EDITORIAL REVIEW

We can make gout management more successful now

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Purpose of review

The purpose of this editorial review is to identify and comment on factors contributing to the current less-than-optimal state of gout management and to emphasize immediate opportunities to improve management practices affecting many patients with gout.

Recent findings

Numerous publications document deficits in the current management and clinical outcomes of gout despite detailed understanding of the pathogenesis and pathophysiology of the disorder, the ability to establish the diagnosis with certainty, and the likely effectiveness, for most patients, of available lifestyle and pharmacological interventions. Among impediments to successful gout management are diagnostic inaccuracy; a paucity of validated management recommendations to guide care providers; incomplete patient education about gout and the aims and modalities of management; suboptimal patient adherence, even to demonstrably effective therapeutic recommendations; comorbidities and drug interferences that complicate treatment of gout; patient groups at special risk for progression to chronic tophaceous gout; and limited urate-lowering alternatives.

Summary

Recent publication of evidence-based recommendations for the diagnosis and management of gout and the impending availability of new urate-lowering agents suggest that this is an opportune time to initiate professional and patient education efforts toward improved management of this increasingly common disorder.

Keywords

diagnosis and management, evidence-based management guidelines, gout, lifestyle and pharmacological interventions, urate crystals, urate-lowering agents

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Introduction

In this editorial review we wish to identify and comment on some of the factors contributing to what we perceive as an ongoing less-than-optimal state of gout management. Our colleagues, Wortmann and Ryan [1], point out that although treatment of gout should be successful and satisfying because the pathogenesis and pathophysiology of the disease are understood, gout can be diagnosed with certainty, and therapies that are safe and effective have long been available for most gout patients, poor clinical outcomes are not uncommon. Articles in the literature [2–4,5•,6,7,8•,9•] (M.A. Becker, H.R. Schumacher, K.L. Benjamin *et al.*, unpublished data) and our clinical experience confirm the validity of this contention and document a range of adverse clinical outcomes of gout, including repeated gout flares, the development of tophi and chronic arthropathy [3,5•,6,7], recurrent urolithiasis and, frequently, diminished quality of life (M.A. Becker, H.R. Schumacher, K.L. Benjamin *et al.*, unpublished data), work disability (M.A. Becker, H.R. Schumacher, K.L. Benjamin *et al.*, unpublished data), increased rates of myocardial infarction [8•,9•], and reduced longevity [9•].

Gout is a chronic disorder affecting from 3 to 5 million individuals in the US [10] and increasing (apparently worldwide) in both incidence and prevalence [11–13]. The great majority of patients with gout in the US are treated by primary care providers and specialists in fields other than rheumatology. We speculate that poor clinical outcomes in gout largely reflect two influences: first, limited patient and provider familiarity with the concept of gout as a potentially disabling disorder, most often following a prolonged progression from sporadic acute flares of arthritis to a chronic deforming tophaceous arthropathy, with or without residual acute flares; and, second, the existence of a number of obstacles, often acting in combination, that conspire to compromise even the most appropriate efforts to pursue

currently recommended gout management. These obstacles include

(1) diagnostic inaccuracy,
(2) paucity of management guidelines,
(3) incomplete patient education about gout and the aims and modalities of management,
(4) suboptimal patient adherence to therapeutic recommendations,
(5) comorbidities and drug interferences,
(6) patient groups at special risk for progression to chronic tophaceous gout,
(7) limited urate-lowering alternatives.

Clearly, the key to overcoming the first influence is education about the disease: diagnosis and course, the distinctive therapeutic modalities employed, circumstances likely to promote or mark progression, the significance of comorbid associations, and means to monitor therapy and maximize adherence to therapeutic recommendations. With regard to removal of the obstacles to successful management, the picture is more unclear. There are legitimate differences in opinion regarding many aspects of gout management, and resolution of these differences will require evidence provided by controlled clinical investigations of approaches already in clinical use and therapeutic testing to affirm or deny the efficacy of novel interventions. Nevertheless, the recent emergence of evidence-based quality of care indicators [14] and diagnostic [15••] and management [16••] recommendations for gout and the advent of promising new urate-lowering agents in trial [17,18] indicate that progress is being made.

We believe that the time has arrived for the rheumatology community to utilize its clinical and educational specialist roles in this disease to promote among our primary care provider colleagues the knowledge to address issues such as the following: how to improve diagnostic accuracy; how to identify and promote nonpharmacological (lifestyle) interventions; how to determine which patients warrant urate-lowering pharmacotherapy and how to employ these agents; how to monitor the progress and effectiveness of gout management; and what circumstances warrant subspecialty consultation or referral. Information imparted in all of these areas should, ultimately, meet validation criteria, but we contend that the best of currently available information offers immediate opportunities to improve management practices affecting many patients with gout.

Impediments to successful gout management

We discuss the following impediments to successful gout management.

Diagnostic uncertainty

The clinical manifestations of gout result from urate or uric acid crystal deposition. Urate crystal identification by polarized light microscopy of joint or tophus aspirates at any time in the course of the disease is the gold standard for the diagnosis of gout [15••,19,20]. Unfortunately, the necessary procedural expertise, equipment, and technician training [21] required for joint aspiration or for accurate crystal analysis are not widely available to the primary care providers who manage up to 90% of the patients with gout in the US. As a result, less definitive clinical, biochemical, and imaging criteria sets for establishing the diagnosis of gout continue to be employed, but the specificities and sensitivities for gout associated with combinations of these criteria require further validation [22]. In a study at one major teaching institution, an initial clinical diagnosis of an acute inflammatory arthritis as gout (prior to arthrocentesis with crystal analysis) was changed to an alternative diagnosis 26% of the time after this procedure (H.R. Schumacher Jr, personal communication). We propose that until clinical diagnostic criteria are validated specifically for use in this country, an educational goal for rheumatologists should be to provide primary care providers with diagnostic guidance, an activity that may begin with disseminating (in a form with more immediate clinical applicability) the recently published European League Against Rheumatism (EULAR) evidence-based recommendations relevant to gout diagnosis (Table 1) [15••]; and with offering consultation (for crystal-based diagnosis) in patients who are potential candidates for initiation of lifelong urate-lowering pharmacotherapy.

A paucity of management guidelines, incomplete patient education, and suboptimal patient adherence

An important obstacle healthcare professionals have faced in treating gout and instructing patients about the details of disease management has been a lack of well documented management guidelines for accomplishment of therapeutic aims. Recently, the EULAR multidisciplinary guideline development group offered 12 recommendations for management of gout on the basis of research-based and expert consensus [16••]. Table 2 lists these recommendations, modified, when appropriate, to accord with laboratory values or available drug dosages in the US.

Conceptually, the clinical manifestations of gout can be viewed as potentially unfolding in a sequence from acute, intermittent attacks of gouty arthritis separated by asymptomatic intervals of varying but generally diminishing length before evolving into a more chronic, sometimes disabling, arthropathy, often accompanied by tophaceous bone, joint and cartilage destruction. Uric acid urolithiasis may punctuate this course at any point, even arising as the first clinical feature, especially in younger affected individuals. An important concern, warranting surveillance and therapeutic response as appropriate, is that each of the features of the metabolic syndrome and all forms of

Table 1 European League Against Rheumatism (EULAR) evidence-based recommendations for gout diagnosis: strength of recommendations (SORs) and likelihood ratios (LRs)

Recommendation	SOR (95% CI) VAS 100	LR (95% CI)
In acute attacks, rapid development of severe pain, swelling, and tenderness, reaching peak at within 6–12 h is highly suggestive of crystal inflammation, though not specific for gout	88 (80–96)	2.4 (1.1–1.5)
For typical gout presentations (e.g. recurrent podagra), a clinical diagnosis of gout is reasonably accurate but not definitive unless crystal confirmed	95 (91–98)	31 (21–46)
Demonstration of MSU crystals in synovial fluid or tophus aspirates permits a definitive gout diagnosis	96 (93–100)	567 (35–9054)
A routine search for MSU crystals is recommended in all synovial fluid aspirates from inflamed joints	90 (83–97)	
Identification of MSU crystals from asymptomatic joints may allow gout diagnosis between attacks	84 (78–91)	15 (1–230)
Gout and sepsis may coexist; if sepsis is suspected, Gram stain and culture of synovial fluid should be carried out even if MSU crystals are identified	93 (87–99)	
Although the most important risk factor for gout, serum urate levels do not confirm or exclude gout	95 (92–99)	
Hyperuricemia (>mean + 2 SD) as a marker in acute gout		10 (8–13)
Radiographs may be useful for differential diagnosis and may show typical features in chronic gout; they are not useful in confirming a diagnosis of early or acute gout	86 (75–94)	4–6 (3–14)
Risk factors for gout and associated comorbidity should be assessed, including features of metabolic syndrome	93 (88–98)	

Order of recommendations is according to topic: clinical; crystals; biochemical; radiographic; risk factors/comorbidities. Each recommendation was graded by all members of the EULAR Task Force on the basis of a review of research evidence and their clinical expertise, using a 100 mm visual analogue scale (VAS 100). The higher the mean SOR rating, the greater the agreement with the respective recommendation. LRs are calculated values [sensitivity/(1 − specificity)] created to assess the validity of diagnostic test measurements. The LR summarizes how many times more (or less) likely patients with gout are to test positive than patients without gout. LR > 1 indicates that the test result is associated with the presence of gout, and conversely, LR < 1 indicates that the test is associated with the absence of gout. LR values >10 or <0.1 are considered, under most circumstances, strong evidence to rule in or out, respectively, a diagnosis. Data modified from [15••]. CI, confidence interval; MSU, monosodium urate.

Table 2 European League Against Rheumatism (EULAR) evidence-based recommendations for gout management: strengths of recommendations (SORs)

Recommendation	SOR (95% CI) VAS 100
Optimal treatment of gout requires nonpharmacological and pharmacological modalities and should be tailored to specific risk factors (levels of serum urate, previous attacks, radiographic signs), clinical phase (acute/recurrent gout, interval gout chronic tophaceous gout), general risk factors (age, obesity, alcohol consumption, urate raising drugs, drug interaction, comorbidities)	96 (93–98)
Patient education and appropriate lifestyle advice regarding weight loss (if obese), diet, and reduced alcohol (especially beer) are core aspects of management	95 (91–99)
Associated comorbidity and risk factors such as hyperlipidemia, hypertension, hyperglycemia, and smoking should be addressed as an important part of the management of gout	91 (86–97)
Oral colchicine or NSAIDs are the first-line agents for systemic treatment of acute attacks; unless contraindicated, a NSAID is a convenient and well accepted option	94 (91–98)
High doses of colchicine lead to side effects, and low doses (for example 0.6 mg three times daily) may be sufficient for some patients with acute gout	83 (74–92)
Intraarticular aspiration and injection of a long-acting steroid is an effective and safe treatment for an acute attack	80 (73–87)
Urate-lowering therapy is indicated in patients with recurrent acute attacks, arthropathy, tophi, and radiographic changes of gout	97 (95–99)
The therapeutic goal of urate-lowering therapy is to promote crystal dissolution and prevent crystal formation; this is achieved by maintaining serum urate levels below the saturation point (~6.8 mg/dl) for monosodium urate; in practice, a serum urate level < 6.0 mg/dl should be sought	91 (86–96)
Allopurinol is an appropriate long-term urate-lowering drug; it should be started at a low dose (for example, 100 mg daily) and increased by 100 mg every 2–4 weeks as required to achieve a goal serum urate level; dose must be adjusted downward 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 with mild rash)	91 (88–95)
Uricosuric agents such as probenecid (or sulfinpyrazone – no longer available in the US) can be used as an alternative to allopurinol in patients with normal renal function but are contraindicated in patients with urolithiasis; benzbromarone (not available in the US) can be used in mild to moderate renal insufficiency but carries a risk of hepatotoxicity	87 (81–92)
Prophylaxis against acute attacks during the first months of urate-lowering therapy can be achieved by colchicine (0.6–1.2 mg daily) or a NSAID (with gastroprotection, if indicated)	90 (86–95)
When gout is associated with diuretic therapy, consider stopping the diuretic, if possible and as long as an effective antihypertensive regimen is available and affordable; for hypertension and hyperlipidemia, consider use of losartan and fenofibrate, respectively (both have modest uricosuric effects)	88 (82–94)

Order based on topic: general; acute management and chronic management. Each recommendation was graded by all members of the EULAR Task Force on the basis of a review of research evidence and their clinical expertise, using a 100 mm visual analogue scale (VAS 100). The higher the mean SOR rating, the greater the agreement with the respective recommendation. Data modified from [16••]. CI, confidence interval.

acquired cardiovascular disease accompany hyperuricemia and gout with increased frequency.

The aims of gout management are rapid and safe termination of acute attacks of gouty arthritis; protection against further attacks prior to and during urate lowering; and establishment and long-term maintenance of subsaturating serum urate levels that will eventually normalize the extracellular urate pool. Although easily enunciated, it is important to bear in mind that these aims are approached by means of distinctive modalities (antiinflammation; prophylaxis, and urate-lowering, respectively) that employ different nonpharmacological or pharmacological interventions and that the clinical courses of gout often do not necessitate (or even permit) their sequential pursuit.

Patients with a single gout flare or several flares spaced over many years may be managed appropriately with anti-inflammatory treatment of individual flares, supplemented by lifestyle modifications (e.g. diet change, reduced alcohol intake, weight reduction) that may reduce serum urate levels without resorting to specific urate-lowering pharmacotherapy [23]. In contrast, under the best of circumstances, management of gout patients requiring long-term pharmacological urate-lowering follows a sequence from control of the initial acute flare through prophylaxis and successful induction and maintenance of subsaturating urate levels. In both instances, the caregiver must be able to distinguish among the aims and means applied at each stage of the sequence and to transmit the respective rationales to the patient in understandable terms. This understanding and communication skill is particularly critical, because the sequential approach to gout management is frequently disrupted by limitations due to comorbidities or concomitant drug therapies and, even more frequently, because successful urate-lowering paradoxically increases the risk of recurrent gout flares in the early months of treatment [17,24]. Gout flare at the outset of urate-lowering therapy is an outcome that may strain the credibility of the caregiver who has not alerted the patient to this possibility and has either not (as recommended in Table 2) prescribed concomitant flare prophylaxis [16••,24] or, alternatively, not initiated urate-lowering medication at low dose, with dose titration to reach a goal serum urate level in the subsaturating range [16••].

Two further obstacles may impact gout patient education and adherence to management recommendations. First, primary care providers are often constrained to devote most of the time-limited patient visit to the frequently serious comorbidities typically present in gout patients (see Hak and Choi, pp. 179–186; Puig and Martinez, pp. 187–191). Second, in common with other medications prescribed for chronic diseases that are asymptomatic for long periods during successful treatment, patient adherence to urate-lowering regimens is suboptimal [25,26]. In one study [25], less than 40% of individuals prescribed allopurinol were adherent with the drug (received or used allopurinol for 80% or more of the days during 2 years of follow up). This problem probably reflects shortcomings in patient understanding or instruction about the need for prolonged maintenance of subsaturating serum urate levels.

Management guidelines and professional and patient education about gout, then, will be key determinants of any successful effort to improve gout management. In addition, we believe that the history of physician and patient education initiatives in other rheumatologic disorders (e.g. rheumatoid arthritis) suggests that a major impetus to provider and patient education in gout will be directly or indirectly therapy driven, if and when newer drug and biological agents for urate-lowering and, possibly, for acute flare management are accepted for clinical use in gout.

Comorbidities and drug interferences

The current universe of individuals with gout includes but extends beyond the classical depiction of the 'typical' gout patient as a middle age, obese, hypertensive man with a fondness for port wine and gluttony. Nevertheless, large studies of hyperuricemic or gouty patients confirm the association of hyperuricemia and gout with the component features of the metabolic syndrome and the predisposition to cardiovascular disease (see Hak and Choi, pp. 179–186; Puig and Martinez, pp. 187–191). (Whether or not hyperuricemia is a causal risk factor for these disorders is controversial and under active investigation [27].) Hypertension and obesity are established risk factors for the development of gout [28], and chronic kidney disease, hyperlipidemia, and alcohol use are all much overrepresented in gouty populations. Efforts to manage these associated disorders can provoke expression of gout or complicate gout treatment, as, for example, the use of thiazide diuretic agents, which independently increase gout susceptibility. In addition, available urate-lowering therapies (allopurinol, uricosuric agents) are commonly avoided or prescribed at suboptimal doses in patients with chronically impaired kidney function [29], either because of concerns about efficacy or fear of increased risk for severe adverse reactions [30,31], respectively. Negotiating safe and effective treatment pathways for managing chronic gout and its associated comorbidities is challenging. Common results of failure to do so, however, appear to be inadequate or no urate-lowering therapy at all (with reliance instead placed on repeated or chronic anti-inflammatory, steroid, or narcotic analgesic use), and an increased risk for progression to tophaceous disease and chronic arthropathy.

Patient groups at special risk

With an aging population and increased longevity among patients with chronic kidney disease and congestive heart

failure, gout in the elderly has emerged as a major contributor to the increased prevalence of the disease and, by virtue of an atypical clinical profile in some of these patients, to the pool of gouty individuals at increased risk for progression to chronic tophaceous disease [32,33]. Among older patients, the male-dominant gender disparity in new-onset gout is reduced, with women relatively more often affected than is the case in younger individuals [13,34]. In patients of either sex, but especially among women [34], gout flares may, for example, present in the upper rather than the lower extremity, as in a preexisting osteoarthritic node. Neither female gender nor an unusual presentation of an inflammatory arthritis nor a silent joint/skin nodule should preclude consideration and pursuit of the diagnosis of gout.

Among other groups at increased risk for progression of gout are patients who have received kidney or heart transplants and are receiving antirejection therapy with cyclosporine A, often along with diuretics [35,36]; patients with intolerance to available urate-lowering agents or whose comorbid disease status precludes doses of urate-lowering agents sufficient to achieve serum urate levels that are subsaturating [29,37]; and patients who do not adhere to a recommended treatment regimen [3]. Some patients in the latter group contend that urate-lowering agents provoke gout flares and refuse to take them; in such individuals, introduction of flare prophylaxis, for which efficacy of low-dose colchicine has been demonstrated [24], may prevent flares and restore patient adherence.

Limited urate-lowering alternatives

No agent with a primary indication for reduction of the hyperuricemia of gout has been introduced in the US since 1965 when allopurinol was approved by the US Food and Drug Administration at a dose range of 100–800 mg daily. Over 90% of urate-lowering therapy in this country is undertaken with allopurinol, but daily administration in excess of 300 mg daily is uncommon (<10% of patients treated), despite evidence that half or more of gout patients do not achieve serum urate levels less than 6.0 mg/dl while receiving this dose of allopurinol [17,38]. Two factors that likely contribute to underutilization of allopurinol are, first, concerns about allopurinol drug interactions, gastrointestinal intolerance, and, especially, rashes (ranging from mild to life threatening) and the rare but frequently fatal hypersensitivity syndrome [39]; and, second, compliance with published [30] (but recently disputed [29,31]) recommendations for allopurinol dose reduction in states of renal functional impairment. Allopurinol dose titration, carried out in 50–100 mg increments every 2–4 weeks with monitoring of serum urate (goal of <6.0 mg/dl) and creatinine levels is likely to yield improved efficacy. It is worth noting, however, the absence of any published randomized controlled trials establishing the urate-lowering (and clinical) efficacy and safety of allopurinol at doses exceeding 300 mg daily. Such trials are critically needed.

Progression of gout refractory to treatment with currently available agents to severe joint disease, with impairment of quality of life and of function, is well documented and increasingly encountered. There is a compelling medical need among such affected patients for novel agents for the treatment of chronic gout. Recently, additional urate-lowering agents have been developed and are currently undergoing clinical trials. These include febuxostat, a xanthine oxidase inhibitor, structurally distinct from allopurinol and metabolized mainly in the liver [40]; and pegylated recombinant uricases, biological agents that replace activity of uricase (urate oxidase), the urate-degrading enzyme lacking in humans [41]. Febuxostat and pegloticase (pegylated recombinant porcine uricase) have shown urate-lowering efficacy [17,18] and do not appear to require dose reduction in patients with mild to moderate chronic kidney disease [42]. The clinical efficacy (reduced gout flare incidence; reduction in tophus size and number; improvement in quality of life) and the safety of these agents are under evaluation.

Although less immediately on the therapeutic horizon, novel uricosuric agents with efficacy comparable, for example, to benzbromarone (but lacking that agent's limiting toxicity) can be expected to follow the elegant delineation of renal uric acid transport processes as a result of the cloning of urate transporters [43]. Among additional approaches to reducing uric acid production, inhibition of the enzyme purine nucleoside phosphorylase may provide an alternative metabolic site to exploit for the aim of urate-lowering therapy. Finally, recent advances in the understanding of gouty inflammation have indicated a potent proinflammatory role for several cytokines, most prominently interleukin-1B, in the pathophysiology of acute gout [44]. Early stage clinical trials are in progress with agents that inhibit interleukin-1 action to assess their efficacy and safety in terminating acute gouty arthritis and, perhaps, in the longer term reduction of low-grade chronic urate crystal-induced inflammation.

Conclusion

In summary, we believe that enhanced professional and patient education and the introduction of novel urate-lowering agents are the key elements necessary to improve clinical outcomes in gout. Toward optimal achievement of the former goal, refinement for use in this country (or the de-novo development) of evidence-based guidelines for gout diagnosis [15••] (Table 1) and management [16••] (Table 2) is a high priority. We believe, however, that much can be done now by rheumatologists to supplement the knowledge of our primary care colleagues toward achieving accurate diagnosis, expediting safe and effective

therapy, selecting appropriate candidates for chronic urate-lowering pharmacotherapy, and identifying circumstances in which subspecialty consultation is warranted.

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