A Specialty Networks Company

CLINICAL PRACTICE GUIDELINE

Gout

Version 1.1.2023
February 2023

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Abbreviations

AASCAR	Allopurinol-associated severe cutaneous adverse reaction
ACP	American College of Physicians
ACR	American College of Rheumatology
AHRQ	Agency for Healthcare Research and Quality
CBC	Complete blood count
CKD	Chronic kidney disease
CT	Computed tomography
CV	Cardiovascular
DASH	Dietary Approaches to Stop Hypertension
DECT	Dual energy computed tomography
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
GI	Gastrointestinal
IM	Intramuscular
IV	Intravenous
MACE	Major adverse cardiovascular event
MI	Myocardial infarction
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 the 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.

Gout is one of several disorders known as crystal deposition diseases. In addition to gout, these disorders include calcium pyrophosphate dihydrate crystal deposition disease (pseudogout) and hydroxyapatite (basic calcium) crystal deposition disease.

The prevalence of gout in the United States (US) was thought to be increasing up until 2007. A 1975 report 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. Two papers published in 2019 based on the National Health and Nutrition Survey from 2007 to 2008 and 2015 to 2016, demonstrated that the prevalence of gout did not significantly change between these two study intervals.[3, 4] The authors used slightly different definitions of elevated serum urate but concluded that the prevalence of gout was essentially unchanged between 2007 and 2016. In both studies the prevalence of gout was 3.9%.

Gout occurs more frequently in men[5] and often begins between the ages of 40 and 60. In women, gout usually begins to appear after the age of 60. A recent study[6] conducted in a single county in Minnesota, compared the incidence of gout from 1989 to 1992 to that from 2009 to 2010. The authors found the incidence of this disease to have almost doubled in the 20-year interval between the study groups (with 158 new cases of gout in the first study period and 278 cases during the second study period, resulting in an incidence of 66.6/100,000 in the earlier group and 136.7/100,000 in the second). In addition, the group studied from 2009 to 2010 had more comorbidities than the earlier group. The incidence of high blood pressure increased by 15%, diabetes by 19%, obesity by 19%, kidney disease by 17%, and hyperlipidemia by 40%.

Gout is associated with serum uric acid (SUA) levels at or above 6.8 mg/dL (the saturation point of MSU). In the 2020 American College of Rheumatology (ACR) guidelines for the management of gout[7] it was stated that the target SUA for successful treatment of this disease should be ≤6.0 mg/dL. This is consistent with the 2016 European League Against Rheumatism (EULAR) recommendations for treatment of gout,[8] the 3Es Initiative (Evidence, Expertise, Exchange),[9] and the British Society for Rheumatology which goes even further by suggesting that the target for good control of gout is an SUA of <5 mg/dL.[10] However, the EULAR 2016 guidelines advocate keeping uric acid levels <5 mg/dL for those with severe gout[8] in order to lower the SUA levels more quickly in patients with tophi, frequent flares and chronic arthropathy.[8]

Not everyone with elevated SUA levels develops gout. In 2011, Zhu et al.[11] reported that the prevalence of hyperuricemia in the US was approximately 21.4%.

When the SUA level is reduced to less than the saturation point of MSU (6.8 mg/dL), the crystals slowly resorb from both the joints and soft tissues which can lead to stabilizing bone erosions, increasing resorption of tophi and decreasing the incidence of flares.

If not properly treated (SUA <6 mg/dL), patients with gout can develop urate crystal deposits in joints, bone erosions and/or 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 the olecranon bursae of the elbow, fingertips, wrists, knees (including the patella bursae), and around the 1st MTP joint and Achilles' tendon. Tophi can also be seen in the cartilage of the ear, vocal cords, nose, and around the spine. Tophi are not always palpable; but at times, may be quite large. Tophi can cause bone erosions, joint deformities, and tendon damage. Large tophi can on rare occasion result in ulceration of the skin.[12]

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,[13] which can eventually 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.[14] 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 annually.

The economic burden of gout for employers (annual health benefit costs for medical and drug claims, sick leave, short- and long-term disability, decreased productivity 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.[15]

Li et al.[16] reported that, between 2002 and 2008, there were more than 50 million (7.2 million annually) ambulatory visits for gout in the US, 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.,[17] visits to emergency rooms for gout-related problems were estimated to cost between $128 and $166 million between 2006 and 2008.

A more recent review of the cost of caring for gout patients was published in 2015[18] which concluded that gout patients, especially the elderly and those refractory to treatment, incurred higher direct and indirect costs when compared to individuals without gout. The higher the SUA levels, the greater the number of flares during a year and the greater the cost of care. All-cause direct costs of care were reported as $4733 for employed patients, $16,925 for the elderly and $18,362 for those not responding to treatment.

In June 2016, Lim et al.[19] published a study of 254,982 hospitalizations for gout-related problems 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 incidence of gout and suboptimal care. Some of the decreased cost of hospitalization for patients with RA could be related to earlier diagnosis and treatment with more effective medications.

Gout is often first diagnosed and treated by primary care physicians. Several studies have documented a high rate of missed or wrong diagnoses, inadequate treatment, and failure to reach the target SUA level of □6 in patients with gout treated by primary care providers.[19-23]

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

- Hypertension not related to traditional risk factors[24]
- Hyperlipidemia
- Type 2 diabetes[25]
- Metabolic syndrome[26]
- Chronic kidney disease (CKD)
- Cardiovascular (CV) disease, including coronary artery disease, transient ischemic attacks, stroke, and angina[27]
- Obesity with a body mass index ≥30 kg/m^2 [28]
- 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 providers treat many of these comorbidities and should be aware of the association 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:[13]

- Asymptomatic hyperuricemia
- Acute intermittent gout
- Advanced gout

Asymptomatic Hyperuricemia

This is the earliest detectable stage of gout. 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.[13]

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 (often the 1st MTP joint). The flare 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. An acute gout flare often has 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 shortens and the duration of the flare 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 nonpalpable tophi may be detected by ultrasound.[13]

Acute flares of gouty arthritis can be triggered by trauma, dehydration, alcohol use, congestive heart failure, deep venous thrombosis, and anything else that causes an increase in SUA levels.[13]

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 joint deformity develops along with stiff, swollen, and painful joints. 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.[13]

The causes of gout are complex and probably related to a combination of genetic, hormonal, metabolic, and pharmacologic issues as well as the comorbidities listed above—particularly, renal disease.[29] Approximately 20% of patients with gout have a family history of the disorder. Recently there has been increasing interest in the relationship between gout and genetics.

Multiple genes are associated with the familial risk of gout. Some are associated with increased uric acid production; others are associated with diminished excretion of uric acid by the kidneys.[30] The most common heritable cause of hyperuricemia is diminished excretion of urate by the kidneys. A discussion of these relatively new and complex genetic findings is beyond the scope of this guideline. If the reader is interested in a more in-depth discussion of the genetics of gout, the following papers may be of interest:

> Merriman TR. An update on the genetic architecture of hyperuricemia and gout. *Arthritis Res Ther* 2015;17:98[31]
>
> Major TJ, Dalbeth N, Stahl EA, et al. An update on the genetics of hyperuricaemia and gout. *Nat Rev Rheumatol* 2018;14:341–353[32]
>
> Dalbeth N, Stamp LK, Merriman TR. The genetics of gout: towards personalised medicine? *BMC Med* 2017;15:108[33]

In addition, other causes of hyperuricemia include the following:[13, 34]

- High ingestion of ○ Alcohol, particularly beer
  - ○ High-fructose corn syrup found in energy drinks/bars and soft drinks[35-37]
- 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 loop diuretics ○ Low-dose aspirin ○ Niacin
  - ○ Cyclosporine, tacrolimus 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.[13]

Diagnosis

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

In 2015, ACR and EULAR published new gout classification criteria.[38] 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, in order 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 demonstrating MSU crystals in synovial fluid is considered the gold standard for the diagnosis of gout, it is performed in less than 10% of patients. The procedure can be difficult, 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 joint 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 (see Table 1 below), the healthcare provider can classify a patient as having gout without joint aspiration. The scoring of the criteria becomes more accurate the 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.[38]

A Web calculator is available on the University of Auckland website. 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 ensure some consistency of diagnosis for patients entering clinical trials. Their utility in diagnosing an individual patient is variable. The criteria, however, demonstrate important things about the signs and symptoms of gout (Table 1).[38]

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	**Category**	**Points**

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 including 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
Domains to be used when sufficient criterion is not met	**Category**	**Points**
Clinical evidence of tophus Draining or chalk like subcutaneous nodule under transparent skin located in any of the following: • Joints • Ears • Olecranon bursae • Fingertips • Tendons	• Present	4

Laboratory tests • SUA measured by uricase method* (highest level ever) • Synovial fluid analysis from 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 but not both) • 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 but not both
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 quickly, the urate crystals move which has been described as a “snowstorm” 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 region. 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.[38] Ultrasound can also detect urate crystals floating in synovial fluid, synovial hypertrophy, synovitis, 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.[39] 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 no urate crystals in synovial fluid or aspirated from subcutaneous nodules. The study used the US findings described above (snowstorm 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.[39]

Although DECT is not yet widely available, it is 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. In order to meet the imaging domain in the classification criteria DECT must document urate deposits.

DECT can also be used to follow resorption of urate deposits during treatment with urate-lowering drugs. It has also been used for the detection of uric acid renal calculi. The chemical composition of MSU crystals has specific attenuation coefficients 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.[39] 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 and a diagnosis of gout was established if either intra- or extracellular MSU crystals were identified. DECT 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.[39]

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 gout and include bone erosions with overhanging edges and sclerotic margins. Large tophi can also be detected on radiographs.[40]

Gout patients have an increased incidence of not only arthritis but renal calculi as well. Many of these stones can be identified as uric acid stones and these patients may benefit from an evaluation by a nephrologist.[28]

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

In 2018, EULAR looked at its criteria for the diagnosis of gout again.[41] The task force made the following eight recommendations:

1. Demonstration of MSU crystals in synovial fluid or a tophus is the gold standard for the diagnosis of gout and the presence of either is sufficient to make a definitive diagnosis of gout.
2. Gout should be included in the differential diagnosis of an adult patient presenting with acute monoarticular arthritis. Synovial fluid analysis in these patients is preferred but if it cannot be performed or the patient refuses, a clinical diagnosis of gout should be considered if the patient has: monoarticular arthritis in the foot or ankle; similar complaints in the past; severe pain and swelling which usually reaches its peak in 6 to 12 hours but can take up to 24 hours to reach its peak; redness of the affected joint; male gender and elevated SUA and CV disease.
3. Patients with undiagnosed inflammatory arthritis should have synovial fluid analysis for MSU crystals. If a septic joint is suspected, arthrocentesis is strongly recommended. In addition to looking for MSU crystals, the specimen should be sent for gram stain and culture to rule out infection.
4. If gout is suspected and synovial fluid sampling cannot be done, then imaging (especially ultrasound) can be used to look for MSU crystal deposition or any possible diagnosis other than gout. Ultrasound may demonstrate the so called “double contour sign” documenting the deposit of crystals in the articular cartilage or tophi not found on physical examination
5. X-rays are limited for the diagnosis of a gout flare but could be helpful in the search for MSU crystals in synovial fluid or in the outer articular cartilage. The “double contour sign” which is specific for MSU deposits can sometimes be seen on plain films but should not be confused with chondrocalcinosis (calcifications seen in the cartilage itself). Other X-ray findings in gout include: bone erosions with overhanging edges and a sclerotic rim, bony overgrowth, narrowing of the joint space and soft tissue tophi. The findings detected on X-rays are usually found when a patient has had gout for many years. Early on in the course of the disease X-rays may appear normal. Ultrasound changes can be detected before radiographic changes are seen. For patients with early signs of gout, X-rays should probably not be done. Ultrasound on the other hand may be helpful if the diagnosis is unclear.
6. Elevated SUA alone is not adequate to diagnose gout. Hyperuricemia alone with joint involvement can occur and is insufficient to diagnose gout.
7. Elevated SUA could be related to obesity, chronic renal disease, medications such as some loop diuretics, low dose aspirin, cyclosporine or tacrolimus, consumption of excess alcohol, or foods containing high fructose corn syrup.

8. Once a diagnosis of gout is established, patients should be evaluated for comorbidities such as renal disease, obesity, high blood pressure, diabetes, ischemic cardiac disease and elevated cholesterol.

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:[13, 42]

- Family history of gout
- 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 diabetes
- Determination of burden of disease—palpable tophi, frequency of flares
- Screen for comorbidities ○ Renal disease ○ CV disease ○ Heart failure ○ Stroke ○ Peripheral arterial disease
  ○ Obesity ○
  Hyperlipidemia ○
  Smoking

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).[13]

Treatment

Gout, like RA, should be managed with a treat-to-target paradigm.[42-44] The target should include the following:

- Ending an acute flare
- Preventing future flares
- Slowing or preventing the formation of tophi and renal calculi
- Preventing joint destruction and/or stabilizing any bony changes already present
- SUA level maintained at □6 mg/dL; for those with severe gout, the target SUA should be <5 mg/dL in order to see a more rapid resorption of tophi and urate crystals in the joint.[8]

SUA 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 present and include modification of medication doses for the treatment of those medical problems, when appropriate.[8]

There have been several recent papers which document that the quality of care of patients with gout is suboptimal. It is important to have guidelines for the management of gout and/or asymptomatic hyperuricemia that are easily accessed, read and understood by all healthcare providers regardless of specialty. In the US, more gout patients are treated by primary care providers (internists and family practitioners) than by rheumatologists.[9, 45-47] Comparing the guidelines for the treatment of gout from ACR[7] to guidelines from the American College of Physicians (ACP)[48, 49] demonstrates significant differences in approach and treatment (see following section entitled A Note About the American College of Physicians Gout Management Guidelines).

It is very important that patients understand that it is necessary to adhere to both non-pharmacologic and pharmacologic treatments at the same time in order to get the best results as quickly as possible.

United Rheumatology strongly recommends adherence to its management guidelines for gout which follow.

Patient Education and Non-Pharmacologic Management

Patient education is essential. It is important to encourage lifestyle and diet changes that can contribute to better health. However, it is also important for patients to understand that these changes alone are not sufficient for the management of gout. It is also very important that the patient does not perceive the discussion as "patient blaming".[7]

Obese/overweight patients and those with metabolic syndrome should be encouraged to lose weight. Certain foods may be found to "trigger" flares and should be avoided. Avoidance of these triggers may decrease the incidence of flares but will not stop the progression of gout. Diet modifications may have a minimal effect on lowering SUA.[7, 9] Low-fat dairy products and good hydration should be encouraged.[42] The best approach is to suggest a healthy balanced diet such as the Dietary Approaches to Stop Hypertension (DASH) diet[50, 51] or the Mediterranean diet.[52, 53]

In addition, limiting intake of alcohol, or foods or drinks containing high fructose corn syrup, may be helpful.[7, 9]

For patients with hypertension treated with loop diuretics, a change in medication should be considered in consultation with the healthcare provider monitoring the patient's blood pressure. According to the 2020 ACR guidelines, losartan, if tolerated, is a good alternative anti-hypertensive medication. The ACR guidelines also suggest that low dose aspirin may be appropriate for certain patients. Regular exercise, when possible, should be encouraged for all patients with gout.[7, 13, 28, 42, 54] Healthcare providers should also consider stopping or changing other prescription medications that are associated with increased SUA levels (see above).

Laboratory Evaluation

Prior to initiation of pharmacologic management, the following laboratory assessments should be obtained if not recently performed:

- Electrolytes
- CBC

- Renal function tests, including estimated glomerular filtration rate
- Liver function tests
- SUA level
- HLA-B58*01 in patients of southeast Asian descent (positive in 6% to 12% of the population) and African-American descent (4% to 6% of the population)

Pharmacologic Management

Gout can be thought of as both an acute and 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. Management decisions should always be the result of an in-depth discussion between the patient and the physician. Shared decision making has the possibility of increasing patient buy-in to the program resulting in increased compliance.

Management of Acute Gout Flares (Table 2)

The treatment target for an acute flare includes elimination of pain, termination of the attack as quickly as possible.[13] The earlier treatment is initiated the better patient-reported outcomes.[55] An acute attack of gouty arthritis should ideally be treated within 24 hours of the onset of symptoms or as soon as possible after the onset of symptoms. To ensure early treatment of the flare, a patient should have a supply of the anti-inflammatory medication readily available at his/her house and office (the pill-in-pocket approach). Any previously prescribed urate-lowering therapy (ULT) should be continued during treatment of an acute flare.

Initial treatment of an acute gout flare begins with either oral nonsteroidal anti-inflammatory drugs (NSAIDs), or oral, intravenous (IV), or intramuscular (IM) steroids, and/or colchicine (Table 2). Initially, colchicine should be started at a low dose. Medication dose 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; oral NSAIDs, or steroids, or colchicine may be adequate. Combination therapy consisting of NSAIDs and colchicine, or steroids (oral, IV or IM) and 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.[7, 8, 42, 55] Healthcare providers 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 (2 tablets) 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. It should be continued for 7 to 10 days or until the flare has resolved. (It is **inappropriate to repeat colchicine every hour until the pain has resolved or other "high-dose" colchicine regimens**). The dose of colchicine should be adjusted based on the patient's other comorbidities and medications.[28, 55] Low-dose corticosteroids or NSAIDS can be used in conjunction with colchicine for severe flares. If NSAIDs are chosen as the initial drug to treat an acute flare, the ACR recommends that they be used at the maximum 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. If necessary, a proton pump inhibitor can be used with NSAIDs to protect the stomach.

Aspirin or salicylates should not be used, because they may increase the SUA level, but low dose aspirin can be continued based on comorbidities if needed.

Oral steroids (prednisone or prednisolone) can be used instead of NSAIDs for acute gout flares. They are usually given at a dose of 0.5 mg/kg/day for 5 to 10 days and then stopped, or 0.5 mg/kg/day for 2 to 5 days and tapered over the next 7 to 10 days. A methylprednisolone dose-pack may also be used.[55] For patients unable to take oral medications, intramuscular or subcutaneous or IV administration can be used.[7, 55] Providers may also consider triamcinolone (or equivalent) 60 mg IM for a single dose. Intraarticular injections may also be helpful, and the dose should be adjusted according to the size of the joint. Examples of appropriate doses for intra-articular steroids in different joints are as follows:[13]

- 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 1st MTP joint

All glucocorticoid doses should be adjusted as appropriate for individual patients. Icing the joint may also be helpful to decrease pain.

Healthcare providers must be aware of the contraindications and toxicities associated with the drugs mentioned above and of a patient's comorbidities, which may require dose modification.

If a short course of steroids is used to control an acute flare, there is the possibility of a rebound flare when they are stopped. Whenever possible, low-dose colchicine should be given with steroids during an acute flare.[13]

Anti-inflammatory Prophylaxis (Table 2)

When ULT is initiated, anti-inflammatory prophylaxis should be started 1–2 weeks prior to starting ULT.[7, 13, 55] The prophylaxis should be continued:

- for at least 3 to 6 months after the last gout flare OR
- for 3 months after the patient achieves a target SUA level (□6 mg/dL or <5 mg/dL for severe gout) and has no detectable tophi on examination OR
- for 6 months after the patient achieves a target SUA level (□6 mg/dL or <5 mg/dL for severe gout) and at least one tophus is found on physical examination

OR

- patient continues to have gout flares

Some patients do not adequately respond to these medications. For those with an acute flare who fail to quickly respond to standard therapy with one drug, a different drug or a combination of drugs should be tried—for severe and recalcitrant cases, IL-1 inhibitors (anakinra or canakinumab),[8, 56] may be helpful but providers should be cognizant of the risks of using these drugs. Treatment of gout with IL-1 medications is considered to be an off-label use of these medications.[57] However, there are papers in peer-reviewed journals which have shown that IL-1 inhibitors might be helpful for patients who do not respond to

standard treatment of an acute gout flare.[58-60] A decision to recommend IL-1 drugs should include a discussion with the patient, not only about the medical indications and potential risks, but also the cost.

Urate-lowering Therapy (ULT)

Despite the ACR 2020 gout guidelines recommendation[7] that ULT for an initial gout flare "**is conditionally recommended *against***" (Page 4), United Rheumatology strongly supports the initiation of ULT early, even before a second flare. ULT lowers SUA levels and helps in the resorption of tophi. The indications that should be considered in making a decision to use ULT to lower SUA levels include but are not limited to the following:[8, 9]

- First gout flare especially in those younger than 40 or with SUA levels >8 mg/dL
- Recurrent gout flares
- Gouty arthritis
- Tophi detected by clinical exam or by imaging (X-ray, ultrasound, or CT)
- Urate renal calculi
- Overproduction of uric acid
- Two or more gout flares per year
- Imaging evidence of bone destruction consistent with gout
- ≥1 tophus detected by clinical exam or by imaging (X-ray, ultrasound, or CT)
- For patients with a first gout flare plus an elevated serum urate level or urate renal calculi or stage 3 or higher chronic renal disease, ULT can be considered according to the ACR.

According to the 2020 ACR guidelines for gout,[7] ULT has been shown to have good results in lowering the frequency of flares, decreasing serum urate levels, and reducing the size of tophi.

ULT **should generally not** be considered in patients with asymptomatic hyperuricemia as the incidence of gout in these patients is low according to the ACR and the 3e Initiative.[7, 9] Sustained serum urate levels that are >11–12 mg/dL may justify treatment for patients who have not had gout symptoms because of the high likelihood of gout or nephrolithiasis in the near future.

Allopurinol, a xanthine oxidase inhibitor (see Table 3), is considered to be the drug of choice when starting ULT even in patients with chronic renal disease stage 3 or greater.[7] Allopurinol is started at ≤100 mg per day. It can be increased by 100 mg every 2 to 4 weeks up to a maximum dose of 800 mg per day or until the desired SUA level (≤6 mg/dL or <5 mg/dL for severe gout) is achieved. In patients with chronic renal disease the starting dose should be ≤50 mg/day and dose escalation should be slower and in increments of no more than 50 mg at a time.[28]

Allopurinol hypersensitivity syndrome (AASCARs or allopurinol-associated severe cutaneous adverse reactions) occurs in about 1 in 1000 people in the US. It 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.[61] The reported mortality rate for AASCARS ranges between 20% to 32%.[61, 62] The genetic risk of allopurinol hypersensitivity is associated with HLA-B*5801 allele. The carriage rate for this genetic susceptibility is 6% to 12% in Asians; 4% to 6% in African-Americans; and 1% in Caucasians and Latinos. Another known risk factor for developing AASCARs is the initiation of allopurinol at doses >100 mg/day. Subsequent dose escalation does not appear to enhance the risk of AASCARs.

The 2020 ACR guidelines for gout recommend testing for HLA-B*5801 in all patients with Southeast Asian or African-American heritage. If a patient fails to respond to allopurinol or cannot tolerate dose escalation or there is reason to believe that the individual is at high risk for allopurinol hypersensitivity syndrome, the ACR suggests febuxostat, another xanthine oxidase inhibitor. It is recommended that this drug should be started at a low dose (20 to 40 mg once a day) which is titrated up to a maximum of 80 mg a day or until the target SUA (≤6 mg/dL or <5 mg/dL) is achieved.[7] Providers should be aware of the FDA required boxed warning for febuxostat warning providers of a possible "increased risk of heart-related death" with this agent.[63] Please see the section below discussing febuxostat and the CARES and FAST trials.

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.[28] Patients should be instructed to notify your office and discontinue the drug for any rash occurring in the first 3 months of treatment.

If allopurinol and febuxostat are contraindicated or not tolerated or do not result in an SUA level of ≤6 mg/dL, then probenecid, a uricosuric agent, can be added. It is generally ineffective in patients with creatinine clearances of less than 50 mL/min. Because of possible 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 two or three divided doses.

A combination of a uricosuric agent and a xanthine oxidase inhibitor can be used if a xanthine oxidase inhibitor alone has not achieved the targeted serum urate level. In this case, probenecid can be used. 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.[29] The use of weak uricosuric agents for lowering SUA is an off-label use and should only be used if absolutely necessary and with the agreement of the patient.

ULT should be continued indefinitely after the target SUA level has been achieved, even if all tophi have been resorbed and no clinical symptoms persist.

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 continue to have their renal function tests monitored.

ULT should not be stopped or adjusted during an acute flare.

Pegloticase and Immunomodulation for the Treatment of Chronic Refractory Gout

In patients refractory to xanthine oxidase inhibitors and/or uricosuric agents, or who cannot tolerate these drugs, pegloticase (Krystexxa®) can be used. Uricase or uric acid oxidase is the final purine catabolic enzyme in all mammals except for humans and higher primates. In a multistep process, uricase opens up the purine ring structure of uric acid and converts it to the very soluble allantoin. Pegloticase employs a recombinant porcine–baboon uricase that is covered by covalently attached polyethylene glycol. This drug was developed and approved for use in patients with severe refractory gout who have failed all other standard treatments.[64, 65] Pegloticase is the only biologic currently available for the treatment of gout (another biologic, pegadricase, is still under investigation and has not yet been approved by the FDA). All

biologics and biosimilars are immunogenic and can elicit an anti-drug antibody response often interfering with the drug's efficacy and tolerability. They also may be associated with infusion reactions.[66, 67]

Pooled data from replicate Phase 3 trials showed that all subjects receiving pegloticase dropped their SUA levels to 1 mg/dL or less.[65] Later in the studies, some patients lost their response to the drug and were found to have SUA levels >6 mg/dL. Persistent responders were defined as having an SUA level <6 mg/dL for the 6 months of the trial. In these trials non-responders had an SUA level <6 mg/dL for approximately 10 weeks but after that SUA levels >6 mg/dL were seen. A significant decrease of the size of tophi and both the number of tender and swollen joints was seen in responders to pegloticase. However, adverse events were reported in many of the patients (responders and non-responders). The most common adverse event was a gout flare in both the pegloticase treated and placebo groups. The second most common adverse event was an infusion reaction, which was seen in 26% of patients receiving an infusion of pegloticase every 2 weeks, 42% of those getting the drug monthly and 5% of those receiving a placebo. Infusion reaction was the most common reason that the drug was discontinued. All of the infusion reactions resolved; however, some were considered serious but did not require hospitalization. Antibodies to pegloticase were detected in 134 of 150 patients treated with it. Only 2% of patients with antibody titers of >1:2430 were able to maintain a urate lowering response to the drug. Eighty two percent of patients with an antibody titer of <1:2430 were able to maintain the response to the drug. Patients who had high antibody titers also had high rates of infusion reactions.

Small studies have reported that if an anti-proliferative and/or immunosuppressive agent such as methotrexate, azathioprine, leflunomide or mycophenolate mofetil was given before infusions of pegloticase the number of responders increased and the incidence of infusion reactions decreased.[68-72] However, if a patient is found to have two consecutive SUA levels of >6 mg/dL with or without the use of an immunomodulator drug, it may be necessary to stop pegloticase because the drug may be ineffective and there is a risk of an infusion reaction. Before stopping pegloticase, the provider should have a discussion with the patient about the risks of continuing the drug.

Currently, the use of immunomodulators with pegloticase is still a work in progress but it appears to be very promising. It has not been determined which drug is preferred and at what dose. Most of the published studies have used oral or subcutaneous methotrexate.

A New Warning for Febuxostat [Uloric®]

The CARES Trial[73]

Febuxostat (Uloric) was approved by the FDA in 2009 as a ULT in the treatment of gout. Over its 10 years of utilization, febuxostat has garnered slightly less than 10% of the urate-lowering medication market.

Most patients receiving febuxostat have previously taken allopurinol but for a number of reasons were switched febuxostat. During the Phase III clinical trials, there was a signal for CV events for febuxostat that was not statistically significant. However, the FDA required a warning in the prescribing information that said, "A higher rate of cardiovascular thromboembolic events was observed in patients treated with ULORIC than allopurinol in clinical trials. Monitor for signs and symptoms of MI [myocardial infarction] and stroke"(Page 1).[74] The FDA also required a post-marketing CV safety trial that compared febuxostat to allopurinol.

The Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial with nearly 6200 patients with gout who were at high risk for CV disease was a long-term, randomized, double-blind study with a 1:1 randomization to either febuxostat (40 to 80 mg daily) or allopurinol (200 to 600 mg daily). Both groups had an initial 3-month period when therapy was up-titrated to achieve a target SUA of <6.0 mg/dL. Patients were followed for up to 85 months, with a median follow-up of 32 months. The primary endpoint of the trial was the occurrence of a major adverse cardiovascular event (MACE) in either treatment group. The secondary endpoints were the individual MACE components (CV death, nonfatal MI, nonfatal stroke, and unstable angina requiring urgent revascularization). All-cause mortality was also analyzed.

The primary endpoint of the trial was not significantly different between febuxostat (10.8%) and allopurinol (10.4%). However, within the secondary endpoints, CV death was significantly different in the febuxostat (4.3%) and allopurinol (3.2%) groups. This, in turn, resulted in a higher all-cause mortality for the febuxostat group. These results were published in the *New England Journal of Medicine* in March 2018[73] and presented to the FDA Arthritis Advisory Committee in January 2019. The result of that hearing was a new FDA-approved black box warning in the Uloric prescribing information. That warning states, "Gout patients with established cardiovascular (CV) disease treated with ULORIC had a higher rate of CV death compared to those treated with allopurinol in a CV outcome study" (Page 1).[74] The warning further recommends: (1) to consider the risk/benefit of Uloric when prescribing or continuing patients on Uloric, (2) to only use Uloric in patients with an inadequate response or intolerance to allopurinol, or (3) to use in patients for whom allopurinol is not advisable.

Many questions remain about the meaning of the CARES study. This is the first CV safety trial for any type of medication where an increase in CV death was not paralleled by an up-tick in one or more of the other MACE components. Mechanisms for the observed increased death rate were extensively investigated by the sponsoring company and the cardiologist who adjudicated this trial. To date, no physiologic mechanism has been detected. Similarly, there was no subset within the treatment cohort of gout patients with existing CV disease that seems to be at particular risk for this outcome. The other unusual aspect of this trial is that most patients who experienced CV death were not on medication (either febuxostat or allopurinol) when death occurred.

The CARES trial had flaws in both its design and execution. The lack of a placebo-controlled arm in this study, while probably being the correct ethical approach, leaves us wondering if CARES demonstrated true cardiotoxicity for febuxostat, or whether febuxostat is simply not as cardioprotective as allopurinol. The study was also flawed in its execution by the very high rate of premature treatment discontinuation and discontinued follow-up for both arms of the trial.

The new FDA-approved warning for febuxostat is a prudent reflection of our current knowledge about CV risk when using this drug. The recommendation for the use of febuxostat only after an earnest trial of allopurinol is in keeping with how febuxostat is already being used in this country. Perhaps the results of another large, on-going, prospective study comparing allopurinol and febuxostat will help to clarify the real meaning of the CARES findings.

***The FAST Trial*[75]**

Long-term CV safety of febuxostat compared with allopurinol in patients with gout (FAST): a multicenter, prospective, open-label, non-inferiority trial[75] was recently published. The study design and endpoints were similar to the CARES trial. The study population was primarily northern European whereas the CARES

trial was a US study. In this study, 6128 patients (mean age 71, 85% men, and 33.4% had previous CVD) were followed for a mean of 4 years (the range of follow up was from 2.8 to 5.6 years). The retention rate for subjects in this study was far superior to that reported in the CARES trial, making interpretation of the FAST data more meaningful. The reported MACE were 2.05 per 100 patient years in the group treated with allopurinol and 1.72 events per 100 patient years in the group treated with febuxostat. This study found that, in contrast to the CARES study described above, treatment with febuxostat was not associated with an increase in CV death or all-cause mortality.

For patients who fail to respond to allopurinol, febuxostat should be considered as long as the patient understands that there is a black-box warning for febuxostat's use in patients with CV disease – even if the reasons for that warning are not entirely justified.

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 ○ MI, stroke ○ Impaired renal function • Contraindications ○ Class 3 to 5 CKD ○ Anticoagulant therapy
Colchicine (Colcrys®, Mitigare®, Gloperba® liquid, 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 Methylprednisolone dose pack Intravenous or intramuscular steroids Methylprednisolone (or equivalent)	• Prednisone 0.5 mg/kg/day ○ 5 to 10 days at full dose then stop ○ OR 2 to 5 days at full dose then taper for 7 days • 0.5–2 mg/kg IV or IM	• 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 ○ Insomnia ○ Facial flushing

Intra-articular steroids Triamcinolone (or equivalent)	• 40 mg for the knee • 20 mg for ankle, wrist, or elbow • 10 mg for small joints	
Prophylaxis for ULT*		
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 ○ MI, stroke ○ Renal impairment
Oral steroids (use only if both NSAIDs and colchicine 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

*See text for duration of anti-inflammatory prophylaxis

AEs, adverse events; BP, blood pressure; CKD, chronic kidney disease; GI, gastrointestinal; IM, intramuscularly; IV, intravenously; MI, myocardial infarction; NSAIDs, nonsteroidal anti-inflammatory drugs; ULT, urate-lowering therapy

Table 3. Drugs and doses used for ULT

Drug	Dose	AEs or Contraindications
Allopurinol (Zyloprim®)	• <100 mg/day to start • For patients with chronic renal disease, 50 mg/day to start • Dose escalation up to 800 mg/day can be tried until desired SUA levels are achieved in patients without chronic renal disease	• 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 • 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
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	

Drug	Dose	AEs or Contraindications
Uricosuric Agents		
Probenecid (Benemid®)	• 250 mg twice daily	• Must have normal renal function and normal urine uric acid levels
	• With escalation of dose up to a maximum of 3 grams/day given in divided doses May • be used in combination with allopurinol	• 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
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
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 • Immunomodulator drug, such as methotrexate or mycophenolate mofetil, should be started weekly 2–4 weeks prior to first infusion of pegloticase and maintained for the entire course of pegloticase therapy	• Allergy-like infusion reactions ○ Chest discomfort ○ Vomiting ○ Flushing ○ Dyspnea ○ Erythema ○ Sweating ○ Back or flank pain ○ Change in BP ○ Congestive heart failure • Prior anaphylactic reaction to pegloticase

*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

Follow Up

Initially, patients should be seen at 2- to 4-week intervals for the evaluation of SUA, renal function tests and size of tophi. Medication adjustment should be made if appropriate. Once the SUA is stable at ≤6 mg/dL or ≤5 mg/dL,[9] as appropriate, the patient may be seen every 6 months for a check of SUA values,

renal function tests and size of tophi. However, if a patient develops an acute flare he/she should be seen as soon as possible.

A Note about the American College of Physicians Gout Management Guidelines

In 2016, the 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.[48]
- Management of acute and recurrent gout: a clinical practice guideline from the American College of Physicians.[49]

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:[76]

Effective treatments for acute gout include colchicine, NSAIDs, and corticosteroids/animal-derived adrenocorticotropic hormone formulation. ULT 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).[48] 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,[49] 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 are 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
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:[49]

> 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-avoidsymptoms 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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Document Updates

Document Version	Description of Changes	Approval Date
1.1.2016	Creation of first version	13 Jan 2017
1.1.2017	2017 review	Aug 2017
1.1.2018	2018 review	Apr 2018
1.1.2019	2019 review	Apr 2019
1.1.2020	2020 review	Feb 2021
1.1.2021	2021 review	Apr 2021
1.1.2023	2023 review	Feb 2023