

Diagnosis of Acute Gout: A Clinical Practice Guideline From the American College of Physicians

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Description: The American College of Physicians (ACP) developed this guideline to present the evidence and provide clinical recommendations on the diagnosis of gout.

Methods: This guideline is based on a systematic review of published studies on gout diagnosis, identified using several databases, from database inception to February 2016. Evaluated outcomes included the accuracy of the test results; intermediate outcomes (results of laboratory and radiographic tests, such as serum urate and synovial fluid crystal analysis and radiographic or ultrasonography changes); clinical decision making (additional testing and pharmacologic or dietary management); short-term clinical (patient-centered) outcomes, such as pain and joint swelling and tenderness; and adverse effects of the tests. This guideline grades the evidence and recommendations by using the ACP grading system, which is based on the GRADE (Grading

of Recommendations Assessment, Development and Evaluation) method.

Target Audience and Patient Population: The target audience for this guideline includes all clinicians, and the target patient population includes adults with joint inflammation suspected to be gout.

Recommendation: *ACP recommends that clinicians use synovial fluid analysis when clinical judgment indicates that diagnostic testing is necessary in patients with possible acute gout. (Grade: weak recommendation, low-quality evidence)*

Ann Intern Med. 2017;166:52-57. doi:10.7326/M16-0569 www.annals.org
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This article was published at www.annals.org on 1 November 2016.

Gout is caused by excess urate crystals accumulating in body tissues and fluid, resulting in inflammatory arthritis. Patients have joint swelling and pain during gout attacks, the initial stages of which are called acute gouty arthritis or acute gout flares. Progression to chronic gout may be accompanied by the accumulation of monosodium urate (MSU) crystals (known as tophi) in joints, cartilage, tendons, bursae, bone, and soft tissue. Risk factors associated with gout include male sex, overweight or obesity, hypertension, excess alcohol intake, diuretic use, a diet rich in meat and seafood, and poor kidney function (1-4). The self-reported prevalence of ever receiving a gout diagnosis is estimated to be 3.9% in U.S. adults older than age 20 (5); this prevalence increased by 1.0% between about 1990 and 2007 (5). An estimated \$1 billion is spent annually on ambulatory care for gout, largely on treatments and prescription medications (6).

Correctly diagnosing gout and differentiating it from other inflammatory arthritic conditions, such as rheumatoid arthritis, septic arthritis, and inflammatory episodes of osteoarthritis, is important, because treatment of these conditions differ. The reference standard for diagnosing acute gout is joint aspiration with synovial fluid analysis for MSU. However, most patients initially are seen in the primary care or emergency medicine setting, where synovial fluid analysis rarely is performed. Synovial fluid analysis is also underutilized in rheumatology (7). Additional approaches for diagnosing acute gout include clinical algorithms that incorporate patient signs and symptoms, ultrasonography, dual-energy computed tomography (DECT), computed tomography, and plain radiography.

GUIDELINE FOCUS AND TARGET POPULATION

The purpose of this American College of Physicians (ACP) guideline is to provide guidance on diagnosing acute gout in patients with gout symptoms, including joint inflammation. This guideline does not apply to adults who have chronic gout that was diagnosed previously by identification of MSU and who present with a flare and no suggestion of a concurrent problem, such as a septic joint. These recommendations are based on a background evidence review paper (8) and an evidence review sponsored by the Agency for Healthcare Research and Quality (AHRQ) (9).

See also:

Related articles. 27, 37, 58
Editorial comments 71, 73
Summary for Patients. I-16

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* This paper, written by Amir Qaseem, MD, PhD, MHA; Robert M. McLean, MD; Melissa Starkey, PhD; and Mary Ann Forciea, MD, was developed for the Clinical Guidelines Committee of the American College of Physicians. Individuals who served on the Clinical Guidelines Committee from initiation of the project until its approval were Mary Ann Forciea, MD† (Chair); Thomas D. Denberg, MD, PhD† (Immediate Past Chair); Michael J. Barry, MD†; Cynthia Boyd, MD, MPH†; R. Dobbin Chow, MD, MBA†; Nick Fitterman, MD†; Linda L. Humphrey, MD, MPH†; Devan Kansagara, MD, MCR†; Scott Manaker, MD, PhD†; Robert M. McLean, MD†; Sandeep Vijan, MD, MS†; and Timothy J. Wilt, MD, MPH†. Approved by the ACP Board of Regents on 7 November 2015.

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METHODS

Systematic Review of the Evidence

The evidence review was conducted by the AHRQ's Southern California Evidence-based Practice Center-RAND Corporation. Additional methodological details may be found in the **Appendix** (available at www.annals.org) as well as in the accompanying article (8) and full report (9). Reviewers searched several databases for studies published from database inception through February 2016 and included prospective and cross-sectional studies. The study population included all adults aged 18 years or older with suspected gout (such as an acute episode of joint inflammation).

The systematic review evaluated diagnostic tests for gout. Evaluated outcomes included accuracy of the test results (sensitivity, specificity, and positive and negative predictive value); intermediate outcomes (results of laboratory and radiographic tests, such as serum urate and synovial fluid crystal analysis and radiographic or ultrasonography changes); clinical decision making (additional testing and pharmacologic or dietary management); short-term clinical (patient-centered) outcomes, such as pain and joint swelling and tenderness; and adverse effects of the tests.

Grading the Evidence and Developing Recommendations

This guideline was developed by the ACP Clinical Guidelines Committee (CGC) according to the ACP guideline development process, details of which may be found in the methods paper (10). The CGC used the evidence tables in the accompanying systematic review (8) and full report (9) when reporting the evidence and graded the recommendations by using the ACP system, which is based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) method (Table).

Peer Review

The AHRQ evidence review was sent to invited peer reviewers and posted on the AHRQ Web site for public comments. The guideline was peer reviewed through the journal and posted online for comments from ACP Regents and Governors, who represent ACP members at the regional level.

ACCURACY OF TESTS, ALGORITHMS, AND CLASSIFICATION SYSTEMS

Clinical Algorithms Incorporating Clinical Signs and Symptoms

Eleven studies assessed the sensitivity and specificity of clinical algorithms versus evaluation of synovial fluid MSU crystals for diagnosing gout (11–21) and reported widely varying results. Evaluated algorithms included the Rome criteria, New York criteria, American Rheumatology Association criteria, Janssens diagnostic rule, Clinical Gout Diagnosis criteria, monoarthritis of the first metatarsophalangeal joint, SUGAR (Study for Updated Gout Classification Criteria), and 2015 American College of Rheumatology and European League Against Rheumatism gout classification criteria.

Table. The American College of Physicians' Guideline Grading System*

Quality of Evidence	Strength of Recommendation	
	Benefits Clearly Outweigh Risks and Burden or Risks and Burden Clearly Outweigh Benefits	Benefits Finely Balanced With Risks and Burden
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or risks		

* Adopted from the classification developed by the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) workgroup.

Moderate-quality evidence showed that several clinical algorithms based on clinical signs and symptoms have good specificity and sensitivity (>80%) for diagnosing gout compared with assessment of synovial fluid MSU crystals. Many algorithms had a higher sensitivity in patients with a longer history of flares (>2 years) than in those with more recent-onset symptoms (≤ 2 years). The components of the clinical algorithms varied; however, most included the following clinical characteristics: more than 1 attack of acute arthritis, maximum inflammation developing within 1 day, redness observed over joints, painful or swollen first metatarsophalangeal joint, proven or suspected tophi, and the comorbid risk factor of hyperuricemia. Details on each algorithm are provided in the accompanying evidence review (8).

DECT

Low-quality evidence from 3 observational studies (20–22) showed that DECT had a sensitivity of 85% to 100% and specificity of 83% to 92% for predicting gout compared with assessment of synovial fluid MSU crystals or clinical algorithms.

Ultrasonography

Low-quality evidence (20, 23–27) showed that ultrasonography had a wide range in sensitivity and specificity for diagnosing acute gout compared with assessment of synovial fluid MSU crystals or clinical algorithms. Pooled sensitivity from 4 trials (12, 17, 19, 28) showed 74% sensitivity (95% CI, 52 to 88) and 88% specificity (95% CI, 68 to 96).

DIAGNOSTIC ACCURACY BASED ON JOINT SITE AND NUMBER OF JOINTS

Insufficient evidence exists regarding whether the joint site or number of joints involved affected the accuracy of diagnostic tests based on clinical signs and symptoms because no studies were identified that directly tested this association.

DIAGNOSTIC ACCURACY BASED ON SYMPTOM DURATION

Insufficient evidence exists regarding the effect of symptom duration (that is, time since beginning of flare) on the accuracy of gout diagnosis based on clinical signs and symptoms.

Figure. Summary of the American College of Physicians guideline on diagnosis of gout.



Summary of the American College of Physicians Guideline on Diagnosis of Gout

Disease/Condition	Acute gout
Target Audience	All clinicians
Target Patient Population	Adults with joint inflammation suspected to be gout
Interventions Evaluated	Clinical history and physical examination, serum urate assessment, ultrasonography, DECT, computed tomography, plain radiography, joint aspiration by physicians and synovial fluid analysis using polarizing microscopy, combinations of aforementioned tests as identified in the literature
Outcomes Evaluated	Accuracy of the test results (sensitivity, specificity, positive and negative predictive value); intermediate outcomes (results of laboratory and radiographic tests, such as serum urate and synovial fluid crystal analysis and radiographic or ultrasonography changes); clinical decision making (additional testing, pharmacologic or dietary management); short-term clinical (patient-centered) outcomes, such as pain, joint swelling, and tenderness; and adverse effects of the tests, including pain, infection, radiation exposure, and effects of false-positive or -negative results
Potential Benefits	Accurate diagnosis of gout, leading to appropriate treatment
Potential Harms	None reported for DECT. No studies reported for ultrasonography or clinical examination/algorithms Synovial fluid aspiration for MSU analysis associated with nonserious adverse events, such as mild postprocedure pain Misdiagnosis or delayed diagnosis, leading to inadequate or inappropriate treatment
Recommendation	<i>Recommendation: ACP recommends that clinicians use synovial fluid analysis when clinical judgment indicates that diagnostic testing is necessary in patients with possible acute gout. (Grade: weak recommendation, low-quality evidence)</i>
Clinical Considerations	Synovial fluid analysis is considered the reference standard for gout diagnosis, although it may be difficult to perform in primary care. Synovial fluid analysis should be used in the following clinical circumstances: The joint can be aspirated without substantial patient discomfort by an experienced clinician who can minimize the risk of infection. A reliable and accurate source (including a polarizing microscope and a trained operator) is available to detect the presence of urate crystals. The clinical situation is ambiguous, and a probability of infection exists. Clinical algorithms are shown to have sensitivities and specificities >80%, although little evidence exists that they can be used to distinguish septic joints.

DECT = dual-energy computed tomography; MSU = monosodium urate.

FACTORS AFFECTING THE ACCURACY OF SYNOVIAL FLUID ASPIRATION AND CRYSTAL ANALYSIS

Insufficient evidence exists to determine what factors influence the accuracy of gout diagnosis from 3 studies that reported conflicting results (29–31).

ADVERSE EFFECTS OF DIAGNOSTIC TESTS

Insufficient evidence exists regarding adverse effects associated with diagnostic tests for gout. Evidence from 1 observational study from a referral center procedure clinic (21) reported no adverse events associated with DECT or with aspiration of synovial fluid, although procedures for detecting adverse events were not reported. One study assessed adverse events asso-

ciated with synovial fluid aspiration for MSU analysis and reported 1 occurrence of septic arthritis and 11 nonserious adverse events, such as mild postprocedure pain (32). None of the identified studies reported adverse effects from other diagnostic tests (ultrasonography or clinical examination). Evidence from 1 observational study from Korea (30) that assessed factors associated with misdiagnosis or delayed diagnosis of acute gout showed that misdiagnosis or delayed diagnosis may result in longer hospitalization and delays in joint aspiration after a gout attack begins. Reviewers found no evidence for patient-reported outcomes, such as pain and subsequent infection from joint aspiration and synovial fluid analysis, the accuracy and reliability of synovial fluid analysis in primary care, or how often joint aspiration is difficult or impossible in primary care.

SUMMARY

Although synovial fluid analysis has been the reference standard for gout diagnosis, it often is difficult to perform in primary care and even rheumatologic settings. Furthermore, accurate detection of urate crystals requires a polarizing microscope and a trained operator. Evidence for alternatives to synovial fluid MSU crystal analysis for diagnosing acute gout would be helpful but is limited. An accurate clinical algorithm that could be used in primary care would be especially valuable. The evidence review found moderate-quality evidence that several clinical prediction tools have sensitivities and specificities greater than 80% for diagnosing early-onset gout compared with the reference standard of synovial fluid MSU crystal analysis. Evidence on whether clinical algorithms can rule out such conditions as septic joints is limited. Evidence showing variation in the sensitivity and specificity of both DECT and ultrasonography for diagnosing acute gout is also limited, leading to uncertainty about the usefulness of these tests in the primary care setting.

The **Figure** summarizes the recommendations and clinical considerations.

RECOMMENDATION

ACP recommends that clinicians use synovial fluid analysis when clinical judgment indicates that diagnostic testing is necessary in patients with possible acute gout. (Grade: weak recommendation, low-quality evidence)

Synovial fluid analysis has been the reference standard for gout diagnosis. Misdiagnosis or delayed diagnosis of acute gout may result in unnecessary surgery; hospitalization; delays in adequate treatment, such as antibiotics for septic joints; and unnecessary prescribing of long-term treatment. In the absence of an evidence-based alternative, joint aspiration and synovial fluid analysis should be done if the joint can be aspirated without substantial patient discomfort by an experienced clinician who can minimize the risk for infection; a reliable, accurate source (including a polarizing microscope and a trained operator) is available to detect the presence of urate crystals; the clinical situation is ambiguous; and a significant probability of infection exists.

If these criteria cannot be met, the clinician should either refer the patient to a source that can meet the criteria or use his or her clinical judgment. Clinical judgment is especially appropriate in situations that are less clinically ambiguous and where there is not a significant probability of infection. For example, joint aspiration would not be essential in a patient with podagra, a history of appropriate risk factors (such as age), and no sign of an overlying skin wound. This patient may appropriately be considered to have gout and treated appropriately (see accompanying guideline on gout management [33]). The current evidence is insufficient to recommend a single clinical algorithm for diagnosing gout. However, several promising algorithms showed sensitivities and specificities greater than 80%.

Current evidence is insufficient to support the use of DECT or ultrasonography to diagnose acute gout.

AREAS OF INCONCLUSIVE EVIDENCE

Insufficient evidence exists to determine the clinical utility of serum urate alone, computed tomography, or plain radiography for diagnosing gout. Evidence also is insufficient to determine the effects of joint site, number of affected joints, duration of symptoms, or practitioner type on the diagnostic accuracy of various tests. Further validation of clinical algorithms is needed.

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Note: Clinical practice guidelines are “guides” only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians' judgment. All ACP clinical practice guidelines are considered automatically withdrawn or invalid 5 years after publication or once an update has been issued.

Disclaimer: The authors of this article are responsible for its contents, including any clinical or treatment recommendations.

Financial Support: Financial support for the development of this guideline comes exclusively from the ACP operating budget.

Disclosures: Dr. Barry reports grants and personal fees from Informed Medical Decisions Foundation and Healthwise, outside the submitted work. Dr. Boyd reports royalties from UptoDate, outside the submitted work. Dr. Manaker reports personal fees from work as a grand rounds speaker, lecturer, consultant, and expert witness on documentation, coding, billing, and reimbursement to hospitals, physicians, departments, practice groups, professional societies, insurers, and attorneys (defense, plaintiff “qui tam,” U.S. attorneys general, and the Office of the Inspector General); personal fees from work as an expert witness in workers' compensation and medical negligence; dividend income from stock held by his spouse in Pfizer and Johnson and Johnson; and meal and travel expenses for serving on the CMS Hospital Outpatient Panel, the American Medical Association/Specialty Society Relative Value Unit Update Committee, and the Board of Directors of CHEST Enterprises, a subsidiary of the American College of Chest Physicians. Authors not named here have disclosed no conflicts of interest. Authors followed the policy regarding conflicts of interest described at www.annals.org/aim/article/745942. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M16-0569. All financial and intellectual disclosures of interest were declared, and potential conflicts were discussed and managed. No CGC members were recused from voting on this guideline due to conflicts. A record of disclosures and management of conflicts of interest is kept for each CGC meeting and conference call and can be viewed at www.acponline.org/about-acp/who-we-are/leadership/committees-boards-councils/clinical-guidelines-committee/disclosure-of-interests-for-clinical-guidelines-committee.

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APPENDIX: DETAILED METHODS

The evidence review was conducted by the Southern California Evidence-based Practice Center-RAND Corporation to address the following key questions:

Key Question 1

a. What is the accuracy of clinical signs and symptoms and other diagnostic tests (such as serum urate, ultrasonography, computed tomography, DECT, and plain radiography), alone or in combination, compared with synovial fluid analysis in diagnosing acute gouty arthritis, and how does the accuracy affect clinical decision making, clinical outcomes and complications, and patient-centered outcomes?

b. How does the diagnostic accuracy of clinical signs and symptoms and other tests vary by affected joint site and number of joints?

c. Does the accuracy of diagnostic tests for gout vary by duration of symptoms (that is, time from the beginning of a flare)?

d. Does the accuracy of synovial fluid aspiration and crystal analysis differ by the type of practitioner who is performing the aspiration or the crystal analysis?

Key Question 2

a. What are the adverse effects (including pain, infection at the aspiration site, radiation exposure) or harms (related to false-positive, false-negative, and indeterminate results) associated with tests used to diagnose gout?

Search Strategy

The systematic literature search included studies identified by using PubMed (from 1946), EMBASE (from 1972), the Cochrane Library (from 1945), and the Web of Science (from 1949) through February 2016 as well as unpublished or non-peer-reviewed studies identified through ClinicalTrials.gov and the Web of Science. Studies were not limited to those published in English.

Quality Assessment

The QUADAS-2 (Revised Quality Assessment of Diagnostic Accuracy Studies) was used to assess the quality of individual studies for risk of bias (34, 35); AMSTAR (A Measurement Tool to Assess Systematic Reviews) was used to assess the quality of existing systematic reviews (36). This guideline rates the evidence and recommendations by using the ACP guideline grading system, which is based on GRADE (Table 1).

Population Studied

Studies were limited to adults aged 18 years or older with suspected gout (such as an acute episode of joint inflammation).

Interventions Evaluated

Studies evaluated clinical history and physical examination, serum urate assessment, ultrasonography, DECT, computed tomography, plain radiography, joint aspiration by physicians and synovial fluid analysis using polarizing microscopy, and combinations of the aforementioned tests as identified in the literature.

Comparators

Interventions were compared with joint synovial fluid aspiration and microscopic assessment for MSU crystals performed by practitioners (such as rheumatologists and laboratory personnel) with different levels of expertise or experience.

Outcomes

Outcomes evaluated included accuracy of the test results (sensitivity, specificity, and positive and negative predictive value); intermediate outcomes (results of laboratory and radiographic tests, such as serum urate and synovial fluid crystal analysis and radiographic or ultrasonography changes); clinical decision making (additional testing and pharmacologic or dietary management); short-term clinical (patient-centered) outcomes, such as pain and joint swelling and tenderness; and adverse effects of the tests, including pain, infection, radiation exposure, and effects of false-positive or -negative results.

Timing

Studies considered timing in terms of symptom relief (1 to 2 days minimum), whether symptoms occurred early versus later or after a flare, and whether adverse outcomes occurred immediately.

Setting

The studies were conducted in primary care (outpatient) or acute care settings or outpatient rheumatology practices or academic medical centers.

Target Audience

The target audience for this guideline includes all clinicians.

Target Patient Population

The target patient population includes adults presenting with symptoms suggesting acute gout (such as an acute episode of joint inflammation), with or without a previous gout diagnosis.

Peer Review

The AHRQ evidence review was sent to invited peer reviewers and posted on the AHRQ Web site for public comments. The guideline was peer reviewed through the journal and posted online for comments from ACP Governors and Regents. All comments were read and carefully considered by the authors, and important issues were discussed by the CGC.

Details of the ACP guideline development process are provided in the ACP methods paper (10).

Web-Only References

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