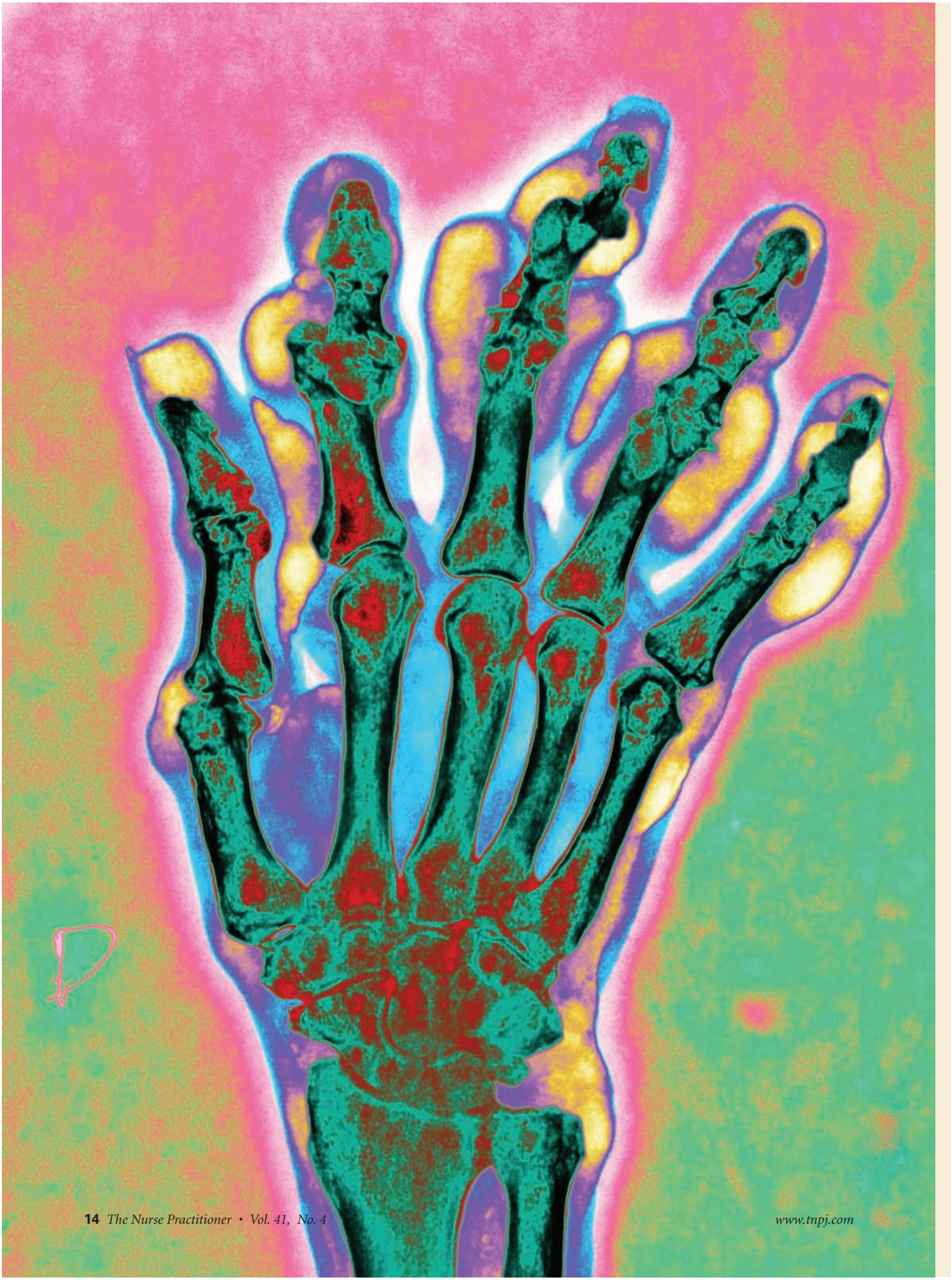


CE 2.5 CONTACT HOURS Rx 2.5 CONTACT HOURS

An update on Gout for primary care providers

Abstract: *This article discusses the current beliefs regarding the pathogenesis of gout and reviews the 2012 guidelines from the American College of Rheumatology regarding diagnostic testing, optimal treatments, and lifestyle modifications. Implementing these guidelines will assist clinicians in resolving acute episodes and managing gout long term, improving outcomes and quality of life.*

By Mariann Harding, PhD, RN, CNE

There has been a renewed interest in gout treatment and management. The incidence of gout, a painful inflammatory arthritic disorder related to hyperuricemia, has been rising at a substantial rate, with its prevalence more than doubling in the United States over the past 20 years. At least 8.3 million individuals in the United States (3.9%) are currently living with gout.[1] This rise is attributed to increasing rates of conditions promoting hyperuricemia, including hypertension, metabolic syndrome, type 2 diabetes mellitus, and chronic kidney disease.[2] The economic burden, including medical costs and disability, is also increasing as the afflicted live with gradually diminishing quality of life and utilize healthcare resources to treat gout and associated comorbidities.[3]

Resolving hyperuricemia is associated with significant improvement in clinical outcomes, including a reduction in acute episodes, tophi resolution, and improved quality of life.[4] However, despite recent advances in gout management, many patients do not achieve adequate symptom control because of major gaps in quality of care and patient education.[5] This article will review the 2012 recommendations from the American College of Rheumatology (ACR) for diagnostic testing, treatment, and lifestyle modifications for patients with gout to help close these gaps.

Pathophysiology

Gout is a metabolic disorder that causes joint inflammation. Uric acid in the form of urate (a byproduct of the metabolism of purines) is a chemical present in all body tissues and many foods. The body is continually metabolizing purines, breaking them down and reusing or excreting the byproducts. Most urate is excreted renally. The body maintains a stable balance between production and excretion, keeping the serum uric acid level between 4 mg/dL and 6.8 mg/dL. Hyperuricemia, variably defined as a serum uric acid level greater than either 6.8 mg/dL or 7.0 mg/dL, occurs when either the kidneys cannot excrete enough urate or too much urate is being produced for the kidneys to handle effectively.[5]

Not everyone with hyperuricemia develops gout. Two processes are essential for hyperuricemia to progress to gout: crystallization and inflammation. As urate levels increase and saturate the synovial fluid or soft tissues, the excess urate coalesces into crystals. This leads to tissue damage and tophi development (monosodium urate crystal accumulation in

Keywords: allopurinol, colchicine, gout, hyperuricemia, probenecid, urate-lowering therapy

hard white nodules that deposit in subcutaneous tissue, synovial membranes, tendons, and soft tissues). These crystals are potent inflammation triggers. Monocytes and macrophages try to remove the crystals via phagocytosis, releasing inflammatory mediators into the surrounding area and triggering a cascade of further inflammation and tissue damage.[6]

Clinical gout begins with an acute episode of intense, painful arthritis possibly triggered by alcohol ingestion, trauma, surgery, drug use, dietary excess, or infection. The first episode is usually monoarticular and associated with few other symptoms. Most have increasingly frequent, longer lasting, and more severe inflammatory episodes as time progresses. Episodes may become polyarticular and eventually resolve incompletely. This leads to a chronic, erosive, and deforming arthritis that slowly progresses to a crippling disease on which acute exacerbations are superimposed.[3,6] There is evidence that hyperuricemia accompanying chronic gout is related to an increase in myocardial infarction, stroke, kidney failure, metabolic syndrome, and overall mortality.[3,7,8]

Gout is likely caused by the interaction of several factors outside of the few patients with genetic disease. The most important factors include: a metabolic cluster of obesity, insulin resistance, hypertension, hyperlipidemia, diet, medication use, and conditions that increase uric acid production or decrease uric acid excretion (see *Conditions associated with gout*).

Younger men have a higher risk for gout than women; however, the gender difference dissipates with men and women over 60 years having an equal risk.[9] Recent studies confirm several foods and beverages promote gout, including meat, seafood, alcohol, and high-fructose and sugar-sweetened drinks.[10] The use of thiazide and loop diuretics, low-dose aspirin, cyclosporine, beta-blockers, and niacin increase uric acid levels.[10]

Conditions associated with gout[10]

Overproduction of urate

- Myelo- and lymphoproliferative disorders
- Polycythemia
- Psoriasis
- Hemolytic anemia
- Tumor lysis syndrome
- Sarcoidosis
- Sickle cell disease

Decreased urate secretion

- Kidney dysfunction
- Diabetic ketoacidosis
- Alcohol use
- Lead toxicity

Clinical presentation and diagnosis

A careful history and physical exam should aid in a gout diagnosis. Patients presenting with an episode of acute inflammation typically complain of rapidly developing severe pain in a single joint, most often the metatarsophalangeal joint of the big toe. Other joints that may be affected include the heels, ankles, wrists, fingers, knees, or elbows. The affected joint(s) may be reddened, warm, swollen, and tender to palpation. There may be systemic signs of inflammation, including fever and complaints of malaise, headache, and chills.

Other causes of joint pain should be considered in the differential diagnosis if the presentation is less clear (see *Differential diagnosis*). While the presence of urate crystals in a joint fluid or tophus sample remains the gold standard of diagnosing gout, synovial fluid analysis is rarely obtained in primary care unless necessary in differentiating gout from pseudogout, psoriatic or rheumatoid arthritis, or a septic joint.[11] A presumptive diagnosis is acceptable in many instances based on certain elements being present, including rapid symptom onset, unilateral metatarsophalangeal joint involvement, redness and swelling of the joint involved, and similar prior episodes.[12,13]

Negating a diagnosis when the serum uric acid level is below 6.8 mg/dL is a common issue when diagnosing gout. Up to 49% of patients experiencing an acute episode have a normal serum uric acid level.[13] Serum uric acid levels are important for monitoring, and a baseline should be obtained after the episode resolves. The long-term goal is to achieve a serum uric acid level below 6.0 mg/dL, which generally improves manifestations.[5] The ACR suggests a target serum uric acid level below 5 mg/dL is necessary to achieve optimal clinical outcomes in patients with palpable and visible tophi.[5]

It should be determined if there is a family history of gout. Any medication use as well as the presence of conditions associated with hyperuricemia should be assessed for. Clinicians should evaluate if any comorbidities, including hypertension and metabolic syndrome, are present. Laboratory studies, such as urinalysis, complete blood cell count, and comprehensive metabolic panel, may be indicated.[5]

It is important to gauge the frequency and severity of acute episodes and to assess for the presence, size, and location of tophi. Tophi may occur on the outer ear, the ulnar surface of the forearms, on skin overlying joints, and along the wrist, knee, Achilles tendon, and nasal cartilage. They are hard, irregular, and painless. Tophi may erode through the skin and drain a chalk-like substance. Clinicians should note the number and location of any joints involved, evaluating for swelling, deformities, and limited mobility.

Managing gout

The ACR recommended interventions are intended to help reduce serum uric acid levels to the therapeutic target and prevent or reverse hyperuricemia consequences (see *Overall hyperuricemia management*). Nonpharmacologic management relies on lifestyle interventions that reduce modifiable risk factors.[14] Clinicians should review the patient's current medications, and if any are associated with hyperuricemia, they should be substituted with another drug if possible. Clinicians should also screen for any associated conditions, including hypertension, diabetes mellitus, obesity, and alcohol abuse, and if present, manage these appropriately. Lifestyle education regarding gout management should also be provided.

Differential diagnosis[6]

- Pseudogout
- Septic arthritis
- Trauma
- Cellulitis
- Lyme disease
- Osteoarthritis
- Psoriatic arthritis
- Sarcoidosis
- Rheumatoid arthritis

Urate-lowering therapy

Urate-lowering therapy (ULT) is the cornerstone of gout management and is required in most patients to achieve disease control. It should be considered in patients with tophi, two or more acute episodes of inflammation per year, chronic kidney disease ([CKD] stage 2 or worse), or a history of urolithiasis.[5] ULT is initiated with a xanthine oxidase inhibitor (XOI). Either allopurinol or febuxostat can be used; however, allopurinol is the first-line therapy, mainly because of its low cost.[14] The dose of allopurinol is gradually titrated up every 2 to 5 weeks until reaching the target serum uric acid level. Allopurinol should be started at a lower dosage in patients with significant kidney disease (CKD stage 4 or worse); consult the manufacturer's product label for complete dosage recommendations.

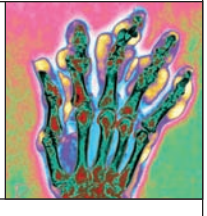
The low starting dose reduces the potential for the patient to experience an acute episode of gout associated with initiating therapy and allows close monitoring for hypersensitivity reactions.[5] Although many patients experience mild adverse reactions, significant adverse reactions can occur, including agranulocytosis, aplastic anemia, and severe skin conditions (such as Stevens-Johnson syndrome and toxic epidermal necrolysis).[14] Clinicians should consider screening for the HLA-B*5801 allele, a genetic test that predicts the risk of a severe allergic reaction to allopurinol in high-risk patients, such as Korean patients with kidney disease or those of Han Chinese or Thai ancestry.[5]

Febuxostat may be preferred in some cases, does not require dose adjustment in kidney disease, and has fewer drug-drug interactions that may limit efficacy or safety. It may be safely used in patients who have had or are at risk for an allopurinol hypersensitivity reaction and are not candidates for allopurinol treatment.[14] Febuxostat is dosed once daily and is titrated up until the target serum uric acid level is reached.[9]

The ACR recommends monotherapy with the uricosuric probenecid if allopurinol or febuxostat is contraindicated or the patient has intolerance to either.[5] Probenecid is contraindicated in patients with a history of urolithiasis or a creatinine clearance below 50 mL/minute. Have patients discontinue using aspirin, as it negates the effects of probenecid.

The ACR recommends anti-inflammatory prophylaxis with the alkaloid colchicine or low-dose nonsteroidal anti-inflammatory drugs (NSAIDs), such as naproxen, when initiating therapy due to the high rate of acute inflammation early in ULT.[15,16] Colchicine requires a dose adjustment downward for patients with kidney disease; the manufacturer's product label should be consulted for complete dosage recommendations for patients with severe kidney failure.

Urate-lowering therapy is the cornerstone of gout management and is required in most patients to achieve disease control.



An alternative is low-dose prednisone or prednisolone in patients who are intolerant to or have a contraindication to colchicine or NSAIDs; however, the ACR encourages careful evaluation before using corticosteroid therapy given the risks of prolonged use.[16]

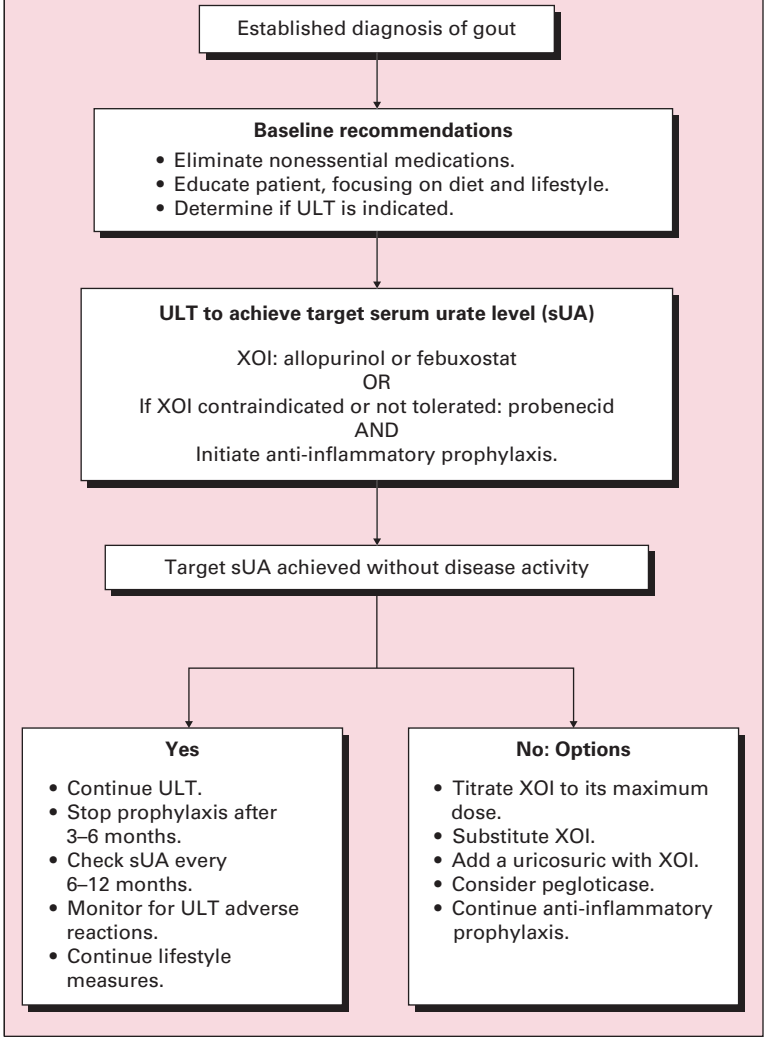
Prophylaxis should be continued while any signs of gout are present. Therapy duration depends on whether tophi were present after the target serum uric acid level has been achieved. Prophylaxis may stop after 3 months in patients without tophi; prophylaxis should continue for 6 months if tophi were present.[15]

Several options are available if the target serum uric acid level is not achieved or the patient experiences continued gout manifestations. Clinicians should confirm that

the initial XOI is titrated to the maximum appropriate dose; the next option is to substitute febuxostat for allopurinol or vice versa. A uricosuric should be added with the XOI, titrating both to their maximum appropriate doses. The ACR recommends not only using probenecid but also other medications with less noticeable uricosuric effects, including the antilipemic agent fenofibrate and the angiotensin II receptor blocker losartan (both drugs are FDA off-label use for gout).[5] Losartan may have the added benefit of decreasing the risk of the patient developing associated hypertension.[10]

Pegloticase is a recombinant form of uricase, the natural enzyme that converts uric acid to more soluble allantoin.[16] Pegloticase therapy is an option in patients who did not reach target serum uric acid level with other ULTs; are unable to tolerate other therapies; are still having frequent episodes; or show chronic gouty arthropathy.[4] Pegloticase should not be used in combination with another urate-lowering agent. Treatment involves an I.V. infusion given every two weeks, usually for a minimum of 6 months. Life-threatening anaphylactic and infusion reactions can occur during and after infusion, necessitating premedication with an antihistamine or corticosteroid. Although therapy is effective, the cost of pegloticase is substantial and a major factor limiting its use.

Overall hyperuricemia management[5,16]



Managing an episode of acute inflammation

The use of pharmacotherapy to reduce inflammation and pain and terminate the episode is the mainstay of treating an acute episode of inflammation.[8] Therapy is based upon severity of pain and the number of joints involved. For an acute episode of mild-to-moderate severity (pain less than or equal to 6 of 10 on a 0 to 10 analogue scale [particularly those involving 1 or a few small joints or 1 or 2 large joints]), the ACR recommends monotherapy with an oral NSAID, systemic corticosteroid, or colchicine (see *Pharmacotherapy for an episode of acute inflammation*).[16]

In more severe disease (with severe pain and a polyarticular presentation), combination therapy is appropriate with colchicine and an NSAID, an oral corticosteroid and colchicine, or intra-articular corticosteroid joint injections with any of the other options. The choice of therapies is at the provider's discretion and based on patient's preference, prior response to pharmacotherapy, and any comorbidities.[16] When therapy is initiated is more important than the choice of drug. The sooner any therapy starts, the faster a response will be attained. In most cases, an acute episode resolves within a few days of initiating treatment. Alternative diagnoses should be considered if any acute episodes do not resolve.[6]

Naproxen, indomethacin, and sulindac are FDA-approved NSAIDs for treating acute episodes.[16] The selection is the provider or patient's choice, as there is no evidence that any is more effective. Since gastrointestinal (GI) toxicity is a concern, clinicians should administer these drugs with a proton pump inhibitor, especially for those with peptic ulcer disease or high risk for GI bleeding.[8] Other NSAIDs may be effective; the ACR recommends therapy with the COX-2 inhibitor celecoxib (FDA off-label for gout) in patients intolerant or with

Pharmacotherapy for an episode of acute inflammation[16]

Drug*	Adverse reactions	Precautions
NSAID		
• Indomethacin oral dose • Naproxen oral dose • Sulindac oral dose	GI bleeding, kidney dysfunction	• Use with caution in patients with CKD, peptic ulcer disease, ulcerative colitis, or GI bleeding. • Monitor kidney and liver function tests. • Coadminister a proton pump inhibitor. • Teach the patient to take with food.
Alkaloid		
Colchicine oral dose	GI bleeding, abdominal pain, nausea, vomiting, diarrhea	• Use with caution in patients with CKD or those taking cyclosporine, macrolide antibiotics, calcium channel blockers, and statins. • Stop drug therapy at the first sign of GI adverse effects. • Monitor kidney function tests. • Teach the patient to take with food.
Corticosteroids		
• Prednisone oral dose • Methylprednisolone oral dose pack or I.V.	Hyperglycemia, hypertension, fluid and sodium retention, nausea, headache	• Use with caution in patients with diabetes mellitus. • Useful for patients who cannot have other therapies or with polyarticular involvement. • Monitor BP, weight, chemistry panel. • Teach the patient to limit sodium intake.
Methylprednisolone intra-articularly at the appropriate site	None generally reported	• Particularly useful for flares of a single large joint. • Rule out joint infection prior to administration. • Advise patient to rest joint for 24–48 hours after injection.
Triamcinolone acetonide I.M. injection	Redness, irritation, pain at injection site	• Useful in patients with known contraindications to NSAIDs. • Requires follow-up therapy with oral prednisone or prednisolone.
ACTH		
ACTH subcutaneous injection	Hypokalemia, hyperglycemia, edema	• Avoid use in patients with recent use of systemic corticosteroids.

* Consult the manufacturers' product labels for complete prescribing information.

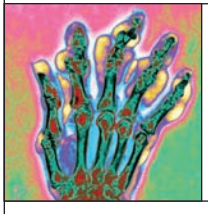
contraindications to the other NSAIDs.[16] Colchicine can be used if the onset of the episode is no greater than 36 hours prior to treatment initiation.[16] It is important to note that a positive response to colchicine is not particular to acute gout. A clinical response can be seen in patients with pseudogout, sarcoidosis, and psoriatic arthritis.[13]

The number of joints involved is the primary consideration when selecting corticosteroids as initial therapy. The ACR recommends short-term therapy with oral corticosteroids for 1 or 2 joints; intra-articular corticosteroids are an option when only 1 or 2 large joints are involved. Intra-articular dosing is based on the size of the involved joint(s) and should be used in combination with an NSAID, colchicine, or oral corticosteroid. Administering subcutaneous adrenocorticotropic hormone (ACTH) or triamcinolone acetonide I.M. injection followed by oral corticosteroid therapy is another approach

for patients who are taking nothing orally or those who are less adherent to an oral regimen.[16]

Pain management is of primary concern during an acute episode. The ACR recommends topical ice application to the affected joint for 30 minutes four times daily.[16] Any inflamed joints should be rested as much as possible for 1 to 2 days, and bed rest may be appropriate in a severe case. The affected joints need to be protected from the weight of the bed sheets.

Some patients may benefit from referral to a rheumatologist. Clinicians should consider referring patients who present with an unclear etiology of hyperuricemia; have polyarticular disease with uncontrolled episodes or signs of destructive tophi; are not reaching the target serum uric acid level, particularly if they have kidney impairment; or those who have experienced multiple and/or serious adverse reactions from ULT.[5] This is particularly true in older adults when comorbidities, polypharmacy, drug interactions, or contraindications to ULT make management challenging.[11]



Pharmacotherapy to reduce inflammation and terminate the episode is the mainstay of treating an acute episode of inflammation.

Patient education

Clinicians have a responsibility to provide patient education. Teaching self-care measures to decrease the risk of acute episodes and avoid long-term complications is highly influential on the patient's quality of life and clinical outcome. All patients should be informed regarding gout and its treatment (including the risks and benefits of drug therapy), how to prevent and handle episodes, and the importance of lifestyle and dietary issues related to gout. Patients should also understand how comorbid conditions, including hypertension and diabetes mellitus, could affect gout and its treatment.

Adherence is a problem with ULT. The patient needs to be adherent to the prescribed regimen, as recurring acute episodes can result in significant long-term effects. Clinicians should review the dosing schedule, administration instructions, and adverse reactions of prescribed medications. Some patients stop therapy due to episodes associated with initiating therapy. Patients should be taught early signs of an acute episode and how to manage them. Patients need to understand that it is important to keep appointments for ongoing monitoring of serum uric acid levels.

Clinicians should provide counseling regarding factors that can precipitate acute episodes. This includes the avoidance of all forms of aspirin and niacin (which may be present covertly in over-the-counter products), as their use can precipitate an acute episode. Patients should be taught that excessive physical or emotional stress, surgery, and acute illness can exacerbate gout. Patients should reduce alcohol use as much as possible, with no more than two servings for men and one serving for women per day. All alcohol should be avoided during an acute episode.[5]

Dietary recommendations are divided into three groups. Patients should avoid eating organ meats (sweetbreads, liver, kidneys), sugar-sweetened, nondiet soft drinks, and foods or fruit juices containing high-fructose corn syrup. Foods to limit include large portions or concentrations of beef, lamb, pork, and seafood; naturally sweet fruit juices; sugar-sweetened foods; and table salt. Promote low-fat or nonfat dairy products, nuts, legumes, vegetables and fruits high in vitamin C, and whole grains.[5] These foods are not only protective against hyperuricemia but reduce comorbidity by reducing insulin resistance.[1] The low-fat dairy products, along with citrus foods and cranberry juice, also help increase urinary pH, decreasing the likelihood of uric acid-related lithiasis. Encourage patients to drink enough fluids to maintain a urinary output of at least 2,000 mL each day.

Clinicians should address any lifestyle considerations associated with coexisting conditions, including obesity, diabetes mellitus, hyperlipidemia, and hypertension. Advise obese patients to follow a balanced, calorie-controlled diet that will result in weight loss. This may entail lowering sodium, fat, and cholesterol intake and will lead to a reduction in gout symptoms and decrease effects associated with coexisting metabolic conditions.[4] Caution patients not to participate in crash-dieting or follow popular high-protein, low-carbohydrate diets, as the increased animal protein intake can exacerbate gout.

The patient should follow a moderate exercise program, avoiding joint trauma. Wearing proper footwear is important. Footwear that has inadequate stability, poor cushioning, and limited stability may increase foot pain and disability.[17] Having shoes fit by a shoe-fitting specialist will help insure shoe size and width are accurate and that shoes have adequate support and cushioning. Good footwear choices include athletic sneakers, walking shoes, or oxfords.

Moving forward

With the prevalence of gout increasing, clinicians need to recognize gout as a chronic disease and provide comprehensive management to optimize clinical outcomes and quality of life. Effective management focuses on reaching and

maintaining a target serum uric acid level below 6.0 mg/dL, lowering the risk of advanced disease, and the development of comorbid conditions. This is best accomplished through a combination of ULT and patient education addressing medication adherence and lifestyle changes tailored to the patient and the presence of coexisting conditions. Using the recent ACR guidelines will help clinicians select the optimum ULT anti-inflammatory prophylaxis, and acute episode management strategies to treat patients with gout.

REFERENCES

1. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. *Arthritis Rheum*. 2011;63(10):3136-3141.
2. Krishnan E. Chronic kidney disease and the risk of incident gout among middle-aged men: a seven-year prospective observational study. *Arthritis Rheum*. 2013;65(12):3271-3278.
3. Wertheimer A, Morlock R, Becker MA. A revised estimate of the burden of illness of gout. *Curr Ther Res Clin Exp*. 2013;75:1-4.
4. Perez-Ruiz F, Herrero-Beites AM. Evaluation and treatment of gout as a chronic disease. *Adv Ther*. 2012;29(11):935-946.
5. Khanna D, Fitzgerald JD, Khanna PP, 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(10):1431-1446.
6. Firestein GS, Budd RC, Gabriel SE, McInnes IB, O'Dell JR. *Kelley's Textbook of Rheumatology*. 9th ed. St. Louis, MO: Saunders; 2012.
7. Seminog OO, Goldacre MJ. Gout as a risk factor for myocardial infarction and stroke in England: evidence from record linkage studies. *Rheumatology (Oxford)*. 2013;52(12):2251-2259.
8. Ruoff G. The treatment of gout. *J Fam Pract*. 2012:11-15.
9. Laine C, Turner BJ, Williams S. Gout. *Ann Intern Med*. 2010;152(3):ITC2.2-ITC2.16.
10. Roddy E, Choi HK. Epidemiology of gout. *Rheum Dis Clin North Am*. 2014;40(2):155-175.
11. Zychowicz ME, Pope RS, Graser E. The current state of care in gout: addressing the need for better understanding of an ancient disease. *J Am Acad Nurse Pract*. 2010;22(suppl 1):623-636.
12. Perez-Ruiz F, Castillo E, Chinchilla SP, Herrero-Beites AM. Clinical manifestations and diagnosis of gout. *Rheum Dis Clin North Am*. 2014;40(2):193-206.
13. Terkeltaub R. *Gout & Other Crystal Arthropathies*. St. Louis, MO: Saunders; 2012.
14. Chaichian Y, Chohan S, Becker MA. Long-term management of gout: nonpharmacologic and pharmacologic therapies. *Rheum Dis Clin North Am*. 2014;40(2):357-374.
15. White S, Mounsey A, Tillett J. Clinical inquiry: which prophylactic therapies best prevent gout attacks? *J Fam Pract*. 2014;63(4):216-217.
16. Khanna D, Khanna PP, Fitzgerald JD, 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(10):1447-1461.
17. Rome K, Frecklington M, McNair P, Gow P, Dalbeth N. Footwear characteristics and factors influencing footwear choice in patients with gout. *Arthritis Care Res (Hoboken)*. 2011;63(11):1599-1604.

Mariann Harding is an associate professor of nursing at Kent State University, Tuscarawas, New Philadelphia, Ohio.

The author and planners have disclosed that they have no financial relationships related to this article.

DOI-10.1097/01.NPR.0000481510.32360.fa