Rheumatology for the Internist: When did Gout get so complicated?

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ACP Clinical Guidelines Committee 2015-19

ACP Delaware Chapter meeting February 8, 2020
Regarding Guidelines & Gout

- I have no conflicts of interest to disclose
- ...Just my biases as a rheumatologist
ACP Guidelines Definition

The goal of the ACP is to provide clinicians with clinical guidelines based on the best available evidence; to make recommendations on the basis of that evidence; to inform clinicians of when there is no evidence; and finally, to help clinicians deliver the best health care possible.

2 types of clinical recommendations:

- **Clinical practice guidelines**: Clinical practice guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances.

- **Clinical guidance statements**: Involve review and critique of available guidelines.
ACP Guideline process overview

- Key questions and scope for the evidence-review papers are developed with input from the Clinical Guidelines Committee.
- The evidence-review paper is a comprehensive systematic review or meta-analysis that addresses the clinical topic area under review.
- Quality of evidence is evaluated by using the ACP's Guideline Grading System, which is adopted from the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system.
- Evidence reviews provide information about whether the studies included are reliable and accurate and provide reasonable assessments of potential adverse events.
Institute of Medicine reports 2011

**Finding What Works in Health Care: Standards for Systematic Reviews**

- Established optimal practice for systematic reviews and clearly distinguishes an systematic review of the evidence from other types of literature reviews.
- Systematic reviews are rigorous protocol-driven literature reviews that summarize evidence by identifying, selecting, assessing, and synthesizing the findings of similar but separate studies.
- Help clarify what is known and not known about the potential benefits and harms of drugs, devices, and other health care services.

**Clinical Practice Guidelines We Can Trust**

- Clinical practice guidelines are statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options.
- The new definition provides a clear distinction between the term “Clinical practice guidelines” and other forms of clinical guidance derived from widely disparate development processes:
  
  *consensus statements, expert advice, appropriate use criteria*
Standards for Developing Trustworthy Clinical Practice Guidelines

1. Establishing Transparency--processes by which a Clinical Practice Guideline is developed and funded should be detailed explicitly and publicly accessible.

2. Management of Conflict of Interest

3. Guideline Development Group Composition- should be multidisciplinary and balanced, comprising a variety of methodological experts and clinicians, and populations expected to be affected by the Guideline; Patient and public involvement should be facilitated by including a current or former patient, and a patient advocate or patient/consumer organization representative

5. Establishing Evidence Foundations for and **Rating Strength of Recommendations**

6. Articulation of **Recommendations in a standardized form** detailing precisely what the recommended action is, and under what circumstances it should be performed.

7. **External Review**- should comprise a full spectrum of relevant stakeholders, including scientific and clinical experts, organizations (e.g., health care, specialty societies), agencies (e.g., federal government), patients, and representatives of the public.

8. **Updating**- publication date, date of pertinent systematic evidence review, and proposed date for future Guideline review should be documented in the Guideline; Literature should be monitored regularly following Guideline publication to identify the emergence of new, potentially relevant evidence and to evaluate the continued validity of the Guideline.
The Development of Clinical Guidelines and Guidance Statements by the Clinical Guidelines Committee of the American College of Physicians: Update of Methods

Anton Gaseeem, MD, PhD, MPH; Devon Kassapis, MD, MCR; Jennifer S. Lin, MD, MCR; Bacon A. Mustafa, MD, MPH; PhD; and Timothy J. West, MD, MPP, for the Clinical Guidelines Committee of the American College of Physicians*

The American College of Physicians (ACP) was one of the first organizations in the United States to develop evidence-based clinical guidelines and has been developing guidelines since 1981. ACP’s Clinical Guidelines Committee (CGC) in collaboration with staff from the Clinical Policy Department, develops clinical guidelines and guidance statements and continues to refine and enhance its methodology. This article presents an update of the CGC’s 2010 paper outlining policies, methods, and presentation format of ACP’s clinical guidelines and guidance statements. Updated methods include more stringent policies about disclosure of interests and conflict management, inclusion of public perspectives, full adoption of GRADE (Grading of Recommendations Assessment, Development and Evaluation) methods, more standardized reporting formats that consider value of care, patient-centered conditions, patient values and preferences, and costs, and further clarification of guidance statement methods.

This article was published in Annals on 11 June 2019.

Disclosure of Interests and Management of Conflicts of Interest in Clinical Guidelines and Guidance Statements: Methods From the Clinical Guidelines Committee of the American College of Physicians

One of the hallmarks of a trustworthy clinical guideline or guidance statement is a comprehensive process for disclosure of interests (DOI) and management of conflicts of interest (COI). The American College of Physicians (ACP) Clinical Guidelines Committee (CGC) aims to disclose all health care-related interests and manage conflicts in a manner that is transparent, proportional, and consistent. Any person involved in the development of an ACP clinical guideline or guidance statement must disclose all financial and intellectual interests related to health care from the previous 3 years. Persons complete disclosures at the start of their participation and are required to update them over the course of their involvement with the CGC, including before each CGC meeting. ADO, COI, review, and Management Panel reviews the disclosures, flags potential conflicts, guides the COI as low, moderate, or high-level, and manages the person’s participation accordingly. A high-level COI results in recusal from authorship, voting, and all committee discussions. Participants with a moderate-level COI are excused from authorship and voting for clinically relevant topics but may participate in all discussions. A low-level COI results in no role restrictions. All disclosures and COI management decisions are publicly reported.

This article was published in Annals on 11 August 2019.

Any actual bias during clinical guideline development and to ensure credibility and public trust in ACP clinical guidelines by reducing the potential for perceived bias. Some subjectivity is inherent to the development of any guideline or guidance statement. Systematic reviewers make judgments when assessing the quality of studies, and the included studies may balance benefits against harms and costs to make recommendations (6). The threat of COI influencing these judgments var...
**Table.** Additions and Changes in the 2019 CGC Methods Paper Compared With the 2010 CGC Methods Paper

| Enhanced and more stringent DOI and COI policies and management |
| Inclusion of public perspective in clinical guideline development |
| Full adoption of GRADE methods, including evidence-to-decision tables |
| Standardized reporting formats that consider value of care, patient comorbid conditions, patient values and preferences, and costs |
| Further details on methods for guidance statement development |

CGC = Clinical Guidelines Committee; COI = conflict of interest; DOI = disclosure of interest; GRADE = Grading of Recommendations Assessment, Development and Evaluation.
Overview of ACP development and approval process

AGREE II = Appraisal of Guidelines for Research and Evaluation II;
CGC = Clinical Guidelines Committee;
PICO = population, interventions, comparators, and outcomes.
GRADE = Grading of Recommendations Assessment, Development, and Evaluation

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<th>Grading Certainty of Evidence</th>
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<tr>
<td>High</td>
<td>Confident that the true effect is close to the estimated effect.</td>
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<tr>
<td>Moderate</td>
<td>Moderately confident in the effect estimate: The true effect is likely close to the estimated effect, but there is a sizable possibility that it is substantially different.</td>
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<tr>
<td>Low</td>
<td>Confidence in the effect estimate is limited: The true effect may be substantially different from the estimated effect.</td>
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<th>Grading Recommendations</th>
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<tr>
<td>Strength</td>
<td>Certainty of Evidence</td>
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<tr>
<td>Strong</td>
<td>High or moderate</td>
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<td>Low only in very rare circumstances</td>
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<td>Balance of Benefits and Harms</td>
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<td>Confidence that benefits clearly outweigh risks and burden or vice versa.</td>
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<td></td>
<td>Applicable Patient Population</td>
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<td></td>
<td>Applies to most patients in most circumstances.</td>
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<td>Policy Implication</td>
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<td>Only strong recommendations could be considered for use as performance measures.</td>
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*Example from ACP’s guideline on treatment of major depressive disorder: “ACP recommends that clinicians select between either cognitive behavioral therapy or second-generation antidepressants to treat patients with major depressive disorder after discussing treatment effects, adverse effect profiles, cost, accessibility, and preferences with the patient (Grade: strong recommendation, moderate-quality evidence)” (7).*

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<tr>
<td>Conditional</td>
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<td>Balance of Benefits and Harms</td>
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<td>Benefits probably outweigh risks and burden, or vice versa, but there is appreciable uncertainty.</td>
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<td>Applicable Patient Population</td>
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<td>Applies to many patients but may differ depending on circumstances or patients’ values and preferences.</td>
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<td></td>
<td>Policy Implication</td>
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<tr>
<td></td>
<td>Policymaking will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.</td>
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*Example from ACP’s guideline on noninvasive treatments of acute, subacute, and chronic low back pain: “In patients with chronic low back pain who have had an inadequate response to nonpharmacologic therapy, clinicians and patients should consider pharmacologic treatment with nonsteroidal anti-inflammatory drugs as first-line therapy, or tramadol or duloxetine as second-line therapy. Clinicians should only consider opioids as an option in patients who have failed the aforementioned treatments and only if the potential benefits outweigh the risks for individual patients and after a discussion of known risks and realistic benefits with patients. (Grade: weak recommendation, moderate-quality evidence)” (8).*
Key Question 1- Acute Gout Treatment

a. What are the benefits and harms of different pharmacologic therapies?

b. Does effectiveness (benefits and harms) differ according to patient baseline demographic characteristics & comorbid conditions (including renal function)?

c. Does effectiveness (benefits and harms) differ according to disease severity, including initial clinical presentation (e.g., extent of joint involvement & time since start of flare) and laboratory values (serum uric acid)?
Key Question 2- Dietary and Lifestyle Management of Gout

a. What are the benefits and harms of different dietary therapies and lifestyle measures on intermediate (serum uric acid levels) and final health outcomes (including recurrence of gout episodes and progression, development of tophi)?

b. Does effectiveness and comparative effectiveness of dietary modification differ according to disease severity (including presence of tophi and baseline serum uric acid level), underlying mechanisms of hyperuricemia, or baseline demographic and comorbid characteristics?
ACP Guideline Process Example
Key questions: Management of Gout

Key Question 3- Pharmacologic Management of Hyperuricemia in Patients With Gout

a. What are the benefits & harms of different pharmacologic therapies on intermediate (serum uric acid levels) and long-term clinical health outcomes (recurrence of gout episodes/progression)?

b. Does effectiveness & comparative effectiveness of uric acid-lowering therapy differ according to disease severity (including presence of tophi & baseline serum uric acid), underlying mechanisms of hyperuricemia, or baseline demographic and comorbid characteristics?

c. What is the effect of dietary modification in combination with pharmacologic therapy?
ACP Guideline Process Example
Key questions: Management of Gout

Key Question 4- Treatment Monitoring of Patients With Gout

a. Does monitoring serum uric acid levels with pharmacologic treatment and/or dietary and/or lifestyle change measures (e.g., adherence) improve treatment outcomes?

b. Is achieving lower subsequent serum uric acid levels (<5 vs. 5-7 mg/dL) associated with decreased risk for recurrent acute gout attack, progression to chronic arthritis or disability, resolution of tophi, or other clinical outcomes (including risk for comorbidities or progression of comorbidities) or patient-reported outcomes?
Key Question 5 - Discontinuation of Pharmaceutical Management for Patients Receiving Acute or Chronic Gout Medications

Are there criteria that can identify patients who are candidates for discontinuing:

i. Urate-lowering therapy?

ii. Anti-inflammatory prophylaxis against acute gout attack, for patients receiving urate-lowering therapy after an acute gout attack?
ACP Recommendations

**Recommendation 1:** ACP recommends that clinicians choose corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), or colchicine to treat patients with acute gout.

(Grade: strong recommendation, high-quality evidence)

**Recommendation 2:** ACP recommends that clinicians use low-dose colchicine when using colchicine to treat acute gout.

(Grade: strong recommendation, moderate-quality evidence)
**Recommendation 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)

**Recommendation 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)
A Clinical Practice Guideline by definition is supposed to tell you:

“what does good evidence suggest or support we should do for a given condition or clinical situation?”

But what we actually want to know is:

“what should we do for a given condition or clinical situation?”
The Challenges and Why Guidelines might differ

• What if the Systematic Review does not find answers to the Key Questions?
• What if studies that other guidelines quote are not felt adequate for consideration?
• What if other guideline-developing entities rely on “expert opinion” in their process rather than pure evidence review?
• What if other entities do not have stringent DOI/COI policies?
What did ACP say for Gout management?

Following a treat-to-target approach is wrong.

OR

ACP cannot endorse the Treat-to-target approach because there is not strong enough evidence to tell us it is the right thing to do.

Of course,

Treating the pain of acute gout (Treat-to-avoid-symptoms) is appropriate, in ways that have proven effective.
What ACP Gout Guideline did NOT say

- Treat only to avoid symptoms and do not use urate-lowering therapy
- Do not base any treatment decisions based on serum uric acid levels

- BUT, those were conclusions attributed to ACP guidelines

Stating “there is not evidence to clearly endorse” is NOT the same as saying “do not do that”
ACP stated need for additional evidence

Key questions from ACP Process could not be answered due to areas of inconclusive evidence

*Treatment Strategy for Patients With Gout Receiving Urate-Lowering Therapy: No study has compared a Treat-to-Target strategy to a Treat-to-avoid-symptoms strategy
*Effect of Urate-Lowering Treatment on Adverse Health Outcomes Beyond Acute Gout
*Duration of Urate-Lowering Treatment
*Treatment in Different Patient Groups
*Effect of Dietary Treatments
*Long Term effects of Febuxostat
So When Guideline Controversy Seems to Occur

The questions to ask:

• Is there a Systematic Review and how was it constructed?
• Is the same evidence being evaluated?
• Is expert opinion being given a role?
• Is stringent DOI/COI process present, for participants as well as sponsoring entity?
Quiz Question #1

Which one of the following statements accurately represents a conclusion from the ACP gout guidelines?

a. Treat only to avoid symptoms, and do not use urate-lowering therapy
b. A Treat-to-target approach cannot be endorsed because there is not strong enough evidence that it is the right thing to do
c. Do not make any treatment decision based on serum uric acid levels
d. Following a treat-to-target approach is wrong and should never be used
Case for Quiz #2

64 yo WM seen by you as his PCP 1 week after he was seen in ED for severe acute pain and swelling of left base great toe starting 2 days previously. He had taken OTC naproxen 220 mg twice in previous day with minimal improvement. He was told that x-ray showed soft tissue swelling but no bone/joint changes

Past Hx: HTN on lisinopril and HCTZ, type 2 DM on metformin, mild knee DJD and takes occasional naproxen OTC 2-3 types per week as needed. NKDA.

Labs in ED with normal CBC and chem panel, uric acid 8.0
Case for Quiz #2

ED physician gave him diagnosis of gout (“podagra”), and gave Rx for methylprednisolone dosepak to take for typical 6 day course, and also gave him indomethacin 50 mg to take BID prn if the methylprednisolone was not making him a lot better after 24-48 hours

In office today, he reports that he finished methylprednisolone yesterday, and the foot is now 90% better. Other joints are fine, and foot appears normal.
Quiz Question #2

In this patient with recent acute gout, the best next management plan right now would be:

a. start allopurinol 100 mg per day
b. give a 2nd course of a methylprednisolone dosepak
c. start colchicine 0.6 mg BID for 1 week then decrease to QD
d. give longer course of tapering oral steroids as prednisone, 30 mg QD for 5 days then taper by 10 mg every 5 days (20 mg x 5 d, 10 mg x 5 d, then stop)
Thank you!

Live neither in the past nor in the future, but let each day absorb all your interest, energy, and enthusiasm. The best preparation for tomorrow is to live today superbly well.

- Sir William Osler

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