ACR Publishes Guidelines for Pharmacologic and Nonpharmacologic Treatment of Gout

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Gout is one of the most common rheumatic diseases in adults, and is the most common cause of inflammatory arthritis in U.S. adults, with an estimated prevalence of 3.9% (approximately 8.3 million persons). The disease is characterized by deposits of monosodium urate monohydrate crystals in the extracellular fluids of the joints and other sites. Typically, gout initially presents as acute episodic arthritis, although it can also manifest as chronic arthritis of one or more joints.

The American College of Rheumatology (ACR) has developed recommendations for the management of gout. The recommendations call for a systematic nonpharmacologic and pharmacologic management approach that is intended to be applicable to all patients with gout. This summary addresses recommendations regarding urate-lowering therapy, analgesic and anti-inflammatory management of acute gouty arthritis, and pharmacologic anti-inflammatory prophylaxis of gouty arthritis.

Urate-Lowering Therapy: Nonpharmacologic Treatments

Patients with gout should stay well hydrated, and should exercise regularly to achieve physical fitness and to prevent or manage comorbidities such as coronary artery disease, obesity, metabolic syndrome, diabetes mellitus, and hypertension. If a patient with gout is obese, he or she should participate in a weight loss program to achieve a body mass index that promotes general health. Patients with gout who smoke should be encouraged to stop smoking.

Patients with gout should avoid eating organ meats that are high in purines, such as sweetbreads, liver, or kidneys. They should also avoid drinking sodas and other beverages that contain high fructose corn syrup, and avoid overuse of alcohol, especially beer (no more than two servings per day for men or one serving per day for women). Patients should have no alcohol during gout attacks, or if they have advanced gout that is poorly controlled.

Patients with gout should limit their intake of beef, lamb, pork, sardines, shellfish, naturally sweet fruit juices, sugar-sweetened foods, table salt, and salty sauces and gravies. They should be encouraged to eat low-fat or nonfat dairy products, and vegetables; evidence suggests that increased vegetable intake may reduce serum urate levels and decrease risk factors for urolithiasis.

Urate-Lowering Therapy: Pharmacologic Treatments

Physicians should consider causes of hyperuricemia in all patients with gout. In particular, physicians should screen for uric acid overproduction in patients younger than 25 years and in those who have a history of urolithiasis.

Physicians should consider eliminating nonessential medications such as niacin, loop diuretics, calcineurin inhibitors, and thiazides that may induce hyperuricemia. However, elimination of these medications should be done only on a case-by-case basis.

Pharmacologic urate-lowering therapy should be administered to any patient who has an established diagnosis of gouty arthritis and any of the following: presence of tophi on clinical examination or imaging, two or more attacks of gouty arthritis per year, chronic kidney disease at stage 2 or worse, or history of urolithiasis.

First-line treatments for urate-lowering therapy include xanthine oxidase inhibitors such as allopurinol (Zyloprim) and febuxostat (Uloric). The starting dosage of allopurinol should be no more than 100 mg per ▶

day; in patients with stage 4 chronic kidney disease or worse, the recommended starting dosage is 50 mg per day. If at least one of these agents is contraindicated or not tolerated by the patient, an alternative first-line medication is a uricosuric agent such as probenecid; other uricosuric agents available in the United States include fenofibrate (Tricor) and losartan (Cozaar). *Table 1* lists core recommendations related to the use of allopurinol and uricosuric urate-lowering therapy.

Therapy with a combination of an oral urate-lowering agent, a xanthine oxidase inhibitor, and a uricosuric agent is appropriate when a patient's serum urate targets are not met by appropriate dosing with a xanthine oxidase inhibitor alone. Pegloticase (Krystexxa) is appropriate only in patients who have severe gout and intolerance of, or refractoriness to, appropriate doses of oral urate-lowering therapy.

Table 1. Recommendations for the Use of Allopurinol and Uricosuric Urate-Lowering Therapy for Gout

Allopurinol (Zyloprim)
Starting dosage should be no greater than 100 mg per day (50 mg per day in patients with stage 4 or worse chronic kidney disease)
Maintenance dose should be titrated every two to five weeks to the appropriate maximal dose until the serum uric acid target is achieved
Dosage can be increased above 300 mg daily, even in patients with renal impairment, as long as the patient receives adequate instructions and is monitored for drug toxicity (e.g., pruritus, rash, elevated hepatic transaminase levels)
Before therapy is initiated, testing for *HLA-B*5801* should be considered in patients at risk of severe allopurinol hypersensitivity reaction (e.g., those of Korean descent with stage 3 or worse chronic kidney disease; those of Han Chinese or Thai descent, irrespective of renal function)
Uricosuric therapy
Probenecid is the first-line uricosuric agent for urate-lowering monotherapy
In patients with gout and creatinine clearance < 50 mL per minute per 1.73 m^2 (0.83 mL per second per m^2), probenecid is not recommended as first-line urate-lowering monotherapy
Use of agents other than probenecid that have clinically significant uricosuric effects, such as fenofibrate (Tricor) and losartan (Cozaar), can be therapeutically useful as components of a comprehensive urate-lowering strategy
First-line uricosuric urate-lowering monotherapy is contraindicated in patients with a history of urolithiasis
Urinary uric acid should be measured before initiation of uricosuric urate-lowering therapy
Uricosuric urate-lowering therapy is contraindicated in patients with urinary uric acid levels indicative of uric acid overproduction
Urinary uric acid levels should be monitored in patients receiving uricosuric urate-lowering therapy
Urine alkalization (e.g., with potassium citrate) with monitoring of urine pH and increased fluid intake should be considered as a risk-management strategy for urolithiasis

Adapted with permission from 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):1440.*

Acute Gouty Arthritis

Attacks of acute gouty arthritis should be treated with pharmacologic therapy, preferably initiated within 24 hours of onset. Pharmacologic urate-lowering therapy should continue uninterrupted for the duration of the attack. Patients who experience acute attacks of gout should be educated on dietary habits and other potential triggers, and should receive instructions to initiate treatment when symptoms occur, without having to consult with their physician.

The choice of pharmacologic agent for acute gout should be based on the severity of pain and the number of joints involved. Monotherapy is appropriate for mild or moderate attacks, particularly those that involve one or a few small joints, or one or two large joints. Recommended options include low-dose oral nonsteroidal anti-inflammatory drugs (e.g., naproxen [Naprosyn], 250 mg twice daily) or oral colchicine (0.6 mg once or twice daily). If these agents are ineffective, contraindicated, or not tolerated by the patient, second-line options include low-dose prednisone or prednisolone (at least 10 mg daily). Ice may be applied as necessary. Physicians should choose the most appropriate monotherapy based on the patient's preference, previous response to pharmacologic therapy for an acute attack of gout, and associated comorbidities. Initial combination therapy is an appropriate option when the attack is characterized by severe pain, especially in an acute polyarticular gout attack or in an attack that involves one or two large joints. Acceptable approaches to combination therapy include the initial simultaneous use of full doses (or, where appropriate, prophylactic doses) of any of the following: colchicine and nonsteroidal anti-inflammatory drugs; colchicine and oral corticosteroids; or intraarticular steroids with all other modalities.

If monotherapy is successful, the patient should be educated about dietary and lifestyle factors that can contribute to attacks of gout, particularly the role of uric acid ▶

excess, and should receive instruction on self-treatment for subsequent attacks. If the patient has an inadequate response to monotherapy (less than 20% improvement on a visual analog pain score within 24 hours, or less than 50% reduction in pain score at 24 hours or longer), adding a second agent is an acceptable option.

Pharmacologic anti-inflammatory prophylaxis is recommended for all patients when pharmacologic urate-lowering therapy is initiated. Urate-lowering therapy may be started during an acute gout attack, provided that effective anti-inflammatory management has been instituted. Prophylaxis should be continued if there is any clinical evidence of continuing disease or if the patient's serum urate target level has not been achieved.

Unless there is a lack of tolerance or a medical contraindication, oral colchicine is an appropriate first-line prophylactic therapy for gout attacks, including with appropriate dose adjustment in chronic kidney disease and for drug interactions. Prophylaxis should be continued for the greater of the following: six months' duration; three months after achieving target serum urate levels with no tophi detected on physical examination; or six months after achieving target serum urate levels with resolution of tophi previously detected on physical examination.

Treatment Goals

Although serum urate targets should be defined for individual patients, the minimum level is less than 6 mg per dL (357 μmol per L). Lowering serum urate levels below 5 mg per dL (297 μmol per L) may be necessary to improve signs and symptoms of gout. Once preferred serum urate target levels have been reached, long-term management goals include continuance of gout prophylaxis if there are ongoing symptoms or signs of the condition. Physicians should regularly monitor serum urate levels and monitor for adverse effects of urate-lowering therapy. After palpable tophi and all symptoms of acute and chronic gouty arthritis have resolved, patients should continue treatment to maintain serum urate targets below 6 mg per dL.

MICHAEL DEVITT, *AFP* Associate Editor ■

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Q1. C **Q3.** C **Q5.** B
Q2. B, C, D **Q4.** D **Q6.** B