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Management of Acute and Recurrent 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 management of gout.

Methods: Using the ACP grading system, the committee based these recommendations on a systematic review of randomized, controlled trials; systematic reviews; and large observational studies published between January 2010 and March 2016. Clinical outcomes evaluated included pain, joint swelling and tenderness, activities of daily living, patient global assessment, recurrence, intermediate outcomes of serum urate levels, and harms.

Target Audience and Patient Population: The target audience for this guideline includes all clinicians, and the target patient population includes adults with acute or recurrent gout.

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)*

Gout, one of the most common forms of inflammatory arthritis, is caused by accumulation of excess urate crystals (monosodium urate) in joint fluid, cartilage, bones, tendons, bursas, and other sites. Patients experience joint swelling and pain during gout attacks, known as acute gouty arthritis. In some patients, the frequency and duration of acute attacks increase over time and lead to chronic gout, which may be associated with deposits of uric acid crystals known as tophi. Risk factors for gout include overweight or obesity; hypertension; alcohol intake; diuretic use; a diet rich in meat, seafood, and high-fructose food or drinks; and poor kidney function (1–4). About 3.9% of U.S. adults older than 20 years report being told at some point that they had gout (5). This percentage increased by about 1% in the 10 years before 2007, probably because of a parallel increase in conditions associated with hyperuricemia. An estimated $1 billion is spent annually on ambulatory care for gout, largely on treatments and prescription medications (6).

Management of gout includes both pharmacologic and nonpharmacologic approaches. Pharmacologic therapies focus on urate-lowering strategies and anti-inflammatory drugs (Table 1). Nonpharmacologic management focuses on dietary and lifestyle changes, including weight loss and exercise.

GUIDELINE FOCUS AND TARGET POPULATION

The purpose of this American College of Physicians (ACP) guideline is to provide guidance on the management of acute and recurrent gout in adults. These recommendations are based on a background evidence paper (7) and a systematic evidence review sponsored by the Agency for Healthcare Research and Quality (AHRQ) (8). For guidance on the diagnosis of gout, please refer to the accompanying ACP guideline (9).

Table 1. Pharmacologic Agents for Treatment of Gout

Agent, by Drug Class	Usual Dosage*	Cost†
Anti-inflammatory drugs		
Nonsteroidal anti-inflammatory drugs		
Ibuprofen	800 mg 3–4 times daily	$15 per 90-d supply
Naproxen	750 mg, then 250 mg every 8 h	$7 per 60-d supply
Diclofenac	75 mg twice daily	$21 per 30-d supply
Indomethacin	50 mg 3 times daily	$10 per 30-d supply
Cyclooxygenase-2 inhibitors	–	$76 per 30-d supply‡
Corticosteroids		
Prednisolone	30–40 mg/d	$11 per 50-d supply of 15-mg dosage
Methylprednisolone	0.5–2.0 mg/kg of body weight intravenously or intramuscularly once	$26 per 21-d supply
Other		
Animal-derived corticotropin	40 IU	$34 724 per injection
Colchicine (generic)	1.2 mg orally, then 0.6 mg 1 h later	$137 per 30-d supply
Colcrys (Takeda Pharmaceuticals)	1.2 mg orally, then 0.6 mg 1 h later	$192 per 30-d supply
Uricosuric drugs		
Probenecid	500 mg orally twice daily	$35 per 60-d supply
Xanthine oxidase inhibitors		
Allopurinol	50–100 mg/d (lower dose if renal function is impaired) and increase by 50–100 mg/d every few weeks	$10 per 30-d supply
Zyloprim (Burroughs Wellcome)	50–100 mg/d (lower dose if renal function is impaired) and increase by 50–100 mg/d every few weeks	$130 per 30-d supply
Febuxostat	40–80 mg orally once daily	NA
Uloric (Takeda Pharmaceuticals)	40–80 mg orally once daily	$272 per 30-d supply
Combination agents		
Colchicine–probenecid	Oral, 1 tablet daily for 1 wk	$42 per 60-d supply

NA = not available.
* Derived from DynaMed Plus (www.dynamed.com) or the Agency for Healthcare Research and Quality report (8).
† Derived from the Healthcare Bluebook Fair Price (www.healthcarebluebook.com).
‡ For celecoxib.

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 can be found in the **Appendix** (available at www.annals.org), as well as in the accompanying article (7) and full report (8). Reviewers searched several databases for studies published from January 2010 to March 2016. Reviewers combined data when possible using meta-analysis and assessed risk of bias and quality of studies according to established methods. The study population included all adults (aged ≥18 years) diagnosed with gout.

The review evaluated nonpharmacologic interventions, including dietary interventions, dietary supplements, and alternative treatments; pharmacologic interventions, including anti-inflammatory drugs, colchicine, urate-lowering therapies, and combination drug bxtherapies; and combinations of drug and dietary or alternative treatments. Evaluated outcomes included intermediate outcome of serum urate levels; health outcomes, such as recurrence, pain, joint swelling and tenderness, activities of daily living, patient global assessment, and development of tophi; and harms.

Grading the Evidence and Developing Recommendations

This guideline was developed by ACP's Clinical Guidelines Committee (CGC) according to ACP's guideline development process, details of which can be found in the methods paper (10). The CGC used the evidence tables in the accompanying systematic review (7) and full report (8) when reporting the evidence and graded the recommendations by using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach (**Table 2**). The authors of the evidence review considered prior physiologic knowledge and indirect and direct evidence when grading the evidence (11, 12).

Peer Review

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

PHARMACOLOGIC TREATMENT OF ACUTE GOUT

Effectiveness (Benefits and Harms) of Pharmacologic Treatments

A total of 28 studies assessed pharmacologic gout treatments (13–40).

Colchicine

Six existing systematic reviews (41–46) reported on the efficacy (health outcomes) of colchicine in treating

Table 2. 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.

acute gout from 5 randomized, controlled trials (RCTs) (17, 18, 47–49). High-quality evidence showed that colchicine reduces pain in patients with acute gout (17, 18). Moderate-quality evidence from 1 study (17) showed that lower doses of colchicine (initial dose of 1.2 mg followed by 0.6 mg after 1 hour) are as effective as higher doses (1.2 mg followed by 0.6 mg/h for 6 hours) for reducing pain and are associated with fewer gastrointestinal adverse effects (for diarrhea: 77% in the high-dose group, 23% in the low-dose group, and 14% in the placebo group). Colchicine is also associated with other gastrointestinal adverse effects, including nausea, vomiting, cramps, and pain (50), and is infrequently associated with headache and fatigue.

Nonsteroidal Anti-inflammatory Drugs

One placebo-controlled trial of tenoxicam (40 mg once daily) showed that it reduces pain but is no different from placebo for swelling in patients with acute gout. High-quality evidence from 1 RCT (38) and observational data showed that nonsteroidal anti-inflammatory drugs (NSAIDs) reduce pain in patients with acute gout. These drugs have known anti-inflammatory activity and have been shown to reduce pain in many conditions. Further, they have been successfully used to prevent gout flares during urate-lowering therapy. The main harms of NSAIDs are gastrointestinal adverse effects ranging from minor (dyspepsia) to serious (perforations, ulcers, and bleeding). Long-term use of higher doses can cause chronic renal insufficiency.

Corticosteroids

There were no placebo-controlled trials of oral corticosteroids. High-quality indirect evidence suggested that systemic corticosteroids reduce pain in patients with acute gout. Although there was no direct evidence assessing the efficacy of systemic corticosteroids to treat gout, corticosteroids have a proven anti-inflammatory effect and were shown to be equivalent to NSAIDs for various outcomes in 6 RCTs (15, 24, 28, 35, 36, 40). Long-term use of corticosteroids is associated with adverse effects that are dose- and duration-dependent and affect almost all organs of the body.

These include dysphoria, mood disorders, elevation of blood glucose levels, immune suppression, and fluid retention.

Animal-Derived Corticotropin

Although no placebo-controlled RCTs were identified, moderate-quality evidence suggested that parenteral corticotropin reduces pain in patients with acute gout. Corticotropin has known anti-inflammatory activity, and evidence from 2 comparative effectiveness trials showed that it was similar to NSAIDs (29) and corticosteroids (30) for various outcomes. Harms of corticotropin are likely similar to those for corticosteroids, due to similar biologic activities.

Comparative Effectiveness (Benefits and Harms) of Pharmacologic Treatments

NSAIDs Versus NSAIDs

Moderate-quality evidence from 16 RCTs (13, 14, 16, 19–23, 25–27, 31–34, 39) showed no clinically important differences in comparisons of different types of NSAIDs with one another in patients with gout.

Corticosteroids Versus Corticotropin

One RCT (30) showed no difference in the duration of acute gout attacks or the number of joints affected when comparing corticotropin with intramuscular triamcinolone.

Corticosteroids Versus NSAIDs

Six RCTs (15, 24, 28, 35, 36, 40) showed no difference in time to resolution of symptoms, clinical joint status at follow-up, or pain reduction between NSAIDs and corticosteroids. However, NSAIDs were associated with more frequent gastrointestinal, nongastrointestinal, and serious adverse events (46).

NSAIDs Versus Selective Cyclooxygenase-2 Inhibitors

Four RCTs showed no difference in pain, joint swelling, global improvement, and health-related quality of life when comparing NSAIDs and cyclooxygenase-2 inhibitors. Cyclooxygenase-2 inhibitors were associated with fewer total adverse events (38% vs. 60%) and fewer withdrawals due to adverse events (3% vs. 8%) than NSAIDs.

NSAIDs Versus Parenteral Corticotropin

One RCT (29) showed that time to pain relief was shorter with corticotropin than with indomethacin, 50 mg 4 times daily (3 vs. 24 hours). No adverse effects were reported for patients treated with corticotropin, whereas NSAIDs were associated with abdominal discomfort or dyspepsia (55%) and headache (38%).

Effectiveness Based on Subgroups

No studies presented effectiveness data for subgroups based on sex, acute episode, history of gout, HLA-B*5801 status, tophi, or comorbidities.

DIETARY AND LIFESTYLE MANAGEMENT OF GOUT

Effectiveness (Benefits and Harms) of Dietary and Lifestyle Management

Evidence from 4 systematic reviews of RCTs (42, 51–53) and 2 new RCTs (54, 55) was insufficient to determine the efficacy of dietary therapies on symptomatic outcomes. Low-quality evidence from 1 systematic review (52) of 13 trials with high heterogeneity showed that vitamin C supplementation reduced serum urate levels (−20.8 µmol/L [−0.35 mg/dL] [95% CI, −39.3 to −1.8 µmol/L {−0.66 to −0.03 mg/dL}]).

Low-quality evidence from 1 study (54) showed that gout-specific counseling about dietary changes (such as reducing intake of red meat, shellfish, and yeast-rich foods and increasing intake of low-fat dairy products, vegetables, and cherries) is not more effective than general dietary counseling (promoting weight loss and reducing alcohol intake) for reducing serum urate levels in patients with gout.

Evidence from 5 systematic reviews (41, 56–59) was insufficient to determine the effectiveness of traditional Chinese medicine, including herbs and acupuncture, on symptomatic outcomes.

Effectiveness Based on Subgroups

There were no effectiveness data based on sex, acute episode, history of gout, HLA-B*5801 status, tophi, or comorbidities.

PHARMACOLOGIC MANAGEMENT OF HYPERURICEMIA TO REDUCE RECURRENT GOUT OR OTHER HEALTH OUTCOMES

Effectiveness (Benefits and Harms) of Pharmacologic Therapy

High-quality evidence from 4 RCTs (60–63) showed that urate-lowering therapy (allopurinol and febuxostat) reduces serum urate levels. High-quality evidence from 2 RCTs showed that urate-lowering therapy does not reduce the risk for gout attacks within the first 6 months. There were no long-term RCTs that compared gout flares between patients treated versus those not treated with urate-lowering therapy. Observational evidence from follow-up of 2 RCTs (64) and several retrospective cohort studies (65–67) consistently showed that patients with lower serum urate levels had fewer flares than those with higher levels. Together with the fact that urate crystalizes at a level greater than about 416 µmol/L (7 mg/dL), the evidence is graded as moderate-quality that longer-term urate-lowering therapy (>1 year) reduces gout flares. We consider the magnitude of this reduction uncertain.

The most common adverse event with allopurinol is rash. Most of the serious adverse effects associated with allopurinol (≥40 years of history) are rare, mild, and reversible; however, fatal hypersensitivity reactions have also been reported with the drug (68). Persons with the HLA-B*5801 haplotype, which is prevalent in Asian persons (including those of Han Chinese and Thai descent) and in Korean persons with stage 3 or worse chronic kidney disease, may have an increased risk for serious adverse effects with allopurinol (69–75). The most commonly reported adverse events from limited trials of febuxostat were abdominal pain, diarrhea, and musculoskeletal pain. There is more uncertainty about the harms of febuxostat because there are no large data-based studies and the clinical experience with this drug is more limited than with older urate-lowering medications.

Comparative Effectiveness (Benefits and Harms) of Pharmacologic Therapy

Evidence was gathered from 4 high-quality systematic reviews (76–79) comparing the efficacy of febuxostat and allopurinol. Gout flare incidence was higher at high doses of febuxostat (120 or 240 mg/d) compared with allopurinol (100 to 300 mg/d). There was no difference in gout flare incidence between lower doses of febuxostat (40 or 80 mg/d) and allopurinol (100 to 300 mg/d). The evidence was inconclusive with regard to changes in tophi. High-quality evidence from 1 RCT showed no difference between febuxostat (40 mg/d) and allopurinol (300 mg/d) for decreasing serum urate levels, and 80 mg of febuxostat per day was more effective than either 40 or 300 mg of allopurinol per day for decreasing serum urate levels (62).

Evidence comparing harms between allopurinol and febuxostat was inconclusive, partly because of limited information about the adverse effects of febuxostat.

Prophylactic Therapy Against Acute Gout Flares in Patients Initiating Serum Urate–Lowering Therapy

High-quality evidence from 1 RCT (47) and observational evidence from 3 RCTs (60–62) showed that use of low doses of colchicine (0.6 mg twice daily) or NSAIDs for prophylactic therapy reduces risk for gout attacks in patients initiating urate-lowering therapy. Moderate-quality evidence from 1 RCT (59) and indirect evidence from 3 RCTs (51, 52, 80) suggests that use of prophylactic colchicine or NSAIDs for longer durations (>8 weeks) is more effective at reducing gout flares than use for shorter durations in patients initiating serum urate–lowering therapy.

Effectiveness Based on Subgroups

Low-quality evidence from subgroup analyses of 1 RCT (81) showed no difference in the efficacy of febuxostat or allopurinol for decreasing serum urate levels based on age (82) or race (83). Evidence was insufficient for sex, baseline tophi, baseline serum urate level, or comorbidities. No studies presented data on HLA-B*5801 status.

Monitoring Serum Urate Levels in Patients With Gout

No studies have assessed the effect of monitoring serum urate levels in patients with gout on adherence or treatment outcomes.

Evidence was insufficient to conclude whether the benefits of escalating urate-lowering therapy to reach a serum urate target ("treat to target") outweigh the harms associated with repeated monitoring and medication escalation. There is no evidence from an experimental study that examined the health outcomes of treating to one serum urate level versus another, nor is there a trial comparing a strategy of basing treatment on attaining a specific urate level versus basing treatment on reduction in symptoms (such as gout flares). The evidence review looked for other studies to evaluate whether achieving lower subsequent serum urate levels (<297 vs. 297 to 416 μmol/L [<5 vs. 5 to 7 mg/dL]) is associated with decreased risk for recurrent gout attack, progression to chronic arthritis or disability, resolution of tophi, or other clinical outcomes. A post hoc observational analysis (64) from 2 large trials (60, 61) showed that patients who attained a urate level less than 357 μmol/L (<6.0 mg/dL) had fewer gout flares at 12 months than those who did not (about 5% of patients with serum urate level <6.0 mg/dL vs. 10% to 15% of those with levels >6.0 mg/dL). Eight other retrospective cohort studies (65, 67, 84–89) found similar associations. Although these studies showed an association between lower urate levels and fewer gout flares, they did not establish that urate-lowering therapy rather than other underlying patient characteristics caused the reduction in flares. Further, even if urate-lowering therapy does reduce gout flares, these studies do not help us understand the tradeoff between the magnitude of benefit and the harms and costs incurred by treatment and monitoring. Thus, we remain uncertain about the value of a treat-to-target strategy compared with a strategy of basing treatment intensity on minimizing symptoms.

DISCONTINUATION OF PHARMACOLOGIC TREATMENT OF ACUTE OR CHRONIC GOUT

Treatment of Hyperuricemia

Evidence was insufficient to determine criteria for discontinuing urate-lowering therapy. Three prospective observational studies (90–92) showed that urate-lowering therapy can be discontinued without increasing the risk for acute gout attacks in some patients, but there were no applicable RCTs. One cohort study showed that urate-lowering therapy can be discontinued in asymptomatic patients who have maintained serum urate levels less than 416 μmol/L (<7 mg/dL) after 5 years of treatment and in whom annual serum urate levels remained below this level (91).

Prophylaxis During Urate-Lowering Therapy

Moderate-quality indirect evidence from comparisons of 3 RCTs (60–62) suggests continuing prophylaxis during urate-lowering therapy using low-dose colchicine or low-dose NSAIDs for more than 8 weeks to prevent acute gout flares. Evidence showed that the rate of acute gout flares approximately doubled when anti-inflammatory prophylaxis was discontinued after 8

weeks (60, 61). Acute gout flares did not increase in a trial that continued prophylaxis for 6 months (62).

SUMMARY

Evidence was insufficient for gout-specific dietary advice or therapies (such as reduced intake of red meat, fructose, and alcohol) to improve symptomatic outcomes. Although 1 systematic review (52) and 1 RCT (55) found that dietary changes reduced urate levels, no study examined the effect of any dietary intervention on clinical outcomes, such as acute gout flares. Low-quality evidence showed that gout-specific dietary advice is similar to general dietary counseling with regard to the effect on serum urate levels in patients with gout.

Evidence from placebo-controlled trials and head-to-head comparisons showed that colchicine, NSAIDs, corticosteroids (high-quality evidence for each), and animal-derived corticotropin (moderate-quality evidence) are effective for reducing pain in patients with acute gout. Lower doses of colchicine are as effective as higher doses and are associated with fewer adverse effects. Evidence also showed that NSAIDs are effective as a class, regardless of choice of the individual drug. Harms associated with colchicine include gastrointestinal adverse events, such as diarrhea, nausea, cramps, and vomiting. Nonsteroidal anti-inflammatory drugs are associated with dyspepsia and potential gastrointestinal perforations, ulcers, and bleeding. Corticosteroids are associated with mood disorders and dysphoria, elevation of blood glucose levels, immune suppression, and fluid retention. Corticotropin is less well-studied; thus, harms are largely unknown but are likely to be similar to those associated with corticosteroids due to similar biologic activity. Fair prices are highest for corticotropin, and colchicine is currently the most expensive nonbiologic.

High-quality evidence showed that urate-lowering therapy does not reduce the risk for acute gout attacks in the first 6 months in patients with gout. Observational evidence showed that patients who attained lower urate levels after 1 year of urate-lowering therapy had fewer gout flares. High-quality evidence showed no difference between lower doses of febuxostat and allopurinol for gout flares. The most common adverse events are rash with allopurinol and abdominal pain, diarrhea, and musculoskeletal pain with febuxostat. Febuxostat is associated with higher costs than allopurinol. High-quality evidence shows that prophylactic therapy with low-dose colchicine or low-dose NSAIDs effectively reduces acute gout flares in patients initiating urate-lowering therapy, and moderate-quality evidence supports continuing prophylactic therapy for more than 8 weeks. Evidence was insufficient about whether urate-lowering therapy can be safely discontinued after 5 years.

Evidence is insufficient for monitoring of serum urate levels in patients with gout.

Target thresholds for serum urate levels rely on the chemistry of urate, which is soluble up to a concentra-

tion of about 404 μmol/L (6.8 mg/dL), above which precipitation may occur. However, this threshold is not absolute because patients with higher serum urate levels may still be asymptomatic, and some may have acute flares below this threshold. Although there is an association between lower urate levels and fewer gout flares, the extent to which use of urate-lowering therapy to achieve various targets can reduce gout flares is uncertain. The Figure summarizes the recommendations and clinical considerations.

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)

High-quality evidence showed that corticosteroids, NSAIDs, and colchicine are effective treatments to reduce pain in patients with acute gout. Gout symptoms are mostly caused by inflammatory reaction to the deposition of urate crystals, which results from an increase in serum urate level above its saturation point in the blood. Hence, most medications that are used to target anti-inflammatory responses help to reduce the symptoms. Contraindications, harms, and costs vary among treatments.

Corticosteroids should be considered as first-line therapy in patients without contraindications because they are generally safer and a low-cost treatment option. Steroids are among the most effective anti-inflammatory medications available and have been shown to be as effective as NSAIDs for managing gout, with fewer adverse effects. Prednisolone at a dose of 35 mg for 5 days has been successfully used to treat acute gout (15). Adverse effects associated with long-term use of corticosteroids include dysphoria, mood disorders, elevation of blood glucose levels, immune suppression, and fluid retention. Corticosteroids are contraindicated in patients with systemic fungal infections or known contraindications.

Moderate-quality evidence showed no difference between different types of NSAIDs, including indomethacin. Adverse effects associated with NSAIDs include dyspepsia and potential gastrointestinal perforations, ulcers, and bleeding. Patients in whom NSAIDs may be contraindicated include those with renal disease, heart failure, or cirrhosis. Although indomethacin is commonly considered as the first-line NSAID for treatment of acute gout, there is no evidence that it is more efficacious than other NSAIDs, such as naproxen and ibuprofen.

A generic formulation of colchicine is now available for gout treatment, but it is still more expensive than NSAIDs or corticosteroids. Adverse effects associated with colchicine include gastrointestinal issues (such as diarrhea, nausea, vomiting, cramps, and pain) and, infrequently, headache and fatigue. Colchicine is contraindicated in patients with renal or hepatic impairment who are using potent cytochrome P450 3A4 inhibitors or P-glycoprotein inhibitors.

Recommendation 2: ACP recommends that clinicians use low-dose colchicine when using colchicine to treat acute gout. (Grade: strong recommendation, moderate-quality evidence)

Moderate-quality evidence suggests that lower doses of colchicine (1.2 mg followed by 0.6 mg 1 hour later) are as effective as higher doses (1.2 mg followed by 0.6 mg/h for 6 hours) at reducing pain and are associated with fewer gastrointestinal adverse effects.

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)

Although evidence supports the benefits of using urate-lowering therapy for shorter durations to reduce gout flares, the benefits of long-term use (≥12 months) in patients with a single or infrequent gout attacks (<2 per year) have not been studied. Urate-lowering therapy is not necessary in cases where the patient would have no or infrequent recurrences. In cases of recurrent gout (≥2 episodes per year) or problematic gout (for example, gout associated with tophi, chronic renal disease, or urolithiasis), shared decision making with the patient is warranted to review possible harms and benefits of urate-lowering therapy.

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)

After resolution of acute gout, some patients may have recurrent episodes. Some patients have no or few attacks over many years, whereas others have more frequent attacks. Although evidence is inadequate to predict which patients will have more problems, those with higher serum urate levels (especially >476 μmol/L [>8 mg/dL]) are at greater risk. Some may prefer to initiate long-term therapy to prevent future gout attacks, whereas others may prefer to treat flares if they occur. Patients who decide not to initiate urate-lowering therapy can revisit their decision if they have multiple recurrences of acute gout.

Febuxostat (40 mg/d) and allopurinol (300 mg/d) are equally effective at decreasing serum urate levels. However, these drugs are associated with adverse effects, including rash with allopurinol and abdominal pain, diarrhea, and musculoskeletal pain with febuxostat.

Data on the most appropriate duration of urate-lowering therapy are insufficient. Moderate- to high-quality evidence suggests that urate-lowering therapy reduces the risk for acute gout attacks after 1 year, but not within the first 6 months of treatment.

Figure. Summary of the American College of Physicians guideline on management of acute and recurrent gout.

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Summary of the American College of Physicians Guideline on Management of Acute and Recurrent Gout

Disease/Condition	Acute or recurrent gout
Target Audience	All clinicians
Target Patient Population	Adults with acute or recurrent gout
Treatments Evaluated	Dietary interventions; other lifestyle measures (smoking cessation, exercise, hydration); dietary supplements and alternative treatments (vitamin C supplementation, traditional Chinese medicine); pharmacologic agents, including anti-inflammatory drugs (NSAIDs, corticosteroids), colchicine, and urate-lowering therapies (xanthine oxidase inhibitors, uricosuric agents); combination drug therapies; or combination drug and dietary or alternative treatments
Outcomes Evaluated	Efficacy, including short-term (pain, joint swelling, and tenderness) and long-term (serum urate levels, pain, joint swelling, and tenderness) outcomes; activities of daily living; patient global assessment; recurrence; intermediate outcome of serum urate levels; and harms
Benefits	Acute gout treatment (colchicine, NSAIDs, corticosteroids, corticotropin): reduction of pain Prophylaxis during serum urate–lowering therapy (low-dose colchicine and low-dose NSAIDs): reduced acute gout flares

Harms and Adverse Effects	Colchicine: gastrointestinal adverse effects, such as diarrhea, nausea, cramps, and vomiting
	
	NSAIDs: dyspepsia and potential gastrointestinal perforations, ulcers, and bleeding
	
	Corticosteroids: mood disorders and dysphoria, elevation of blood glucose levels, immune suppression, and fluid retention
	
	Corticotropin: unknown, but probably similar to those of corticosteroids
	
	Serum urate–lowering therapy:
	
	  Febuxostat: abdominal pain, diarrhea, and musculoskeletal pain
	
	  Allopurinol: rash and reactions (including potentially serious ones)

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)* High-quality evidence showed that corticosteroids, NSAIDs, and colchicine are effective treatments to reduce pain in patients with acute gout. *Recommendation 2: ACP recommends that clinicians use low-dose colchicine when using colchicine to treat acute gout. (Grade: strong recommendation, moderate-quality evidence)* Lower doses of colchicine (1.2 mg followed by 0.6 mg 1 h later) are as effective as higher doses (1.2 mg followed by 0.6 mg/h for 6 h) at reducing pain and are associated with fewer gastrointestinal adverse effects. *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)* Although evidence supports the benefits of using urate-lowering therapy for shorter durations to reduce gout flares, the benefits of long-term use (≥12 mo) in patients with a single or infrequent gout attacks have not been studied. *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)* Upon resolution of acute gout, some patients have no or few attacks over many years, whereas others have more frequent or recurrent attacks. Febuxostat (40 mg/d) and allopurinol (300 mg/d) are equally effective at decreasing serum urate levels, and prophylactic therapy with low-dose colchicine or low-dose NSAIDs reduces the risk for acute gout attacks in patients initiating urate-lowering therapy.
High-Value Care	Clinicians should select from among corticosteroids, NSAIDs, or colchicine as first-line therapy on the basis of costs when treating patients with acute gout who do not have contraindications to these drugs. Colchicine, including the current generic version, is the most expensive of these medications. Clinicians should also carefully consider and discuss the benefits, harms, and costs of initiating urate-lowering therapy with the patient immediately after an episode of acute gout and if the patient has recurrent flares. The intensity of urate-lowering therapy and monitoring of urate levels should be based on discussions with individual patients, given the uncertainties of different treatment strategies.
Clinical Considerations	Treatment of gout flares should be started as soon as possible for quicker resolution of symptoms. Not all patients with elevated serum urate levels have gout symptoms or recurrent gout attacks, and some patients with urate levels below the commonly identified threshold of 357 μmol/L (6 mg/dL) may have symptoms. Allopurinol is associated with an increased risk for serious adverse events in persons with the HLA–B*5801 haplotype, which is prevalent in certain Asian populations.

NSAID = nonsteroidal anti-inflammatory drug.

High-quality evidence showed that prophylactic therapy with low-dose colchicine or low-dose NSAIDs reduces the risk for acute gout attacks in patients initiating urate-lowering therapy. Moderate-quality evidence also showed that continuing prophylactic treatment for more than 8 weeks was more effective than shorter durations to help prevent gout flares in patients initiating urate-lowering therapy.

AREAS OF INCONCLUSIVE EVIDENCE

Treatment Strategy for Patients With Gout Receiving Urate-Lowering Therapy

A paradigm has developed that monitoring serum urate levels and targeting therapy to achieve a specific urate level (treat to target) reduces acute gout attacks and subsequent joint damage. An alternative strategy bases the intensity of urate-lowering treatment on the goal of avoiding recurrent gout attacks ("treat to avoid symptoms"), with no monitoring of urate levels. Comparative effectiveness studies that evaluate the incremental benefits and harms of a treat-to-target strategy over a treat-to-avoid-symptoms strategy should be a priority.

Effect of Urate-Lowering Treatment on Adverse Health Outcomes Beyond Acute Gout

The importance of decreasing urate levels to prevent adverse health outcomes beyond acute gout is uncertain.

Duration of Urate-Lowering Treatment

Insufficient evidence suggests that some patients with annual urate levels less than 416 μmol/L (<7 mg/dL) may be able to stop urate-lowering treatment after about 5 years.

Treatment in Different Patient Groups

Evidence is insufficient to determine whether treatment of patients with gout should vary according to such variables as patient demographic characteristics, comorbidities, gout severity, clinical presentation, or laboratory values.

Effect of Dietary Treatments

Although many patients are counseled to change various dietary factors or supplements, we found insufficient evidence to recommend these changes.

Long-Term Effects of Febuxostat

Although patients may be prescribed this medication for longer periods, we have little evidence about its long-term benefits or harms.

HIGH-VALUE CARE

Clinicians should select from among corticosteroids, NSAIDs, or colchicine as first-line therapy on the basis of costs when treating patients with acute gout who do not have contraindications to one of these drugs. Colchicine, including the recently introduced generic version, is the most expensive of these medications. Clinicians should also carefully consider and discuss the benefits, harms, and costs of initiating urate-

lowering therapy with the patient after an episode of acute gout and if the patient has recurrent flares. The intensity of urate-lowering therapy and monitoring of urate levels should be based on discussions with individual patients, given the uncertainties of different treatment strategies.

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.

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APPENDIX: DETAILED METHODS

The evidence review was conducted by the Southern California Evidence-based Practice Center–RAND Corporation.

Key Questions Addressed

Key Question 1: Acute Gout Treatment

a. In patients with acute gout, what are the benefits and harms of different pharmacologic therapies?

b. Does effectiveness (benefits and harms) differ according to patient baseline demographic characteristics and 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 and time since start of flare) and laboratory values (serum urate [UA] levels)?

Key Question 2: Dietary and Lifestyle Management of Gout

a. In adults with gout, what are the benefits and harms of different dietary therapies and lifestyle measures on intermediate (serum UA levels) and final health outcomes (including recurrence of gout episodes and progression [e.g., development of tophi])?

b. Does effectiveness and comparative effectiveness of dietary modification differ according to disease severity (including presence of tophi and baseline serum UA level), underlying mechanisms of hyperuricemia, or baseline demographic and comorbid characteristics?

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

a. In adults with gout, what are the benefits and harms of different pharmacologic therapies on intermediate (serum UA levels) and long-term clinical health outcomes (including recurrence of gout episodes and progression)?

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

c. What is the effect of dietary modification in combination with pharmacologic therapy?

Key Question 4: Treatment Monitoring of Patients With Gout

a. In adults with gout, does monitoring serum urate levels with pharmacologic treatment and/or dietary and/or lifestyle change measures (e.g., adherence) improve treatment outcomes?

b. Is achieving lower subsequent serum urate levels (<297 vs. 297 to 416 µmol/L [<5 vs. 5 to 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

a. In adults with gout, 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?

Search Strategy

The systematic literature search included studies published between 1 January 2010 and 1 March 2016, identified using PubMed, EMBASE, the Cochrane Library, and the Web of Science (also for unpublished or non–peer-reviewed studies), as well as ClinicalTrials.gov (from inception until 1 March 2016). Manufacturers of prescription medications used to treat gout were contacted in July 2014 for recently completed studies and unpublished or non–peer-reviewed study findings. Studies were not limited to those published in English.

Quality Assessment

The Cochrane risk-of-bias tool was used to assess the quality of individual studies for risk of bias, and AMSTAR (A Measurement Tool to Assess Systematic Reviews) was used to assess the quality of existing systematic reviews (93, 94). This guideline rates the evi-

dence and recommendations by using the ACP's guideline grading system (Table 2).

Population Studied

The population included all adults aged 18 years or older with a diagnosis of gout.

Interventions Evaluated

Nonpharmacologic

Nonpharmacologic interventions included dietary interventions (low-purine diet, fructose restriction, other carbohydrate restriction, ethanol restriction, sour cherry juice, dairy products and vegetables, Mediterranean diet, and DASH [Dietary Approaches to Stop Hypertension] diet), other lifestyle measures (smoking cessation, exercise, and hydration), and dietary supplements and alternative treatments (vitamin C supplementation and traditional Chinese medicine).

Pharmacologic

Pharmacologic interventions included anti-inflammatory drugs (NSAIDs and corticosteroids), colchicine, urate-lowering therapies (xanthine oxidase inhibitors and uricosuric agents), and combination drug therapies.

Co-interventions

Co-interventions included combination drug and dietary or alternative treatments.

Comparators

Comparators included placebo or usual care, other interventions, usual diet or level of activity, and early initiation of treatment.

Outcomes

Diet and Lifestyle Therapy

Outcomes included intermediate outcomes of serum urate tests; health outcomes, such as recurrence; and harms.

Acute Gout

Outcomes included efficacy, including short-term health outcomes of pain and joint swelling and tenderness; long-term outcomes, including serum urate level, pain, joint swelling and tenderness, activities of daily living, patient global assessment, and recurrence; and safety, including gastrointestinal and renal adverse effects, steroid-induced osteoporosis, and diabetes.

Chronic Gout

Outcomes included intermediate outcomes (serum urate level), final health outcomes (pain, joint swelling, tenderness associated with the development of tophi, activities of daily living, patient global assessment, risk for comorbidities or death, and recurrence of gout attacks), and safety (inflammatory, hematologic, cardiovascular, liver dysfunction, and renal dysfunction).

Timing

Studies of short-term treatment (24 to 72 hours' follow-up), long-term treatment (any follow-up time), and delayed versus immediate treatment were included.

Setting

Studies in primary care settings, including urgent care clinics and emergency departments, were included. If evidence from primary care was limited, studies of patients in specialty clinics and emergency departments were included.

Target Audience

The target audience for this guideline includes all clinicians.

Target Patient Population

The target patient population includes adults diagnosed with acute or chronic gout.

Peer Review

The AHRQ evidence review was guided by a technical expert panel that included rheumatology and general medicine specialists and methodologists. These same consultants also examined and commented on the draft final review. The draft final review was posted on the AHRQ Web site for public comments. The guideline went through a peer review process through the journal and was posted online for comments from ACP Governors and Regents. All comments were read and carefully considered by the authors, and important issues were also discussed by the CGC.

Details of the ACP guideline development process can be found in ACP's methods paper (10).

Web-Only References

93. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al; Cochrane Bias Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011; 343:d5928. [PMID: 22008217] doi:10.1136/bmj.d5928
94. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007;7:10. [PMID: 17302989]