



The Open Urology & Nephrology Journal

Content list available at: www.benthamopen.com/TOUNJ/

DOI: 10.2174/1874303X01609010022



Gout Transitions from Medieval Times into the 21st Century

Puja P. Khanna*

Division of Rheumatology, Department of Internal Medicine, 300 North Ingalls, Ste. 7C27, Ann Arbor, MI 48109-5422, USA

Abstract: Gout is the most treatable arthritis in the Western World—the pathophysiology of which is related to uric acid metabolism and there are effective medications available to treat both acute arthritis and chronic hyperuricemia. Despite this many patients continue to suffer from tophaceous gout with major detrimental effects on patient-reported outcomes and substantial economic impact. Poor adherence to medications is considered an important attribute in developing disability due to gout. This review summarizes recommendations from various national and international guidelines with an update on the therapeutics.

Key Points

- NSAIDs, COX-2 inhibitors, corticosteroids, colchicine, and IL-1 inhibitors have strong evidence to suggest efficacy in the treatment of acute gout.
- Urate lowering therapy, with allopurinol or febuxostat as first line agents, is warranted for chronic management of gout.
- All guidelines recommend a ‘treat-to-target’ strategy to achieve serum urate of at least 6 mg/dL or lower.

Keywords: Allopurinol, corticosteroids, guidelines, gout, treatment update, urate lowering therapy.

INTRODUCTION

Gout has been known since the time of Hippocrates in the 5th century BCE. Prior to the turn of the 19th century, urate crystals were identified as the predominant component of tophaceous deposits. The primary treatments for gout have been available to clinicians since 1814 (colchicine) and 1963 (allopurinol). Though often referred to as “curable,” study of clinical cohorts demonstrates that there are dramatic deficiencies in the quality of care provided to patients with gout [1] some of whom go on to develop permanent disability due to chronic gout.

The American College of Rheumatology (ACR) most recently published guidelines for the management of acute and chronic gout [2] and are developing quality measures based on these guidelines. The guidelines were developed using the RAND/UCLA consensus process, a commonly applied methodology to bridge the gap between evidence-based literature and expert opinion. The guidelines highlight new recommendations for safer use of old familiar drugs, use of newer gout therapeutics and non-pharmacologic interventions.

TREATMENT GUIDELINES FOR ACUTE GOUT ATTACKS

Management of gout is complicated due to the episodic nature of the disease and underlying comorbidities of patients. The guidelines advocate that treatment for an acute attack should be initiated within 24 hours of onset when possible. For patients who are on established urate-lowering therapy (ULT), the ULT should be continued during the attack else the attack may be exacerbated. Either colchicine, NSAIDs, or corticosteroids may be used as first-line agents with selection based on patient preference, prior response, comorbidities, and for colchicine the time of onset of flare (preferably within first 24 hours of the attack) [3]. When colchicine is used, the loading dose should be limited to

* Address correspondence to this author at the Division of Rheumatology, Department of Internal Medicine, 300 North Ingalls, Ste. 7C27, Ann Arbor, MI 48109-5422, USA; E-mail: pkhanna@med.umich.edu

2.4 mg in a 24 hour period; use of higher loading doses is associated with increased adverse effects without incremental benefit. Inadequate response to the initial agent warrants addition of a second drug; however, clinicians should avoid concurrent use of NSAIDs and systemic corticosteroids due to their synergistic gastrointestinal tract toxicity. In the event of severe polyarticular joint involvement or refractory flares, combination therapy with simultaneous use of full doses of colchicine and NSAIDs, or oral corticosteroids and colchicine, or intra-articular steroids with any of the other modalities.

URATE-LOWERING THERAPY (ULT)

Allopurinol (xanthine oxidase inhibitor, XO) and Probenecid (uricosuric) have been used for the treatment of gout for 50 years. Febuxostat, (XOI) has been recently added to the ULT armamentarium. Despite familiarity with these drugs, patient and physician factors lead to sub-optimal usage as summarized in recent reviews [4, 5]. The guidelines provide recommendations to avoid common prescribing errors. The “treat to target” paradigm is one of the key recommendations and emphasizes that for patients in need of ULT, the target serum urate level should be less than 6 mg/dL; and even lower to less than 5 mg/dL in patients with frequent flares and large tophaceous burden.

Allopurinol and febuxostat are described as equivalent first line agents in the guidelines. However, the RAND/UCLA methodology specifically excludes consideration of costs, an important limitation of the analysis. There is limited cost-effectiveness data to guide the clinician [6, 7], and no cost-effectiveness analyses using either non-protocol patients or comparator trials based on guideline-endorsed dosing of allopurinol. For patients with refractory serum urate levels despite adherence, combination ULT with both xanthine oxidase inhibitor and probenecid can be used. Combination of two xanthine oxidase inhibitors should not be used.

Due to frequently reported errors and its more common use, the ACR gout guidelines give special attention to Allopurinol usage. For allopurinol, the guidelines recommend, “starting low” (no more than 100 mg per day, lower in CKD 4 or worse) and titrate up frequently (every 2-5 weeks) to achieve target serum urate. Serum urate reaches new equilibrium within days of ULT dose change. In contrast, the common initial prescribing dose of 300 mg per day can increase the risk of acute gout flare associated with ULT initiation leading to non-adherence and contribute to morbidity by increasing the risk of Allopurinol Hyper-sensitivity Syndrome.

Studies have documented that 97% of non-protocol patients in cohorts never exceed Allopurinol doses of 300 mg per day [4] which is problematic as the mean dose required to lower serum urate < 6 mg/dL has been shown to greater than 370 mg per day [8]. The dose should be titrated up based on serial serum urate results and patient tolerance (*e.g.*, absence of drug rash or hepatic toxicity). These doses can exceed 300 mg per day in most patients and can exceed doses previously outlined by Hande and colleagues [9] for patients with renal disease.

New genetic studies have identified an association between HLA haplotype and the risk for Allopurinol Hypersensitivity Syndrome. The guidelines recommend that select ethnicities, Koreans with CKD stage 3 or worse, Han Chinese, or Thai descent, should be screened for HLA-B*5801 prior to initiating allopurinol to reduce the risk of Allopurinol Hypersensitivity Syndrome.

For patients with disabling symptoms and refractory to maximally tolerated oral therapies, pegloticase and/or specialty referral should be considered. With any initial ULT prescription, patient education and pharmaceutical prophylaxis against acute gout attacks are key critical components. Clinicians should review patient comorbidities and concurrent medications, take action where indicated and educate patients about how their diet, medications and comorbidities can affect their gout. Patients’ understanding of the disease process, factors that affect serum urate and consequences of untreated gout are all considered essential for adherence to therapy and efficacy of the drugs used to treat gout.

PROPHYLAXIS AGAINST ACUTE GOUT ATTACKS

Patients are at increased risk for acute gout flare with initiation of any ULT; therefore they should be started on concomitant acute gout prophylaxis to reduce the risk of acute flare with expected change in serum urate. ULT can be initiated once adequate anti-inflammatory treatment has been initiated. Low-dose colchicine or NSAIDs are preferred regimens. Duration of prophylaxis should continue for at least 6-months in patients without tophi. However, for those with tophi on exam, prophylaxis should be offered for 6-months past resolution of the tophi. Low-dose steroids can be used when above medications are not tolerated or contraindicated, but only for a shorter duration.

NON-PHARMACOLOGIC MANAGEMENT

Lifestyle measures and low-purine diet are cornerstones of preventing acute gout attacks and lowering urate levels. Purine breakdown from meat, seafood and alcohol are known to trigger gout flares. The guidelines outline clear dietary recommendations delineating dietary products as “avoid”, “limit”, or “encourage”. Abstinence from alcohol consumption other than for cardio-protective purposes, weight loss, and avoidance of products rich in high fructose corn syrup are advocated based on epidemiologic data.

PUBLISHED GUIDELINES - THEIR APPLICABILITY AND IMPACT

In the last two decades, there have been several rheumatologic societies who have developed guidelines for management of gout including national and international guidelines - British Society of Rheumatology (BSR), European League Against Rheumatism (EULAR), American College of Rheumatology (ACR), and 3e Initiative - Multinational Evidence, Exchange and Expertise group; the 2014 EULAR update is available only as an abstract (see Table 1 for summary and comparison of acute and chronic therapies) [2, 10 - 13]. All have emphasized patient education as the central theme for improving patient-related outcomes [14]. Despite published guidelines, there are significant disparities in approaches to gout management, prescribing patterns of providers and lack of uniform standard of care for chronic treatment of gout [2, 10 - 12, 15, 16]. The latest systematic review of medication adherence in gout showed that less than 50% of gout patients in the real-world setting are adherent to their treatment [5]. It is interesting to note how some of these recommendations have evolved over the years. Most of the guidelines, EULAR, ACR and 3e initiative were all given very low marks for applicability, which by definition describes the following: ‘the guideline describes a) facilitators and barriers to its application, b) provides advice and/or tools on how the recommendations can be put into practice, c) the potential resource implications of applying the recommendations have been considered, and finally d) presents monitoring and/or auditing criteria’ [17].

Table 1. Comparison of guidelines for the treatment of gout.

Society	1 st Line for Acute Attack	Target Uric Acid Level	Treatment of Asymptomatic Hyperuricemia	Allopurinol Dose Recommendations	Prophylaxis when Starting Allopurinol	Febuxostat	Use of Uricosuric Agents	Other	Lifestyle Modification Included
ACR 2012	NSAIDs, corticosteroids, or Colchicine	6 mg/dL (360 µM)	N	Start at 100 mg, may uptitrate beyond 300 mg	Colchicine/NSAIDs recommended for all patients	First line option	Second line or in combination	Pegloticase for refractory cases	Yes
BSR 2007	NSAIDs, Coxibs or colchicine	5 mg/dL (300 µM)	N	100 mg, may uptitrate to up to 900 mg	Colchicine/NSAIDs/coxibs for 6 months	Not addressed	Second line	Opiates as an adjunctive	Yes
3E 2013	Colchicine NSAIDs	6 mg/dL (360 µM)	N	Decrease dose in renal impairment	Colchicine should be considered or else NSAIDs, steroids if contraindications	Renal impairment	Second line		Yes
EULAR 2006	NSAIDs, colchicine also an option	6 mg/dL (360 µM)	N	100 mg starting dose, decrease in renal impairment	Colchicine “reasonable”, less evidence for NSAIDs	Not addressed	Second line	Losartan and fenofibrate when appropriate	Yes
JSGNM 2011	Colchicine or NSAIDs	6 mg/dL (360 µM)	Yes > 8 with lifestyle, > 9 with edications	50 mg starting dose	Colchicine recommended	Not addressed	Option as first line therapy		Yes
DCGP 2002	NSAIDs first, then colchicine, then corticosteroids	Not addressed	N	Recommended for high uric acid excretors	Colchicine maintenance not advised	Not Addressed	Option as first line therapy		Yes

Adapted with permission from Current Opinions in Rheumatology; ACR - American College of Rheumatology, BSR - British Society of Rheumatology, EULAR - European League against Rheumatism, JSGNM - Japanese Society of Gout and Nucleic Acid Metabolism, 3E - Multinational Evidence, Exchange and Expertise Group, DCGP - Dutch College of General Practitioners, NSAIDs - Non-Steroidal Anti-Inflammatory Drugs.

The guidelines were purported to shift the current paradigm of treatment by creating a change in the practice patterns of providers so that they initiate ULT early in the management of chronic gout. However, the impact of

guidelines in day-to-day practice is difficult to gauge due to factors such as lack of measurement tools to assess patient adherence to treatment, the change brought upon by the introduction of guidelines, short timespan after release of guidelines, and finally a lack of education in primary care providers of the appropriate use of uric acid-lowering therapies. Concerted effort is needed to develop tools to better assist primary care providers implement these recommendations to help improve patient compliance with medications and change long-term outcomes in gout.

CONCLUSION

Treatment of acute gout attacks and management of hyperuricemia have received a lot of attention over the last decade with publication of the four international guidelines. There are several new recommendations for the proper use of old familiar drugs, and newer agents for the management of gout. This is a major step towards addressing the growing impact of the disease burden in gout, increase adherence to therapy, and thus improve patient outcomes. Hence, a reflection on the gout era when there is a clear need to shift the treatment paradigm and improve quality of care. Changes in these recommendations reflect some evolutionary aspects in the management of gout and other subtle differences. Despite these differences, the primary themes remain consistent about the importance of ULT in patients with indications and the 'treat to target' concept.

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

- [1] Singh JA. Quality of life and quality of care for patients with gout. *Curr Rheumatol Rep* 2009; 11(2): 154-60. [<http://dx.doi.org/10.1007/s11926-009-0022-4>] [PMID: 19296889]
- [2] Khanna D, Fitzgerald JD, Khanna PP, *et al.* American College of Rheumatology. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res (Hoboken)* 2012; 64(10): 1431-46. [<http://dx.doi.org/10.1002/acr.21772>] [PMID: 23024028]
- [3] Khanna PP, Gladue HS, Singh MK, *et al.* Treatment of acute gout: a systematic review. *Semin Arthritis Rheum* 2014; 44(1): 31-8. [<http://dx.doi.org/10.1016/j.semarthrit.2014.02.003>] [PMID: 24650777]
- [4] Edwards NL. Quality of care in patients with gout: why is management suboptimal and what can be done about it? *Curr Rheumatol Rep* 2011; 13(2): 154-9. [<http://dx.doi.org/10.1007/s11926-010-0154-6>] [PMID: 21161617]
- [5] De Vera MA, Marcotte G, Rai S, Galo JS, Bhole V. Medication adherence in gout: a systematic review. *Arthritis Care Res (Hoboken)* 2014; 66(10): 1551-9. [<http://dx.doi.org/10.1002/acr.22336>] [PMID: 24692321]
- [6] Meltzer M, Pizzi LT, Jutkowitz E. Payer decision-making with limited comparative and cost effectiveness data: the case of new pharmacological treatments for gout. *Evid Based Med* 2012; 17(4): 105-8. [<http://dx.doi.org/10.1136/ebmed-2011-100065>] [PMID: 22345034]
- [7] Jutkowitz E, Choi HK, Pizzi LT, Kuntz KM. Cost-effectiveness of allopurinol and febuxostat for the management of gout. *Ann Intern Med* 2014; 161(9): 617-26. [<http://dx.doi.org/10.7326/M14-0227>] [PMID: 25364883]
- [8] Perez-Ruiz F, Alonso-Ruiz A, Calabozo M, Herrero-Beites A, García-Erauskin G, Ruiz-Lucea E. Efficacy of allopurinol and benzbromarone for the control of hyperuricaemia. A pathogenic approach to the treatment of primary chronic gout. *Ann Rheum Dis* 1998; 57(9): 545-9. [<http://dx.doi.org/10.1136/ard.57.9.545>] [PMID: 9849314]
- [9] Hande KR, Noone RM, Stone WJ. Severe allopurinol toxicity. Description and guidelines for prevention in patients with renal insufficiency. *Am J Med* 1984; 76(1): 47-56. [[http://dx.doi.org/10.1016/0002-9343\(84\)90743-5](http://dx.doi.org/10.1016/0002-9343(84)90743-5)] [PMID: 6691361]
- [10] Jordan KM, Cameron JS, Snaith M, *et al.* British Society for Rheumatology and British Health Professionals in Rheumatology Standards, Guidelines and Audit Working Group (SGAWG). British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout. *Rheumatology (Oxford)* 2007; 46(8): 1372-4. [<http://dx.doi.org/10.1093/rheumatology/kem056a>] [PMID: 17522099]
- [11] Sivera F, Andrés M, Carmona L, *et al.* Multinational evidence-based recommendations for the diagnosis and management of gout: integrating systematic literature review and expert opinion of a broad panel of rheumatologists in the 3e initiative. *Ann Rheum Dis* 2014; 73(2): 328-35. [<http://dx.doi.org/10.1136/annrheumdis-2013-203325>] [PMID: 23868909]

- [12] Zhang W, Doherty M, Bardin T, *et al.* EULAR Standing Committee for International Clinical Studies Including Therapeutics. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCSIT). *Ann Rheum Dis* 2006; 65(10): 1312-24. [<http://dx.doi.org/10.1136/ard.2006.055269>] [PMID: 16707532]
- [13] Zhang W, Doherty M, Pascual E, *et al.* EULAR Standing Committee for International Clinical Studies Including Therapeutics. EULAR evidence based recommendations for gout. Part I: Diagnosis. Report of a task force of the Standing Committee for International Clinical Studies Including Therapeutics (ESCSIT). *Ann Rheum Dis* 2006; 65(10): 1301-11. [<http://dx.doi.org/10.1136/ard.2006.055251>] [PMID: 16707533]
- [14] Rees F, Hui M, Doherty M. Optimizing current treatment of gout. *Nat Rev Rheumatol* 2014; 10(5): 271-83. [<http://dx.doi.org/10.1038/nrrheum.2014.32>] [PMID: 24614592]
- [15] Singh JA, Hodges JS, Toscano JP, Asch SM. Quality of care for gout in the US needs improvement. *Arthritis Rheum* 2007; 57(5): 822-9. [<http://dx.doi.org/10.1002/art.22767>] [PMID: 17530682]
- [16] Wall GC, Koenigsfeld CF, Hegge KA, Bottenberg MM. Adherence to treatment guidelines in two primary care populations with gout. *Rheumatol Int* 2010; 30(6): 749-53. [<http://dx.doi.org/10.1007/s00296-009-1056-7>] [PMID: 19590874]
- [17] Nuki G. An appraisal of the 2012 American College of Rheumatology Guidelines for the Management of Gout. *Curr Opin Rheumatol* 2014; 26(2): 152-61. [<http://dx.doi.org/10.1097/BOR.000000000000034>] [PMID: 24492863]

Received: April 18, 2015

Revised: April 30, 2015

Accepted: April 30, 2015

© Puja P. Khanna; Licensee *Bentham Open*.

This is an open access article licensed under the terms of the Creative Commons Attribution-Non-Commercial 4.0 International Public License (CC BY-NC 4.0) (<https://creativecommons.org/licenses/by-nc/4.0/legalcode>), which permits unrestricted, non-commercial use, distribution and reproduction in any medium, provided the work is properly cited.