSAIDs with regard to renal adverse effects [67]. COX-2 inhibitors appear to be associated with an increased risk of myocardial infarction when used at high doses in the long term. Some have argued that this effect extends to all NSAIDs. The relationship between NSAIDs, COX-2 inhibitors and CVD remains controversial. Nonetheless, NSAIDs/COX-2 inhibitors should be used at the lowest effective dose for the shortest period.

NSAIDs have multiple drug interactions, which may be of particular relevance in patients with renal impairment and cardiac disease. The combination of an NSAID, diuretic and an ACE inhibitor is of particular concern because of the combined effects on blood pressure and renal function. Therefore NSAIDs need to be used with caution and, in most cases, avoided in the setting of significant cardiac and/or renal disease.

#### Colchicine

Colchicine is commonly used in acute gout, despite the fact that there are only two placebo-controlled trials. In the largest and most recent study, the Acute Gout Flare Receiving Colchicine Evaluation study, placebo, low-dose colchicine (1.8 mg total) and high-dose colchicine (4.8 mg total) were compared. Although both colchicine regimens were effective in reducing pain, low-dose colchicine was associated with significantly fewer adverse effects [68].

Colchicine is relatively contraindicated in those with CrCL < 60 ml/min. Gastrointestinal adverse effects, which can occur even at a low dose, can be severe and may be poorly tolerated in those with borderline cardiac or renal function. Colchicine myotoxicity typically affects males aged 50–70 years, receiving maintenance low-dose colchicine [69]. Renal impairment (CrCL ≤ 50 ml/min) is an important risk factor [70]. Thus the dose of colchicine should be adjusted for renal impairment, and significant renal impairment should be considered a relative contraindication to colchicine use.

Drug interactions between colchicine and CYP3A4 and P-glycoprotein inhibitors (e.g. diltiazem, verapamil, clarithromycin) have been recently highlighted. CYP3A4 is involved in the conversion of colchicine to its inactive metabolites, whereas P-glycoprotein is thought to limit gastrointestinal absorption of colchicine. Thus CYP3A4 or P-glycoprotein inhibitors may lead to accumulation of colchicine. A recent study examined the effects of CYP3A4 and P-glycoprotein inhibitors on colchicine pharmacokinetics and recommended a reduction in

colchicine dose of 33–66% for the treatment of acute gout and 50–75% for prophylaxis [71]. Our recommendation for colchicine is commencing therapy within 12–24 hours of the onset of the acute attack and to use in low dose (i.e. 1.2 mg stat followed by 0.6 mg 1 hour later) [68].

#### Corticosteroids

Oral, intravenous, intra-articular and intra-muscular corticosteroids can all be effective in the management of acute gout. If only one or two joints are involved, intra-articular corticosteroids are useful. Where more joints are affected or the joints are not amenable to injection, oral prednisone is as effective as NSAIDs [72]. In patients with concomitant diabetes, there is reluctance to use corticosteroids. However, these patients frequently have renal impairment, which precludes the use of NSAIDs or colchicine. The increase in blood sugars resulting from corticosteroids can be managed in the short-term while the acute episode is treated. In most patients with significant renal and/or CVD, short-term therapy for acute gout with corticosteroids may be the lesser of the three evils.

#### IL-1 inhibitors

IL-1 is a key cytokine in the inflammatory response to MSU crystals [73]. IL-1 inhibitors are emerging as a therapy for acute gout and have been shown to be effective in small studies [74–76]. Canakinumab is effective in the treatment of gout flares [76] and prevents gout flares during the initiation of allopurinol [77]. Adverse effects of IL-1 inhibition include infection and injection site reactions. Further data will be required on the use of these agents in patients with multiple comorbidities, and the cost of these agents may also preclude their widespread use.

#### Urate-lowering therapy

Sustained reduction of SU is critical to the long-term management of gout. The recommended target SU is <0.36 mmol/l, and achievement of this over time results in dissolution of MSU crystals, suppression of acute gout attacks and resolution of gouty tophi [78, 79]. Reduction of SU can be achieved by decreasing production (XO inhibitors: allopurinol, febuxostat), increasing excretion of uric acid (uricosurics: benzbromarone, probenecid) or metabolism of uric acid to allantoin, which is more water soluble (recombinant uricases: pegloticase, rasburicase).

#### Xanthine oxidase inhibitors: allopurinol

Allopurinol is the most commonly used ULT, as it is effective, easy to administer (once daily dosing), inexpensive and generally well tolerated. However, many patients are prescribed sub-therapeutic doses of allopurinol. One of the reasons for such under-prescribing is concern about the rare, but potentially fatal allopurinol hypersensitivity syndrome (AHS), which is characterized by rash (e.g. toxic epidermal necrolysis, exfoliative dermatitis), eosinophilia, leucocytosis, fever, hepatitis and progressive renal failure. The true incidence of AHS is unknown, although it is estimated to be ~0.1%.

A number of studies have reported that recent commencement of allopurinol therapy [80–83], renal impairment [80, 81, 83–86] and diuretic use [80, 81, 84–86] are risk factors for the development of AHS. The presence of *HLA-B\*5801*, particularly in those of Asian descent, has been associated with AHS [83, 87–89]. Whether *HLA-B\*5801* typing can prevent AHS remains to be determined. The Taiwan Department of Health recommends consideration of *HLA-B\*5801* testing before commencing allopurinol, given the high prevalence of *HLA-B\*5801* in the Taiwanese population. Such recommendations have not been made elsewhere. The starting dose of allopurinol has also been reported to be a risk factor for AHS [90].

Allopurinol has also been reported to be the most common cause of drug reaction with eosinophilia and systemic symptoms [91], which is characterized by fever, rash, eosinophilia, multi-organ involvement and lymphocyte activation. There is some debate as to whether drug reaction with eosinophilia and systemic symptoms is a separate clinical entity from other drug-induced reactions such as AHS [92].

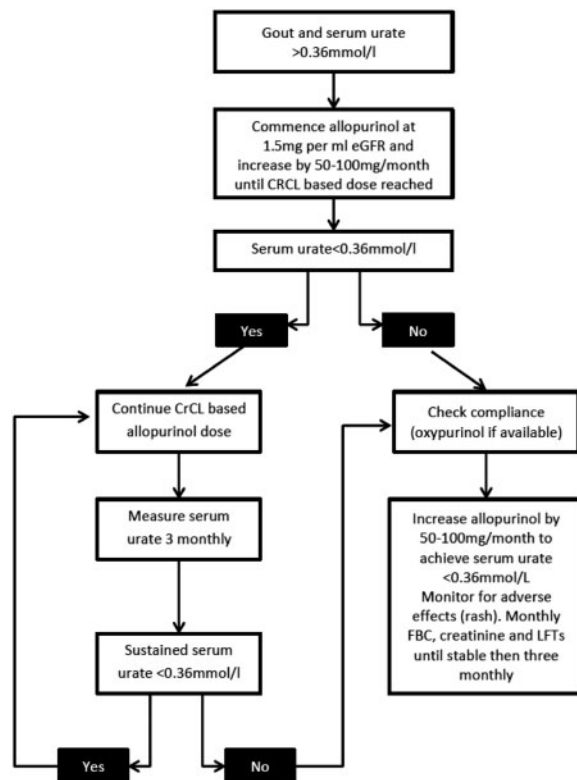
The observation by Hande *et al.* [80] that most patients with AHS had pre-existing renal impairment and were treated with full doses of allopurinol ( $\geq 300$  mg daily) along with studies of oxypurinol clearance in patients with renal impairment led to the development of allopurinol dosing guidelines based on CrCL. However, the relationship between elevated oxypurinol concentrations and AHS has not been confirmed, and no study has demonstrated that administration of lower doses of allopurinol in patients with renal impairment reduces the risk of AHS. Furthermore, these CrCL-based dosing guidelines have resulted in the failure of adequate urate lowering in many patients [93].

The optimal allopurinol dosing regimen remains controversial, particularly in patients with renal impairment. Recent data would suggest that allopurinol should be commenced at 1.5 mg/ml eGFR [90] and increased at monthly intervals until the CrCL-based dose has been reached. If the target SU is not achieved, compliance should be assessed; measurement of plasma oxypurinol may aid in this regard. If compliance is ensured, increasing the dose above the CrCL-based dose, even in patients with renal impairment, has been shown to be effective in lowering SU [94] (Fig. 1). Although there were no cases of AHS within this small study, larger long-term safety data will ultimately be required for this approach to be accepted by many clinicians. An alternative approach is to add or change to another urate-lowering agent. Combination therapy with allopurinol and probenecid [95, 96] or allopurinol and benzbromarone [97, 98] results in additional urate lowering.

There are a number of important drug interactions with allopurinol, including diuretics (thiazides and furosemide), warfarin, AZA, aspirin and ACE inhibitors (Table 2). Furosemide decreases urinary uric acid excretion and results in an increase in SU. The increase in SU occurs within a few days of commencing diuretics and persists for the duration of therapy [9]. Patients with gout on



**Fig. 1** Dosing with allopurinol using the treat-to-target rationale.



furosemide require higher doses of allopurinol relative to their renal function to attain an SU <0.36 mmol/l compared with those not on furosemide [94]. Patients on allopurinol receiving concomitant furosemide have higher plasma oxypurinol concentrations, despite similar doses of allopurinol, suggesting that allopurinol becomes less effective [99]. The clinical indications for furosemide are unclear in many cases, and in many cases alternative agents that do not have an effect on SU could be used. Clinicians should review the need for furosemide in patients with gout on a regular basis.

#### *XO inhibitors: febuxostat*

Febuxostat, a non-purine XO inhibitor, was approved by the European Medicines Agency in 2008 and the FDA in 2009. In the clinical studies to date, febuxostat has been shown to have a superior urate-lowering effect compared with allopurinol; however, in these studies the allopurinol dose was fixed, with a maximum of 300 mg/day in patients with normal renal function and 100–200 mg/day in patients with mild to moderate renal impairment. This study design may have overestimated the relative urate-lowering efficacy of febuxostat compared with allopurinol, and there is a need for head-to-head comparator trials where the dose of allopurinol is titrated to achieve the target SU. In the interim, there is the potential for patients to be changed to febuxostat based on apparent allopurinol failure or

because of concern regarding AHS. One perceived advantage of febuxostat is that dose adjustment is not required for patients with mild to moderate renal impairment (CrCL > 30 ml/min). Fixed dosing of 80 mg/day, increasing to 120 mg/day after 2 weeks if the target SU is not achieved, is recommended. However, there are few data on the use of febuxostat in patients with more severe renal impairment (CrCL < 30 ml/min). Previous AHS is not a contraindication to therapy with febuxostat, although there is a potential for hypersensitivity reactions with febuxostat, therefore this group of patients needs to be closely monitored [100]. Another unresolved issue is the possible increased risk of cardiovascular events in patients receiving febuxostat. The CONFIRMS study reported similar cardiovascular event rates in patients on febuxostat 80 mg/day and allopurinol 200 or 300 mg/day [101]. However, this was a short-term study (52 weeks) and a 120 mg/day febuxostat dose was not assessed. In the long-term extension EXCEL study, there was no significant difference in cardiovascular event rates between allopurinol and febuxostat [102]. Although a causal relationship has not been identified, further cardiovascular safety data are required, and febuxostat should be used with caution in patients with a known history of CVD.

#### *Uricosurics: probenecid, sulphinpyrazone, benzbromarone*

Benzbromarone, probenecid and sulphinpyrazone lower SU by increasing renal urate excretion. Benzbromarone remains effective in patients with CrCL > 20 ml/min, despite treatment with diuretics [103, 104]. However, the efficacy of probenecid declines as renal function declines, and it is generally ineffective with CrCL < 60 ml/min. Benzbromarone is not available in many countries because of concerns about hepatotoxicity. This appears to be rare, with no cases reported in 200 patients treated with 75–125 mg/day of benzbromarone for a mean of 5 years [105]. A risk-benefit assessment concluded that the risks of hepatotoxicity could be reduced by a gradual dose increase and regular monitoring of liver function tests [106]. Whether there is an association between viral hepatitis and benzbromarone is unclear, but it is prudent to screen for viral hepatitis before commencing benzbromarone. Sulphinpyrazone is rarely used, as it is poorly tolerated and ineffective, even when mild renal impairment is present [107].

A complication of uricosuric therapy is the deposition of MSU crystals within the kidney, which can result in urate nephropathy and/or the formation of uric acid stones. A gradual increase in dose, maintaining adequate urine volume of ≥1500 ml/day, and attaining alkaline urine can help prevent these complications. [108]. In many patients with significant cardiac impairment, strict fluid restrictions mean that maintaining adequate urine volume may be challenging. Furthermore, in patients with renal impairment, acute obstruction due to renal calculi may be poorly tolerated. Thus, in many cases, uricosurics may have the potential for more adverse effects than XO inhibitors.

**TABLE 2** Important drug interactions to consider when treating patients with gout

	Drugs that may interact	Effect	Dosing adjustment	Monitoring required
NSAIDs	Warfarin ACE inhibitors	Increased risk of gastrointestinal bleeding Hypertension and potential for deterioration in renal function		Creatinine
Colchicine	CYP3A4 and P-glycoprotein inhibitors, e.g. diltiazem, verapamil, ciclosporin, clarithromycin	Increased risk of colchicine-induced toxic effects	Reduce colchicine dose by 33–66%	Full blood count, creatine kinase
Allopurinol	Furosemide Thiazide diuretics	Increased plasma oxypurinol concentration, increase in SU Increased SU	May require higher doses of allopurinol to achieve target SU May require higher doses of allopurinol to achieve target SU	Creatinine
	AZA Probenecid	Increased 6-mercaptopurine concentrations resulting in myelosuppression Reduced plasma oxypurinol concentrations, reduced SU	Reduce AZA by 50–75% and use lower dose of allopurinol	Regular full blood count while on combination therapy
	Warfarin ACE inhibitors	May increase anticoagulant effects May increase risk of allergic reaction to allopurinol		Monitor INR Monitor clinically
	Theophylline	Increased serum half-life of theophylline		Monitor serum theophylline concentrations Monitor clinically
Febuxostat	Penicillins AZA	May increase risk of skin rash Not formally documented but likely increase in 6-mercaptopurine concentrations due to XO inhibition, resulting in myelosuppression	Avoid combination	
Probenecid	Aspirin, high dose MTX Penicillins and cephalosporin	Decreases uricosuric effect Increases MTX concentrations Increases antibiotic concentrations		Monitor for MTX adverse effects

*Recombinant uricases: pegloticase, rasburicase*

Urate oxidase catalyses the conversion of uric acid to allantoin, which is more water soluble and hence readily excreted via the kidney. The absence of uricase in humans allows the development of hyperuricaemia. Pegylated-uricase (pegloticase), a recombinant uricase, reduces SU and reduces the size of tophi in patients who have failed other ULTs [109, 110]. Adverse effects of pegloticase include gout flares and infusion reactions. Exacerbation of cardiac failure has been observed in a small number of patients, thus pegloticase should be used with caution in patients with cardiac failure [111]. A number of issues remain with the use of recombinant uricases, including the optimal duration of therapy and long-term safety and efficacy.

## Management of gout in patients with solid organ transplants

Hyperuricaemia is known to occur in up to 80% of transplant recipients receiving ciclosporin [112]. Gout is less common, occurring in up to 28%. Although the same therapies are used for the management of gout as in the general population, careful consideration must be given to adverse effects and drug interactions with immunosuppressive therapies in transplant recipients. There is a significant interaction between XO inhibitors and AZA, which results in myelosuppression. Further discussion is beyond the scope of this review, but the literature has been reviewed recently [113].

## Role of other agents in urate lowering in patients with metabolic syndrome

As noted earlier, patients with gout frequently have metabolic syndrome. Medications used to treat elements of the metabolic syndrome, such as hypertension and hyperlipidaemia, may have effects on SU, and physicians should use agents for these conditions that can lower SU rather than those that can increase SU.

### Anti-hypertensive agents

Losartan inhibits the renal urate transporter *URAT1*, thereby increasing urinary uric acid excretion and lowering SU [114]. Other angiotensin II receptor blockers do not have effects on SU, and switching from other angiotensin II receptor blockers to a combination of losartan and low-dose hydrochlorothiazide results in a significant reduction in SU ( $6.0 \pm 1.3$  mg/dl vs  $5.7 \pm 1.3$  mg/dl;  $P < 0.0039$ ) without adverse effects on blood pressure control [115]. Amlodipine also reduces SU through an increase in renal uric acid clearance [7]. The exact mechanism is not known. It is likely that the increase in renal uric acid clearance occurs through non-specific actions on the renal circulation. The effects of amlodipine on *URAT1* are unknown.

### Lipid-lowering agents

Fenofibrate reduces plasma lipids, particularly triglycerides. Fenofibrate, but not other fibrates, has been shown

to reduce SU through increased renal uric acid clearance [13, 116, 117]. In patients with gout receiving allopurinol or benzbromarone, the addition of fenofibrate results in additional SU lowering [14, 15, 118]. The combination of fenofibrate and losartan has been shown to be additive with regard to urate lowering [119].

## Summary

Patients with gout frequently have associated medical conditions that may enhance the development of gout and make management more challenging. The choice of therapy for both acute gout and gout prophylaxis needs to be tailored according to the individual patient's comorbidities and their co-prescribed medications. Many cardiovascular medications result in an increase in SU, and in patients with troublesome or refractory gout, consideration should be given to using alternative therapies with no deleterious or possibly beneficial effects on SU. Sustained urate reduction to  $<0.36$  mmol/l is critical for the long-term management of gout. There is now more choice regarding ULT and better data on the optimal use of established therapies such as allopurinol.

### Rheumatology key messages

- Comorbidities, including hypertension, renal impairment, diabetes and CVD are common in patients with gout.
- Medications for comorbidities may have an adverse effect on SU concentrations in patients with gout.
- When choosing gout therapies, physicians need to consider the individual patient's comorbidities and potential drug interactions.

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