

Gout and Hyperuricemia

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Dr Esherrick, Dr Blount, Ms LaRocque, and Ms Gangel have returned disclosure forms indicating that they have no financial interest in or affiliation with any commercial supporter or providers of any commercial services discussed in this educational material.

Learning Objectives

After reading this *CME Bulletin*, you should be able to:

- Utilize the evidence-based diagnostic criteria for gout in all individuals presenting with swollen, red, warm joints consistent with inflammatory arthritis.
- Propose therapy plans for individuals with acute gout and recurrent gout using uric-acid-lowering agents, nonsteroidal anti-inflammatory drugs, colchicine, and other drugs that are alternatives when comorbidities are present.
- Understand the complications of chronic hyperuricemia and gout.

Introduction

Gout, previously known as the *disease of kings* because of its association with the excessive consumption of alcohol, red meat, and seafood that only the wealthy could once afford, is now a common form of inflammatory arthritis. The incidence of gout has doubled over the past 2 decades, yet there have been few advances in the management of the disease in the past 50 years.^{1,2} Research on this topic continues to be limited.

Epidemiology of Gout

Approximately 2 to 6 million individuals in the United States have been diagnosed with gout.³ The increase in incidence of gout may be the result of a number of factors including dietary trends; increased longevity; increases in organ transplantation; increased prevalence of hypertension, end-stage renal disease, and metabolic syndrome; and the increased use of certain drugs such as thiazide, loop diuretics, and low-dose aspirin.⁴ A review of data from the Third National Health and Nutrition Examination Survey (NHANES III) showed that the prevalence of metabolic syndrome in study participants with gout was greater than 60%; the prevalence in participants without gout was approximately 25%.⁵ In the United States, changes in demographics (eg, the increasing black population, in which incidences of metabolic syndrome and hypertension are higher) may also be responsible for an increase in prevalence.⁴

Gout is a chronic disease directly related to the presence of hyperuricemia. Hyperuricemia, defined as a serum urate level >6.8 mg/dL, is a metabolic disorder caused by an imbalance in the production and excretion of uric acid; this imbalance can result from overproduction, underexcretion, or both.^{6,7} Inefficient renal excretion is thought to account for 80% to 90% of hyperuricemia.^{6,8}

Gout affects approximately 2% of men older than 30 years and 2% of women older than 50 years, and is the most common form of inflammatory joint disease in men older than 40 years. Serum urate levels are, on average, 0.5 to 1.0 mg/dL higher in men than women, making male sex a risk factor for hyperuricemia and gout. Lower serum urate levels in women are associated with the presence of estrogen, which is thought to act as an antihyperuricemic.⁶ When gout occurs before age 30 years in men, or before menopause in women, renal disease or an inherited enzyme defect should be considered.⁹ Incidence of gout begins to equalize among men and women at age 65 years.⁶

Gouty arthritis is caused by intense inflammation resulting from monosodium urate (MSU) crystal deposition in joints. Because a direct causal relationship exists between serum urate levels and the risk of gout, any systemic factor that increases the risk of hyperuricemia can also increase the risk of gout.^{1,10} Modifiable risk factors include consumption of purine-rich meats and foods or beverages containing excessive fructose, alcohol consumption (particularly beer and liquor), increased body mass index, and changes in pH levels or body temperature.^{5,6,10,11}

Fructose consumption has been recently identified as a risk factor for gout. Fructose induces hyperuricemia by accelerating the catabolism of adenine nucleotides.^{6,12} An analysis of NHANES-III data examined the relationship between the consumption of soft drinks and hyperuricemia and found a significant increase in serum uric acid levels as fructose-sweetened soft drink consumption increased.¹²

Common triggers for acute gout include infection, intravenous contrast media, acidosis, and rapid fluctuations in serum uric acid concentrations associated with trauma, surgery, psoriatic flares, chemotherapy initiation, diuretic therapy, and stopping or starting the xanthine oxidase inhibitor allopurinol.¹⁰ There is an association between hyperuricemia and gout, and insulin resistance syndrome and related comorbid conditions.¹

Hyperuricemia and Gout

Asymptomatic Hyperuricemia

In asymptomatic hyperuricemia, uric acid levels are elevated, but individuals experience no symptoms of gout. The risk of a gouty attack increases as the uric acid level increases. Most individuals with asymptomatic hyperuricemia will have elevated uric acid levels for years before the first attack, or they may never experience an attack.¹³



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Although treatment is not necessary for asymptomatic hyperuricemia, years of sustained elevated uric acid levels can lead to gout and/or nephrolithiasis; therefore, physicians should adjust or correct the underlying causes of hyperuricemia.⁹ Medical treatment of asymptomatic hyperuricemia should be restricted to specific circumstances, such as:¹³

- Initiation of chemotherapy or radiation therapy
- History of kidney stones
- History of gouty attack, tophi, and moderate renal function impairment (creatinine clearance [CrCl] <42 mL/min)
- Markedly elevated uric acid levels (≥ 12 mg/dL in men or women)

Acute Gout

Long-term hyperuricemia can lead to the deposition of small sodium urate crystals in and around joint spaces (tophi), resulting in an acute gout flare.¹⁴ In an acute gout flare, an individual experiences sudden onset of pain, erythema, limited range of motion, and swelling of the affected joint; pain and sensitivity are so significant that the individual often cannot wear socks or tolerate the touch of bed sheets.^{9,10} An attack can last for days or weeks and be followed by a long, symptom-free (ie, intercritical) period.

Gout manifestations can be monoarticular, polyarticular, symmetrical, or asymmetrical, and may involve joints in the lower or upper extremities.² Approximately 90% of first gout attacks are monoarticular.⁹ In more than 50% of individuals who experience acute gout, the first metatarsophalangeal (MTP) joint (podagra) is the initial affected joint, and that joint is eventually affected in 90% of individuals with gout.⁹ Other areas that are commonly affected include the instep/forefoot, ankle, knee, wrist, and fingers.⁹ Low-grade fever (temperature of 38.3°C [101°F]), chills, carpal tunnel syndrome, and malaise can also accompany acute attacks.¹⁴ Symptoms often begin in the early morning, then increase and peak within 24 to 48 hours; attacks generally subside within 5 to 7 days.¹⁰

Acute gout can cause fever and peripheral leukocytosis (sometimes $>40,000$ white blood cells/mm³ [40×10^9 per L]) and can be difficult to distinguish from acute septic arthritis.¹⁰ When a high-grade fever is present or an individual is immunocompromised, evaluation for septic arthritis via synovial fluid aspiration must be performed immediately. If aspiration cannot be performed in the office setting, immediate referral to a facility where it can be performed is required.²

Diagnosis of Gout

Serum Urate Level

Serum urate levels may or may not be elevated during an attack and therefore are not necessary to confirm a diagnosis of gout¹⁰; however, measuring serum urate levels at the time of the attack provides a baseline from which to initiate urate-lowering therapy and to compare subsequent levels to determine whether therapy is effective.¹⁵

Once an attack of acute gout subsides, 24-hour uric acid levels should be measured to determine whether hyperuricemia is the result of urate overproduction or underexcretion; this determination will aid in choosing the appropriate drug to control the associated hyperuricemia.^{2,14} A serum urate level is not part of many chemistry panels and must be requested separately. Because the serum urate level is normal in approximately 50% of individuals experiencing an attack of acute gout, the most accurate measurement of serum urate can be obtained at least 2 weeks after the attack.² If the serum urate level is not elevated during an attack, it will likely be elevated 2 weeks later in individuals with gout; conversely, a diagnosis of gout is unlikely in individuals whose serum urate levels are low (<4 mg/dL) 2 weeks after an attack.¹⁵

Imaging

Specific x-ray features (tophi) for gout generally manifest late in the disease, typically 15 years after disease onset; therefore, x-rays are not considered useful in confirming the diagnosis of early or acute gout.^{16,17} Ultrasound (US) can be used to evaluate cartilage, soft tissues, urate crystal deposition, and synovial membrane inflammation.¹⁷ Recent studies have shown that US can provide enough detail for an initial diagnosis of tophaceous gout in the office setting.¹⁸ Dual energy computed tomography (DECT) scan, a relatively new noninvasive technology that uses two x-ray tubes capable of simultaneously producing different energies, assesses urate deposits by producing color displays that help identify subclinical tophi and measure total body urate burden. The role of US and DECT in the primary care management of gout is not yet established.^{17,19,20}

Synovial Fluid Analysis

Synovial fluid analysis and the identification of needle-shaped, negatively birefringent MSU crystals under compensated polarized microscopy is currently considered the gold standard for diagnosis of acute gout.² Synovial fluid white blood cell count usually is 10,000 to 70,000/ μ L, but can be as low as 1,000/ μ L.¹⁴ Studies can be performed with only 1 to 2 mL of synovial fluid.⁵

In the absence of synovial fluid analysis, criteria developed by the American College of Rheumatology can be used to diagnose an attack of acute gout. Six of the 12 criteria listed below must be present in order to confirm a diagnosis.^{2,4}

- Asymmetric swelling within joint on x-ray
- Hyperuricemia
- Joint fluid culture negative for organisms during attack
- Maximum inflammation developed within a day
- Monoarthritis
- More than one attack of acute arthritis
- Painful/swollen first MTP joint
- Redness over joints
- Subcortical cysts without erosions on x-ray
- Tophus (proved or suspected)
- Unilateral attack of first MTP joint
- Unilateral attack of tarsal joint

Major differential diagnostic considerations include Lyme disease, painful osteoarthritis, pseudogout, psoriatic arthritis, rheumatoid arthritis, septic arthritis, and spondyloarthropathy.⁴

Treatment of Acute Gouty Attack

The primary goal during an acute attack of gout is to relieve pain and return an individual to normal function.

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are considered first-line agents for an acute gout attack and should be initiated immediately to achieve the best outcome.²¹ Ninety percent of individuals experience a complete resolution of symptoms within 5 to 8 days of starting NSAID therapy.⁹ Maximum doses should be initiated immediately and continued for 2 to 5 days, then tapered to approximately 50% to 25% once the attack is resolved.¹⁴ NSAID use is associated with an increased risk of gastrointestinal bleeding and may have cardiovascular and renal toxicity; it should be avoided in individuals with chronic renal failure, liver disease, peptic ulcer disease, poorly compensated congestive heart failure, and those receiving anticoagulation therapy.^{9,21} Risk of adverse effects is greatest in elderly individuals; therefore, if used in this population, early administration during a gout attack is recommended to limit dosage and duration of exposure.²² In lower doses, aspirin is associated with an increased risk of gout; low-dose aspirin causes retention of uric acid; but higher doses (>3 g/day) may be uricosuric.²³

Oral Colchicine

Colchicine, which was approved by the Food and Drug Administration (FDA) in July 2009 for the treatment of gout, has been used for centuries and is considered a first alternative when NSAIDs are contraindicated.^{24,25} It is most effective if administered within the first 24 hours of an attack.⁹ Fifty percent to 80% of individuals using oral colchicine experience adverse effects that can include diarrhea, nausea, and vomiting.²² Colchicine should be used cautiously in elderly or debilitated individuals because of susceptibility to cumulative toxicity. The risk of neuromuscular toxicity and rhabdomyolysis is increased in elderly individuals with or without concomitant renal or hepatic dysfunction. The maximum dosage for elderly individuals is 2.4 mg/day.²⁵

Oral colchicine is an FDA pregnancy category C agent and should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus. Colchicine is contraindicated in individuals with hepatic or renal impairment who are also taking P-glycoprotein inhibitors and/or strong CYP3A4 inhibitors and should be used cautiously in individuals with bone marrow disorders or dental disease. Due to toxicity, intravenous colchicine is no longer available in the United States.²⁵

Corticosteroids

Oral corticosteroids are appropriate for individuals who cannot tolerate NSAIDs or colchicine and can be particularly beneficial for elderly individuals. Long-acting, intra-articular corticosteroids can be used for single-joint involvement if no infection is present.^{14,21} When corticosteroids are used in individuals with diabetes, changes in insulin, oral antidiabetic agent dosage, and/or diet may be required.²⁶

Table 1 lists drugs for treatment of acute gout attack.

Intercritical Gout

Gout attacks are typically intermittent. During the intercritical period, no symptoms are present and joints function normally.^{9,10,13} To protect against future flares, initiate strategies to control underlying hyperuricemia—risk-factor management and urate-lowering therapy—once an acute attack has subsided.

Lifestyle Modifications

Nonpharmacologic treatment of hyperuricemia should target modifiable risk factors including diet and alcohol intake. Individuals should be encouraged to limit consumption of red meat and seafood (4-6 oz/day) and increase consumption of low-fat dairy products, which are associated with a reduced risk of gout.^{27,28} Alcohol (beer and liquor, but not wine) consumption promotes purine metabolism and uric acid production, and may also reduce uric acid excretion; therefore, individuals with gout should limit (1 drink 3 times/week) or eliminate alcohol intake.²¹ Weight loss should be encouraged in overweight and obese individuals.²⁸

Vitamin C intake has been associated with reduced serum urate levels. It may affect reabsorption of uric acid by the kidneys and increase the speed at which the kidneys function or protect against inflammation. A 20-year study of 47,000 men found that gout risk was greater among individuals taking less than 250 mg/day of vitamin C compared with those taking 500 to 999 mg/day. The incidence of gout decreased with increasing total and supplemental vitamin C intake; for every 500-mg increase in vitamin C intake, gout risk fell by 17%.²⁹

Lifestyle and dietary changes and weight loss may be beneficial to individuals with early-stage gout and limited elevation of serum urate levels, but these measures generally do not negate the need for urate-lowering therapy (ULT) in patients with existing gout. When possible, diuretics being used in the treatment of hypertension should be replaced with alternative antihypertensives.¹⁰

Table 1. Treatment of Acute Gout

Drug	Dosage
Nonsteroidal anti-inflammatory drugs	
Indomethacin	50 mg 3 times/day for 10 days
Naproxen	500 mg 2 times/day for 4-10 days
Sulindac	200 mg 2 times/day for 4-10 days
	Maximum doses should be initiated immediately, then tapered to 1/2 - 1/4 once attack resolves.
Colchicine	0.6 mg
	If creatinine clearance
	≥50 mL/min: 2 times/day
	35-49 mL/min: Daily
	10-34 mL/min: Every 2 or 3 days
	<10 mL/min: Avoid
Corticosteroids	
Prednisone	20-60 mg/day 2-3 days; taper over 10-14 days
Intra-articular methylprednisolone	20-40 mg once
Intramuscular methylprednisolone	80-120 mg once

Adapted with permission from Eggebeen AT. Gout: An Update. *Am Fam Physician*. 2007;76(6): 801-808 [Review].

Urate-Lowering Therapy

The goal of ULT is to maintain a serum urate level of <6 mg/dL, prevent urate crystal formation, and promote crystal dissolution.²¹ Indications for ULT include:¹¹

- Advanced gouty arthritis
- Daily urinary urate excretion >1,000 mg
- Gout with chronic kidney disease (CrCl <60 mL/min)
- 3 or more gout flares per year
- Recurring renal stones
- Tophi
- Urate overproduction

After initiating ULT, serum urate levels should be measured every 2-4 weeks and urate-lowering agents titrated upward to doses that will achieve the targeted level (ie, <6.0 mg/dL).²² Non-adherence to ULT can result in recurring attacks and tophi development and therefore, individuals with hyperuricemia should be encouraged to continue urate-lowering therapy for life.² Three types of urate-lowering agents are xanthine oxidase inhibitors, uricosurics, and urate oxidases.

Xanthine Oxidase Inhibitors

Allopurinol is currently the xanthine oxidase inhibitor of choice for ULT.^{2,30} Ideal candidates for treatment with allopurinol include uric acid overproducers (24-hour urinary uric acid excretion >800 mg on a general diet, or >600 mg on a purine-restricted diet); individuals with renal insufficiency (CrCl <50 mL/min), nephrolithiasis, or tophaceous gout; or those at risk of developing uric acid nephropathy (eg, individuals being treated for myeloproliferative or lymphoproliferative disorders).^{31,32} Allopurinol therapy should not be initiated during an acute attack but should be continued in individuals who are established on this therapy.² Allopurinol is an FDA pregnancy category C agent.³³ While it is generally well tolerated, severe or fatal hypersensitivity to allopurinol has been documented; individuals who develop a skin rash should discontinue its use and seek immediate medical attention.¹⁰

Febuxostat, the first new oral antihyperuricemic treatment approved by the FDA since the early 1960s, is a nonpurine xanthine oxidase inhibitor similar to allopurinol.³⁴ Febuxostat is cleared primarily through the liver and may be useful in lowering serum urate levels when allopurinol is contraindicated, or in individuals with chronic renal insufficiency because minimal amounts of the drug are cleared renally.^{7,10,23} Like allopurinol, febuxostat has been associated with an increased risk of gout flare during initiation of therapy and is classified as an FDA pregnancy category C agent.³⁵

Prophylaxis against acute attacks during the first months of ULT can be achieved with concomitant use of colchicine (0.6 to 1.2 mg daily) or an NSAID (with gastroprotection if indicated).^{2,21} Because of the potential for toxicity, colchicine or NSAID use should be discontinued 6 months after a serum urate level of <6 mg/dL has been maintained for 6 months or tophi have resolved.²

Uricosurics

Approximately 80% to 90% of individuals with gout are underexcretors (24-hour urinary uric acid excretion <800 mg on an unrestricted diet, or <600 mg on a purine-free diet). Uricosurics (eg, probenecid) increase renal urate excretion and therefore are considered first-line agents for individuals who have decreased renal urate excretion.^{11,22} Uricosurics are considered second-line therapy for individuals who cannot tolerate allopurinol.^{2,21} Uricosuric therapy is contraindicated in individuals with a history of nephrolithiasis and is not effective in individuals with a creatinine clearance of <50 mL/min.² To obtain the maximum benefit from uricosuric therapy, individuals should consume at least 2 liters of fluid daily and should not have a history of urolithiasis or excessive urine acidity (urine pH <6).¹³

Pegloticase

Pegloticase is an experimental drug that breaks down uric acid with a recombinant form of the enzyme urate oxidase; it lowers

uric acid concentrations by converting uric acid into allantoin, which is easily excreted in the urine.³⁶ Its use in treating individuals whose hyperuricemia and severe gout symptoms are inadequately managed by another urate-lowering therapy is currently being investigated. Pegloticase is in Phase III clinical trials at the time of this publication.^{37,38}

Table 2 lists practice recommendations for the diagnosis and treatment of acute gout.

Chronic Tophaceous Gout

If untreated, prolonged hyperuricemia can develop into chronic tophaceous gout, which is characterized by pain, soft-tissue damage and deformity, joint destruction, and nerve compression syndromes.¹⁰

The most commonly affected sites for tophi include the joints of the hands or feet. Less common locations include the helix of the ear, the olecranon bursa, and the Achilles tendon.⁹ Articular tophaceous gout can lead to destructive arthropathy and chronic secondary osteoarthritis. The time between the first attack and recognizable tophaceous disease ranges from 3 to 42 years (mean: 12 years).⁹ Tophaceous gout is more likely to occur in individuals who have a polyarticular manifestation, a serum urate level >9.0 mg/dL, and whose first attack occurred before age 40.5 years.⁹ Treatment of tophi with urate-lowering therapy and management of serum urate levels can help prevent disease progression.¹¹

Other Complications of Hyperuricemia and Gout

Uric acid stones are more common in individuals with gout, and the risk of stone formation increases with increasing serum urate levels and urine excretion rates. The overall prevalence of urate nephrolithiasis in individuals with gout is approximately 22%. Uric acid nephrolithiasis should be considered in an individual with a history of gout who presents with flank pain, urinary frequency, and dysuria.³⁷ Allopurinol is the drug of choice for individuals with hyperuricemia who develop uric acid stones.³¹

Chronic urate nephropathy was once thought to be common, but studies have shown that the condition is rare. Some deterioration in renal function secondary to hyperuricemia occurs in approximately 10% of individuals with leukemia and lymphoma who have undergone intensive chemotherapy and radiation.³⁹ Intravenous rasburicase, a recombinant urate oxidase, facilitates the conversion of urate into the readily excretable metabolite allantoin and is approved for use in preventing hyperuricemia during the tumor lysis syndrome.^{31,36}

Conclusion

Although gout is the best understood and most manageable form of inflammatory arthritis, the incidence and prevalence in the United States is increasing due to a combination of factors including increased longevity, the diseases associated with longevity, and the trend toward a purine- and fructose-rich diet. Early diagnosis together with lifestyle modifications and pharmacologic intervention to manage serum urate levels can help individuals with hyperuricemia and gout live more comfortable lives.

Table 2. SORT: Key Practice Recommendations

Clinical Recommendation	Evidence Rating
Serum uric acid measurements are useful in the evaluation of gout but should not be used alone to confirm or exclude the diagnosis of gout. ¹	B
Synovial fluid analysis is the gold standard for diagnosis of gout. ¹	A
Nonsteroidal anti-inflammatory drugs and colchicine are effective treatments for acute gout. ¹	A
Intra-articular corticosteroids are effective in relieving pain of acute gouty monoarthritis. ¹	B
In patients with gout, modifiable risk factors such as obesity, diuretic use, high-purine diet, and alcohol intake should be addressed. ¹	B
Urate-lowering therapy is recommended for patients with recurrent gout attacks, tophi, or ongoing arthropathy with joint damage seen on x-ray. ¹	A
Allopurinol is the recommended first-line agent for urate-lowering therapy. ¹	A
During urate-lowering therapy, the target serum uric acid level is <6 mg per dL (355 μmol per L). ²	B

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SORT=Strength of Recommendation Taxonomy: A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series.

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Note About Drugs and Off-label Uses: *The faculty for this activity have made all reasonable efforts to ensure that information contained herein is accurate in accordance with the latest available scientific knowledge at the time of accreditation. Information regarding drugs (eg, administration, dosages, contraindications, adverse reactions, interactions, special warnings, and precautions) and delivery systems is subject to change; and the reader is advised to check the manufacturer's insert and medical references for information concerning recommended dosage and potential problems or cautions prior to dispensing or administering any medication.*

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Self-Assessment Quiz

- Which of the following statements about gout is true?
 - Gout is a chronic disease directly related to hyperuricemia.
 - Overproduction of uric acid accounts for 80% to 90% of all cases of hyperuricemia.
 - The incidence of gout has decreased by half over the past 2 decades.
 - Gout is more common in men until age 40 years.
- Consumption of which of the following has been recently identified as a risk factor for gout?
 - Low-fat dairy products
 - Beer and liquor
 - Fructose-sweetened soft drinks
 - Purine-rich meats
- Which test result confirms the diagnosis of acute gout?
 - An elevated serum uric acid level greater than 6.8 mg/dL
 - A 24-hour urine uric acid level less than 800 mg
 - Synovial fluid WBC count greater than 10,000/ μ L
 - Synovial fluid analysis demonstrating negatively birefringent monosodium urate crystals
- Which of the following drugs should be used cautiously in elderly individuals because of the potential for cumulative toxicity?
 - Non-steroidal anti-inflammatory drugs
 - Oral colchicine
 - Oral corticosteroids
 - Parenteral colchicine
 - Intra-articular corticosteroids
- Which of the following is NOT an indication for urate-lowering therapy?
 - >3 acute gouty attacks in a 12-month period
 - Serum uric acid level >11 mg/dL
 - 24-hour urinary excretion <1000 mg
 - Creatinine clearance of <60 mL/min

Answers: 1. A, 2. C, 3. D, 4. B, 5. C

Members: To complete the quiz, see instructions for AAFP members at right.

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