Clinical Practice Guideline

Gout

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Abbreviations

ACP	American College of Physicians
ACR	America College of Rheumatology
ACTH	Adrenocorticotropic hormone
AHRQ	Agency for Healthcare Research and Quality
CBC	Complete blood count
CKD	Chronic kidney disease
CRP	C-reactive protein
CT	Computed tomography
DECT	Dual energy computed tomography
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
GI	Gastrointestinal
IM	Intramuscular
IV	Intravenous
MSU	Monosodium urate
MTP	Metatarsophalangeal
NSAIDs	Nonsteroidal anti-inflammatory drugs
RA	Rheumatoid arthritis
SUA	Serum uric acid
ULT	Urate-lowering therapy
US	United States

Introduction

Gout is both an acute and chronic, progressive inflammatory arthritis caused by the deposition of monosodium urate (MSU) crystals in and around joints, soft tissues, cartilage, and kidneys. It usually presents with recurrent episodes (also known as flares) of severe pain, swelling, tenderness and, in some cases, erythema of a lower-extremity joint. Early on, the first metatarsophalangeal (MTP) joint is commonly involved, but the ankle and/or knee can be affected as well. Initially, the painful flares are usually short in duration, lasting 5 to 7 days. As the disease progresses, flares may last for more than 14 days, and the pain-free interval between flares becomes shorter.[1] Synovial hypertrophy, synovitis, and bone and cartilage destruction occur over time.

The prevalence of gout has been increasing in the United States (US) for at least the past 50 years. In 1975, it was estimated that 2.6 in 1000 people suffered from gout; by 2007, the prevalence had almost doubled to 4.7 in 1000 people,[2] which is equivalent to 3.9% of the US population or 8.3 million people. The disease occurs more frequently in men (6.1 million) than in women (2.2 million)[3] and often begins between the ages of 40 and 60 years in men and after the age 60 years in women.

Gout usually occurs when serum uric acid (SUA) levels exceed 6.8 mg/dL (hyperuricemia), but only one in five people with hyperuricemia will develop gout. In 2008, hyperuricemia was estimated to occur in approximately 43.3 million people in the US.[4] Gout is one of several disorders known as crystal deposition diseases which include calcium pyrophosphate dihydrate crystal deposition disease (pseudogout) and hydroxyapatite (basic calcium) crystal deposition disease.

If not properly treated, patients with gout can develop tophi, which are nodular masses of MSU crystals in the soft tissues. The development of tophi is related to both the duration of hyperuricemia and the level of SUA. Tophi can occur anywhere but are most commonly seen in olecranon bursae of the elbow, finger tips, wrists, knees (including the patella bursae), and around the first metatarsal phalangeal joint and Achilles' tendon. Tophi can also develop in the cartilage of the ear, vocal cords, nose, and around the spine. Tophi are not always palpable.

Some gout patients develop uric acid or calcium oxalate renal stones. In severe cases, gouty nephropathy can develop secondary to deposition of urate crystals in the renal interstitium,[5] which may lead to renal failure.

Gout is the most common form of inflammatory arthritis in the US. It negatively impacts the quality of life of patients. Acute gout flares and chronic inflammatory arthritis result in absenteeism from work, decreased productivity, and increased hospitalizations. A 2013 article by Wertheimer et al.[6] indicates that employees with gout miss approximately 5 days more of work per year than those without the disorder. In this study, the average cost of care for patients with gout exceeded $3000.

The economic burden of gout for employers (annual health benefit costs for medical and drug claims, sick leave, short- and long-term disability, and workmen's compensation) was studied in 300 000 employees, 1171 of whom were identified as having gout. The annual employer cost for an employee with gout was

approximately $6870 between 2001 and 2004; the employer costs for those without gout averaged $3705 during the same time period. Interestingly, only 0.9% of the employees with gout were responsible for 20% of the gout-specific costs.[7]

Li et al.[8] reported that, between 2002 and 2008, there were more than 50 million (7.2 million annually) ambulatory visits for gout, with visits in 2008 more than double those in 2002. Most of the visits were to primary care physicians' offices. It was also estimated that the combined annual cost of caring for patients with gout was close to $1 billion, with drug costs accounting for 61% of the total. According to Garg et al.,[9] visits to emergency rooms for gout-related problems were estimated to cost between $128 and $166 million between 2006 and 2008. This cost represented 0.7% of all emergency room visits with a primary or secondary diagnosis of gout.

In June 2016, Lim et al.[10] published a study of 254 982 hospitalizations for gout-related problems taking place between 1993 and 2011 and compared them to 323 649 hospitalizations for patients with rheumatoid arthritis (RA). They reported that the annual hospitalization rate for RA decreased from 13.9 to 4.6 per 100 000 US adults (an overall decrease of 67%) while the hospitalization rate for those with gout increased from 4.4 to 8.8 (a 100% increase) per 100 000 US adults. Hospitalizations for joint replacement fell from 8.4 to 2.1 per 100 000 people in the US overall; but for patients with gout, joint replacements rose from 0.096 to 0.17 per 100 000 people. The costs of hospitalization for patients with gout rose from $34 457 in 1993 to $58 003 in 2011, while the cost of hospitalizations for RA fell from $84 350 in 1993 to $55 988 in 2011. The increased costs for caring for patients with gout was attributed to the increased prevalence of gout, combined with suboptimal care. Some of the decreased cost of hospitalization for patients with RA could be related to earlier diagnosis and treatment with more effective pharmacologic agents.

Gout is often first diagnosed and treated by primary care professionals. Several studies have documented a high rate of missed or wrong diagnoses, inadequate treatment, and failure to reach the target SUA level of $\leq$6 in patients with gout treated by primary care professionals.[10-14]

Gout is associated with many comorbidities including but not limited to:

- Hypertension not related to traditional risk factors[15]
- Hyperlipidemia
- Type 2 diabetes[16]
- Metabolic syndrome[17]
- Chronic kidney disease (CKD)
- Cardiovascular disease, including coronary artery disease, transient ischemic attacks, stroke, and angina[18]
- Obesity with a body mass index $\geq$30 kg/m^2 [19]
- Medications including but not limited to
    - Thiazide and loop diuretics
    - Low-dose aspirin
    - Niacin

- Cyclosporine and other calcineurin inhibitors
- Antiretroviral drugs
- Anti-tuberculosis medications such as ethambutol, pyrazinamide

Primary care professionals treat many of these comorbidities and should be aware of the associations between these comorbidities and gout in at-risk patients. If the diagnosis of gout is established early, treatment is more effective, and later disability may be limited or averted.

Stages of Gout

There are three stages of gout:[5]

- Asymptomatic hyperuricemia
- Acute intermittent gout
- Advanced gout

Asymptomatic Hyperuricemia

This is the earliest detectable stage of the disorder. It is characterized by elevated SUA levels (>6.8 mg/dL) with urate crystals accumulating in joints, articular cartilage, and the soft tissues around the joints. At this stage, patients do not complain of pain. If the clinical situation continues untreated, painful flares and, eventually, cartilage and bone destruction may develop. The duration of asymptomatic hyperuricemia is quite variable ranging from a few years to a few decades.[5]

Acute Intermittent Gout

Acute intermittent gout is characterized by recurrent acute gout flares. The first flare is usually, but not always, limited to one joint in the lower extremities. The attack may be accompanied by a low-grade fever, chills, and malaise. Leukocytosis, elevated erythrocyte sedimentation rate and elevated C-reactive protein may also occur. Most of the early flares last for 5 to 7 days and gradually resolve. The primary clinical characteristics of a gout flare include a very rapid onset of severe pain, associated with intense erythema and the inability to use the affected joint or limb. During an acute flare, SUA may drop by as much as 1 mg/dL to 2 mg/dL from baseline due to the uricosuric effect of the pro-inflammatory cytokine IL-6. Between acute flares, the patient is asymptomatic. Over time, the interval between attacks decreases and duration increases. An acute flare can last for more than 2 weeks. If SUA levels are not controlled during this stage, tophi may begin to develop. Initially, tophi are small and not detected on clinical examination. However, even at this stage, they can cause bone destruction. Small non-palpable tophi may be detected by ultrasound.[5]

Acute flares of gouty arthritis can be triggered by trauma, dietary indiscretion, dehydration, alcohol use, congestive heart failure, deep venous thrombosis, and anything that causes a fluctuation in SUA levels.[5]

Advanced Gout

If left untreated or under-treated, the acute intermittent phase of gout progresses to advanced gout. During this stage, there are no pain-free intervals. Chronic progressive arthritis with synovial hypertrophy, bone destruction, and deformity; and stiff, swollen, and painful joints develop. During this stage, upper-extremity joint symptoms become more prevalent. In patients with nodal osteoarthritis, tophi have a tendency to develop in Heberden's and Bouchard's nodes.[5]

The causes of gout are complex and probably related to a combination of genetic, hormonal, metabolic, pharmacologic, and dietary issues as well as the comorbidities listed above—particularly, renal disease.[20] Approximately 20% of patients with gout have a family history of the disorder. Multiple genes are associated with a familial risk of gout. Some of these genes are associated with increased uric acid production; others are associated with diminished excretion of uric acid by the kidneys.[21] The most common heritable cause of hyperuricemia is diminished excretion of urate by the kidneys.

In addition to these genetic factors, other reasons for hyperuricemia include the following:[5]

- High ingestion of
  - Alcohol, particularly of beer
  - Red meat and shellfish, anchovies, and sardines
  - High-fructose corn syrup found in energy drinks/bars and soft drinks
- Disorders associated with high cell turnover
  - Psoriasis
  - Paget's disease of bone
  - Myeloproliferative disorders
  - Tumor lysis syndrome
- Medications that may cause decreased renal excretion of uric acid
  - Thiazides or other loop diuretics
  - Low-dose aspirin
  - Niacin
  - Cyclosporine and other calcineurin inhibitors
  - Antiretroviral drugs
  - Anti-tuberculosis medications such as ethambutol and pyrazinamide
  - Chemotherapy

Gout is also commonly seen in heart-, renal-, and liver-transplant patients who have been treated with cyclosporine and other calcineurin inhibitors. In these patients, gout progresses quickly from asymptomatic hyperuricemia to advanced gout.[5]

Diagnosis

An acute single episode of gout can be confused with other inflammatory arthritides, septic arthritis, pseudogout, trauma, and cellulitis.

In 2015, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) published new gout classification criteria.[22] These classification criteria should only be used for patients who have been symptomatic at some time. The classification criteria are divided into eight domains:

1. Pattern of joint or bursal involvement
2. Characteristics of flares
3. Time course of flare
4. Presence or absence and location of tophi
5. SUA level
6. Synovial fluid analysis
7. Imaging evidence of urate crystal deposition
8. Imaging evidence of joint damage related to gout

According to the classification criteria, for gout to be considered in the differential diagnosis, a patient must have had at least one episode of peripheral joint or bursal pain, swelling, or tenderness. If a patient has an acute flare (acute attack of pain, erythema, or joint swelling) and joint aspiration reveals MSU crystals in the fluid or a tophus is identified then a definitive diagnosis of gout can be established.

Although the finding of MSU crystals in synovial fluid is considered the gold standard for the diagnosis of gout, it is performed in less than 10% of the patients. The procedure can be challenging, and patients may refuse to undergo the procedure because of existing joint pain and tenderness. If the differential diagnosis includes a septic joint then aspiration is very strongly encouraged. Ultrasound guidance facilitates the aspiration by allowing the provider to see the position of the aspirating needle in real-time, decreasing the time and discomfort associated with the procedure.

The 2015 Classification Criteria have a sensitivity of 0.92 and specificity or 0.89 for the diagnosis of gout when all domains are scored. Using these criteria and scoring system, the healthcare professional can classify a patient as having gout without joint aspiration. The scoring of the criteria becomes more accurate with more domains included in the calculation. If imaging is not done or is not available and synovial fluid analysis is not done, the sensitivity and specificity of the criteria decrease to 0.85 and 0.78, respectively.

The results of imaging, either with ultrasound or dual energy computed tomography (DECT) and plain films are part of the scoring process for gout.[22]

A Web calculator is available at http://goutclassificationcalculator.auckland.ac.nz. A score of eight or more of 23 possible points is sufficient to classify a patient as having gout.

Like all classification criteria, the ACR/EULAR 2015 Gout Classification Criteria were developed and designed to insure some consistency of diagnosis for patients entering clinical trials. Their utility in diagnosing an individual patient is variable. The criteria, however, do tell us important things about the signs and symptoms of gout (Table 1).[22]

Table 1. The 2015 ACR/EULAR classification criteria for gout

Criterion	Category	Points
Entry criterion	Must have at ≥1 episode peripheral joint or bursa pain, swelling, or tenderness	
Sufficient to establish the diagnosis of gout	MSU crystals detected in symptomatic joint or bursa fluid or tophus	
Domains to be used when sufficient criterion is not met		
Pattern of joint or bursa involvement during any symptomatic episode	• Mono- or oligo-articular pain, swelling, or tenderness of the ankle or midfoot not involving the 1st MTP joint • Mono- or oligo-articular pain, swelling, or tenderness of the 1st MTP joint	1 2
Characteristics of symptomatic joint Erythema over symptomatic joint—can be patient reported or provider observed Cannot tolerate any touch or pressure to the affected joint Difficulty walking or inability to use symptomatic joint	• Any 1 characteristic • Any 2 characteristics • Any 3 characteristics	1 2 3
Time course of episode(s) at any time Must have ≥2 of the following symptoms at some time, despite the use of anti-inflammatory treatment: <24 hours to maximum pain <14 days to resolution of symptoms Complete resolution of symptoms or return to baseline symptoms	• 1 typical episode • >1 typical episode	1 2
Clinical evidence of tophus Draining or chalk like subcutaneous nodule under transparent skin located in any of the following: Joints Ears Olecranon bursae Finger tips Tendons	• Present	4

Criterion	Category	Points
Laboratory tests SUA measured by uricase method* (highest level ever) Synovial fluid analysis from (ever) symptomatic joint or bursa†	• <4 mg/dL • >4 to <6 mg/dL • 6 to 8 mg/dL • 8 to <10 mg/dL • >10 mg/dL • Not done • MSU crystals negative	-4 0 2 3 4 0 -2
Imaging Imaging findings of MSU deposition in the symptomatic joint at any time:‡ Ultrasound finding of a double contour sign or DECT demonstrating urate deposition	• Ultrasound or DECT findings present (either modality) • Ultrasound and/or DECT not available or not done • Plain film findings present • Plain films not available or not done	4 0 4 0

*If possible, test when patient is not taking a uric acid-lowering medication and when 4 weeks have passed from the start of a flare; if possible retest under the above conditions. The highest value, regardless of timing, should be scored.

†Must be performed with polarizing microscopy.

‡Plain films of the hands or feet demonstrating at ≥1 erosion (i.e. cortical break with sclerotic margins and overhanging edges excluding distal interphalangeal joints) that is consistent with gout. Plain films are not useful in the early or acute gout attacks and, in those cases, should be performed only if a fracture is suspected.

ACR, American College of Rheumatology; DECT, dual energy computed tomography; EULAR, European League Against Rheumatism; MSU, monosodium urate; MTP, metatarsophalangeal; SUA, serum uric acid.

Imaging for gout is divided into two parts in this classification system:

1. High-resolution ultrasound **or** DECT
2. Conventional radiography

A high-frequency ultrasound transducer (more commonly available than DECT) can demonstrate the presence of urate crystals in synovial fluid. Although not as specific as the evaluation of joint fluid by a polarizing microscope, ultrasound findings are considered to be very reliable. Urate deposits in synovial fluid appear as hyperechoic spots measuring under 1 mm and demonstrating posterior acoustic shadowing. In addition, when light pressure is applied to the joint and released, the urate crystals move which has been described as a “snow storm” appearance.

The most reliable ultrasound sign of gout is the double contour sign. This is seen as a hyperechoic line on the anterior margin of the cartilage (normally iso- or hypo-echoic) separated from the normally seen hyperechoic line along the posterior margin of the cartilage by a thin hypoechoic level. The appearance is the result of urate crystal deposition on the surface of the cartilage. This is the only ultrasound finding currently included in the ACR/EULAR Classification Criteria.[22] Ultrasound also detects urate crystals

floating in synovial fluid, synovial hypertrophy, synovitis, urate crystal deposition on the surface of the cartilage, and bone erosions before they can be seen on plain X-rays.

A recent multi-institutional, international study examined ultrasound findings in 824 patients with at least one swollen joint or a subcutaneous nodule (possible tophus) and a potential diagnosis of gout.[23] All individuals had arthrocentesis or nodule aspiration for the evaluation of MSU crystals, which was considered to be the gold standard for the diagnosis of gout. The group was divided into 416 patients with MSU crystals in synovial fluid and 408 controls with urate crystals neither in synovial fluid nor aspirated from subcutaneous nodules. The study used the US findings described above (snow storm in joint fluid, double contour sign, and the presence of a tophus) as compatible with gout. The authors reported that when one or more of these findings was present, ultrasound had a high specificity for gout and a high positive predictive value, especially in those with a longer history; but even in those with a short history and no evidence of tophi on physical examination, the specificity was high. Most of the patients who were positive for MSU crystals had a least one ultrasound finding compatible with gout. In the control group, 92% of patients had no sonographic findings of gout. Only 23% of the patients with MSU crystals had no sonographic findings of gout.[23]

Although DECT is not yet widely available, it is also a better imaging technique than plain films for the detection of early gout. It can detect tophaceous urate crystal deposition in the soft tissues and bones. This imaging technique can also be used to follow resorption of these deposits during treatment with urate-lowering drugs. DECT has been used for the detection of uric acid renal calculi. The chemical composition of MSU crystals has a specific attenuation coefficient at high- and low-kilo voltage computed tomography (CT). With appropriate software, DECT can reliably distinguish uric acid stones from other renal calculi. Using the same technique, researchers prospectively studied 40 patients with gout and 41 patients with other joint problems to determine the sensitivity and specificity of DECT for the diagnosis of gout.[24] The study included patients with no prior history of gout, patients with symptoms for less than 6 weeks, and patients with a long history of the disease. Patients with clinical evidence of tophaceous gout were excluded. All patients in the study had either an injection or aspiration of a peripheral joint. The aspirated fluid was evaluated by two experienced rheumatologists using a polarizing microscope. A diagnosis of gout was established if either intra- or extracellular MSU crystals were identified. Dual energy computed tomography was performed within 2 weeks of the joint aspiration. Of the original group of patients, ten (three with gout and seven in the control group) did not have a DECT examination. The results demonstrated that DECT had a sensitivity of 0.90 and a specificity of 0.83 for the diagnosis of gout. There were four false-negative cases in the gout group, and all of these patients had experienced symptoms for less than 6 weeks. In the control group with negative synovial fluid analysis, DECT found evidence of intra-articular MSU crystals in seven patients, all of whom had osteoarthritis and MSU crystal deposition in menisci and not in the synovial fluid. The authors also studied another group of 30 patients with nonspecific inflammatory arthritis or tendinitis; 22 of these had negative synovial fluid aspiration for MSU crystals and eight were not candidates for aspiration. In 14 of these patients, DECT identified joints with a suspicion of MSU crystal deposition in or around the joint. Ultrasound-guided aspiration was performed in 12 of these 14 patients and MSU crystals were identified in eleven. Of the 30 patients with inflammatory

arthritis or tendinitis, almost one third were diagnosed with gout. The authors concluded that, in these two studies, DECT demonstrated high accuracy in establishing a diagnosis of gout.[24]

Plain films of symptomatic joints may be useful in establishing the diagnosis of gout or excluding gout. They can be especially helpful when there is concern for a possible fracture, including a stress fracture. The classic conventional radiographic findings occur late in the course of the disease and include bone erosions with overhanging edges and sclerotic margins. Large tophi can also be detected on radiographs.[25]

As mentioned above, the first healthcare professional to see a patient with a possible diagnosis of gout is often a primary care physician. Clinical criteria for diagnosis should be used to assist the primary care physician to determine which patients require referral to a rheumatologist for further work-up, including but not limited to joint aspiration, high-resolution ultrasound and/or DECT.

Patient Assessment

The first step in the evaluation of a patient with proven or suspected gout is a detailed medical history, including but not be limited to the following:[5]

- Family history
- Dietary patterns
- Alcohol consumption
- Medications
- Complete blood count (CBC)
- Physical examination, including blood pressure
- History of hypertension
- Urinalysis
- Laboratory tests, including but not limited to electrolytes, SUA level, renal- and liver-function tests
- Screening for the comorbidities listed above
- Screening for diabetes

During the work-up, it is important to exclude any other condition that may result in the over production or under excretion of uric acid (see list of comorbidities and medications in Introduction).[5]

Treatment

Gout, like RA, should be managed with a treat-to-target paradigm.[26, 27] The target includes the following:

- Ending an acute flare
- Preventing future flares
- Slowing or preventing the formation of tophi and renal calculi
- Preventing joint destruction or stabilizing any bony changes already present
- Serum uric acid level maintained at <6 mg/dL

Serum uric acid level in patients with severe gout (tophi or frequent flares) should be maintained at <5 mg/dL Treatment consists of both nonpharmacologic and pharmacologic management. Any management plan should consider all comorbidities of the patient and include modification of medication doses for the treatment of those medical problems, when appropriate.

Patient Education

Patient education is essential to encourage both lifestyle and dietary changes that can contribute to better disease control. However, it is important for the patient to understand that these changes alone are not sufficient for the management of gout. It is also helpful if the patient understands the disease process and the purpose and importance of pharmacologic therapy.

Early on in the course of the disease; particularly in asymptomatic hyperuricemia, weight loss, a diet high in vegetables, nuts, and whole-grain foods, and avoidance of foods with a high sugar content (especially high-fructose corn syrup) can be very helpful. Alcohol consumption should be limited and patients encouraged to drink enough water to avoid dehydration. For patients with hypertension treated with either thiazides or loop diuretics consideration should be given to changing these medications after consultation with the healthcare professional monitoring the patient's blood pressure. Healthcare professionals should also consider stopping or changing any other prescription medications that are associated with increased SUA levels. Regular exercise, when possible, should be encouraged for all patients with gout.[5, 19, 28, 29]

Laboratory Evaluation

Prior to initiation of pharmacologic management, the following laboratory assessments should be ordered:

- Electrolytes
- CBC
- Renal function tests
- Liver function tests
- SUA level
- HLA-B58*01 in patients of southeast Asian descent (positive in 6% to 12% of the population)

Pharmacologic Management

Gout can be thought of as both an acute and a chronic disorder that requires long-term treatment and monitoring. If acute flares are not managed properly and the SUA level is not controlled, the disease can ultimately result in severe disabling joint destruction and renal failure.

Treatment of gout has two major goals:

1. Elimination of the pain of an acute attack and resolution of the attack
2. Prevention of disease progression by lowering the SUA level to ≤6 mg/dL, which, over time, prevents most acute flares, increases the resorption of tophi, and decreases and/or slows the progression of joint destruction.[5] In patients with advanced disease, it may be necessary to lower the SUA level to <5 mg/dL to improve the flares and resorb tophi.

Management of Acute Gout

The treatment target for an acute flare includes both the elimination of pain and the termination of the attack as quickly as possible.[5] Early initiation of treatment is associated with better patient-reported outcomes.[30] According to the ACR, an acute attack of gouty arthritis should ideally be treated within 24 hours of the onset of symptoms. Any previously prescribed urate-lowering drug therapy should be maintained.

Initial treatment of acute gout begins with either oral nonsteroidal anti-inflammatory drugs (NSAIDs), oral or intramuscular (IM) steroids, or colchicine (if started within 36 hours of the attack) (Table 2). Therapy should be adjusted, based on the intensity of the attack and the number of joints involved. If only one or two large joints or several small joints are involved; monotherapy with either oral NSAIDs, steroids, or colchicine is appropriate. Combination therapy consisting of NSAIDs and colchicine, or steroids and colchicine, or intra-articular or IM steroids and NSAIDs or colchicine can be considered for patients with severe pain and involvement of one or two large joints or for those with an inadequate response to monotherapy.[30] Healthcare professionals should be aware of contraindications to all of the medication mentioned above.

When colchicine is used for an acute attack, an initial dose of 1.2 mg is given as soon as possible, followed an hour later by an additional 0.6 mg. Colchicine should be continued at a dose of 0.6 mg once or twice a day, 24 hours after the second acute dose for 7 to 10 days or until the flare has resolved. (It is inappropriate to repeat colchicine every hour until the pain has resolved). The dose of colchicine should be adjusted, if appropriate, based on the patient's other medical problems.[19, 30]

If NSAIDs are chosen as the initial drug to treat an acute flare, the ACR recommends that they be used at the full dose approved by the Food and Drug Administration (FDA) for anti-inflammatory and/or analgesic effects until the attack resolves. Currently naproxen, indomethacin, and sulindac are FDA approved for the treatment of acute gout; however, any NSAID can be used for the management of an acute flare. Healthcare professionals should appropriately adjust the NSAID dose for each patient, depending on comorbidities.[30]

Aspirin or salicylates should not be used, because they may increase the SUA level.

Another choice for the treatment of an acute gout flare is oral steroids, usually prednisone or prednisolone at a dose of 0.5 mg/kg/day. A methylprednisolone dose-pack may also be used.[30] Steroids may also be administered intramuscularly or subcutaneously as follows:[5]

- Triamcinolone (or equivalent) 60 mg IM for a single dose
  OR
- Methylprednisolone (or equivalent) 100 mg to 150 mg intravenous (IV) initially, followed by 50 mg to 75 mg orally twice daily for several days

Intra-articular injections may also be used. The dose should be adjusted according to the size of the joint and, in addition, NSAIDs, oral steroids, or colchicine should be used. Examples of appropriate doses for intra-articular steroids in different joints are as follows:[5]

- 40 mg triamcinolone acetonide (or equivalent) for a large joint such as the knee
- 20 mg triamcinolone acetonide (or equivalent) for a medium-sized joint such as ankle, wrist, or elbow
- 10 mg triamcinolone acetonide (or equivalent) for small joints such as the first MTP joint

All glucocorticoid doses should be adjusted as appropriate for individual patients. Icing the joint may be helpful as an additional strategy for reducing pain.

Intra-articular injections are contraindicated if there is any suspicion of joint infection.

Healthcare professionals must be aware of the contraindications and toxicities associated with the drugs mentioned above as well as a patient's comorbidities, which may require dose modification. It may be necessary to avoid or modify the dose of colchicine in patients with chronic renal disease.

If a short course of steroids is used to control an acute flare there is a risk of a rebound flare. Whenever possible, low-dose colchicine should be given with steroids during an acute flare.[5]

Some patients do not adequately respond to these regimens. For those who fail to quickly respond to standard monotherapy for an acute flare, a different monotherapy or combination therapy should be tried—for severe and recalcitrant cases, IL-1 inhibitors (anakinra 100 mg subcutaneously daily for 3 days or canakinumab 150 mg subcutaneously one time) or adrenocorticotropic hormone (ACTH)-gel 80 IU subcutaneously. These three treatments are considered to be off-label uses.

For hospitalized patients who are nothing by mouth, medications for an acute gout flare can be given intravenously or intramuscularly.

Urate-lowering Therapy (ULT)

Urate-lowering therapy should be considered during the first gout flare. Indications for initiating therapy to lower SUA levels are the following:

- History of any gout flare
- Advanced gouty arthritis
- Tophi detected by clinical exam or by imaging (X-ray, ultrasound, or CT)
- Gout with chronic renal disease
- Gout with a major organ transplant
- Nephrolithiasis
- Overproduction of uric acid

Prior to initiating ULT, patients should be started on anti-inflammatory prophylaxis, which should be continued for at least 6 months. Prophylactic drugs include oral colchicine (0.6 mg orally either once or twice a day) and low-dose NSAIDs with gastrointestinal protective agents.[30] Healthcare professionals should adjust the dose of each medication, based on an individual's comorbidities such as impaired renal function.

The consensus of the ACR Task Force was that the use of combination therapy (colchicine plus low-dose NSAIDs) did not prevent all gout flares after the initiation of ULT.[30] If combination therapy with colchicine and NSAIDs is either ineffective or contraindicated, daily prednisone or prednisolone at a dose under 10 mg/day (or equivalent) should be considered. In view of the long-term complications of steroid use, doses exceeding 10 mg/day of prednisone (or equivalent) were considered to be inappropriate by the ACR.[30]

If there are no signs or symptoms of gout while on ULT, anti-inflammatory prophylaxis (Table 2) should be given:[5, 30]

- For at least 3 to 6 months after the last gout flare
  OR
- For 3 months after the patient achieves an acceptable SUA level and has no detectable tophi on examination
  OR
- For 6 months after the patient achieves an acceptable SUA level and at least one tophus is found on physical examination

Xanthine oxidase inhibitors such as allopurinol or febuxostat are the initial drugs of choice for ULT (Table 3). Allopurinol is started at $\leq$100 mg/day, unless the patient has Stage 4 CKD or worse, in which case the dose should be decreased to 50 mg/day. In patients without moderate or severe renal disease, allopurinol may be increased by 100 mg every 2 to 4 weeks up to a maximum dose of 800 mg/day or until the desired SUA level is achieved. In patients with Stage 4 or 5 CKD, dose escalation should be slower and in increments of no more than 50 mg at a time.[19]

Allopurinol hypersensitivity syndrome occurs in about 1 in 1000 people in the US and is manifested by Stevens-Johnson syndrome or toxic epidermal necrolysis as well as eosinophilia, leukocytosis, fever, vasculitis, rash, or acute hepatic toxicity with elevated liver function tests. The reported mortality rate between 20% and 25%.[31] Patients who are genetically at risk for allopurinol hypersensitivity reactions include patients of south-east Asian descent. These patients may be tested for HLA-B58*01. A positive test indicates that allopurinol should not be used.[29]

If febuxostat is chosen as the initial urate-lowering drug, it is started at 20 mg to 40 mg daily and increased slowly to 80 mg daily if the target SUA level is not achieved after treatment for 2 weeks or longer.

Allopurinol and febuxostat should not be used in combination!

After starting ULT with either allopurinol or febuxostat, liver- and renal-function tests, SUA levels, and CBC should be monitored at 2- to 4-week intervals to screen for drug toxicity. These blood tests should be repeated every 2 to 4 weeks after any dose escalation.[19]

If allopurinol and febuxostat are contraindicated or not tolerated then probenecid, a uricosuric agent, can be used as monotherapy. However, it is generally ineffective in patients with creatinine clearances of less than 50 mL/min. Because of gastrointestinal (GI) intolerance, probenecid is usually initiated at a dose of 250 mg twice daily and gradually increased up to a maximum dose of 3000 mg daily given in 2 or 3 divided doses.

A combination of a uricosuric agent and a xanthine oxidase inhibitor can be used if monotherapy with a xanthine oxidase inhibitor alone has not achieved the targeted serum urate level. In this case, either probenecid or lesinurad can be used. Lesinurad is only used in combination with a xanthine oxidase inhibitor and dosed at 200 mg daily. Other weak uricosuric agents such as losartan, fenofibrate, or vitamin C can be added to either mono or combination ULT to help achieve the target serum urate level.[20] The use of these weak uricosuric agents for urate lowering is off-label and should only be used if otherwise medically indicated.

In patients refractory to xanthine oxidase inhibitors or uricosuric agents, or who have not achieved the target SUA level (5 mg/dL to 6 mg/dL), pegloticase can be used every 2 weeks at a dose of 8 mg per infusion. In addition, in patients with a large tophaceous burden or severely advanced or debilitating disease, pegloticase can be used as induction therapy. Treatment with pegloticase can last for 3 to 4 months to achieve control. Then, the patient may be switched to more standard ULT. Because there is a significant incidence of infusion and anaphylactic reactions, this drug should only be administered in an infusion center under the supervision of an appropriately trained healthcare professional. Serum uric acid levels should be measured prior to any infusion, because diminished uric acid-lowering ability of pegloticase is predictive of an infusion reaction.[5, 19, 29]

Urate-lowering therapy should be continued indefinitely when the target SUA level has been achieved, even if all tophi have been resorbed and no clinical symptoms persist. There is no recommendation for the duration of pegloticase administration.[29]

When the correct dose and type of medication has been established then SUA levels should be monitored every 6 to 12 months. Patients whose ULT includes a uricosuric agent should be continually monitored for urinary uric acid levels.[29]

Urate-lowering therapy should not be stopped or adjusted during an acute flare.

Table 2. Anti-inflammatory medications for use in acute gout flares and for prophylaxis when initiating ULT

Acute Gout Flare		
Anti-inflammatory Medications	**Dose**	**AEs or Contraindications**
NSAIDs (any NSAID may be used) Naproxen Indomethacin Ibuprofen Sulindac Diclofenac	• Maximum recommended dose to start (e.g., naproxen 500 mg twice daily for the first 3 days), then taper over next 4 to 5 days • Use with GI protective agent (proton pump inhibitor) – especially for prolonged use	• Dyspepsia, peptic ulcer disease, and GI bleeding • Increased risk for o MI, stroke o Impaired renal function • Contraindications o Class 3 to 5 CKD o Anticoagulant therapy
Colchicine (Colcrys® or Colbenemid)	• 1.2 mg as soon as possible; followed, one hour later, by 0.6 mg; and continued at a dose of 0.6 mg once or twice daily for 7 to 10 days or until flare has resolved	• Abdominal cramping, nausea, vomiting, and diarrhea • Bone marrow depression • Myopathy and neuropathy with prolonged use
NSAID plus colchicine	• Low-dose combinations of both NSAID and colchicine	• Combination therapy may allow patients intolerant to the full dose of either medication to achieve adequate anti-inflammatory response
Steroids **Oral Steroids** Prednisone Prednisolone Methylprednisolone dose pack **Intravenous or Intramuscular Steroids** Triamcinolone (or equivalent) Methylprednisolone (or equivalent) **Intra-articular Steroids** Triamcinolone (or equivalent)	• 0.5 mg/kg/day • 60 mg IM for a single dose • 100 to 150 mg IV initially, followed by 50 to 75 mg orally, twice daily, for several days • 40 mg for the knee • 20 mg for ankle, wrist, or elbow • 10 mg for small joints	• Weight gain • Increased risk of infections • High blood sugar • Increased BP • Bone loss or osteoporosis • Fluid retention with swelling of lower legs • Thinning of the skin • In addition to the adverse events mentioned above, parenteral steroids can be associated with o Insomnia o Facial flushing

Prophylaxis for Urate-lowering Therapy (ULT) (see text for duration of anti-inflammatory prophylaxis)		
Anti-inflammatory Medications	**Dose**	**AEs or Contraindications**
Low-dose NSAIDs and/or Low-dose Colchicine	• Use with GI protective agents	• Dyspepsia, peptic ulcer disease, and GI bleeding • Increased risk for o MI, stroke o Renal impairment
Oral Steroids (use only if both colchicine and NSAIDs are not effective) Prednisone (or equivalent) Prednisolone (or equivalent)	• <10 mg orally, as needed • Use with GI protective agents	• Weight gain • Increased risk of infections • High blood sugar • Increased BP • Bone loss or osteoporosis • Fluid retention with swelling of lower legs • Thinning of the skin

AEs, adverse events; BP, blood pressure; GI, gastrointestinal; IM, intramuscularly; IV, intravenously; MI, myocardial infarction; NSAIDs, nonsteroidal anti-inflammatory drugs

Table 3. Drugs and doses used for urate-lowering therapy (ULT)

Drug	Dose	AEs or Contraindications
Xanthine Oxidase Inhibitor		
Allopurinol (Zyloprim®)	• <100 mg/day • For patients with chronic renal disease, 50 mg/day • Dose escalation up to 800 mg/day can be tried until desired SUA levels are achieved	• Prior history of hypersensitivity reaction to allopurinol or known positive HLA-B58*01 • Headaches, drowsiness, diarrhea, vomiting and GI discomfort • Swelling of the mouth and lips, rash, eye irritation, hepatitis, hematuria, dysuria, jaundice, easy bruising, ecchymosis, decreased urine output
Febuxostat (Uloric®)	• 20 to 40 mg/day • May be escalated up to 80 mg/day if desired SUA level is not achieved after at least 2 weeks of therapy	• MI, abnormal LFTs, weakness or numbness of the arms or legs, hives, swelling of the face, lips or tongue, difficulty breathing, skin rash • Should not be used with azathioprine or mercaptopurine • There is a higher risk of CV mortality with febuxostat compared to allopurinol
Uricosuric Agents		
Probenecid (Benemid®)	• 250 mg twice daily • With escalation of dose up to a maximum of 3 grams/day given in divided doses • May be used in combination with allopurinol	• Must have normal renal function and normal urine uric acid levels • Follow-up urinary uric acid should be obtained • History of renal calculi and blood dyscrasias
Colbenemid (combination of 0.5 mg colchicine and 500 mg probenecid)	• 1 tablet, orally, for 1 week, then 1 tablet, orally, twice daily	• Avoid grapefruit or grapefruit juice
Lesinurad (Zurampic®)	• 200 mg/day in combination with a xanthine oxidase inhibitor	• Should only be used in combination with a xanthine oxidase inhibitor • Causes a reversible elevation of serum creatinine to >1.5 times baseline in 5 to 6% of patients
Fenofibrate* (Tricor®, Lofibra®, Lipidil® Supra)	• May be helpful in doses >200 mg/day, especially in patients who also have dyslipidemia	• Use in gout is off label • Contraindicated in patients with Stage 3 or worse renal disease

Drug	Dose	AEs or Contraindications
Uricosuric Agents		
Losartan* (Cozaar®)	• Maximum dose is 50 mg/day	• Use in gout is off label • Uricosuric effect may be transitory • Use appropriate medical monitoring
Biologic		
Pegloticase (Krystexxa®)	• 8 mg administered IV every 2 weeks	• Allergy-like infusion reactions o Chest discomfort o Vomiting o Flushing o Dyspnea o Erythema o Sweating o Back or flank pain o Change in BP o Congestive heart failure • Prior anaphylactic reaction to pegloticase
Combination Drug Xanthine Oxidase Inhibitor + Uricosuric Agent		
Duzallo® (combination of allopurinol and lesinurad) 300 mg allopurinol + 200 mg lesinurad 200 mg allopurinol + 200 mg lesinurad	• For either combination. 1 tablet orally, on demand	• Known allergy to allopurinol • Do not start if creatinine clearance is <30 to 45 mL/min • May cause a reversible elevation of serum creatinine to >1.5 times baseline in 5 to 6% of patients

*Not FDA-approved as urate-lowering treatment in gout

AEs, adverse events; BP, blood pressure; GI, gastrointestinal; IM, intramuscularly; IV, intravenously; MI, myocardial infarction; LFTs, liver function tests; SUA, serum uric acid

A Note about the American College of Physicians Gout Management Guidelines

In 2016, the America College of Physicians (ACP) published its guidelines for the diagnosis and management of gout in two manuscripts:

- Diagnosis of acute gout: a clinical practice guideline from the American College of Physicians.[32]
- Management of acute and recurrent gout: a clinical practice guideline from the American College of Physicians.[33]

These guidelines are based on a requested systematic review of the literature by the Agency for Healthcare Research and Quality (AHRQ), through its evidence-based practice centers which were released in draft form in May 2015. The data source was Medline, EMBASE, the Cochrane Collection, and the Web of Science with articles published between January 1, 2010 and April 28, 2014. The conclusions of the AHRQ were:[34]

> Effective treatments for acute gout include colchicine, NSAIDs, and corticosteroids/animal-derived ACTH formulation. Urate-lowering therapy achieves its goal of lowering serum urate levels. Urate lowering should lead to a reduction in gout attacks, but that has yet to be directly demonstrated, because initiation of urate-lowering-therapy is itself a risk factor for gout flare (attack). Patient preferences and other clinical circumstances are likely to be important in decisions about treating patients with gout (Page vii).

In the ACP guideline publication on the diagnosis of acute gout, the sole recommendation was "… that clinicians use synovial fluid analysis when clinical judgement indicates that diagnostic testing is necessary in patients with possible acute gout" (Page 54).[32] This was graded as a weak recommendation with low-quality evidence.

This guideline is a fairly innocuous document with little new or surprising content intended to support the general approach of primary care physicians to not perform arthrocentesis. It does not give guidance to primary care physicians relating to which clinical circumstances would justify performing a synovial fluid analysis for crystals or even for referring patients to specialists for such testing.

Similarly, in the ACP's second gout guideline publication,[33] there were four very bland treatment recommendations, including: (1) corticosteroids, NSAIDs, or colchicine to treat acute gout; (2) if colchicine is used to treat acute gout, low-dose regimens are recommended, because they is as "effective as higher doses … at reducing pain and are associated with fewer gastrointestinal adverse events" (Page 63); (3) against long-term ULT in most patients after a first gout attack or in patients with infrequent attacks; and (4) for clinicians to discuss benefits, harm costs, and individual preferences with patients with gout before initiating ULT, including concomitant prophylaxis, in those patients with recurrent gout.

Controversial information of the ACP Gout Treatment Guideline was included in that same article under the heading *Areas of Inconclusive Evidence* and involved treatment strategies for patients with gout receiving ULT. In this section the authors state:[33]

> *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 therapy 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"* (Page 65).

There are no specific recommendations on how to facilitate the treat-to-avoid-symptoms strategy. It offers no guidance on the strength or duration on ULT; however, it clearly states that serum urate levels should not be monitored in patients taking these medications. These recommendations run counter to all other published gout treatment guidelines produced by other American and international medical professional groups. The ACP gout treatment guideline ignores known scientific underpinnings of the disease process; long-term follow-up trial data with ULT that clearly show regression of flare frequency, reduced use of NSAIDs, colchicine, and corticosteroids with monitored urate levels; and the recommendations of experts on its own guideline writing committee. For these reasons, and because they are simply a reversion to the typical under treatment that has epitomized gout therapy for decades, gout specialists from around the world have chosen to ignore this set of ACP guidelines.

United Rheumatology does not support the ACP guidelines for the diagnosis and management of gout.

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