Advances and unmet needs in gout

Gout is a common condition representing the most frequent inflammatory arthritis occurring in men with an overall prevalence of approximately 1–3%. Epidemiological studies have reported an increase in the incidence and prevalence of gout over the past few decades, underscoring gouty arthritis as a growing public health problem. Novel therapies, including pegloticase, febuxostat and agents targeting IL-1, hold promise in the treatment of both acute and chronic gout. Despite recent advances in our understanding of gout epidemiology and the development of novel treatments, gout care continues to be characterized by suboptimal care. This article reviews several recent advances in gout, and points out potential 'unmet needs' warranting further investigation.

KEYWORDS: epidemiology ■ gout ■ quality of care ■ treatment

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Gout is a common disorder characterized by chronic hyperuricemia and recurrent attacks of acute inflammatory arthritis, affecting approximately 1–3% of the population. Recently, gout has received increased attention partly owing to the development of new therapies (including the first approved gout treatment in more than 40 years) and an improved understanding of its pathophysiology. Recent research has also shed important insight into its epidemiology, including several novel environmental and genetic risk factors for the development of hyperuricemia and gout. Despite being described by the Egyptians in 2640 BC [1], and recognizing recent substantive gains in research, gout continues to be characterized by suboptimal treatment resulting in high morbidity and unacceptable societal costs. This article discusses the current status of gout, highlighting the many 'unmet needs' that continue to beleaguer the care of these patients.

Epidemiology

Significant progress has been made with several recent studies examining gout epidemiology, including seminal investigations of gout frequency, its risk factors, and the relationship of hyperuricemia and gout with disease-related comorbidity and mortality.

■ Incidence & prevalence

Data from the National Health and Nutrition Examination Survey (NHANES)-III estimated the prevalence of gout to be 2.7% in the USA, with the highest rates observed in elderly men (11% in men 70–79 years of age) [2]. A slightly lower gout frequency was observed using the national UK General Practice Research Database (GPRD), with a prevalence of 1.4% in 1999 [3]. Similar to results from NHANES-III, gout was most common among elderly men with a prevalence rate of approximately 7% in men over the age of 65 years [3]. These reports also confirm a striking male predominance of gout with male-to-female ratios approaching 4:1, ratios that decline dramatically in older age groups as gout incidence (which is exceedingly low in younger women) increases in postmenopausal women.

Importantly, it appears both the incidence and prevalence of gout have increased worldwide over the past few decades [4–6]. Investigators from the Rochester Epidemiology Project (MN, USA) observed a more than twofold increase in the incidence of primary gout (patients without diuretic exposure) over a 20-year period ending in 1996 [4]. Similar increases in gout frequency have been reported in both New Zealand [6] and the UK [5]. While reasons for the apparent increase in gout burden are not known, there has been substantial speculation that this reflects trends in select gout risk-factor prevalence, including increased rates of obesity and metabolic syndrome (see below) [7–9].

The incidence and prevalence of gout have been difficult to define with precision owing to diagnostic uncertainty and the frequent reliance on self-reported disease or diagnostic codes in epidemiological studies [3–6,9], which are methods associated with substantial misclassification. Gout classification criteria (Box 1), developed for such studies, are often cumbersome and impractical to apply in research practice. With rheumatologist assessment as the 'gold standard', use of

Box 1. Gout classification criteria.

1963 Rome criteria
- Painful joint swelling; abrupt onset, clearing in 1–2 weeks
- Serum uric acid: 7 mg or more in males; 6 mg or more in females
- Presence of tophi
- Presence of urate crystals in synovial fluid

1966 New York criteria
- Two attacks of painful limb joint swelling; abrupt onset and remission in 1–2 weeks
- An attack involving a big toe – as described in the above point
- Presence of tophi
- Response to colchicine – major reduction in inflammation within 48 h

1987 American College of Rheumatology criteria
- More than one attack of acute arthritis
- Maximum inflammation within 1 day
- Monoarthritis attack
- Redness observed over joints
- First metatarsalphalangeal painful or swollen
- Unilateral first metatarsalphalangeal joint attack
- Unilateral tarsal joint attack
- Tophus (proven or suspected)
- Hyperuricemia
- Asymmetrical swelling within a joint on x-ray
- Subcortical cysts without erosions on x-ray
- Synovial fluid cultures negative for organisms

Rome or New York criteria: each requires two or more criteria for the diagnosis of gout. The presence of monosodium urate crystals in synovial fluid supercedes this requirement in the New York classification criteria. American College of Rheumatology criteria require either monosodium urate crystals in synovial fluid or 6 out of 12 criteria for the diagnosis of gout.

these criteria yields only modest-to-poor predictive values for identifying gout [10,11]. To accurately define the true public health burden of gout at present, definitive documentation of tophus formation or monosodium urate crystals in synovial fluid is needed, but this is often considered unfeasible. For instance, among incident gout patients identified in the Rochester Epidemiology Project less than a third underwent diagnostic arthrocentesis [4]. In addition to quantifying gout frequency, early diagnosis in gout is important to optimize long-term health outcomes. Problems with the classification or diagnosis of hyperuricemia and gout are further hampered by the lack of standardization in crystal analysis and serum urate measurements. Many clinical laboratories, for instance, still consider serum uric acid levels greater than 6.8 mg/dl (360 µmol/l) to be 'within normal limits', based solely on population norms rather than biologic science. Thus, an improved means of facilitating early and accurate identification of these patients represents a critical unmet need in gout care.

■ **Risk factors for hyperuricemia & gout**

Several recent reports have provided insight into epidemiological risk factors for the development of hyperuricemia and gout, with research from the Health Professional Follow-up Study (HPFS) adding seminal understanding to the relationship of dietary/nutritional factors with gout risk (**Box 2**). Compared to those with low daily intake, individuals in the highest quintile of purine-rich meat and seafood consumption had an approximate 40–50% increased risk for gout [12]. Similarly, the intake of alcoholic beverages was positively associated with gout risk, a risk that appears to be dose dependent and most striking for beer consumption [13]. Conversely, these investigators found that increased intake of dairy products significantly reduced gout risk [12]. In more recent studies, both vitamin C and coffee intake have been shown to be protective against the development of gout [14,15]. Precisely how these various dietary factors influence the synthesis and/or excretion of serum urate and influence gout risk remains to be defined. Further insight into the mechanisms of action underpinning these dietary influences will be critical in informing future gout treatments and prevention.

Of the many dietary factors examined in gout risk, perhaps none have garnered more attention than the intake of high-fructose corn syrup, a factor that has also been implicated in the rapidly rising incidence of obesity and Type 2 diabetes mellitus since its introduction as a food 'supplement' in the late 1960s [7,8,16,17]. It has been suggested that fructose directly leads to hyperuricemia via fructokinase-dependent ATP breakdown and that fructose-induced hyperuricemia plays a causal role in the epidemic of obesity and metabolic syndrome [18]. In addition, high fructose ingestion has been shown to increase blood pressure, leading to features of the metabolic syndrome in otherwise healthy adult males [19]. Interestingly, this increase in blood pressure was blunted by administration of allopurinol, and allopurinol reduced the number of new cases of metabolic syndrome in this population [19]. In the HPFS, individuals with the highest fructose consumption (highest quintile vs lowest quintile) were substantially more likely to develop gout over follow-up (HR: 2.02; 95% CI: 1.49–2.75), an association that was independent of BMI, alcohol use and other gout risk factors [8]. In this study, consumption of two or more soft drinks per day (a common source of dietary fructose) was associated with an approximately 80% increased risk of developing gout. Future studies will be needed to examine the impact that dietary modifications focused on reducing fructose intake might have on reducing gout burden.

Genetic factors have long been implicated in gout risk with reports of familial clustering of disease and observations of 'precocious' gout in patients with rare genetic disorders including Lesch-Nyhan disease (X-linked deficiency in hypoxanthine guanine phosphoribosyltransferase) and familial juvenile hyperuricemic nephropathy (autosomal dominant inheritance of a mutation in uromodulin). Recently, using genome-wide association studies, researchers have identified genetic loci associated with increased uric acid levels and the development of gout in both African–Americans and those of European ancestry [20]. Specifically, single nucleotide polymorphisms in *SLC2A9*, *SLC17A3* and *ABCG2* were associated with modest but significant increases in gout risk. These findings again emphasize the importance of renal handling of urate since these genes code for proteins that are expressed in the renal tubules. Genetic studies of hyperuricemia and gout susceptibility arguably lag behind those conducted in other less common rheumatic diseases, such as rheumatoid arthritis and lupus, where burgeoning data from genome-wide association studies have shed important light on the pathogenesis and potential interventions for these conditions. Similar advances in gout hold substantial promise in advancing our understanding of this ancient disease.

■ Relationship of hyperuricemia & gout with morbidity & mortality

Current research has increasingly focused on the association between hyperuricemia and gout with comorbid conditions including the metabolic syndrome, obesity, hypertension and cardiovascular disease [21,22]. Krishnan *et al.* have demonstrated that gout patients are at a significantly higher risk for both myocardial infarction and cardiovascular mortality compared with those without gout, a risk not observed among individuals with asymptomatic hyperuricemia [23]. Similar results were recently reported by Kuo *et al.* in a longitudinal study of Taiwanese patients [24]. In an intriguing retrospective study of US veterans, urate-lowering therapy with allopurinol was associated with significant survival benefit (HR: 0.78; 95% CI: 0.67–0.91) among patients with hyperuricemia [25]. It is possible that serum urate may have direct effects on other cardiovascular risk factors, particularly since hyperuricemia has been shown to contribute to the development of hypertension in animal models [26], and allopurinol leads to significant, albeit modest, blood pressure reductions among children

with essential hypertension [27]. The studies by Krishnan [23] and Kuo [24] would suggest that gout and secondary inflammation may play a more direct causal role in cardiovascular morbidity and mortality than elevations in serum urate. Studies examining the links between hyperuricemia and gout with cardiovascular morbidity and mortality represent essential steps in reducing disease burden among gout sufferers.

Treatment

Gout has undergone a renaissance of sorts with recent advances in the treatment of both acute and chronic gout. However, it is arguable that healthcare providers have had highly effective options at their disposal for many years, yet gout continues to be characterized by suboptimal quality of care [28–32]. Current treatment options of both acute and chronic gout are summarized in this section, highlighting recent advances in gout care and remaining areas of need. Recent recommendations from the European League Against Rheumatism (EULAR) remind us that both nonpharmacologic and pharmacologic treatment strategies should be optimized in gout patients [33]. Each acute gout flare provides an excellent window of opportunity to address lifestyle modifications (e.g., weight reduction, moderation in alcohol consumption and low purine diet) and medication counseling with a goal of optimizing treatment adherence.

Many previous studies comparing gout treatments utilized outcome measures that were neither validated or standardized, limiting inferences that could be made regarding the utility of specific interventions and rendering comparisons across studies futile. The Outcome Measures in Rheumatology (OMERACT) Special Interest Group on Gout has been instrumental in the early implementation of efforts to improve the measurement of gout outcomes in clinical trials. This group of leading gout experts

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Box 2. Dietary risk factors for the development of hyperuricemia and/or gout.

Increased risk
- Sugar-sweetened soft drinks [8]
- Fructose-rich fruits and juices [8]
- Purine-rich meats [12]
- Purine-rich seafood [12]
- Alcohol (e.g., beer and spirits) [13]

Decreased risk
- Dairy products [12]
- Coffee [15]
- Vitamin C [14]

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has identified key outcome measures for clinical trials examining treatment interventions in both acute and chronic gout [34,35]. In a related effort, Taylor and colleagues are developing a gout flare definition [36], critical because gout flare represents a central outcome in gout treatment trials. To date, this has been a poorly understood outcome, with previous clinical trials relying on patient or investigator reports of flare. While the identification of outcomes is an important first step in improving clinical trials in gout, their validation and implementation in clinical trial design represents an ongoing unmet need.

■ Acute gout

The pharmacologic treatment of acute gouty attacks has historically focused on the use of NSAIDs, colchicine or corticosteroids. Recommendations pertinent to their use are largely empiric, and adequate studies comparing efficacy and cost–effectiveness of different treatment strategies are sorely lacking. Although NSAIDs are frequently considered to be first-line agents for acute gout, there has been only one placebo-controlled, randomized controlled trial evaluating the use of NSAIDs in acute gout. In this study, tenoxicam was shown to provide superior pain control at day 1 versus placebo, but both groups were equal by day 4 [37]. Many other studies (primarily open-label studies and case series) have compared different NSAIDs and shown equal efficacy [38–40], indicating class effectiveness. Indomethacin has historically been the NSAID of choice; however, indomethacin and all nonselective NSAIDs are fraught with potentially serious side effects, often rendering them suboptimal for administration in the population most affected with gout, including elderly patients and those with significant comorbid illness. Early enthusiasm that selective COX-2 inhibitors (e.g., rofecoxib and celecoxib) would prove safer than traditional nonselective NSAIDs has been dampened following observations of increased cardiovascular events associated with their use [41], a problem already increased in the context of gout.

Colchicine is recognized as an effective therapy for the treatment and prevention of acute gout, with reports of colchicine use as long as 2000 years ago [1]. Despite its long and venerable history in gout care, the first controlled trial of colchicine was not published until 1987 [42]. In this small study, 43 patients with acute gout received either placebo or high-dose colchicine (1 mg initially followed by 0.5 mg every 2 h until toxicity or resolution of symptoms) with the colchicine group demonstrating significant

reduction in pain at 48 h versus placebo. Perhaps more striking was the finding that all patients receiving colchicine suffered gastrointestinal adverse events that included vomiting or diarrhea [42]. The poor tolerability of high-dose colchicine has frequently led healthcare providers to try alternative dose schedules with hopes of decreasing its side-effect profile. Reported in abstract form, investigators recently evaluated the use of low-dose (1.8 mg given as 1.2 mg initially followed by 0.6 mg in 1 h) and high-dose (4.8 mg given as 1.2 mg followed by 0.6 mg hourly for 6 h) colchicine with placebo in the treatment of acute gout. Its authors reported comparable efficacy in both colchicine groups, with the low-dose group showing similar rates of diarrhea to the placebo arm (23 vs 14%; OR: 1.86; 95% CI: 0.74–4.69) [43]. The low-dose treatment studied by Terkeltaub and colleagues corresponds with the EULAR recommended dosing strategy of 0.5 mg three times daily [33].

Corticosteroids have also been used successfully in the treatment of acute gout, especially in patients with complications or contraindications to NSAIDs and/or colchicine. As with all treatment strategies in acute gout, the use of corticosteroids has been poorly studied. No studies have evaluated the use of steroids versus placebo for the treatment of gout. At least one small study compared steroids to NSAIDs and adrenocorticotropic hormone [44], but evidence has been lacking to recommend corticosteroids as first-line therapy, until recently. In a recent randomized controlled trial, investigators compared the use of prednisolone 35 mg daily for 5 days to naproxen 500 mg twice daily (b.i.d.) in patients with acute crystal-proven gout [45]. At 90 h, the reduction of pain as evaluated using a 100-mm visual analog scale was equivalent amongst the two groups. The authors concluded that prednisolone should be considered as a 'first-line therapy' for acute gout, based on a safer short-term side-effect profile than naproxen and potential cost savings with prednisolone. Corticosteroids have the added benefit of an intra-articular route of administration, limiting the risk of systemic toxicity. One study evaluated the use of low-dose intra-articular triamcinolone ($\leq$10 mg) in 19 patients with crystal-proven gouty arthritis. All 19 patients (20 acute gout flares) had complete resolution of pain and swelling at 48 h [46]. Recognizing that studies comparing intra-articular corticosteroids with other systemic therapies are lacking, the former appears to be safe and well tolerated, particularly in patients with monoarticular arthritis.

As the treatment of acute gout continues to evolve, newer therapies, including IL-1 antagonism will probably prove beneficial in patients with difficult-to-treat or refractory acute gout. Recent advances in our understanding of disease pathogenesis have shown that the NALP3 component of the inflammasome plays a central role in acute gout, mediating IL-1β release and promoting acute inflammation (Figure 1). IL-1 antagonists, including anakinra and rilonacept, have been reported in case reports [47,48] and at least two pilot studies [49,50] to improve the symptoms of refractory gout. One pilot study with rilonacept (IL-1 Trap) demonstrated significant decreases in patient self-reported pain scores and high-sensitivity C-reactive protein levels in patients with chronic active gouty arthritis [50]. Experience in rheumatoid arthritis and the autoinflammatory diseases has shown IL-1 antagonism to be relatively well tolerated, with injection site reactions and infection the most commonly reported adverse events. Patients with severe refractory gout often have several comorbid conditions, and the safety and cost–effectiveness of IL-1 antagonism in this population warrants further study, particularly in light of higher costs associated with biologic treatments referent to traditional anti-inflammatory approaches used in acute gout. The role of anti-IL-1 therapy will probably play an increasingly important role in the future of gout treatment.

It is somewhat surprising that a disease with the prevalence and impact of gout has been subject to only scant rigorous scientific study. As a result, studies are critically needed to determine optimal treatment strategies in acute gout, investigations addressing:

▪ Comparative and cost–effectiveness of available treatment options;

▪ The relative safety of available therapies in patients with gout-related comorbidity, particularly patients with renal impairment, hypertension and cardiovascular disease;

▪ The role of 'combination therapies';

▪ The role of novel therapies;

▪ The optimal timing for initiation of uric acid-lowering therapy.

▪ Chronic gout & urate-lowering therapy

It is increasingly clear that the success of urate-lowering therapy is dependent on the adoption of a clear and standardized therapeutic goal. Based on EULAR recommendations, healthcare providers should lower and maintain serum urate levels below 6.0 mg/dl (360 µmol/l) to reduce or even eliminate gout flares in the long term, with the understanding that some patients may require even lower serum urate levels for tophus resolution [33]. 'Rebound' gout flares remain the most common 'adverse effect' associated with the initiation of urate-lowering treatments [51,52], underscoring the need for anti-inflammatory prophylaxis with the initiation of these treatments. Recent Phase III clinical trials have shown that low-dose colchicine (typically 0.6 mg every day to b.i.d.) or naproxen (250 mg b.i.d.) are both effective in reducing gout flares during the initiation of urate-lowering therapy [53,54]. In a placebo-controlled study of

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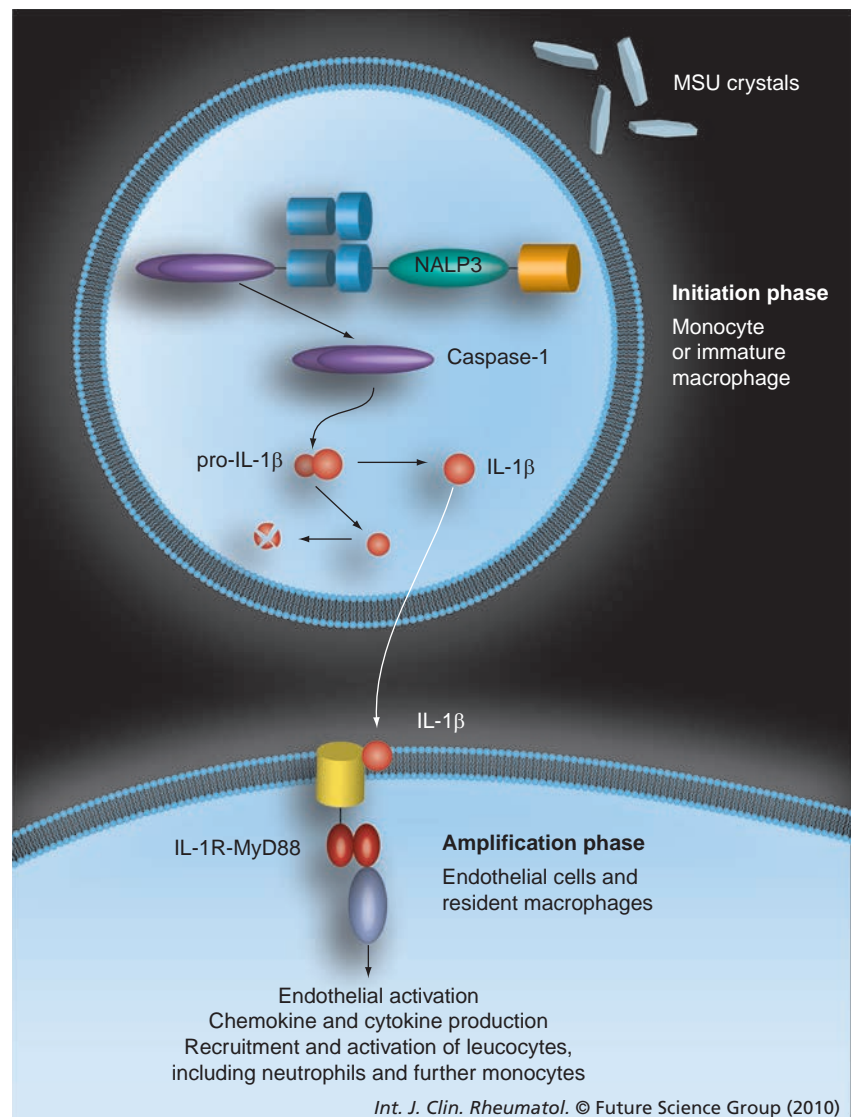
Figure 1. A new paradigm for the pathophysiology of acute gouty inflammation: the central role of the NALP3 inflammasome.
MSU: Monosodium urate.
Adapted with permission from [68].

43 gout patients, Borstad and colleagues found that low-dose colchicine was superior to placebo in reducing gout flares with the initiation of allopurinol, a benefit that extended throughout the duration of the 6-month study [55]. The potential efficacy of other anti-inflammatory agents (i.e., corticosteroids or alternative NSAIDs) and the optimal duration for prophylaxis are unknown, important information that awaits further study.

Allopurinol and uricosuric agents have long been the mainstay of treatment in chronic gout. Relative to uricosurics, allopurinol continues to be the first-line urate-lowering agent based on its effectiveness in both urate overproducers and underexcretors, its ease of administration with once-daily dosing and its potential for use in patients with renal impairment. Although first approved in the 1960s, interest in allopurinol has increased over the last 10 years owing to the development of novel urate-lowering medications, including the recent approval of febuxostat. Allopurinol, a hypoxanthine analog, and its active metabolite oxypurinol, inhibit xanthine oxidase and thus lead to decreased serum and urine urate levels. Allopurinol is approved in doses up to 800 mg daily, but, despite prior dosing recommendations and knowledge that only a limited number of patients on daily doses of 300 mg or less reach appropriate serum urate levels [53,54], allopurinol continues to be routinely underdosed with a mean daily dose of less than 300 mg [56].

The impact of allopurinol 'underdosing' is borne out in recent clinical trials examining the efficacy of 'standard' fixed doses of 300 mg/day. Analysis of Phase III febuxostat trials revealed that only 21–22% of patients on allopurinol 300 mg per day reached the EULAR recommended serum urate level of less than 6.0 mg/dl (360 µmol/l) [53,54], a proportion that decreased to 13% if the strict British recommendations of less than 5 mg/dl (300 µmol/l) were applied [53]. A study evaluating the use of allopurinol versus benzbromarone (a uricosuric agent) highlights the potential efficacy associated with allopurinol doses exceeding 300 mg per day. In this study, dose escalation of allopurinol to 600 mg daily in patients with relatively preserved renal function (creatinine clearance >50 ml/min) significantly increased the percentage of patients achieving a serum urate concentration less than 6.0 mg/dl (360 µmol/l) to 85%, with 78% of patients achieving a serum urate less than 5.0 mg/dl (300 µmol/l) [57].

Allopurinol tolerability, its potential side-effect profile and suboptimal patient adherence all negatively impact the ability to reach therapeutic serum urate levels. An administrative claims-based study reported poor compliance in patients prescribed allopurinol [31], a finding that has been corroborated by others [58]. Concerns of allopurinol hypersensitivity syndrome (AHS) in patients with renal insufficiency also limit the appropriate use of allopurinol. AHS is historically characterized by severe rash, eosinophilia, fever, hepatitis, worsening renal function and leukocytosis [59], with a cumulative incidence of 0.41–0.72% in patients with renal impairment [60]. Risk factors for AHS, reported in a case series, have included allopurinol initiation in the context of renal insufficiency and concurrent diuretic therapy [59]. While the precise cause of AHS is unknown, it is hypothesized that elevated oxypurinol levels may contribute to AHS [59]. Guidelines released in 1984 set out to provide optimal allopurinol dosing based on renal function with the goal of reducing AHS risk. It is important to recognize that these guidelines are based primarily on pharmacokinetic data [59], rather than patient outcomes or the occurrence of drug-related adverse effects. Whether renal dosing of allopurinol reduces AHS risk is not known. In a recent investigation reported in abstract form, allopurinol dose escalation beyond these guideline recommended doses was not associated with an increased incidence of AHS [61]. In the absence of evidence-based guidelines, further studies are clearly warranted to establish optimal allopurinol dosing strategies in gout complicated by chronic kidney disease.

Febuxostat is a potent nonpurine selective xanthine oxidase inhibitor recently approved for use in chronic hyperuricemia resulting in gout, the first agent marketed for the management of chronic gout in decades. Phase III trials comparing standard-dose allopurinol (300 mg) with febuxostat (80, 120 or 240 mg) found febuxostat to be superior to allopurinol in the reduction of serum uric acid concentrations [53,54]. Limited data from these efforts also suggested that febuxostat could have an important role in allopurinol-intolerant or -resistant patients. Febuxostat is primarily metabolized by the liver, with less than 5% excreted unchanged by the kidney [62], with pharmacokinetic and clinical data suggesting that febuxostat is well tolerated in mild-to-moderate renal insufficiency. With only a limited number of patients with renal insufficiency enrolled in Phase III trials of febuxostat (none with serum creatinine concentrations exceeding 2 mg/dl), conclusions regarding its safety in this populationare premature.

It is important to note that these trials compared fixed doses of febuxostat and allopurinol, a practice that is counter to 'real-life' treatment prescribing strategies that are implemented with judicious dose escalation of urate-lowering therapy with a serum urate goal in mind. Trials comparing treatment strategies that use dose escalation of allopurinol versus febuxostat in gout patients (including those with serious comorbidity) are needed. End points, including the proportion of patients achieving goal serum urate levels, gout flares, cardiovascular protective effects, severe adverse events, mortality and cost–effectiveness, would further inform the care of chronic gout sufferers.

The management of treatment failure gout, disease that is refractory to currently available therapies, continues to challenge healthcare providers. Pegloticase, a genetically engineered recombinant PEGylated mammalian uricase, offers potentially important disease-modifying effects. First given orphan drug status in 2001, pegloticase has been shown in Phase II/III trials to significantly reduce serum urate levels versus placebo [63,64]. Secondary end points, including complete tophus resolution and improvement in physician global assessment, were also significantly improved compared with placebo. The role that this agent will eventually play, whether as a 'salvage' therapy in treatment failure gout or as an induction therapy in patients with severe disease, remains to be seen.

Quality of care in gout

Gout is unique among chronic diseases in that its basic science is well understood, appropriate and effective treatments have been available for nearly half a century, and physicians report a high comfort level in treating gout patients. It is perhaps counterintuitive then that gout continues to be characterized by suboptimal care. Recent efforts aimed at improving gout care have focused on the development of evidence- and consensus-based guidelines, quality of care indicators, and the implementation of interventions targeting both patients and providers to ultimately improve gout care.

■ Recommendations for gout diagnosis & treatment

In response to a growing number of reports showing suboptimal gout management, the EULAR Gout Task Force was formed with the aim of developing evidence-based recommendations on issues relevant to the diagnosis and treatment of gout. Results of this important collaborative international effort were released in 2006 in companion reports from the Gout Task Force, a broad initiative that involved 20 experts from 13 European nations [33,65]. The EULAR task force effort resulted in the development of 'key propositions' or recommendations relevant to the diagnosis and management of gout using a combination of best available evidence (based on a systematic literature review of reports published over the previous 50 years) and expert consensus. The EULAR recommendations are summarized in Box 3 & 4.

■ Measuring quality of care in gout

Recognizing the need for a valid means of measuring quality in gout care, gout quality indicators (QIs) were previously published. Similar to

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Box 3. Evidence-based recommendations for gout diagnosis from the European League Against Rheumatism (EULAR) Gout Task Force.

- In acute attacks the rapid development of severe pain, swelling and tenderness that reaches its maximum within just 6–12 h, especially with overlying erythema, is highly suggestive of crystal inflammation although not specific for gout.
- For typical presentations of gout (e.g., recurrent podagra with hyperuricemia) a clinical diagnosis alone is reasonably accurate, but not definitive without crystal confirmation.
- Demonstration of monosodium urate crystals in synovial fluid or tophus aspirates permits a definitive diagnosis of gout.
- A routine search for monosodium urate crystals is recommended in all synovial fluid samples obtained from undiagnosed inflamed joints.
- Identification of monosodium urate crystals from asymptomatic joints may allow definite diagnosis in intercritical periods.
- Gout and sepsis may coexist, so when septic arthritis is suspected, Gram stain and culture of synovial fluid should still be performed even if monosodium urate crystals are identified.
- While being the most important risk factor for gout, serum uric acid levels do not confirm or exclude gout as many people with hyperuricemia do not develop gout and, during acute attacks, serum levels may be normal.
- Renal uric acid excretion should be determined in selected gout patients, especially those with a family history of young-onset gout, onset of gout under the age of 25 years or with renal calculi.
- Although radiographs may be useful for differential diagnosis and may show typical features in chronic gout, they are not useful in confirming the diagnosis of early or acute gout.
- Risk factors for gout and associated comorbidity should be assessed, including features of metabolic syndrome (e.g., obesity, hyperglycemia, hyperlipidemia and hypertension).

Data taken from [65].

Box 4. Evidence-based recommendations for gout management from the European League Against Rheumatism (EULAR) Gout Task Force.

- Optimal treatment of gout requires both nonpharmacological and pharmacological modalities and should be tailored according to:
  – Specific risk factors (e.g., levels of serum urate, previous attacks and radiographic signs)
  – Clinical phase (e.g., acute/recurrent gout, intercritical gout and chronic tophaceous gout)
  – General risk factors (e.g., age, sex, obesity, alcohol consumption, urate-raising drugs, drug interactions and comorbidity)
- Patient education and appropriate lifestyle advice regarding weight loss (if obese), diet and reduced alcohol (especially beer) are core aspects of management.
- Associated comorbidity and risk factors, such as hyperlipidemia, hypertension, hyperglycemia, obesity and smoking, should be addressed as an important part of the management of gout.
- Oral colchicine and/or NSAIDs are first-line agents for systemic treatment of acute attacks; in the absence of contraindications, an NSAID is a convenient and well-accepted option.
- High doses of colchicine lead to side effects, and low doses (e.g., 0.5 mg three times daily) may be sufficient for some patients with acute gout.
- Intra-articular aspiration and injection of long-acting steroid is an effective and safe treatment for an acute attack.
- Urate-lowering therapy is indicated in patients with recurrent acute attacks, arthropathy, tophi or radiographic changes of gout.
- The therapeutic goal of urate-lowering therapy is to promote crystal dissolution and prevent crystal formation; this is achieved by maintaining the serum uric acid below the saturation point for monosodium urate (≤360 µmol/l).
- Allopurinol is an appropriate long-term urate-lowering drug; it should be started at a low dose (e.g., 100 mg daily) and increased by 100 mg every 2–4 weeks if required; the dose must be adjusted in patients with renal impairment; if allopurinol toxicity occurs, options include other xanthine oxidase inhibitors, a uricosuric agent or allopurinol desensitization (the latter only in cases of mild rash).
- Uricosuric agents, such as probenecid and sulphinpyrazone, can be used as an alternative to allopurinol in patients with normal renal function, but are relatively contraindicated in patients with urolithiasis; benzbromarone can be used in patients with mild-to-moderate renal insufficiency on a named patient basis, but carries a small risk of hepatotoxicity.
- Prophylaxis against acute attacks during the first months of urate-lowering therapy can be achieved by colchicine (0.5–1 mg daily) and/or an NSAID (with gastroprotection if indicated).
- When gout associates with diuretic therapy, stop the diuretic if possible; for hypertension and hyperlipidemia consider use of losartan and fenofibrate, respectively (both have modest uricosuric effects).

Data taken from [33].

the EULAR recommendations, their development incorporated a combination of best available evidence and expert consensus [66]. These QIs address issues pertinent to the use of urate-lowering therapies, the use of anti-inflammatory agents, and the need for counseling gout patients regarding behavioral and lifestyle modifications. Using these QIs as a 'measurement tool', several independent groups have qualified gout care as suboptimal. In a study of the UK General Practice Research Database, physician rates of nonadherence for three of the ten approved QIs ranged from 25 to 57% [30]. In a separate retrospective claims analysis of a large regional managed care database, Sarawate *et al.* reported that the vast majority of gout patients initiating allopurinol did not have serum urate levels measured within the first 6 months of therapy, counter to the corresponding QI [56].

■ **Interventions to improve quality of care in gout**
Perhaps the greatest unmet need in gout remains the critical need for novel and effective means of optimizing gout care in the primary-care setting, where the vast majority of gout care occurs. In a 2007 meeting involving primary-care physicians and rheumatologists, participants identified several key areas of need in terms of facilitating the diagnosis and management of gout. Several areas requiring 'educational reinforcement' were addressed, including appropriate treatment goals of urate-lowering therapy, the appropriate use of anti-inflammatory prophylaxis with the initiation of urate-lowering treatments and the inappropriate initiation of allopurinol during acute gouty flares. In all instances, the proportion of primary-care providers making appropriate treatment decisions in gout care rose to 'acceptable' levels following this educational 'intervention' [67]. Although these results suggest that provider education could represent an important means of improving care, it may be naive to suggest that improvements in education will solve the current crisis in gout care. Novel techniques aimed at improving gout care, both in the clinic and the community, need to be developed and tested.

Conclusion & future perspective

Despite many advances in the understanding and treatment of gout, this historic disease continues to represent a major public health problem. With an increasing incidence and prevalence, the burden posed by gout and the 'company it keeps' are likely to grow in the near future. There have been several important

developments in the treatment of both acute and chronic gout in the last few years, including the recent approval of the first agent to treat gout in more than 40 years. Other treatments, including pegloticase (in chronic gout) and agents targeting IL-1 (in acute gout), hold substantial promise. Future studies will be needed to identify the precise role that these agents and others to follow will play in gout treatment. Recognizing these advances and the availability of highly effective treatments in gout, the quality of gout care continues to be characterized as suboptimal. Further research efforts are needed that will allow healthcare providers to individualize and optimize treatment strategies in gout, assuring that gout patients receive care that is effective, safe and of high quality.

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Executive summary

Epidemiology
- While misclassification is probably common in epidemiological studies to date, overall gout prevalence is estimated to be between 1 and 3%.
- Recent studies suggest that gout incidence has increased by approximately twofold over the last few decades.
- Several recent studies have identified dietary risk factors for the development of gout and hyperuricemia.
- Disease-related comorbidity (particularly metabolic syndrome, hypertension and cardiovascular disease) pose a substantial burden in gout; the impact of urate-lowering therapy in these conditions remains to be defined.
- Studies of the genetic epidemiology of gout lag behind those for other rheumatic conditions.

Treatment of acute gout
- Recent efforts have identified the NALP3 inflammasome (and its effect on IL-1) as a key pathway involved in acute gouty inflammation.
- Agents targeting IL-1 hold promise as an alternative strategy for the treatment and prophylaxis of acute gout.
- Studies are urgently needed to identify the optimal treatment strategy for individual patients with acute gout.

Treatment of chronic gout
- Febuxostat, a potent nonpurine xanthine oxidase inhibitor, represents the first approved agent for the treatment of chronic gout in over 40 years.
- Pegloticase, a PEGylated mammalian form of uricase, could soon represent an alternative urate-lowering approach in patients with treatment refractory gout.
- Although available for more than 40 years, optimal dosing strategies and safety of allopurinol in patients with comorbidity (particularly renal failure) remain to be established.
- The role of urate-lowering therapy in the treatment and/or prevention of 'gout-related' comorbidity remains to be defined.

Quality of care in gout
- Studies to date have consistently qualified gout care as suboptimal in terms of quality.
- The development of gout quality indicators and guidelines represents important potential advances in gout care.
- Ongoing efforts have the potential to improve the standardization of clinical studies in gout.
- Studies examining interventions focused on improving the quality of gout care are critically needed.

Conclusion
- There have been substantial recent gains in our understanding of gout epidemiology with important advances in the treatment of both acute and chronic gout.
- Several unmet needs remain in gout research and treatment.

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