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EDITORIAL

Do Not Let Gout Apathy Lead to Gouty Arthropathy

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How do the American College of Physicians gout guidelines differ from rheumatology society guidelines?

During the last decade, there has been no shortage of gout guideline statements, with several publications and updates from various rheumatology specialty societies (1–5). Most recently, the American College of Physicians (ACP) published its version of guidelines for the diagnosis and management of gout (6,7). While there are modest differences between the various international rheumatology guidelines, the ACP management of gout guideline has created much debate, as several recommendations conflict with recommendations provided by the rheumatology specialty societies. Since most gout patients are cared for by primary care providers, the guidelines published by the ACP in the *Annals of Internal Medicine* (6) will likely reach a greater proportion of clinicians caring for patients with gout than will guidelines published in specialty journals. Therefore, it is important to understand what these new guidelines state, how they differ from rheumatology guidelines, and what this means for the field.

How do different groups, reviewing essentially the same evidence, reach such different recommendations? Are the different interpretations akin to the pictorial illusion of the young lady looking away versus the old lady in profile (Figure 1)? This illusion derives its effect from the ambiguity of the image and the perception of the reader.

The conceptual framework and stated purpose of the ACP-developed guidelines are different from those of the American College of Rheumatology (ACR) and other rheumatology society guidelines. The ACP seeks to provide "clinicians with recommendations based on the best available evidence; to inform clinicians of when there is no evidence; and finally, to help clinicians deliver the best health care possible" (8). "If no specific evidence exists to answer a clinical question within a topic, the ACP Clinical Guidelines Committee refrains from making a clinical recommendation" (9). By restricting themselves to statements with the highest level of evidence, the ACP authors produce guidelines with a narrower focus, whereas the ACR and other rheumatology societies have tried to present guidelines that provide broader guidance on clinically relevant issues, at times in the absence of randomized controlled trial (RCT) data.

Based on differences in this conceptual framework, the ACP gout management guideline offers just 4 recommendations (Table 1) versus, for example, the recent European League Against Rheumatism 2016 update, which included 3 overarching and 11 specific recommendations (with many distinct subrecommendations) (4). In addition to including fewer recommendations, the ACP recommendations are quite conservative. The first gout management statement recommends the use of treatments for acute gout attacks that have been the standard of care for decades. The final recommendation is simply to discuss risks, benefits, costs, and harms prior to initiating urate-lowering therapy (ULT) or prophylaxis. In contrast to rheumatology society guidelines, no guidance is provided with regard to when or for whom ULT might be beneficial. Therefore, it is unlikely that these ACP recommendations will impact the often-described poor current practice of care for patients with gout.

What are the concerns about the ACP guidelines?

Aside from conceptual differences, the biggest difference between the ACP's and the various rheumatology societies' guideline statements pertains to the ACP statements about use of ULT. In the ACP guidelines, the

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Figure 1. "The Lady in Profile" illusion (*My Wife and My Mother-In-Law*, W. E. Hill, 1915).

authors argue against treat-to-target (T2T) because of a lack of RCT data to support this approach, and instead propose a concept of "treat to avoid symptoms (T2aS), with no monitoring of urate levels" (6), despite a lack of RCT or other data to support this approach. Rheumatology societies have universally recommended T2T based on the physiologic solubility of urate below a threshold level and results from several large observational studies, including long-term extensions of RCTs, correlating serum urate level with frequency of acute attacks and changes in tophi (10–14). Critics argue that this type of logic led to failed T2T strategies in diabetes (15), anemia of renal disease (16), and hyperlipidemia (17), and there has been pushback against the use of surrogate biologic markers in place of clinical outcomes. Applying inference from these studies to the management of gout, while cautionary, cannot be justified as supporting evidence against the utility of serum urate measurement or T2T in gout.

Extrapolation from these studies fails to acknowledge that urate is the necessary and causative agent in the clinical manifestations of gout. Without deposition of monosodium urate monohydrate crystals, there would be no gout flares and no tophi. In contrast, measures such as hyperglycemia or hyperlipidemia are not the sine qua non of cardiovascular disease. The ACP questions if "the harms associated with repeated monitoring and medication escalation" might outweigh the benefits of the T2T strategy. While a T2T approach does not work for all patients (for example, those with multiple drug intolerance or other contraindications to ULT), allopurinol (the most commonly prescribed ULT) has been in use for decades with a good safety profile (aside from the known but rare and potentially serious hypersensitivity reactions).

The ACP introduction of T2aS is problematic for several reasons. While not bulleted with the other 4 recommendations, it is the most directive statement and arguably may have the most impact on the care of patients with gout. Yet it is introduced without any supporting evidence. In an accompanying editorial (9), one of the ACP authors chastises "many professional organizations, including the ACR… (which) still develop 'guidelines' that are actually consensus expert panel opinions." Simply introducing T2aS in the Discussion section ought not to exempt the recommendation from the same standard the ACP Clinical Guidelines Committee uses to judge itself or other groups.

Furthermore, the T2aS concept is introduced to clinicians who would accept the corollary "don't T2T" recommendation. However, it is introduced without detail to guide those clinicians' management of gout in their patients. There are several clinical situations in which a T2aS strategy would be unclear. What would be the recommendation for a patient with a gout flare 4 months after the initiation of ULT? Might this be an expected flare with ULT initiation? Perhaps instead, there was nonadherence. Without monitoring of serum urate levels, it would be difficult to distinguish these scenarios. If clinicians opt to start patients with a low dose of allopurinol (as recommended in rheumatology guidelines), would there be any upward titration in a T2aS strategy? How would a T2aS approach differ from the current "standard of care"? The only clarity in the ACP discussion about T2aS is that it is not T2T. Finally, the ACP

Table 1. Summary of the American College of Physicians (ACP) gout guideline statements

1. ACP recommends that clinicians choose corticosteroids, nonsteroidal antiinflammatory drugs, or colchicine to treat patients with acute gout. Grade: strong recommendation, high-quality evidence
2. ACP recommends that clinicians use low-dose colchicine when using colchicine to treat acute gout. Grade: strong recommendation, moderate-quality evidence
3. ACP recommends against initiating long-term urate-lowering therapy in most patients after a first gout attack or in patients with infrequent attacks. Grade: strong recommendation, moderate-quality evidence
4. ACP recommends that clinicians discuss benefits, harms, costs, and individual preferences with patients before initiating urate-lowering therapy, including concomitant prophylaxis, in patients with recurrent gout attacks. Grade: strong recommendation, moderate-quality evidence

Clinical Guidelines Committee downgraded the Agency for Healthcare Research and Quality, Evidence-Based Practice Centers (AHRQ-EPC) literature review evidence rating on T2T from low to insufficient.

In addition to the above critique, it is not clear what the moderate strength of evidence is to support the ACP's third (e.g., don't treat first attack or infrequent attacks) or fourth (discuss risk/benefits of treatment) management recommendations. These specific topics were not addressed in key questions or the AHRQ-EPC literature review (18). The ACP assessment of strength of evidence rating appears inconsistent. Nonetheless, despite these methodologic concerns, these 2 recommendations are not inconsistent with existing specialty society guideline statements.

The most concerning implication of the ACP guidelines is their potential for worsening the already suboptimal gout care in the US. Primary hospitalization rates for gout have doubled over the past 2 decades, with significant increased economic burden (19). In an abstract presented at a recent ACR Annual Meeting, it was noted that patients with acute gout attacks are frequently admitted with preliminary diagnoses of septic arthritis or cellulitis (20). The authors judged that 89% of these gout admissions were preventable and identified infrequent use of ULT or prophylactic colchicine, the high prevalence of hyperuricemia, and ULT nonadherence as areas for improvement. Other studies have documented the very poor patient adherence with ULT (21–25). Additional studies document that serum urate monitoring is infrequent (14,23). While these studies would likely be discounted by those who are critical of the use of surrogate markers, another study has shown that serum urate monitoring has been associated with better adherence with ULT (26).

The ACP guidelines define several "do not treat" recommendations (do not treat patients with a first attack or infrequent attacks, do not use T2T). In a short summary on the ACP guidelines for patients, the following description about ULT is provided: "Some medicines are used to lower urate in the blood; however, lowering uric acid below a certain level may or may not prevent a future gout attack" (27). The impact of these messages on clinicians or patients is uncertain, but they are unlikely to reinforce the importance of ULT for those in whom this treatment is recommended, and unlikely to reinforce the importance of adherence to a ULT regimen. Ultimately, the concern is that such messaging will exacerbate the suboptimal management of gout.

Where do we go from here?

As disconcerting as some rheumatologists find the ACP gout guidelines, there are pervasive beliefs about the potential danger of surrogate markers as treatment targets. The only way to overcome these concerns would be through head-to-head comparisons of different treatment strategies (e.g., T2T versus T2aS). There are several potential challenges that would have to be overcome to conduct such a comparative effectiveness trial. T2aS was not described in detail, making design of a comparative study complicated. Without clear definition of a T2aS protocol, outcomes of a comparative study would be subject to critique about the operationalization of the study's T2aS implementation. Furthermore, in a recent editorial about conducting ethical trials in gout, the author stresses that both treatment arms ought to be designed to "receive care that we would want if we were enrolled in the study" (28). Strong proponents of either T2T or T2aS might not consider the two arms to be in equipoise, making recruitment difficult. Finally, the clinical benefits of oral ULT are not observed during the first 6 months of therapy and thus, any such trial comparing clinical end points would require longer follow-up (e.g., 1–2 years).

However, data not considered by the ACP and trials in progress may be able to provide better justification for T2T. As pegloticase infusion therapy is not prescribed by primary care providers, its RCT data were excluded from the AHRQ-EPC review. Nonetheless, these RCTs provide important insights regarding clinically relevant effects of lowering serum urate. A group receiving biweekly pegloticase treatment had a significantly greater frequency of complete resolution of at least 1 tophus, lower flare rates in the final 3 months of the trial, fewer tender joints, and greater improvements in patient-reported outcomes of pain, function, and quality of life compared with patients receiving placebo (29). These clinical end points were very likely mediated by serum urate response to the therapy. In another recently completed RCT in patients with early gout ($\leq$2 gout flares ever and only 1 flare in the past year), participants received febuxostat or placebo for 2 years. The percentage of patients with at least 1 flare was lower in the febuxostat group than the placebo group (29.3% versus 41.4%; $P < 0.05$) (30). A recently completed UK comparative effectiveness trial randomized 517 gout patients seen by general practitioners and compared a nurse-led T2T approach with general practitioner–led usual care in the UK primary care setting over 2 years. The results from this trial are expected in the near future (31). To the extent that primary care providers' delivery of gout care approximates a T2aS strategy, the results of this survey may be able to provide better support for T2T strategies.

Until there is better agreement between the respective societies, individual rheumatologists must serve as an important educational resource for their local primary care providers. As such, rheumatologists must become ambassadors of gout. Do not let gout apathy lead

to gouty arthropathy. Reach out to primary care provider colleagues to help answer questions they may have after the publication of the ACP guidelines.

AUTHOR CONTRIBUTIONS

Drs. FitzGerald, Neogi, and Choi drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

REFERENCES

1. Khanna D, Khanna PP, Fitzgerald JD, Singh MK, Bae S, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2. Therapy and antiinflammatory prophylaxis of acute gouty arthritis. Arthritis Care Res (Hoboken) 2012;64:1447–61.
2. Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, et al. 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;64:1431–46.
3. Zhang W, Doherty M, Bardin T, Pascual E, Barskova V, Conaghan P, et al. EULAR evidence based recommendations for gout. Part II. Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2006;65:1312–24.
4. Richette P, Doherty M, Pascual E, Barskova V, Becce F, Castaneda-Sanabria J, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis 2017;76:29–42.
5. Jordan KM, Cameron JS, Snaith M, Zhang W, Doherty M, Seckl J, et al. on behalf of the 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;46:1372–4.
6. Qaseem A, Harris RP, Forciea MA, for the Clinical Guidelines Committee of the American College of Physicians. Management of acute and recurrent gout: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2017;166:58–68.
7. Qaseem A, McLean RM, Starkey M, Forciea MA, for the Clinical Guidelines Committee of the American College of Physicians. Diagnosis of acute gout: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2017;166:52–7.
8. American College of Physicians. Clinical guidelines and recommendations from the American College of Physicians. URL: https://www.acponline.org/clinical-information/guidelines.
9. McLean RM. The long and winding road to clinical guidelines on the diagnosis and management of gout [editorial]. Ann Intern Med 2017;166:73–4.
10. Perez-Ruiz F, Calabozo M, Pijoan JI, Herrero-Beites AM, Ruibal A. Effect of urate-lowering therapy on the velocity of size reduction of tophi in chronic gout. Arthritis Rheum 2002;47:356–60.
11. Perez-Ruiz F, Atxotegi J, Hernando I, Calabozo M, Nolla JM. Using serum urate levels to determine the period free of gouty symptoms after withdrawal of long-term urate-lowering therapy: a prospective study. Arthritis Rheum 2006;55:786–90.
12. Shoji A, Yamanaka H, Kamatani N. A retrospective study of the relationship between serum urate level and recurrent attacks of gouty arthritis: evidence for reduction of recurrent gouty arthritis with antihyperuricemic therapy. Arthritis Rheum 2004;51:321–5.
13. Sarawate CA, Patel PA, Schumacher HR, Yang W, Brewer KK, Bakst AW. Serum urate levels and gout flares: analysis from managed care data. J Clin Rheumatol 2006;12:61–5.
14. Annemans L, Spaepen E, Gaskin M, Bonnemaire M, Malier V, Gilbert T, et al. Gout in the UK and Germany: prevalence, comorbidities and management in general practice 2000–2005. Ann Rheum Dis 2008;67:960–6.
15. Launer LJ, Miller ME, Williamson JD, Lazar RM, Gerstein HC, Murray AM, et al. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy. Lancet Neurol 2011;10:969–77.
16. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, et al, for the CHOIR Investigators. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med 2006;355:2085–98.
17. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129 Suppl 2:S1–45.
18. Shekelle PG, Newberry SJ, FitzGerald JD, Motala A, O'Hanlon CE, Tariq A, et al. Management of gout: a systematic review in support of an American College of Physicians clinical practice guideline. Ann Intern Med 2017;166:37–51.
19. Lim SY, Lu N, Oza A, Fisher M, Rai SK, Menendez ME, et al. Trends in gout and rheumatoid arthritis hospitalizations in the United States, 1993–2011. JAMA 2016;315:2345–7.
20. Sharma TS, Harrington TM, Olenginski TP. Aim for better gout control: a retrospective analysis of preventable hospital admissions for gout [abstract]. Arthritis Rheumatol 2014;66 Suppl 10:S1014.
21. Halpern R, Mody RR, Fuldeore MJ, Patel PA, Mikuls TR. Impact of noncompliance with urate-lowering drug on serum urate and gout-related healthcare costs: administrative claims analysis. Curr Med Res Opin 2009;25:1711–9.
22. Harrold LR, Andrade SE, Briesacher B, Raebel MA, Fouayzi H, Yood RA, et al. The dynamics of chronic gout treatment: medication gaps and return to therapy. Am J Med 2010;123:54–9.
23. Sarawate CA, Brewer KK, Yang W, Patel PA, Schumacher HR, Saag KG, et al. Gout medication treatment patterns and adherence to standards of care from a managed care perspective. Mayo Clin Proc 2006;81:925–34.
24. Rashid N, Coburn BW, Wu YL, Cheetham TC, Curtis JR, Saag KG, et al. Modifiable factors associated with allopurinol adherence and outcomes among patients with gout in an integrated healthcare system. J Rheumatol 2015;42:504–12.
25. De Vera MA, Marcotte G, Rai S, Galo JS, Bhole V. Medication adherence in gout: a systematic review. Arthritis Care Res (Hoboken) 2014;66:1551–9.
26. Roddy E, Zhang WY, Doherty M. Concordance of the management of chronic gout in a UK primary-care population with the EULAR gout recommendations. Ann Rheum Dis 2007;66:1311–5.
27. Qaseem A, Harris RP, Forciea MA, for the Clinical Guidelines Committee of the American College of Physicians. Management of acute and recurrent gout: a clinical practice guideline from the American College of Physicians: summaries for patients. Ann Intern Med 2017;166:I–16.
28. Shmerling RH. The ethics of recent gout trials [editorial]. Arthritis Rheumatol 2016;68:2057–60.
29. Sundy JS, Baraf HS, Yood RA, Edwards NL, Gutierrez-Urena SR, Treadwell EL, et al. Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: two randomized controlled trials. JAMA 2011;306:711–20.
30. Dalbeth N, Saag KG, Palmer W, Choi HK, Hunt B, MacDonald P, et al. Overall reduction in acute flares during treatment with febuxostat compared with placebo over 2 years in patients with early gout [abstract]. Arthritis Rheumatol 2016;68 Suppl 10. URL: http://acrabstracts.org/abstract/overall-reduction-in-acute-flares-during-treatment-with-febuxostat-compared-with-placebo-over-2-years-in-patients-with-early-gout/.
31. University of Nottingham, sponsor. Arthritis Research UK Gout Treatment trial: phase 2. ClinicalTrials.gov identifier: NCT01477346; 2011.