

## Update on gout: new therapeutic strategies and options

Robert Terkeltaub

**Abstract** | Gout, a disease recognized since antiquity, has increased in prevalence in recent years and the clinical profile of this disease has become increasingly complex, owing to large numbers of cases with iatrogenic factors, multiple comorbidities, advanced age, and hyperuricemia and arthritis refractory to treatment. In this Review, key advances in gout research made during the past decade are summarized. Revised strategies for safe and effective employment of dietary measures and pharmacologic treatments for active gouty arthritis, prevention of gout flares and urate lowering are also reviewed, with an emphasis on dosing of colchicine and allopurinol, and the evidence-based approach to systemic glucocorticosteroid treatment of acute gout. Also discussed are new and emerging treatments for gout and hyperuricemia, and the potential influence of dual energy CT imaging on treatment. In this context, the therapeutic role of febuxostat, and clinical development of pegylated uricase urate-lowering therapy and interleukin 1 antagonism for gouty inflammation are reviewed. Collectively, novel approaches will hopefully lead to improved management of hyperuricemia and gout, and also to improvements in patient-centered outcomes, even for those who have previously failed to respond to treatment.

Terkeltaub, R. *Nat. Rev. Rheumatol.* 6, 30–38 (2010); doi:10.1038/nrrheum.2009.236

### MedscapeCME Continuing Medical Education online

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of MedscapeCME and Nature Publishing Group.

MedscapeCME is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

MedscapeCME designates this educational activity for a maximum of 1.0 **AMA PRA Category 1 Credits™**. Physicians should only claim credit commensurate with the extent of their participation in the activity. All other clinicians completing this activity will be issued a certificate of participation. To participate in this journal CME activity: (1) review the learning objectives and author disclosures; (2) study the education content; (3) take the post-test and/or complete the evaluation at <http://www.medscapecme.com/journal/nrrheum>; and (4) view/print certificate.

### Learning objectives

Upon completion of this activity, participants should be able to:

- 1 Describe the epidemiology and clinical profile of gout.
- 2 Treat acute gout effectively.
- 3 Manage chronic gout effectively.
- 4 Identify the efficacy and safety of new treatments for gout.

### Competing interests

R. Terkeltaub declares associations with the following companies: Altus, Ardea Biosciences, BioCryst Pharmaceuticals, EnzymeRx, Novartis, Pfizer, Regeneron, Savient Pharmaceuticals, Takeda, URL Pharma. See the article online for full details of the relationships. The Journal Editor J. Buckland and the CME question author C. P. Vega declare no competing interests.

### Introduction

Gout is a common metabolic disorder characterized by chronic hyperuricemia, which is defined as urate levels >6.8 mg/dl ( $\geq 360$  mmol/l), the level above which the physiological saturation threshold is exceeded.<sup>1</sup> Gout manifests as microscopic and macroscopic soft tissue deposits of monosodium urate monohydrate crystals (tophi), which characteristically trigger intense but self-limited bouts of acute arthritis with excruciating pain, and articular and periarticular inflammation. Tophi can also promote chronic inflammatory and erosive arthritis.<sup>1</sup> In some patients, gout also manifests as uric acid urolithiasis, promoted in part by urine acidity.<sup>2</sup>

Asymptomatic hyperuricemia is a common but under-recognized clinical entity because measurement of urate levels is not a routine component of the serum chemistry or metabolic panel that physicians perform. The risk of developing gout increases with the extent and chronicity of hyperuricemia, and rises markedly with serum urate levels >9.0 mg/dl; however, only a minority of patients with hyperuricemia actually develop gout.<sup>3</sup> Factors that drive the development of tophi are not completely understood, beyond the mitigating effects of cool temperatures and the undervascularized connective tissue milieu of synovial joints, and a potential role for low-grade inflammation in and around tophi.<sup>4</sup> The advent of dual-energy CT (Figure 1), a noninvasive, highly sensitive and specific advanced imaging modality that can detect both soft tissue monosodium urate crystals and renal uric acid calculi,<sup>5</sup> should improve the understanding of tophus biology, and also provide a novel method of early recognition of gout in hyperuricemic patients.

Rheumatology Section,  
Veterans Affairs  
Medical Center,  
University of California,  
San Diego, 3350  
La Jolla Village Drive,  
CA 92161, USA.  
[rterkeltaub@ucsd.edu](mailto:rterkeltaub@ucsd.edu)

Asymptomatic hyperuricemia that occurs independently of gout might not be benign. Substantial, growing epidemiologic and experimental biologic evidence (reviewed in detail elsewhere)<sup>6</sup> indicates that asymptomatic hyperuricemia is capable of directly promoting hypertension and vascular disease. For example, soluble urate is an antioxidant,<sup>7</sup> but urate also can be converted to pro-oxidants that can affect the disposition of the vasodilator, nitric oxide, and thereby potentially regulate vascular endothelial cell function.<sup>6,8</sup>

This Review focuses on recent advances in genetic, translational and clinical research into gout. New developments in strategies and drugs for the management of hyperuricemia and gouty arthritis are discussed, as are benchmarks to improve outcomes in patients with gout.

### Epidemiology and clinical profile

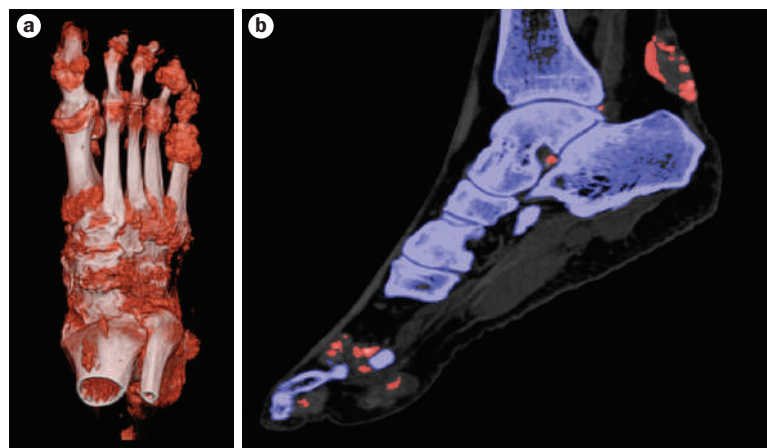
In the past few decades gout has approximately doubled in prevalence in the USA, and is also markedly increasing in prevalence in other countries with established and emerging economies.<sup>9–11</sup> Currently, at least 3 million Americans are thought to have self-reported, active gout, with a self-reported history of gout in up to 3 million more (1–2% of adults).<sup>11</sup> Hyon Choi and colleagues have demonstrated that several features of Western diets (high intakes of meat, seafood, fructose-sweetened beverages and beer) are linked with development of gout in middle-aged men, whereas high intakes of low-fat dairy products, coffee and ascorbate are linked with reduced rates of disease development in the same population.<sup>9</sup> Dietary purines such as guanosine, which is readily absorbed from beer, promote uric acid overproduction, as do certain disorders of increased cell turnover, and (in a small fraction of patients with gout) identifiable mutations in enzymes involved in purine metabolism. In the vast majority of patients with gout, however, hyperuricemia is primarily driven by renal uric acid hypoexcretion, a state that can have multifactorial origins (genetics, high alcohol consumption, decreased glomerular filtration rate, and medications that are being prescribed increasingly commonly, such as diuretics, low-dose aspirin, and niacin [nicotinate]).<sup>7</sup> In this context, a particularly large increase in gout prevalence has occurred in patients over 65 years of age, which is even more striking in those aged over 75 years.<sup>10</sup> In elderly individuals, steadily declining mortality from cardiovascular disease, in conjunction with frequent comorbidities that promote hyperuricemia (for example, chronic kidney disease [CKD], hypertension, metabolic syndrome, congestive heart failure),<sup>7</sup> and widespread prescription of thiazide and loop diuretics, has created a ‘perfect storm’ of new and difficult to manage gout in senior citizens.<sup>7</sup>

### Therapy targets in hyperuricemia

Antihyperuricemic pharmacologic agents (xanthine oxidase inhibitors, uricosurics and uricases) target uric acid generation, renal uric acid excretion and uric acid degradation.<sup>7</sup> Specifically, uric acid, which is generated by the activity of xanthine oxidase, is the end product of purine nucleotide catabolism in humans (Figure 2). Uric

#### Key points

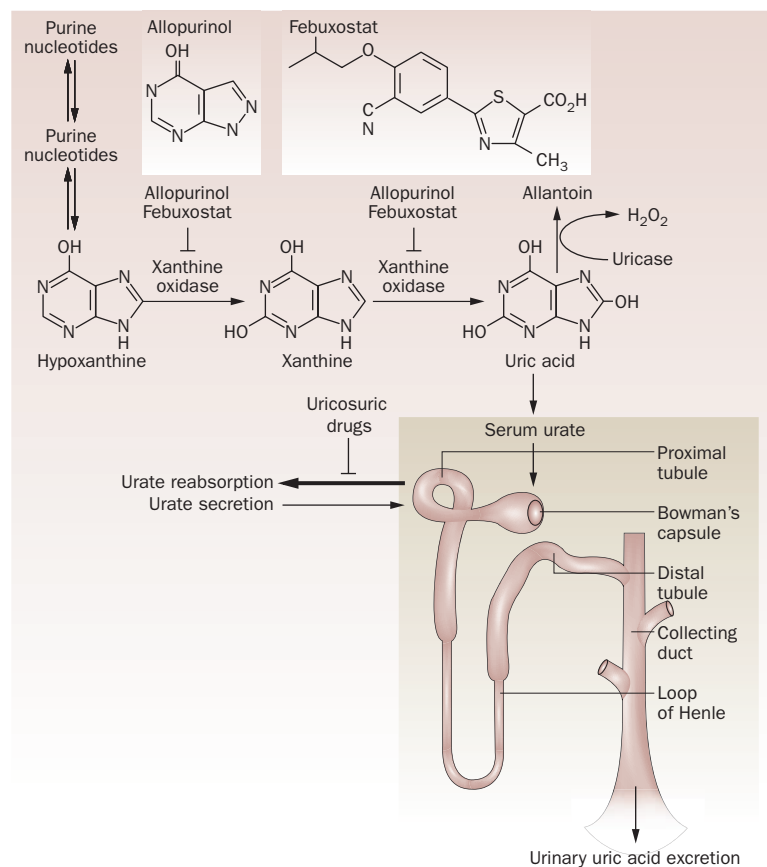
- The prevalence of gout has approximately doubled in the past two decades, along with increases in its severity, treatment complexity and refractoriness
- Major advances have been made in understanding the link between inherited susceptibility to gout and altered renal urate disposition
- These advances have the potential to improve risk stratification for patients with incident gout and to optimize urate-lowering therapy via pharmacogenomics
- Evolution in the evidence base for allopurinol, colchicine and oral glucocorticosteroid administration has validated improved and cost-effective treatment strategies for most patients
- Febuxostat and biologic agents in development (interleukin 1 inhibitors and pegloticase) represent substantial therapeutic advances, particularly for severe, treatment-refractory gout, and patients with comorbidities or intolerance to other drugs



**Figure 1** | Dual-energy CT imaging of tophi in patients with gout. **a** | This volume-rendered, color-coded, three-dimensional, dual-energy CT image of the right foot and ankle of a 71 year old man with a known diagnosis of gout reveals multiple urate deposits (red), indicative of a severe disease burden and subclinical tophaceous disease. **b** | This 74 year old man underwent dual-energy CT to assess erosions associated with an established inflammatory arthritis. This multiplanar reformat sagittal color-coded two-material decomposition (urate and calcium) image of the right foot and ankle reveals urate crystal tophi (red) along the Achilles tendon, sinus tarsi and at the first metatarsophalangeal joint, consistent with gout. These images and descriptions were generously provided (with permission) by Dr Hyon Choi, Boston University Medical School, Boston, MA, USA.

acid levels are delicately balanced in humans, in large part because humans lack the enzyme uricase.<sup>12</sup> In nonhuman mammals, uricase rapidly converts sparingly soluble uric acid to allantoin, which is highly soluble and undergoes efficient renal elimination. In humans, however, uric acid degrades to oxidative intermediates that undergo slow, nonenzymatic conversion to allantoin (Figure 2). This situation is stunningly illustrated by the finding that normal serum urate levels in men and postmenopausal women (~6 mg/dl) are approximately sixfold the levels seen in normal mice; uricase-knockout mice have serum urate levels of ~10 mg/dl.

Major advances in understanding of the interaction between inherited susceptibility to gout and altered renal urate disposition have the potential to improve gout risk stratification (for example, for patients with both obesity and hyperuricemia) and to optimize urate-lowering



**Figure 2 |** Pathways of uric acid metabolism and renal elimination, and primary therapeutic sites of actions of gout medications. Xanthine oxidase generates uric acid as the end product of purine metabolism. Allopurinol and its major active metabolite oxypurinol (which has a much longer half-life than allopurinol, and is primarily eliminated by renal excretion) inhibit activity of xanthine oxidase, and also suppress uric acid generation upstream (mechanisms not shown). Febuxostat acts solely as a selective xanthine oxidase inhibitor, and, in further distinction to allopurinol and oxypurinol, does not have a purine-like backbone (see inset chemical structures). Uricase sparingly oxidizes soluble uric acid to oxidative intermediates that in humans are slowly converted nonenzymatically to highly soluble allantoin, generating the oxidant hydrogen peroxide as a byproduct. Uricase expression is absent in humans and higher primates, which consequently have high baseline serum urate levels versus those of other mammals. Almost all circulating urate is filtered by glomeruli, with only a small fraction (~10%) normally excreted in the urine as uric acid. The proximal tubule is the major site of both urate reabsorption and secretion; uricosuric drugs (for example, probenecid, benzbromarone) primarily act by suppressing urate anion reabsorption by proximal tubule epithelial cells.

therapy via pharmacogenomics. Notable developments include identification of polymorphisms and mutations in genes that encode ion transporters such as SLC22A12 (solute carrier family 22 [organic anion/urate transporter] member 12), SLC2A9 (solute carrier family 2 [facilitated glucose transporter] member 6), SLC17A1 (solute carrier family 17 [sodium phosphate] member 1), and ABCG2 (ATP-binding cassette subfamily G member 2), which have major roles in urate anion disposition by renal proximal tubule epithelial cells (Figure 3).<sup>13–17</sup> The anion exchanger SLC22A12 drives urate anion reabsorption from the tubule lumen at the apical (brush border) plasma membrane.<sup>13</sup> The hexose transporter SLC2A9 carries out voltage-dependent urate anion reabsorption into the

peritubular interstitium at the proximal tubule epithelial cell basolateral membrane, which mediates movement of urate back into the circulation.<sup>14</sup> Some evidence also points to a role for SLC2A9 in urate anion reabsorption at the basolateral membrane in proximal tubule cells.<sup>18</sup> Genetic polymorphisms of *SLC2A9* associated with gout pose new questions about the mechanisms by which hyperglycemia and gout are linked. In general, the contribution of genetic variants of *SLC2A9* to serum urate levels is greater in women than men and is enhanced in individuals with increased BMI.<sup>19</sup> Importantly, the central role of SLC22A12 and SLC2A9 in proximal tubular reabsorption of urate in humans has been underlined by the linkage of marked functional deficiencies of these transporters to hypouricemia of renal etiology.<sup>13,14</sup>

ABCG2 functions as one of the key transporters involved in urate anion secretion into the tubule lumen (Figure 3).<sup>16</sup> The ABCG2 rs2231142 single nucleotide polymorphism (SNP), which has a minor allele frequency of 0.11 in white individuals and is even more common in Asian populations, encodes a Gln141Lys mutation in the nucleotide-binding domain of ABCG2 that inhibits urate transport velocity by ABCG2 by ~50% *in vitro*.<sup>16</sup> The ABCG2 rs2231142 SNP is strongly associated with serum urate levels, and the adjusted odds ratio for gout of 1.68 for this risk allele suggest that this SNP has a significant pathogenic role in ~10% of gout cases in white individuals (and an even higher proportion of cases in Asian people).<sup>16</sup> The 806T>C genotype of the voltage-dependent transporter gene *SLC17A1* was linked with considerable reduction of serum urate levels in obese Japanese men.<sup>17</sup> Interestingly, estrogen, which as a native uricosuric helps to keep serum urate levels substantially lower in premenopausal women than they are in age-matched men, works in part by modulating expression of SLC22A12 and possibly other renal urate transporters; testosterone also modulates expression of some renal urate transporters.<sup>13</sup>

## The pathogenesis of gouty inflammation

Gout, as well as calcium pyrophosphate dihydrate crystal deposition disease (in which an acute synovitis with red, tender, and swollen joints that resembles gouty arthritis is termed pseudogout) and pulmonary silicosis exemplify diseases in which innate immune inflammatory responses are activated by deposits of crystals in tissue.<sup>20–23</sup> In acute gout, monosodium urate crystals liberated from tissue deposits promote an inflammatory cascade that involves complement activation and release of multiple inflammatory cytokines, which culminates in acute but self-limited neutrophilic inflammation.<sup>20–22</sup> At the cellular level, a fundamental mechanism that promotes urate-crystal-induced inflammation is innate immune engagement of the crystals by plasma membrane receptors, including Toll-like receptors (TLRs) 2 and 4, on mononuclear phagocytes.<sup>21</sup> Consequent phagocytosis, and events that seem to include phagolysosome destabilization induced by the membranolytic properties of the crystals,<sup>23</sup> with associated protease release, generation of reactive oxygen species and lowering of intracellular potassium levels, promote activation of the NLRP3 (NLR

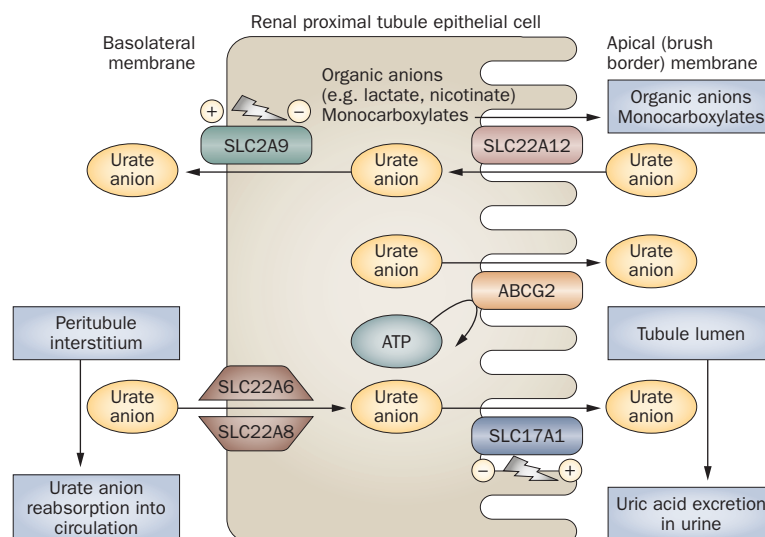
family pyrin domain containing 3; also known as cryopyrin) inflammasome, proteolytic cleavage and activation of caspase 1, proteolytic cleavage and maturation of pro-interleukin 1 $\beta$ , and secretion of mature interleukin (IL) 1 $\beta$  (Figure 4).<sup>22</sup> Other crystal-induced cytokines that promote gouty inflammation include tumor necrosis factor, IL-6, CXC-chemokine ligand (CXCL) 1 and CXCL8.<sup>20</sup>

### Current therapeutic approaches

The fundamental aims of gout treatment are to improve outcomes by short-term suppression and long-term elimination of gout flares, to induce durable resolution of tophi, and also to identify and effectively manage comorbidities, many of which promote hyperuricemia.<sup>24,25</sup> Unfortunately, treatment adherence seems to be poorer in patients with gout than in those with many other chronic diseases.<sup>26</sup> Adherence is particularly poor with regard to urate-lowering therapy in relatively young patients,<sup>27</sup> and reflects not only the behavior patterns of patients with gout, but also systematic deficiencies in education of these patients that need to be rectified. Furthermore, treatment strategies and drugs for hyperuricemia and gouty inflammation had seen limited advancements until recently. The limitations of these therapeutic approaches, together with the aforementioned changes in the epidemiology of gout, have spawned a new generation of patients who present with treatment-refractory tophaceous disease; many of these patients seek medical advice because of intolerance of allopurinol or a lack of effective serum urate-lowering by this drug, frequently owing to use of low, ineffective doses or the presence of stage 3 or worse CKD (defined as creatinine clearance <60 ml/min).<sup>7</sup> Fortunately, recent clinical and translational research has produced both new strategies for use of long-established drugs and emerging therapeutic agents for both gouty arthritis and hyperuricemia.

### Therapeutic advances for gouty arthritis

NSAIDs, glucocorticosteroids and colchicine are evidence-based, cost-effective treatments for acute gout<sup>24,28–30</sup> that nonselectively inhibit pathways of the neutrophil-driven inflammation that is characteristic of acute gout;<sup>20</sup> however, each of these agents is associated with risks of potentially severe adverse effects and drug–drug interactions, particularly in elderly patients and those with comorbidities such as CKD or diabetes mellitus.<sup>24</sup> Over the past decade, selective inhibition of cyclo-oxygenase (COX) 2 was observed to be comparably effective to NSAID therapy for acute gout, with considerably fewer adverse events.<sup>31</sup> The evidence basis for oral glucocorticosteroid treatment of acute gout is now established (with comparable efficacy of 5 day courses of ~30–35 mg daily prednisolone versus NSAIDs).<sup>29,30</sup> Oral glucocorticosteroids are a particularly appropriate primary treatment strategy in patients with moderate-to-severe CKD. Intra-articular glucocorticosteroid injection and systemic adrenocorticotrophic hormone are alternative options for gouty arthritis, but the former is not always feasible and the latter is costly and has limited availability.<sup>24</sup> Interestingly, peripheral

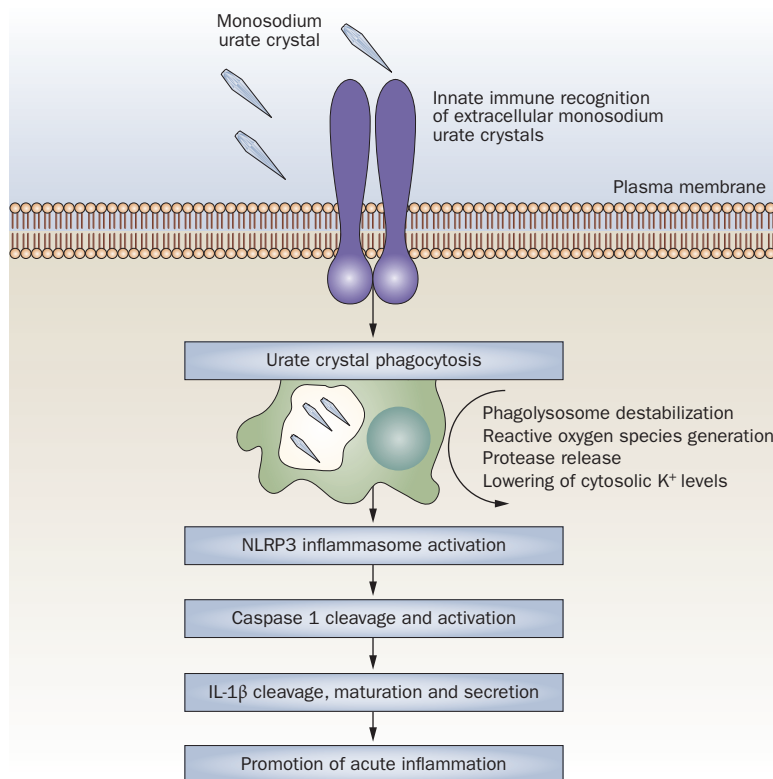


**Figure 3** | Mutations in renal urate transporters that are associated with gout.

The principal transporters in the current model of bidirectional urate anion movement in proximal tubule epithelial cells are shown. The balance between urate reabsorption and secretion is critically linked to net uric acid elimination in urine. This schematic shows the major transporters that are linked with serum urate levels and susceptibility to gout in genetic studies; other transporters at the apical and basolateral membrane (ABCC4 and SLC22A11, not shown) are also implicated in urate disposition. Urate reabsorption at the apical membrane is critically regulated by SLC22A12-mediated exchange of urate for intracellular organic anions (for example, lactate, nicotinate) and monocarboxylates (for example, pyrazinamide metabolites). The purine nucleoside transporter ABCG2 and the voltage-driven transporter SLC17A1 mediate urate secretion at the apical membrane. The hexose transport facilitator SLC2A9 carries out voltage-dependent urate anion transport, which at the basolateral membrane leads to urate reabsorption into the circulation. Some evidence also indicates a role for SLC2A9 at the basolateral membrane in reabsorption of urate anion in proximal tubule cells. Importantly, the uricosuric drugs probenecid and benzbromarone inhibit both SLC22A12 and SLC2A9. Abbreviations: ABC, ATP-binding cassette family member; SLC, solute carrier family member.

anti-inflammatory effects of phagocyte melanocortin receptor 3 agonism (not simply those of adrenal glucocorticosteroid induction) have been suggested to underlie the rapidity of adrenocorticotrophic hormone therapeutic action in gouty arthritis.<sup>31</sup> Moreover, pharmacologic melanocortin receptor 3 agonism by itself suppresses experimental urate-crystal-induced inflammation.<sup>32</sup>

Intravenous colchicine for acute gout was withdrawn from active marketing in the USA by the FDA in 2008, because of inappropriate use and multiple deaths being reported, which has made timely the re-examination of the evidence basis and dosing guidelines for oral colchicine in gout.<sup>28</sup> In colchicine regimens previously advocated for acute gout, several doses of 0.5 mg or 0.6 mg oral colchicine were administered at intervals of 1 h or 2 h until a satisfactory clinical response was achieved, severe gastrointestinal side effects occurred, or a predetermined maximum dose of ~5–7 mg was reached.<sup>28</sup> With such ‘high dose’ regimens, severe diarrhea (and to a lesser degree nausea and vomiting) were dose-limiting factors, since gastrointestinal side effects developed in most patients before a 50% reduction in pain was achieved.<sup>28</sup> Experimentally based guidelines from the European League Against Rheumatism advocate ‘low dose’ colchicine (0.5 mg three times a day) for acute



**Figure 4** | Urate crystal uptake by phagocytes, NLRP3 inflammasome activation, and IL-1 $\beta$  secretion in promotion of gouty inflammation. This schematic depicts the consequences of urate crystal uptake by phagocytes, which is driven by engagement of crystals at the cell surface mediated by innate immune mechanisms. In this model, uptake of urate crystals is followed by phagolysosome destabilization with protease release, reactive oxygen species generation, and lowering of cytosolic potassium levels. These events have the capacity to synergistically promote activation of the NLRP3 (also known as cryopyrin) inflammasome. Consequently, endoproteolytic activation of caspase 1 and cleavage and maturation of IL-1 $\beta$  promote the secretion of IL-1 $\beta$ , which has a central role in driving experimental urate crystal-induced inflammation. IL-1 $\beta$  has also been identified as a therapeutic target in gouty arthritis. Abbreviations: IL, interleukin; NLRP3, NACHT, LRR and PYD domains-containing protein 3.

gout.<sup>25</sup> In a large, randomized controlled, clinical trial, a self-administered 'low dose' colchicine regimen (1.2 mg followed by 0.6 mg 1 h later) that was specifically designed for use in the earliest phase of a gout flare (defined as within 12 h of onset), was considerably better tolerated and equivalent in efficacy to 'high dose' colchicine (4.8 mg over 7 h), and was superior in efficacy and comparably tolerated to placebo.<sup>33</sup>

IL-1 $\beta$  has a more central role than tumor necrosis factor in experimental urate-crystal-induced inflammation.<sup>34</sup> Studies to date indicate favorable results for off-label use of the IL-1 receptor antagonists anakinra and rilonacept to suppress pain and inflammation in small, open-label studies in patients with chronic, treatment-refractory gouty inflammation,<sup>34,35</sup> and for IL-1 inhibition as a strategy for gout flare prophylaxis in a placebo-controlled study of patients who initiated treatment with allopurinol.<sup>36</sup>

#### Therapeutic advances in serum urate lowering

Moderation of alcohol consumption, and diets tailored to control portion sizes, achieve an ideal body weight,

and to lessen insulin resistance (rather than unpalatable low purine diets), are recommended to limit gout flares and suppress hyperuricemia;<sup>7,24</sup> however, the maximum serum urate reduction achieved by diet alone is typically only ~1 mg/dl or up to 15%, which renders pharmacologic options necessary for most patients with gout. For containment of current drug costs in the urate-lowering algorithm for gout (Figure 5), the first choice for pharmacologic lowering of urate levels remains suppression of uric acid generation, using appropriate upward dose-titration of allopurinol,<sup>37</sup> which predominantly acts by xanthine oxidase inhibition.

#### Allopurinol: the 'treat-to-target' strategy

The evidence basis for a pharmacologic serum urate target of <6.0 mg/dl in gout has been established by the results of outcomes studies performed during the past decade, which show reductions of both gout flares and articular urate crystal burdens.<sup>38</sup> A temporarily lower serum urate target, such as <4 mg/dl, seems to be appropriate for limited-term, aggressive, tophus debulking in patients with a large burden of urate and associated, incapacitating chronic gouty arthritis with sizeable tophi.<sup>39</sup> Hence, the therapeutic approach to urate lowering in patients with gout is now 'treat to target' rather than treating to a specific allopurinol dose linked in a calibrated manner to renal function.<sup>38,39</sup>

FDA guidelines for allopurinol administration recommend progressive dose titration from a starting dose of 100 mg daily to a maximum of 800 mg daily, until the target serum urate level (<6.0 mg/dl) is achieved.<sup>37</sup> In clinical trials of hundreds of gout patients who had baseline serum urate levels approaching 10.0 mg/dl, allopurinol 300 mg daily achieved the serum urate target level of <6.0 mg/dl in only a minority (~40%) of patients with normal renal function.<sup>40–42</sup> Yet, in a small clinical study of gout patients, 372 mg was the mean allopurinol dose that normalized serum urate levels,<sup>43</sup> and, in another limited study, an increase in allopurinol dose from 300 mg to 600 mg daily normalized serum urate in ~80% of patients who had preserved renal function.<sup>44</sup> Unequivocally, allopurinol is underdosed in clinical practice, since the vast majority of allopurinol prescriptions are for 300 mg daily or less.<sup>45</sup> This situation reflects the persistence of non-evidence-based dosing guidelines that were originally designed to lessen the incidence of allopurinol hypersensitivity syndrome, which develops in 0.1–0.4% of patients, typically early in therapy, and has substantial mortality.<sup>37</sup> The risk of developing allopurinol hypersensitivity syndrome is increased in patients with CKD and those on thiazide diuretic therapy.<sup>37</sup> Possession of the MHC class I antigen HLA-B58 is a risk factor for severe cutaneous adverse reactions to allopurinol (such as Stevens-Johnson syndrome or toxic epidermal necrolysis) in individuals of European, Han Chinese, and Japanese ancestry;<sup>37</sup> however, HLA-B58 is common in these groups, and severe hypersensitivity reactions to allopurinol cannot be reliably predicted in individual patients.<sup>37</sup>

Clearly, dose adjustment of allopurinol according to renal function not only fails to prevent allopurinol hypersensitivity but also fails to adequately normalize

serum urate levels in most patients.<sup>46</sup> Reduction of the maximum allopurinol dose is advised in patients with severe CKD,<sup>37</sup> a strategy supported by retrospective analyses;<sup>47</sup> however, even after decades of allopurinol use in the clinic, specific dose limits for this drug relative to the glomerular filtration rate in patients with CKD have not been adequately determined, nor has the long-term safety of allopurinol at doses >300 mg daily in populations with either intact or impaired renal function.

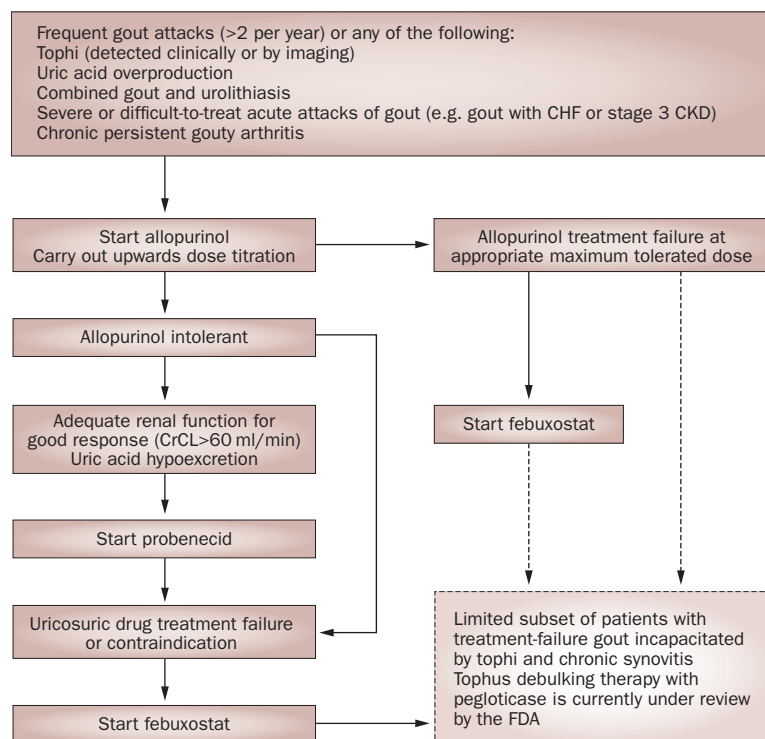
### Febuxostat

The selective xanthine oxidase inhibitor febuxostat,<sup>40,41</sup> unlike allopurinol, does not have a purine-like core structure (Figure 2), and febuxostat is primarily metabolized by hepatic oxidation and glucuronidation. Whereas renal elimination of the active allopurinol metabolite oxypurinol centrally regulates allopurinol pharmacodynamics,<sup>37</sup> renal elimination has a minor role in disposal (and dosing) of febuxostat. In clinical trials, adverse effects associated with febuxostat included rash (<2% incidence), but without reported severe cutaneous reactions. Diarrhea and elevated hepatic transaminases occurred in small proportions of patients.

Febuxostat has been approved at doses of 40 mg and 80 mg daily in the USA, and at up to 120 mg daily in Europe. In current clinical practice, to contain drug costs, primary use of febuxostat is reserved for patients with allopurinol hypersensitivity, intolerance, or treatment failure, including those in whom uricosuric therapy is not indicated or has failed. In randomized, 6–12 month, clinical trials that compared febuxostat to allopurinol in patients with gout who had mean serum urate levels approaching 10.0 mg/dl, 40 mg febuxostat daily achieved the serum urate target level of <6.0 mg/dl in ~45% of patients with preserved renal function. Febuxostat doses of 80 mg and 120 mg both achieved serum urate levels <6.0 mg/dl in most patients (for example, 67–72% of patients at 6 months and ~74% at 12 months for febuxostat 80 mg daily), whereas most patients failed to reach this serum urate target level on 300 mg allopurinol daily in the same trials.<sup>40,42</sup> In a subgroup of patients with stage 2–3 CKD, febuxostat 40 mg or 80 mg daily were both superior to renally dose-adjusted allopurinol (200–300 mg daily) in achieving levels of serum urate <6.0 mg/dl.<sup>42</sup> In small, non-controlled, open-label extension analyses, several years of febuxostat treatment achieved beneficial effects on quality of life parameters in association with marked tapering of gout flares and progressive reductions in the size of tophi.<sup>48</sup> Data from long-term controlled studies of febuxostat that include assessments of patient-centered outcomes and cost-effectiveness, and include a comparison to allopurinol dose-titrated above 300 mg daily, would be valuable.

### Uricosuric therapy in gout

Uricosuric agents enhance renal uric acid excretion, primarily by inhibiting urate anion reabsorption by proximal renal tubule epithelial cells (Figure 3). In patients with adequate renal function, potent uricosuric drugs such as probenecid and benzbromarone can be effective.<sup>49</sup> Moreover, uricosuric therapy can provide additive effects



**Figure 5** | Proposed therapeutic algorithm for serum urate lowering in patients with gout. This algorithm shows the author's recommended strategy for therapeutic serum urate lowering in patients with gout, based on current evidence and cost considerations, and taking into account alternative approaches in the event of therapeutic failure of the first choice (allopurinol). Not shown in the figure is the strategy (discussed in the text) of employing uricosuric therapy to provide additive effects with xanthine oxidase inhibition, since xanthine oxidase inhibitors decrease urinary uric acid excretion. Abbreviations: CHF, congestive heart failure; CKD, chronic kidney disease; CrCL, creatinine clearance.

with xanthine oxidase inhibitors, since the latter decrease urinary uric acid excretion.<sup>50</sup> The use of losartan and fenofibrate, alone or in combination with urate-lowering therapies<sup>7</sup> (which have transitory, moderate and weak uricosuric activity, respectively) could have adjunctive value in the prevention and management of hyperuricemia in patients with hypertension and dyslipidemia; such approaches, however, are not yet sufficiently evidence-based in those with gout.

Uricosuric agents particularly increase the risk of urolithiasis in acid urine.<sup>2</sup> Moreover, acid urine is a common feature of metabolic syndrome that is caused by defective bicarbonate renal output, mediated by insulin resistance. Unmet needs remain for potent uricosuric drugs other than probenecid (which becomes ineffective if creatinine clearance is <50 ml/min) and benzbromarone (which retains efficacy in patients with stage 3 CKD, but is only available outside the USA and on a restricted basis owing to its potential hepatotoxic effects). In my opinion, ideal uricosuric drugs would have once-daily dosing, retain their efficacy in stage 3 CKD, and be designed and formulated to minimize the risk of urolithiasis.

### 'Biologic' uricase agents

Uricase therapies for gout management could enable accelerated resolution of tophi, and such therapies have

been developed and optimized for the prevention of tumor lysis syndrome over the past few decades.<sup>12,51</sup> In pilot studies, however, off-label use of the nonpegylated, recombinant, fungal enzyme rasburicase in patients with severe, chronic gout did not demonstrate sustainable tolerability or efficacy beyond 6–12 months in most circumstances.<sup>51</sup> Pegylation of uricases suppresses their immunogenicity and increases the half-life of these agents.<sup>12</sup> In pivotal, phase III, clinical studies in patients with particularly severe gout, ~70% of whom had visible tophi, treatment with intravenous, pegylated, recombinant, pig–baboon uricase (pegloticase) 8 mg every 2 weeks achieved target serum urate levels of <6 mg/dl at 6 months in ~42% (intent to treat analysis).<sup>52</sup> This regimen also achieved complete resolution of tophi in 20% of patients by 13 weeks and ~40% by 25 weeks.<sup>53</sup> Overall, rates of robust responses to the biologic agent pegloticase compare favorably to those of American College of Rheumatology 70 responses and remission seen for studies of biologic agents in patients with rheumatoid arthritis. As such, pegloticase has the potential to provide a noteworthy clinical advance for patients with the most severe and incapacitating forms of chronic tophaceous gout. Buttressing this assessment are favorable results of controlled analyses of quality of life parameters,<sup>54</sup> and the observation that visible tophi can resolve after weeks to months of pegloticase therapy,<sup>53</sup> as opposed to the 2–5 years or more required to do so using conventional doses of xanthine oxidase inhibitors.

The immunogenicity of uricases, including pegloticase, has, however, limited their tolerability and efficacy. Antibodies to these drugs develop in most patients, despite the use of pegylation, and infusion reactions are common. In the pivotal, phase III, pegloticase trial, fexofenadine, acetaminophen, and hydrocortisone (200 mg) were administered before each infusion to limit infusion reactions.<sup>52,55</sup> Nonetheless, such reactions were observed in more than a quarter of patients, and were classified as moderate to severe in ~10%, though anaphylaxis was uncommon.<sup>52</sup> Over a period of several months, treatment-emergent antibodies to pegloticase impaired the drug's pharmacokinetics and pharmacodynamics in many patients.<sup>55</sup> High titers of antipegloticase antibodies (which were also linked with infusion reactions) were, however, rare in treatment responders—those with serum urate levels <6.0 mg/dl at 6 months.<sup>55</sup> Loss of the urate-lowering response is an indication that uricase therapy should be immediately discontinued. An important point to note is that in the first few months of pegloticase therapy, acute gout flares are frequent (they occur in up to 80% of patients),<sup>56</sup> but taper off with continued therapy in responders.<sup>52</sup> In addition, uricase treatment also has the capability to induce oxidative stress<sup>7</sup> mediated by generation of hydrogen peroxide.<sup>57</sup> The presence of glucose-6-phosphate dehydrogenase deficiency is an exclusion criterion for uricase treatment, to lessen the risk of drug-induced methemoglobinemia and hemolysis. Fortunately, the extent of oxidative stress induced by uricase treatment seems usually to be mitigated by the abundance of active catalase on erythrocytes.<sup>57</sup> Currently, the oxidative

intermediates of uric acid oxidation generated by uricase have no known biologic effects in human plasma.<sup>57</sup>

Short-term and long-term safety are not yet clearly defined for uricase therapy and, given that this treatment is more intensive and expensive than conventional oral urate-lowering drugs, consensus, evidence-based guidelines are needed. My own draft guidelines have proposed that uricase therapy should be reserved for selected patients who could potentially benefit from accelerated tophus debulking, for example to resolve incapacitating tophi linked with active synovitis, or under circumstances where patients have failed to respond to appropriate doses of oral urate-lowering therapies.<sup>51</sup> To date, pegloticase therapy has not yet been approved by the FDA for treatment-failure gout.

### Updated urate-lowering treatment algorithm

Key features of the serum urate-lowering treatment algorithm for gout proposed in Figure 5 are, first, that urate-lowering therapy, once indicated and initiated in patients with gout, should be continued lifelong. Second, to improve patients' outcomes and adherence, studies have validated that a central component of treatment should be gout flare prophylaxis, starting at the time of treatment initiation.<sup>24</sup> In patients commencing allopurinol urate-lowering therapy, low-dose daily oral colchicine prophylaxis of gout flares was demonstrated to reduce flare frequency and duration in a small placebo-controlled clinical trial.<sup>58</sup> Furthermore, phase III clinical trials that compared febuxostat to allopurinol have been particularly instructive with regard to the issue of gout flare prophylaxis, since early gout flares (in the first months of therapy) were more common in the subgroups of patients who demonstrated a superior serum urate-lowering response to either drug.<sup>40,42</sup> Gout flares induced by urate-lowering treatment, which probably reflect proinflammatory effects of synovial tophus destabilization and remodeling, were far more severe when flare prophylaxis with colchicine or low-dose naproxen was stopped at 8 weeks into urate-lowering treatment. Collective evidence supports a minimum of 6 months duration of gout flare prophylaxis in patients who start urate-lowering therapy.

### Conclusions

The prevalence and clinical complexity of gout have increased in recent years, but so has our understanding of the pathogenesis of hyperuricemia and gouty inflammation. Linkage of specific diet-related, alcohol-related and genetic factors with the risk of gout, as well as our increased understanding of the function of renal urate transporters, provide the opportunity for early stratification of the risks associated with incident gout, for the development of new strategies to modify dietary and lifestyle behavior, and for prescription of medicines that promote hyperuricemia. The sensitive and specific capacity of dual-energy CT imaging to detect tophi, by providing information distinct from that of physical examination, joint fluid analysis, plain radiography, ultrasonography and MRI, represents a major advance

that has the potential to reshape the definition of disease in gout by providing a new criterion for the tophus.

Quality of care gaps<sup>59–61</sup> need to be narrowed in patients with established gout, since these individuals exhibit poorer quality of life and physical function metrics, increased comorbidities, greater health care costs, and more adverse outcomes of cardiovascular disease than do matched control patients without gout.<sup>59,62,63</sup> Practitioners need to assess serum urate levels frequently in individuals at risk for gout, and during monitoring of ongoing therapy in patients with established gout, both to ensure treatment targets are achieved and to assess the patient's adherence to therapy.<sup>64</sup> Improved education of patients with gout will be critical to make much-needed improvements in treatment adherence<sup>26,27</sup> and patient-centered outcomes. Large clinical trials in patients with asymptomatic hyperuricemia are urgently needed to improve our understanding of the suggested direct effects of hyperuricemia in the pathogenesis of hypertension and atherosclerosis.

Treating gout flares is expensive,<sup>65</sup> and cost-effectiveness must be considered in these challenging times of financial stress and ongoing health care reform. Updated strategies for using established and inexpensive drugs (allopurinol, colchicine, glucocorticosteroids) have been defined in gout. Moreover, novel, highly selective therapies for

hyperuricemia and for gouty inflammation that are based on identification of specific targets are emerging or at hand; these therapies include febuxostat, biologic agents currently in phase II and III stages of clinical development (pegloticase, IL-1 antagonists), and novel uricosuric drugs. The availability of new options for patients with gout who have previously failed to respond to urate-lowering and anti-inflammatory treatment, and the promise of improved patient-centered outcomes in those with treatment-refractory disease, is the start of a new and exciting era for this ancient disease.

# Review criteria

Published articles for inclusion in this Review were sourced from the literature on epidemiology, clinical features and dietary aspects of gout and hyperuricemia, the treatment of gout and hyperuricemia, collected over the past 10 years. "Gout" and "hyperuricemia" were employed as the primary search terms, with "colchicine", "glucocorticosteroids", "diet", "allopurinol", "uricosuric", "febuxostat", "pegloticase", "uricase", "IL-1", "rilonacept" and "inflammasome" as secondary search terms. Papers discussed here included English-language full-text papers and conference abstracts.

1. Mandell, B. F. Clinical manifestations of hyperuricemia and gout. *Cleve. Clin. J. Med.* **75** (Suppl. 5), S5–S8 (2008).
2. Liebman, S. E., Taylor, J. G. & Bushinsky, D. A. Uric acid nephrolithiasis. *Curr. Rheumatol. Rep.* **9**, 251–257 (2007).
3. Wortmann, R. L. Gout and hyperuricemia. *Curr. Opin. Rheumatol.* **14**, 281–286 (2002).
4. Dalbeth, N. & Haskard, D. O. Mechanisms of inflammation in gout. *Rheumatology (Oxford)* **44**, 1090–1096 (2005).
5. Choi, H. K. *et al.* Dual energy computed tomography in tophaceous gout. *Ann. Rheum. Dis.* **68**, 1609–1612 (2009).
6. Feig, D. I., Kang, D. H. & Johnson, R. J. Uric acid and cardiovascular risk. *N. Engl. J. Med.* **359**, 1811–1821 (2008).
7. Biebert, J. D. & Terkeltaub, R. A. Gout: on the brink of novel therapeutic options for an ancient disease. *Arthritis Rheum.* **50**, 2400–2414 (2004).
8. Zharikov, S. *et al.* Uric acid decreases NO production and increases arginase activity in cultured pulmonary artery endothelial cells. *Am. J. Physiol. Cell Physiol.* **295**, C1183–C1190 (2008).
9. Hak, A. E. & Choi, H. K. Lifestyle and gout. *Curr. Opin. Rheumatol.* **20**, 179–186 (2008).
10. Wallace, K. L., Riedel, A. A., Joseph-Ridge, N. & Wortmann, R. Increasing prevalence of gout and hyperuricemia over 10 years among older adults in a managed care population. *J. Rheumatol.* **31**, 1582–1587 (2004).
11. Lawrence, R. C. *et al.* National Arthritis Data Workgroup. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum.* **58**, 26–35 (2008).
12. Sundy, J. S. & Hershfield, M. S. Uricase and other novel agents for the management of patients with treatment-failure gout. *Curr. Rheumatol. Rep.* **9**, 258–264 (2007).
13. Endou, H. & Anzai, N. Urate transport across the apical membrane of renal proximal tubules. *Nucleosides Nucleotides Nucleic Acids* **27**, 578–584 (2008).
14. Anzai, N. *et al.* Plasma urate level is directly regulated by a voltage-driven urate efflux transporter URATV1 (SLC2A9) in humans. *J. Biol. Chem.* **283**, 26834–26838 (2008).
15. Dehghan, A. *et al.* Association of three genetic loci with uric acid concentration and risk of gout: a genome-wide association study. *Lancet* **372**, 1953–1961 (2008).
16. Woodward, O. M. *et al.* Identification of a urate transporter, ABCG2, with a common functional polymorphism causing gout. *Proc. Natl Acad. Sci. USA* **106**, 10338–10342 (2009).
17. Urano, W. *et al.* Sodium-dependent phosphate cotransporter type 1 (NPT1) sequence polymorphisms in male patients with gout. *Ann. Rheum. Dis.* doi:10.1136/ard.2008.106856.
18. Matsuo, H. *et al.* Mutations in glucose transporter 9 gene SLC2A9 cause renal hypouricemia. *Am. J. Hum. Genet.* **83**, 744–751 (2008).
19. Brandstätter, A. *et al.* Sex-specific association of the putative fructose transporter SLC2A9 variants with uric acid levels is modified by BMI. *Diabetes Care* **31**, 1662–1667 (2008).
20. Cronstein, B. N. & Terkeltaub, R. The inflammatory process of gout and its treatment. *Arthritis Res. Ther.* **8** (Suppl. 1), S3 (2006).
21. Liu-Bryan, R., Scott, P., Sydlaske, A., Rose, D. M. & Terkeltaub, R. Innate immunity conferred by Toll-like receptors 2 and 4 and myeloid differentiation factor 88 expression is pivotal to monosodium urate monohydrate crystal-induced inflammation. *Arthritis Rheum.* **52**, 2936–2946 (2005).
22. Martinon, F., Pétrilli, V., Mayor, A., Tardivel, A. & Tschopp, J. Gout-associated uric acid crystals activate the NALP3 inflammasome. *Nature* **440**, 237–241 (2006).
23. Hornung, V. *et al.* Silica crystals and aluminum salts activate the NALP3 inflammasome through phagosomal destabilization. *Nat. Immunol.* **9**, 847–856 (2008).
24. Terkeltaub, R. A. Clinical practice. Gout. *N. Engl. J. Med.* **349**, 1647–1655 (2003).
25. Zhang, W. *et al.* EULAR evidence based recommendations for gout. Part II: management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann. Rheum. Dis.* **65**, 1312–1324 (2006).
26. Briesacher, B. A., Andrade, S. E., Fouayzi, H. & Chan, K. A. Comparison of drug adherence rates among patients with seven different medical conditions. *Pharmacotherapy* **28**, 437–443 (2008).
27. Harrold, L. R. *et al.* Adherence with urate-lowering therapies for the treatment of gout. *Arthritis Res. Ther.* **11**, R46 (2009).
28. Terkeltaub, R. A. Colchicine Update: 2008. *Semin. Arthritis Rheum.* **38**, 411–419 (2008).
29. Man, C. Y., Cheung, I. T., Cameron, P. A. & Rainer, T. H. Comparison of oral prednisolone/paracetamol and oral indomethacin/paracetamol combination therapy in the treatment of acute gout like arthritis: a double-blind, randomized, controlled trial. *Ann. Emerg. Med.* **49**, 670–677 (2007).
30. Janssens, H. J., Janssen, M., van de Lisdonk, E. H., van Riel, P. L. & van Weel, C. Use of oral prednisolone or naproxen for the treatment of gout arthritis: a double-blind, randomised equivalence trial. *Lancet* **371**, 1854–1860 (2008).
31. Rubin, B. R. *et al.* Efficacy and safety profile of treatment with etoricoxib 120 mg once daily compared with indomethacin 50 mg three times daily in acute gout: a randomized controlled trial. *Arthritis Rheum.* **50**, 598–606 (2004).

32. Getting, S. J., Lam, C. W., Chen, A. S., Grieco, P. & Perretti, M. Melanocortin 3 receptors control crystal-induced inflammation. *FASEB J.* **20**, 2234–2241 (2006).
33. Terkeltaub, R., Furst, D., Bennett, K., Kook, K. & Davis, M. Low dose (1.8 mg) vs high dose (4.8 mg) oral colchicine regimens in patients with acute gout flare in a large, multicenter, randomized, double-blind, placebo-controlled, parallel group study [abstract 1944]. *Arthritis Rheum.* **58** (Suppl.), S879 (2008).
34. So, A., De Smedt, T., Revaz, S. & Tschopp, J. A pilot study of IL-1 inhibition by anakinra in acute gout. *Arthritis Res. Ther.* **9**, R28 (2007).
35. Terkeltaub, R. et al. The IL-1 inhibitor rilonacept in treatment of chronic gouty arthritis: Results of a placebo-controlled, monosequence crossover, nonrandomized, single-blind pilot study. *Ann. Rheum. Dis.* **68**, 1613–1617 (2009).
36. Schumacher, R. H. et al. Placebo-controlled study of rilonacept for prevention of gout flares during initiation of urate-lowering therapy. *Ann. Rheum. Dis.* **68** (Suppl. 3), 680 (2009).
37. Chao, J. & Terkeltaub, R. A critical reappraisal of allopurinol dosing, safety, and efficacy for hyperuricemia in gout. *Curr. Rheumatol. Rep.* **11**, 135–140 (2009).
38. Perez-Ruiz, F. & Lioté, F. Lowering serum uric acid levels: what is the optimal target for improving clinical outcomes in gout? *Arthritis Rheum.* **57**, 1324–1328 (2007).
39. Edwards, N. L. Treatment-failure gout: a moving target. *Arthritis Rheum.* **58**, 2587–2590 (2008).
40. Becker, M. A. et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N. Engl. J. Med.* **353**, 2450–2461 (2005).
41. Schumacher, H. R. Jr, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. *Arthritis Rheum.* **59**, 1540–1548 (2008).
42. Becker, M. et al. A phase 3 randomized, controlled, multicenter, double-blind trial (RCT) comparing efficacy and safety of daily febuxostat (FEB) and allopurinol (ALLO) in subjects with gout [abstract L11]. *Arthritis Rheum.* **58** (Suppl.), (2008).
43. Perez-Ruiz, F. et al. Efficacy of allopurinol and benzbromarone for the control of hyperuricaemia. A pathogenic approach to the treatment of primary chronic gout. *Ann. Rheum. Dis.* **57**, 545–549 (1998).
44. Reinders, M. K. et al. A randomized controlled trial on the efficacy and tolerability with dose-escalation of allopurinol 300–600 mg/day versus benzbromarone 100–200 mg/day in patients with gout. *Ann. Rheum. Dis.* **68**, 892–897 (2009).
45. Sarawate, C. A. et al. Gout medication treatment patterns and adherence to standards of care from a managed care perspective. *Mayo Clin. Proc.* **81**, 925–934 (2006).
46. Dalbeth, N. & Stamp, L. Allopurinol dosing in renal impairment: walking the tightrope between adequate urate lowering and adverse events. *Semin. Dial.* **20**, 391–395 (2007).
47. Perez-Ruiz, F., Hernando, I., Villar, I. & Nolla, J. M. Correction of allopurinol dosing should be based on clearance of creatinine, but not plasma creatinine levels: another insight to allopurinol-related toxicity. *J. Clin. Rheumatol.* **11**, 129–133 (2005).
48. Schumacher, H. R., Jr, Becker, M. A., Lloyd, E., MacDonald, P. A. & Lademacher, C. Febuxostat in the treatment of gout: 5-yr findings of the FOCUS efficacy and safety study. *Rheumatology (Oxford)* **48**, 188–194 (2009).
49. Perez-Ruiz, F., Calabozo, M., Pijoan, J. I., Herrero-Beites, A. M. & Ruibal, A. Effect of urate-lowering therapy on the velocity of size reduction of tophi in chronic gout. *Arthritis Rheum.* **7**, 56–60 (2002).
50. Reinders, M. K., van Roon, E. N., Houtman, P. M., Brouwers, J. R. & Jansen, T. L. Biochemical effectiveness of allopurinol and allopurinol-probenecid in previously benzbromarone-treated gout patients. *Clin. Rheumatol.* **26**, 1459–1465 (2007).
51. Terkeltaub, R. Learning how and when to employ uricase as bridge therapy in refractory gout. *J. Rheumatol.* **34**, 1955–1958 (2007).
52. Sundry, J. S. et al. Efficacy and safety of intravenous (IV) pegloticase (PGL) in subjects with treatment failure gout (TFG): Phase 3 results from GOUT1 and GOUT2 [Abstract]. *Arthritis Rheum.* **58** (Suppl.), S400 (2008).
53. Baraf, H. S. et al. Tophus response to pegloticase (PGL) therapy: pooled results from GOUT1 and GOUT2, PGL phase 3 randomized, double blind, placebo-controlled trials [Abstract]. *Arthritis Rheum.* **58** (Suppl.), S176 (2008).
54. Becker, M. A. et al. Quality of life and disability in patients with treatment-failure gout. *J. Rheumatol.* **36**, 1041–1048 (2009).
55. Becker, M. A. et al. Immunoreactivity and clinical response to pegloticase (PGL): pooled data from GOUT1 and GOUT2 PGL phase 3 randomized, double blind, placebo-controlled trials [abstract 1945]. *Arthritis Rheum.* **58** (Suppl.), S880 (2008).
56. Sundry, J. S. et al. Reduction of plasma urate levels following treatment with multiple doses of pegloticase (polyethylene glycol-conjugated uricase) in patients with treatment-failure gout: results of a phase II randomized study. *Arthritis Rheum.* **58**, 2882–2891 (2008).
57. Terkeltaub, R. Gout. Novel therapies for treatment of gout and hyperuricemia. *Arthritis Res. Ther.* **11**, 236 (2009).
58. Borstad, G. C. et al. Colchicine for prophylaxis of acute flares when initiating allopurinol for chronic gouty arthritis. *J. Rheumatol.* **31**, 2429–2432 (2004).
59. Singh, J. A. Quality of life and quality of care for patients with gout. *Curr. Rheumatol. Rep.* **11**, 154–160 (2009).
60. Mikuls, T. R. Quality of care in gout: from measurement to improvement. *Clin. Exp. Rheumatol.* **25** (Suppl. 47), 114–119 (2007).
61. Neogi, T., Hunter, D. J., Chaisson, C. E., Allensworth-Davies, D. & Zhang, Y. Frequency and predictors of inappropriate management of recurrent gout attacks in a longitudinal study. *J. Rheumatol.* **33**, 104–109 (2006).
62. Singh, J. A. & Strand, V. Gout is associated with more comorbidities, poorer health-related quality of life and higher healthcare utilisation in US veterans. *Ann. Rheum. Dis.* **67**, 1310–1316 (2008).
63. Krishnan, E., Svendsen, K., Neaton, J. D., Grandits, G. & Kuller, L. H. MRIT Research Group: long-term cardiovascular mortality among middle-aged men with gout. *Arch. Intern. Med.* **168**, 1104–1110 (2008).
64. Wall, G. C., Koenigsfeld, C. F., Hegge, K. A. & Bottenberg, M. M. Adherence to treatment guidelines in two primary care populations with gout. *Rheumatol. Int.* doi:10.1007/s00296-009-1056-7.
65. Wu, E. Q. et al. Disease-related and all-cause health care costs of elderly patients with gout. *J. Manag. Care Pharm.* **14**, 64–175 (2008).

## Acknowledgments

Dr Terkeltaub is supported by the Research Service of the US Department of Veterans Affairs. Charles P. Vega, University of California, Irvine, is the author of and is solely responsible for the content of the learning objectives, questions and answers of the MedscapeCME-accredited continuing medical education activity associated with this article.