Quality of care in gout: from measurement to improvement

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ABSTRACT

Gout is a growing health problem, affecting approximately 7% of men and 3% of women over the age of 65 years. Although effective therapies for gout management exist, quality in gout care has been too frequently characterized as being "suboptimal." This review examines issues pertinent to quality of care in gouty arthritis with a focus on initial reports examining suboptimal care, subsequent efforts to develop quality of care indicators for gout management, more recently published evidence-based recommendations for gout diagnosis and treatment, and an ongoing international initiative to develop core outcome measures for acute and chronic gout.

"If you can not measure it, you can not improve it…" – *Lord Kelvin*

Introduction

Given its incumbent associations with advancing age and co-morbidity (1), gout renders patients highly vulnerable to the effects of suboptimal healthcare. Although systematic studies examining quality of care in gout are limited in number and scope, available evidence suggests that the delivery of suboptimal gout care is an all too frequent phenomenon. This fact conflicts with the self-reported "confidence" that healthcare providers indicate in both the diagnosis and management of gout. In a recent survey of healthcare providers, nearly 90% of general practitioners claimed to be confident in their diagnosis and management of gout and, compared to patients with other forms of inflammatory arthritis, gout patients receiving treatment in the primary care setting were far less likely to be referred to rheumatologists or other specialists (2). On the surface, these results suggest that the need for quality improvement efforts in gout care have gone largely unrecognized in the arena where gout care most often takes place.

In addition to the perceived lack of need, quality improvement efforts in gout have been hampered by a lack of consensus regarding standards of care in gout and the appropriate outcome measures that should be adopted in clinical investigations of gout. This review will focus on recent advances that have addressed important barriers to improvements in gout quality of care. Specifically, it will examine issues surrounding quality of care in gout, including initial reports of suboptimal gout care and subsequent comprehensive efforts to develop quality of care indicators for gout management, more recently developed evidence-based recommendations pertinent to both gout diagnosis and management, and an ongoing initiative to develop core outcome measures for acute and chronic gout.

Reports of suboptimal gout care

Reports of inaccurate diagnosis and suboptimal management in gout are not new. Wolfe and Cathey previously reported on the frequency of misdiagnoses in gout and hyperuricemia among consecutive patients seen in an outpatient rheumatology clinic, with a majority of these patients receiving inappropriate therapy as a result (3). Often considered the gold-standard for gout diagnosis, several studies have shown that synovianalysis and microscopic crystal identification suffer greatly from inter-observer variability and resulting diagnostic inconsistencies (4, 5), setting the stage for inappropriate medication use.

In addition to the suboptimal use of diagnostics, reports of suboptimal gout management have been commonplace. In a study by Chin and colleagues examining the frequency of suboptimal medication use among elderly patients presenting to a community-based emergency department, one in ten patients had received at least one inappropri-

ate treatment, with indomethacin (used commonly in the treatment of acute gout) representing the most frequently prescribed inappropriate medication (6). It is noteworthy that gout was among the most commonly cited indications for the administration of inappropriate treatments in this study. In another small investigation of in-patient gout treatments, medication-related errors complicated more than one-fourth of all orders for intravenous colchicine (7). In a case series of 78 patients with severe allopurinol-related toxicity, over one-half of patients were initially given allopurinol for the treatment of asymptomatic hyperuricemia (8), a practice that to date is without evidence-based support. In separate audits of new allopurinol orders (the most frequently used urate-lowering treatment in gout), independent groups reported that the prescribed dose exceeded the recommended dose (based on renal function) in approximately half of patients (9, 10). In another study, 22% of patients receiving a new prescription for allopurinol required a pharmacy-based intervention because of either excessive dosing or lack of an approved drug indication (11).

In a more recent report from our group, we found that gout medication errors occurred in approximately 40% of facilities participating in an Internet-accessible error-reporting program over a five-year surveillance period (12). While uncommon, reports of patient-level harm accompanied some of these medication errors. Compared to errors reported for medications used to treat other musculoskeletal conditions, allopurinol and colchicine-related treatment errors were often ascribable to problems with physician prescribing (7% for others *vs*. 23-39% for gout medications, $p < 0.0001$) and less often to problems with drug administration or nursing error (50% *vs*. 23-27%, $p < 0.0001$).

Evidence-based recommendations for gout diagnosis and treatment

Perhaps in response to a growing number of reports showing suboptimal gout management, the European League Against Rheumatism (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 EULAR effort were released in 2006 in companion reports (13, 14) from the gout task force, an initiative that involved 20 experts from 13 European nations. The EULAR recommendations are among the first guidelines on gout diagnosis to be published since the 1977 American Rheumatism Association (ARA) diagnostic criteria for acute gout (15). Prior to that time, diagnostic guidelines had been promulgated through the Rome (16) and New York (17) criteria, published in 1963 and 1968, respectively. In contrast to older (8, 18) and more recent treatment guidelines (19-21), the EULAR recommendations are based on a broad international effort, employing a rigorous evidence-based methodology. In their seminal work from nearly 20 years ago, Wallace and Singer (1988) provided empiric guidelines for the safe use of intravenous colchicine (18), while Hande and colleagues (1984) proposed initial guidelines for the prevention of severe allopurinol toxicity in gout patients with renal insufficiency (8).

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. Reports from the supporting systematic literature review include a summary on both the safety and efficacy of approved gout therapies (including estimated effect sizes and a pooled summary examining the dose-dependent effect of allopurinol on serum urate levels), a summary of metric properties for various diagnostic tests in gout, and a summary of select disease risk factors and/or co-morbidities with gout. In addition to providing evidence- and expert-based guidelines for gout diagnosis and treatment, the task force developed propositions governing a future research agenda in gout, propositions that certainly merit further investigation.

Consensus regarding the key EULAR propositions was reached using an iterative Delphi technique. Importantly, the strength of each recommendation from the task force was graded using the EULAR ordinal scale (A = fully recommended, B = strongly recommended, C = moderately recommended, D = weakly recommended, and E = not recommended) and a 100 mm visual analogue scale (VAS) (22). Panel members were instructed to determine their "strength of recommendation" ratings based on both the available evidence and their individual clinical expertise. The key propositions/recommendations approved by the EULAR task force, and corresponding strength of recommendation scores, are summarized in Tables I and II.

Quality of care indicators for gout management

Recognizing the need for a valid means of measuring quality in gout care, our group developed ten gout management quality process indicators using a combination of best available evidence and expert consensus (23). Following a systematic literature review, draft process quality indicators (QIs) were developed and reviewed by two separate expert panels using a modified version of the RAND/University of California at Los Angeles (UCLA) appropriateness method (24).

As with process QIs developed across other conditions, it is not expected that high rates of adherence to these QIs will necessarily lead to ideal or even optimal care, although it is possible that, compared to low levels of adherence, high adherence rates may be associated with "higher" levels of quality in gout care. It is also worth noting that there is substantial debate about whether quality measures should focus on processes measures (such as these QIs) or clinical outcomes. Recognizing the limitations to using process-based measures, QIs can be readily measured in "real-time" using a variety of clinical and/or administrative claims data sources, thus circumventing the need to measure other confounding factors that could influence patient outcomes over lengthy follow-up periods such as co-morbidity, concurrent therapies, and patient compliance. Ten gout man-

Table I. Evidence-based recommendations/propositions for gout diagnosis from the European League Against Rheumatism (EULAR) Gout Task Force (from ref. 13).

	Evidence-based proposition/recommendation	Strength of recommendation (95% CI)*	Frequency (%) of strong (A or B) recommendation†
1.	In acute attacks the rapid development of severe pain, swelling, and tenderness that reaches its maximum within just 6-12 hours, especially with overlying erythema, is highly suggestive of crystal inflammation though not specific for gout	88 (80 to 96)	93
2.	For typical presentations of gout (such as recurrent podagra with hyperuricemia) a clinical diagnosis alone is reasonably accurate but not definitive without crystal confirmation	95 (91 to 98)	100
3.	Demonstration of monosodium urate crystals in synovial fluid or tophus aspirates permits a definitive diagnosis of gout	96 (93 to 100)	100
4.	A routine search for monosodium urate crystals is recommended in all synovial fluid samples obtained from undiagnosed inflamed joints	90 (83 to 97)	87
5.	Identification of monosodium urate crystals from asymptomatic joints may allow a definite diagnosis in intercritical periods	84 (78 to 91)	93
6.	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	93 (87 to 99)	93
7.	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	95 (92 to 99)	93
8.	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 age 25, or with renal calculi	72 (62 to 81)	60
9.	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	86 (79 to 94)	93
10.	Risk factors for gout and associated co-morbidity should be assessed, including features of metabolic syndrome (obesity, hyperglycemia, hyperlipidemia, hypertension)	93 (88 to 98)	100

*Based on visual analog scale (0-100 mm)
†Based on the EULAR ordinal scale (A = fully recommended, B = strongly recommended, C = moderately recommended, D = weakly recommended, E = not recommended).

agement QIs were rated to be valid by our expert panels (23). These QIs are shown in Table III and address issues pertinent to the use of urate-lowering therapies, the use of anti-inflammatory agents, and the need for counselling gout patients regarding behavioural/lifestyle modifications.

Quality of care indicators as a measure of gout management quality

Armed with a valid means of measuring and quantifying "quality," recent efforts have focused on quality in gout management and have begun to explore patient-level characteristics that predict suboptimal care. In a study of the UK General Practice Research Database (GPRD) (25), we examined physician adherence to three of the ten approved QIs (23). The three QIs assessed the appropriateness of initial allopurinol dosing based on renal function, inappropriate concomitant use of allopurinol with azathioprine or 6-MP (a potentially life-threatening drug interaction), and the administration of allopurinol for the treatment of asymptomatic hyperuricemia. Rates of non-adherence to the QIs ranged from 25% to 57%. In additional analyses, we also examined the association of patient factors with the receipt of inappropriate treatment for asymptomatic hyperuricemia, finding that male sex, older age, a history of renal impairment, and medication polypharmacy were all significantly associated with increased odds of receiving such treatment. In contrast, both hypertension and diuretic use were associated with lower odds of receiving inappropriate treatment of asymptomatic hyperuricemia.

In a recent retrospective claims analysis of a large regional managed care database, Sarawate *et al*. examined adherence to two of the published QIs including appropriate allopurinol dosing based on renal function and the measurement of serum urate subsequent to treatment initiation (26). In their study, more than half of patients (53%) with renal impairment received inappropriately high allopurinol doses and a majority (83%) of patients initiating allopurinol did not have their serum urate levels measured within the first 6 months of use. Subjects with renal impairment were significantly more likely than those without renal impairment to undergo appropriate serum urate testing (OR = 3.2; 95% CI 0.40–0.63).

In a separate study examining medical, pharmacy, and laboratory claims data from a large national health plan, investigators also observed frequent non-adherence to the published gout management QIs (27). Of eligible gouty subjects, 43% received inappropriately high initial allopurinol doses based on renal function, 40% did not receive appropriate anti-inflammatory prophylaxis during the initiation of urate-lowering therapy, 45% of those deemed eligible for urate-lowering therapy were not receiving treatment, and 68% did not have a serum urate level check dur-

Table II. Evidence-based recommendations/propositions for gout management from the European League Against Rheumatism (EULAR) Gout Task Force (from ref. 14).

	Evidence-based proposition/recommendation	Strength of recommendation (95% CI)*	Frequency (%) of strong (A or B) recommendation†
1.	Optimal treatment of gout requires both non-pharmacological and pharmacological modalities and should be tailored according to: (a) specific risk factors (levels of serum urate, previous attacks, radiographic signs) (b) clinical phase (acute/recurrent gout, intercritical gout, and chronic tophaceous gout) (c) general risk factors (age, sex, obesity, alcohol consumption, urate-raising drugs, drug interactions, and co-morbidity)	96 (93 to 98)	100
2.	Patient education and appropriate lifestyle advice regarding weight loss if obese, diet, and reduced alcohol (especially beer) consumption are core aspects of management	95 (91 to 99)	100
3.	Associated co-morbidity and risk factors such as hyperlipidemia, hypertension, hyperglycemia, obesity, and smoking should be addressed as an important part of the management of gout	91 (86 to 97)	94
4.	Oral colchicine and/or NSAID are first-line agents for the systemic treatment of acute attacks; in the absence of contraindications, an NSAID is a convenient and well-accepted option	94 (91 to 98)	100
5.	High doses of colchicine lead to side effects, and low doses (for example, 0.5 mg three times daily) may be sufficient for some patients with acute gout	83 (74 to 92)	82
6.	Intra-articular aspiration and injection of long-acting steroid is an effective and safe treatment for an acute attack	80 (73 to 87)	88
7.	Urate-lowering therapy is indicated in patients with recurrent acute attacks, arthropathy, tophi, or radiographic changes of gout	97 (95 to 99)	100
8.	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)	91 (86 to 96)	100
9.	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 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)	91 (88 to 95)	100
10.	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	87 (81 to 92)	94
11.	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 gastro-protection if indicated)	90 (86 to 95)	100
12.	When gout associates with diuretic therapy, stop the diuretic if possible; for hypertension and hyperlipidemia consider the use of losartan and fenofibrate, respectively (both have modest uricosuric effects)	88 (82 to 94)	100

*Based on visual analog scale (0-100 mm)
†Based on the EULAR ordinal scale (A = fully recommended, B = strongly recommended, C = moderately recommended, D = weakly recommended, E = not recommended).

ing the first six months after receiving urate-lowering treatment. In contrast, higher rates of adherence were observed for two of the indicators: use of allopurinol rather than a uricosuric agent for those receiving urate-lowering therapy in the context of renal impairment or a history of nephrolithiasis [98% adherence, possibly due to the overwhelming use of allopurinol as the urate-lowering therapy of choice (1)]; and appropriate use of anti-inflammatory treatments for the treatment of acute gout flares (85% adherence).

Taken together, these studies suggest that the recent development of QIs and evidence-based guidelines have yet to make a major impact on the improvement of gout management quality, perhaps not surprisingly given the slow rate at which such guidelines are typically translated into everyday clinical practice. These results also suggest that select patient-level factors are important determinants of appropriate (or inappropriate) care. For instance, data from the GPRD study (25) suggest that future quality improvement initiatives should focus on "high-risk" groups including older men and those receiving multiple concomitant medications. Clearly, additional research is warranted in the area of quality in gout care. Studies to date have focused only on identifying the existence of suboptimal gout care and have only preliminarily begun to define the magnitude of this problem. In addition to examining patient-level factors that determine the quality of care received, future studies must also examine the association of system-level factors with suboptimal/optimal healthcare in gout. Moreover, the cost of suboptimal care must be examined, in terms of both the economic

Table III. Quality of care indicators for gout management (from ref. 23).

Topic Area	Process Indicators
Use of uric acid lowering therapy	1. **IF** a gout patient is receiving an initial prescription for allopurinol AND has significant renal impairment (defined as a serum creatinine ≥ 2 mg/dL or measured/estimated creatinine clearance ≤ 50 mL/min), **THEN** the initial daily allopurinol dose should be less than 300 mg per day **BECAUSE** the risk of allopurinol-related toxicity is increased in the presence of significant renal impairment in gout patients given a daily allopurinol dose equal to or exceeding 300 mg.
	2. **IF** a gout patient is given a prescription for xanthine oxidase inhibitor in the setting of required therapy with EITHER of the following medications: 1) azathioprine (Imuran) OR 2) 6-mercaptopurine (6-MP), **THEN** the dose of azathioprine/6-MP should be reduced by a minimum of 50% **BECAUSE** concurrent use of a xanthine oxidase inhibitor leads to a substantial increase in serum levels of azathioprine (and 6-MP) and increases the risk for severe drug-related myelosuppression.
	3. **IF** a patient with tophaceous gout is given an initial prescription for a urate-lowering medication (xanthine oxidase inhibitor, probenecid, or sulfinpyrazone) AND LACKS BOTH of the following: 1) significant renal impairment (a serum creatinine ≥ 2 mg/dl or measured/estimated creatinine clearance ≤ 50 ml/min) AND 2) peptic ulcer disease, **THEN** a prophylactic anti-inflammatory agent (colchicine or NSAID) should be given concomitantly **BECAUSE** prophylactic anti-inflammatory therapy reduces the risk of rebound gout attacks, which frequently follow the initiation of urate-lowering therapy.
	4. **IF** a patient has asymptomatic hyperuricemia characterized by: 1) no prior history of gouty arthritis or tophaceous deposits AND 2) no prior history of nephrolithiasis or hyperuricosuria AND 3) no ongoing treatment of malignancy, **THEN** urate-lowering therapies should NOT be initiated **BECAUSE** there is currently no widely accepted indication for the treatment of asymptomatic hyperuricemia.
	5. **IF** a gout patient is started on urate-lowering therapy and has EITHER of the following: 1) a history of nephrolithiasis OR 2) significant renal insufficiency (serum creatinine ≥ 2 mg/dl or measured/estimated creatinine clearance ≤ 50 ml/min), **THEN** a xanthine oxidase inhibitor should be started as the initial urate-lowering medication rather than a uricosuric agent (probenecid or sulfinpyrazone) **BECAUSE** in contrast to xanthine oxidase inhibitors, uricosuric agents increase the renal excretion of urate, enhancing the risk of nephrolithiasis, and may have diminished efficacy in the context of significant renal insufficiency.
	6. **IF** a patient has hyperuricemia and gouty arthritis characterized by ANY of the following clinical characteristics: 1) tophaceous deposits, 2) gouty erosive changes on radiographs, or 3) gout attack frequency ≥ 2 attacks per year, **THEN** the patient should be offered treatment with a urate-lowering drug **BECAUSE** urate-lowering drugs have been well-tolerated and effective in decreasing the attack frequency and disease severity for those with severe gout.
	7. **IF** a gout patient is given a prescription for a xanthine oxidase inhibitor, **THEN** a serum urate level should be checked AT LEAST ONCE during the first 6 months of continued use **BECAUSE** periodic serum urate measurements are required for appropriate dose adjustments of xanthine oxidase inhibitors (escalations or reductions).
Behavioral modifications	8. **IF** a patient is diagnosed with gout and has EITHER of the following clinical characteristics: 1) obesity (defined as a body mass index ≥ 28 kg/m^2) or 2) frequent alcohol use (≥ 1 alcoholic beverage per day), **THEN** as part of their overall therapy patients should be advised on the importance of weight loss and/or decreased alcohol use, respectively **BECAUSE** weight loss and reduction of alcohol intake may be beneficial components of gout therapy.
Use of anti-inflammatory agents	9. **IF** a patient has acute gouty arthritis and lacks BOTH of the following relative contraindications to gout treatment: 1) significant renal impairment (a serum creatinine ≥2 mg/dl or measured/estimated creatinine clearance ≤ 50 ml/min) and 2) peptic ulcer disease **THEN** the patient should be treated with an anti-inflammatory agent to include one of the following: 1) NSAID, 2) ACTH or glucocorticoid (either systemic or intra-articular administration), OR 3) colchicine **BECAUSE** anti-inflammatory agents have been shown to be both effective and well-tolerated for the short-term treatment of acute gout. Patients with renal impairment and a history of peptic ulcer disease may be at higher risk for gout medication toxicity.
	10. **IF** a gout patient receives chronic prophylactic oral colchicine (defined as a minimum daily dose of 0.5 mg for a duration of 6 months or longer) and has significant renal insufficiency (serum creatinine ≥2 mg/dl or measured/estimated creatinine clearance ≤ 50 ml/min), **THEN** a complete blood count (CBC) AND creatine kinase (CK) should be evaluated a minimum of one time for every 6 months of continued use **BECAUSE** the risk of colchicine-related myopathy and myelosuppression appears to be substantially increased in the context of reduced renal function.

burden it poses and its direct impact on the patients' quality of life and other relevant long-term outcomes. Such studies represent important intermediate steps before widely adopted, comprehensive quality improvement initiatives can be effectively undertaken.

Patient outcomes in gout

It is widely recognized that the lack of well-validated outcome measures represents a major obstacle to continued advances in gout management. In recognition of this deficit, gout has been a recent focus of the OMERACT (Outcome Measures in RheumAtology Clinical Trials) gout special interest group, which has been charged with the development and validation of core outcome measures for both acute and chronic gout (28). The OMERACT gout special interest group, consisting primarily of academic physicians and scientists from industry, has preliminarily adopted five 'global' outcome domains for acute gout including pain, a measure of inflammation, patient function, global well-being, and treatment safety. Proposed outcome domains for chronic gout include: serum urate

level, gout flare recurrence, tophus regression, radiographic joint damage (or other imaging modality), health-related quality of life, musculoskeletal function, patient global well-being, participation, and treatment safety/tolerability. Although requiring further development – in addition to formal testing for feasibility, discriminatory properties, and validity – the availability of core outcome measures in gout may represent an important watershed in advancing quality in gout care.

Conclusion

Gout represents the most common form of inflammatory arthritis in men and is a frequent problem in the elderly, affecting approximately 7% of men and 3% of women over the age of 65 years (1). Further underscoring it as a disease of the vulnerable, gout and hyperuricemia are strongly associated with several co-morbid conditions including renal failure, hypertension, diabetes, heart disease, dyslipidemia, nephrolithiasis, and metabolic syndrome (1, 13, 29). Recent reports suggest that hyperuricemia and gout are rapidly on the rise, with a more than 2-fold increase in the incidence of primary gout in the US over a 20-year span starting in the mid-1970s (30). A similar rise in disease frequency has been observed in both the UK (31) and New Zealand (32). Its rising incidence, coupled with its co-morbid diseases and a rapidly aging population, suggest that gout and gout care will continue to have important public health implications. In the context of an increasing disease burden, it is important to recognize many recent strides in our understanding of gout epidemiology (29), in addition to significant advances with the development of new state-of-the-art gout treatments (33, 34). Recent gains in our ability to measure and quantify quality in gout diagnosis and treatment may pay even greater dividends in gout care, laying the foundation for important quality improvement initiatives in the near future.

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