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An update on gout diagnosis and management for the primary care provider

Abstract: Gout is the most common inflammatory arthritis in the US, affecting 3.9% of the population. Although many effective gout therapies are available for acute flares and chronic management, it is suboptimally treated worldwide, and recurrent gout flares can cause significant pain and irreversible joint damage.

By Nadine Mbuyi, MD, and Catherine Hood, DNP, FNP

Gout is an inflammatory arthritis that occurs when there is a deposition of monosodium urate (MSU) crystals in the joints and soft tissues that is caused by hyperuricemia. 3.9% of adults in the US have gout, making it the most common inflammatory arthritis nationally.[1,2] Using data from the National Health and Nutrition Examination Survey (NHANES), a recent study found the prevalence of gout in the US to be 4.8% in non-Hispanic Black individuals, 4.0% in non-Hispanic White individuals, and 2% in Hispanic individuals.[1] The estimated prevalence worldwide is 1% to 4% with higher rates in developed countries. Prevalence is more than 10% in some Oceanic countries.[2] The peak age of onset for gout is between 40 and 50 years in males and over 60 years in females.[3] This difference is likely due to the rise of uric acid concentration that occurs with onset of menopause.[4] Gout is more common in men than women, with a prevalence of 5.2% and 2.7%, respectively.[1] This gap between genders decreases with age.[2] Because gout is affected by metabolic syndrome, obesity, and diet, the prevalence is likely to continue to rise.[5]

Keywords: allopurinol, arthritis, colchicine, gout, musculoskeletal ultrasonography (MSUS), primary care, rheumatology, uric acid

Gout management remains suboptimal in the US and abroad despite available effective therapies.[6,7] A recent UK study comparing nurse-led care for patients with gout using a protocol including patient education and engagement, and a treat-to-target approach, versus traditional care by general practitioners showed that patients in the nurse-led group had improved adherence to their urate lowering therapy, lower serum urate levels, and a reduction in flares after 2 years.[7] Due to the current shortage of trained rheumatologists in the US, patients with rheumatic diseases including gout have reduced access to healthcare.[8] Therefore, a multidisciplinary approach with NPs at the center could improve access to care and clinical outcomes for patients with gout.[9,10]

Pathophysiology

Uric acid is a product of endogenous and exogenous purine metabolism and exists primarily as MSU in extracellular fluid.[11] Nearly two-thirds of daily urate produced is excreted through the kidneys.[12] About one-third of it is degraded by intestinal bacteria.[12] Hyperuricemia is defined as serum uric acid level exceeding 6.8 mg/dL, which results from impaired renal urate excretion or from urate overproduction.[13,14] Above this threshold, there is an increased risk for MSU crystal deposition in tissues with its associated clinical consequences including gouty arthritis.[13] Episodes of gouty arthritis can be triggered by MSU crystal deposition in joints.[13] Recognition of MSU crystals by Toll-like receptors on resident macrophages and dendritic cells initiates the inflammatory response leading to activation of the NLRP3 inflammasome, a large cytoplasmic protein complex, resulting in the production of interleukin-1 beta.[15,16] This triggers the production of various cytokines and chemokines including IL-6, IL-8, and tumor necrosis factor-alpha that play a role in the inflammatory response in gouty arthritis.[15]

Presentation

The first episode of gouty arthritis is typically monoarticular, often affecting the first metatarsophalangeal joint—a condition called podagra.[17] Gouty arthritis flares are characterized by the abrupt onset of excruciating joint pain that progresses rapidly over several hours.[18] The pain is so severe that patients often complain of an inability to tolerate even the slightest pressure on the affected joint such as that from a bedsheet.[19] Without any intervention, a gout flare eventually resolves on its own within approximately 7 to 10 days.[20] Over time, the attacks can become more frequent and polyarticular. The ankles, midfoot joints, knees, wrists, fingers, and elbows are the most commonly involved.[3] Gout flares can also affect bursae and tendons such as the olecranon bursa and the Achilles tendon causing gouty bursitis or tendonitis.[20] Interestingly, a few studies have reported that patients with gout or hyperuricemia can have tophaceous deposits in any layer of the eye including the cornea, the iris, the conjunctiva, and the sclera.[21] However, large-scale studies are needed to determine the frequency of ocular manifestations of gout.

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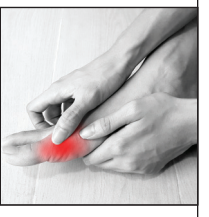


Physical exam

During a flare, patients can have systemic signs of inflammation such as a low-grade fever. The affected joints are warm, erythematous, and extremely tender to touch, and a joint effusion may be present.[22] Periarticular erythema and swelling can develop, resulting in a condition called gouty cellulitis. Over time, the skin overlying the involved joints desquamates as the inflammation resolves.[23]

In patients with chronic gouty arthritis, subcutaneous crystal deposits or tophi can be seen most commonly on the elbows, fingers, hands, knees, feet, or the helix of the ear. On physical exam, they appear as large, chalky, solid bumps under the skin.[20] Tophi can also form in bursae and tendons, and the skin overlying tophi can ulcerate and become infected.[24] Rarely, chronic tophaceous gout can be the first manifestation of gout in the absence of preceding attacks of acute gout.[25] Complications from chronic gouty arthritis can be avoided with early interventions.

Lab evaluation

Various lab abnormalities can be seen in individuals with gout (see *Lab evaluation in gout*). Arthrocentesis should be performed if a joint effusion is present to establish the diagnosis of gout (see diagnosis section) and to rule out alternative or concomitant causes of

joint inflammation such as other crystal-induced arthropathies or septic arthritis.[26] Synovial fluid analysis should include a crystal analysis, cell count and differential, and Gram stain and culture. Because septic arthritis can cause rapid joint destruction and sepsis, it should always be ruled out. In a recent retrospective analysis of patients with coexisting crystal-induced arthritis and septic arthritis, the knee was the most commonly affected joint.[27] A high index of suspicion is required to diagnose patients and provide appropriate treatment.

Hyperuricemia and MSU crystal deposition are hallmarks of gout.[18] Studies have shown that elevated levels of serum uric acid promote the development of coronary heart disease, renal disease, metabolic syndrome, and gout through inflammation, oxidative stress, and endothelial cell damage.[28] Of note, the serum uric acid level can be normal or even low during an acute gout flare.[18] This is in part due to release of interleukin 6 (IL-6) by macrophages during a flare as part of the inflammatory response. IL-6 promotes renal excretion of uric acid.[18] Hence, serum uric acid level should be checked after an acute gout flare has resolved to document the degree of baseline hyperuricemia in patients with gout. Other common but nonspecific lab test abnormalities include an elevation of the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), leukocytosis, and possibly a reactive thrombocytosis.[18]

Imaging—Conventional radiography

Conventional radiography remains the most widely used imaging modality in the workup of gout.[29] It is routinely used to assist in the diagnosis of gout and to monitor disease progression. Classic features of gout on conventional radiography, such as the formation of tophi and marginal erosions with sclerotic margins and overhanging edges, tend to appear late in the disease course.[20] In early gout, radiographs may only show nonspecific changes of soft tissue swelling or joint effusion.[30] Over the past decade, more advanced imaging modalities such as musculoskeletal ultrasound (MSUS), MRI, and dual-energy computed tomography (DECT) have gained popularity due to their ability to detect changes that occur earlier in the disease course.[31-33]

Imaging—Musculoskeletal ultrasound

MSUS is increasingly gaining popularity within rheumatology.[34] It is noninvasive, well tolerated, relatively inexpensive, and can be used as a point-of-care diagnostic and therapeutic tool.[35] It can evaluate both periarticular and intra-articular structures including soft

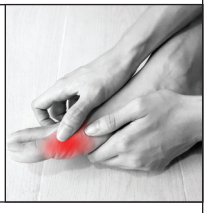
Lab evaluation in gout

Test	Comments
Serum uric acid	May be normal or low during an acute flare of gout
CRP	May be elevated during a gout flare
ESR	May be elevated during a gout flare
CBC	White blood cell count may be slightly elevated during a gout flare Highly elevated white blood cell count may indicate septic arthritis A reactive thrombocytosis can be seen during a gout flare
Renal function	Renal failure is a risk factor for hyperuricemia CKD is a common gout comorbidity Gout medications should be dosed based on creatinine clearance
Serum glucose	Hyperglycemia and diabetes are common gout comorbidities and may complicate gout management Caution is advised when prescribing oral steroid medications or with parenteral administration in patients with diabetes
Liver function tests	May need to adjust dose of gout medications based on liver function
Synovial fluid analysis	Always aspirate a swollen joint to diagnose crystal arthropathies or septic arthritis on initial presentation. Synovial fluid analysis should include a crystal analysis, cell count and differential, and culture and Gram stain

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; CBC, complete blood count; CKD, chronic kidney disease

tissues and bones. Furthermore, in patients with acute gout, using high-resolution MSUS with Doppler allows for evaluation of inflamed joints and tendons; it also enables safe needle guidance during arthrocentesis.[35] MSUS can accurately detect MSU crystal deposits in joints and soft tissues.[36] A recent multicenter study found that ultrasound had a sensitivity of 76.9% and specificity of 84.3% for detecting MSU crystal deposition.[37] Further, a study evaluating patients with gout on urate-lowering medications showed that ultrasound can be used to evaluate response to treatment as disappearance of urate deposits detected by ultrasound was associated with reduced serum uric acid levels.[33]

Computed tomography is an excellent tool to visualize tophi and differentiate them from other subcutaneous nodules.



Imaging—Computed tomography

Computed tomography (CT) is an excellent tool to visualize tophi and differentiate them from other subcutaneous nodules.[31] Additionally, CT is better than both MRI and ultrasound at detecting bony erosions and intra-articular tophi, which makes it particularly useful in assessing chronic gout. However its use is limited by radiation exposure.[31]

Imaging—Dual-energy computed tomography

DECT is a relatively new and noninvasive tool to detect and quantify MSU crystal deposition.[38] MSUS, MRI, and conventional CT can also detect tophi, but DECT provides the most specific images.[39] DECT can detect small MSU crystal deposits, which makes it useful for early diagnosis of gout and to monitor treatment response based on tophus dissolution.[39] A systematic review found the pooled sensitivity and specificity of DECT for gout diagnosis to be 88% and 90%, respectively.[40] Some disadvantages of DECT include higher cost and exposure to radiation.[29]

MRI

MRI can be a useful tool to detect inflammation, erosions, and tophaceous deposits.[41,42] However, given the availability of more inexpensive modalities such as MSUS, the use of MRI is limited in the assessment of gout.

Diagnosis

The gold standard for diagnosis of an acute gout flare is through direct visualization of intracellular MSU crystals from a synovial fluid aspirate.[26,43] MSU crystals are described as needle-shaped, and negatively birefringent under polarized microscopy.[20] Analysis of the synovial fluid should include a crystal analysis, cell count and differential, and Gram stain and culture. The aspirate in gout is inflammatory with at least 2,000 leukocytes/mcL but typically between 20,000 to 50,000 leukocytes/mcL as well as a predominance of neutrophils.

Management

The American College of Rheumatology (ACR) updated its guideline for the treatment of gout in 2020.[44] The new guideline incorporated data from recent clinical trials conducted since the 2012 ACR gout treatment guidelines were published.[45,46] It emphasizes the need to treat acute gout flares with anti-inflammatory therapies and to treat symptomatic hyperuricemia with urate-lowering therapies using a treat-to-target approach with a goal serum uric acid level of less than 6 mg/dL. This goal prevents crystallization of MSU, which occurs above the solubility limit of 6.8 mg/dL.[44]

Pharmacologic interventions—Acute management

Nonsteroidal anti-inflammatory drugs (NSAIDs), systemic or intra-articular corticosteroids, and colchicine are all recommended first-line treatments for an acute gout flare.[44] The choice of therapy depends on the patient's comorbidities. NSAIDs should be used with caution in patients with renal or hepatic impairment, bleeding disorders, peptic ulcer disease, gastrointestinal bleeding history, and cardiovascular disease.[47] NSAIDs are also on the Beers Criteria list of medications to be avoided in patients age 65 and older.[48] Corticosteroids are effective anti-inflammatory medications, but caution must be taken in patients with cardiovascular comorbidities or diabetes as they can cause fluid retention and hyperglycemia.[49] Colchicine is most effective if given in the first 36 hours of a gout flare.[50] It should be used with caution in older adults or patients with renal or hepatic impairment, although the dose can be appropriately adjusted in patients with chronic kidney disease (CKD).[51] Also,

colchicine should not be given to patients who are taking cyclosporine or tacrolimus because of the risk of severe neuromyopathy.[3] When colchicine is selected to manage a gout flare, a low-dose regimen is recommended over a high-dose regimen given its similar efficacy and lower adverse reaction profile including gastrointestinal upset.[44,52] Low-dose colchicine given as a loading dose of 1.2 mg at the onset of a gout flare followed by 0.6 mg 1 hour later is the FDA-approved dosing for treating a gout flare. However, typical recommendation advises to continue 0.6 mg of colchicine once to twice daily until the flare fully resolves.[46] Refer to the package insert for dose adjustments in certain populations.

Another class of effective, but less commonly used treatments for gout flares, due to cost and availability, are interleukin 1 (IL-1) inhibitors such as the IL-1 receptor antagonist, anakinra.[53] A 5-day treatment with a 100 mg subcutaneous injection once daily has been shown to be equally effective at treating gout flares as the other three first-line treatments; however, anakinra is not FDA-approved for the treatment of gout.[53] IL-1 inhibitors should be reserved for patients in whom first-line anti-inflammatories are ineffective, contraindicated, or poorly tolerated.[44]

Finally, in patients who are unable to take oral medications, injected glucocorticoids are recommended but subcutaneous adrenocorticotropic hormone (ACTH) can be considered to treat a gout flare if there is a contraindication to first-line agents (see *Anti-inflammatory therapies for acute gout*).[44,45]

Pharmacologic interventions—Chronic management

Urate-lowering therapy (ULT) should be started in patients who experience two or more gout flares within a 12-month period as well as in those with tophi or radiographic damage secondary to gout.[44] ULT should also be considered in patients with CKD stage 3 or worse or urolithiasis who have had at least one gout flare and in those with infrequent gout flares and marked hyperuricemia (greater than 9 mg/dL).[44]

Allopurinol is the first-line therapy for chronic management of gout, including in patients with CKD.[44] It is a xanthine oxidase inhibitor that decreases

Anti-inflammatory therapies for acute gout

Drug	Comments/precautions
NSAIDs	• First-line agents • Use with caution in patients with renal or hepatic impairment, peptic ulcer disease, history of gastrointestinal bleeding, cardiovascular disease, or clotting disorders • Avoid in patients age 65 and older
Colchicine	• First-line agent • Use with caution in older adult patients or patients with renal or hepatic impairment • Dose should be adjusted based on CrCL • Avoid in patients taking cyclosporine or tacrolimus because of risk of severe neuromyopathy • Risk of myelosuppression
Corticosteroids	• First-line agents • Use with caution in patients with cardiovascular disease or diabetes as they can cause fluid retention and hyperglycemia • Caution should be used in patients with active infections
IL-1 inhibitors	• Second-line agents • Example: anakinra • Used off-label if there is an intolerance or contraindication to first-line anti-inflammatory therapies • Use with caution in patients with active infections or who are immunosuppressed • Must be renally dosed • Consider using in patients who are unable to take oral medications, or in case of intolerance or contraindication to first-line agents
ACTH	• Second-line agent • Subcutaneous injection • Consider using in patients who are unable to take oral medications, or in case of intolerance or contraindication to first-line agents

NSAIDs, nonsteroidal anti-inflammatory drugs; CrCL, creatinine clearance; IL-1, interleukin 1; ACTH, adrenocorticotropic hormone

the production of uric acid.[3] A major concern with allopurinol is the potential for allergic reactions ranging from mild maculopapular eruptions to more severe cutaneous reactions including toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), and a rare but life-threatening systemic reaction called allopurinol hypersensitivity syndrome (AHS), which has a mortality rate ranging from 9 to 20%.[54] Clinical features of AHS include a rash, low-grade fever, leukocytosis with eosinophilia, and liver and renal failure.[54] Risk factors for AHS include renal insufficiency, concomitant diuretic therapy, older age, recent initiation of allopurinol, higher starting dose of allopurinol, and the presence of the HLA-B*58:01 allele.[55] Because this allele is highly prevalent in individuals of certain ethnic backgrounds and based on demonstrated cost-effectiveness, the ACR recommends screening for the presence of HLA-B*58:01 prior to initiating allopurinol in those of Korean, Han Chinese, or Thai descent, and in individuals who identify as Black American.[44,55,56]

To minimize drug toxicity and flare risk, ULT should be started at the lowest possible dose with subsequent gradual titration to achieve a serum uric acid level of less than 6 mg/dL.[44] When a gout flare occurs, the ULT dose should be kept constant throughout a flare.[3]

Febuxostat is a second-line ULT used when patients have an intolerance or contraindication to allopurinol or fail to respond to allopurinol or uricosuric agents.[44] It is a selective xanthine oxidase inhibitor, which decreases the synthesis of uric acid.[3] It is more expensive than allopurinol.[3] Febuxostat can rarely cause a skin rash, and is also associated with a small risk of severe cutaneous adverse reactions such as TEN and SJS, though the risk is lower in comparison with allopurinol.[57] As with allopurinol, the dose of febuxostat should not be increased or decreased during a gout flare and routine lab monitoring should include liver function testing.[44,57,58] Recently, in response to results of the Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial, which suggested greater risk of cardiovascular and all-cause mortality with febuxostat than allopurinol, the US FDA issued a black box warning for increased mortality risk with febuxostat versus allopurinol in patients with established cardiovascular disease.[59,60] The CARES trial highlights the need for shared decision-making between healthcare providers and patients when deciding on the appropriate ULT, and studies are ongoing to validate its results.[61]

As previously stated, the dose of ULT such as allopurinol and febuxostat should be gradually increased until the uric acid goal is met.[44] During this time period, patients should also be on a prophylactic dose of an anti-inflammatory medication. Prophylaxis should be continued for at least 3 to 6 months after initiation of ULT to reduce the risk of flare.[44] Patients who continue to experience flares after cessation of anti-inflammatory prophylaxis should be treated with anti-inflammatory medications as needed.[44]

Probenecid is a uricosuric agent that can be used as a second-line agent to treat chronic gout. It can be used alone or in conjunction with allopurinol or febuxostat in patients who have failed to achieve their target serum uric acid level with optimized doses of allopurinol or febuxostat.[44] Probenecid reduces the serum urate concentration by enhancing renal excretion of uric acid.[62] Like allopurinol and febuxostat, probenecid should not be stopped during an acute gout flare.[44] Probenecid should be avoided in patients with nephrolithiasis, or a creatinine clearance of <30 mL/min.[18] Adequate hydration is advised to reduce risk of nephrolithiasis and it should be used with caution because of multiple medication interactions.[18] It prolongs the half-life of penicillin, dapsone, methotrexate, heparin, and indomethacin.[63]

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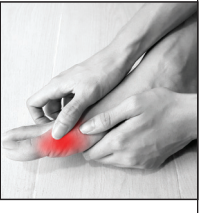

Pegloticase is a urate-lowering drug that is generally reserved for patients with refractory or severe tophaceous gout.[44] Pegloticase, which is costlier than any other ULT, is a recombinant mammalian uricase bound to polyethylene glycol to increase its solubility and half-life.[64] It converts uric acid to allantoin, which is more soluble than uric acid and readily excreted through the kidneys.[64] It is given as an I.V. infusion every 2 weeks and has been shown to lower uric acid levels as well as uric acid crystals in joints and soft

Pharmacologic interventions for hyperuricemia in gout

Urate-lowering therapies	Comments
	When initiating ULT, give with anti-inflammatory flare prophylaxis for at least 3-6 months
Allopurinol	Mode of action: XOI—decreases synthesis of uric acid • First-line therapy for treatment of hyperuricemia in gout • Starting dose: 50-100 mg daily; titrate dose every week based on sUA. Maximum dose: 800 mg daily. Doses larger than 300 mg should be administered in divided doses. Adjust dose based on CrCL • Can cause mild maculopapular rash to severe cutaneous reactions such as TEN or SJS. AHS is a rare but life-threatening systemic reaction • Risk factors for AHS: older age, diuretic use, CKD, HLA-B*58:01 allele, recent initiation of allopurinol, higher starting dose of allopurinol • Individuals who should be screened for HLA-B*58:01 allele: individuals of Korean, Han Chinese or Thai descent, and Black Americans
Febuxostat	Mode of action: XOI—decreases synthesis of uric acid • Second-line therapy for patients who have failed to achieve target sUA with allopurinol or uricosuric agents, or in case of intolerance or contraindication to allopurinol or uricosuric agents. More expensive than allopurinol • Starting dose: 40 mg daily; titrate dose to maximum dose of 80 mg daily after 2 weeks if needed to achieve target sUA • Small risk of allergic reaction (from mild rash to TEN or SJS) • Risk of liver toxicity • No dose adjustment needed if CrCL above 30 mL/min • Black box warning: may increase risk of death in patients with CV disease
Probenecid	Mode of action: Uricosuric agent—Inhibits URAT1 and GLUT9 transporters in the kidneys leading to decreased tubular reabsorption of urate • Second-line agent, used alone or in combination with XOIs in patients who fail to reach target sUA with XOIs • Starting dose: 250 mg daily; titrate dose to maximum of 2g daily divided into two doses to achieve target sUA • Avoid in patients with history of nephrolithiasis or a creatinine clearance of <30 mL/min • Advise adequate hydration to decrease risk of nephrolithiasis
Pegloticase	Mode of action: Pegylated recombinant mammalian uricase—converts uric acid to more soluble compound, allantoin, which is renally excreted • Indicated for patients with chronic tophaceous gout refractory to first- and second-line agents, or chronic gout with recurrent flares despite optimal treatment with XOIs and uricosuric agents • Dose: 8 mg I.V. every 2 weeks • Do not use in patients with heart failure or G6PD deficiency • More costly than other ULT • Risk of infusion reaction and anaphylaxis due to formation of antidrug antibodies • Check sUA before each infusion and if above 6 mg/dL especially if on 2 consecutive occasions, consider discontinuing treatment

ULT = urate-lowering therapy, XOI = xanthine oxidase inhibitor, TEN = toxic epidermal necrolysis, SJS = Stevens-Johnson syndrome, AHS = allopyrinol hypersensitivity syndrome, sUA = serum uric acid, CrCL = creatinine clearance, G6PD = glucose-6-phosphate dehydrogenase, CV = cardiovascular

Note: Always refer to drug labels for complete prescribing information.

tissues.[65] Patients who are on pegloticase should also be on prophylaxis against gout flares because of the increased risk of gout flares on this medication.[3] Pegloticase is not affected by renal function, but it should not be used in patients with heart failure, and patients should be screened for glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to administration.[3] In addition, pegloticase carries a black box warning for anaphylaxis and infusion reactions that can occur during and after administration. About 40% of people treated with pegloticase develop a resistance, and these 40% are at increased risk for infusion reactions such as anaphylaxis due to the formation of antidrug antibodies.[19] When a patient on pegloticase has a uric acid level above 6 mg/dL prior to the next scheduled infusion, especially on 2 consecutive

occasions, this may be a sign that the drug has lost efficacy and discontinuation of treatment should be strongly considered due to the increased risk of adverse reactions.[66] A few small studies have suggested strategies for preserving drug efficacy by using immunosuppressive therapies such as azathioprine or mycophenolate mofetil to reduce pegloticase immunogenicity and prevent the formation of antidrug antibodies.[66,67] However, large-scale prospective studies are needed to determine if immunosuppressive medications should be prescribed with pegloticase (see *Pharmacologic interventions for hyperuricemia in gout*).

Several drugs, such as cyclosporine, thiazide diuretics, furosemide and other loop diuretics, and low-dose aspirin, decrease renal excretion of urate, causing serum elevation of uric acid that can exacerbate gout.[68] Several other drugs can lower uric acid levels including losartan, amlodipine, and fenofibrate.[44] In patients with gout and comorbid hypertension, the 2020 ACR gout treatment guidelines conditionally recommend switching patients taking hydrochlorothiazide to a different antihypertensive when feasible. Losartan is the preferred antihypertensive due to its hypourecemic effects.[44]

Dietary recommendations

For appropriate gout management, patients who are overweight or obese should be encouraged to lose weight to decrease the odds of recurrent gout flares.[44] Patients should also avoid alcohol and foods that are high in purines because they raise the body's uric acid level. Foods that are rich in purine include red meat, organ meat, fish, shellfish, and those with high fructose corn syrup.[69] Some foods that might lower serum uric acid levels include cherries and low-fat dairy products.[70,71] It is difficult to manage gout by diet alone. Purines from one's diet only account for about 1 to 2 mg/dL of the total serum acid concentration, and consequently, if a patient were to eliminate all purines from his/her diet, it would only affect his/her serum uric acid levels by 1 to 2 mg/dL.[72]

Pain

Gout is an inflammatory condition that causes severe joint pain. NSAIDs, colchicine, corticosteroids, and IL-1 inhibitors are effective anti-inflammatory therapies that can rapidly resolve acute gout pain.[20] Opioid medications are generally not indicated to treat gout pain given the lack of evidence of long-term benefit, and the potential for recurrent use and dependence even after a short course of treatment.[73,74] Nevertheless, opioids continue to be widely prescribed to treat gout pain, thus contributing to the current opioid epidemic.[73,75] This represents an opportunity for healthcare providers to reduce the burden of opioid use and combat the opioid epidemic.

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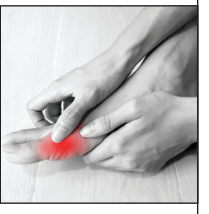

Ice has also been shown to alleviate pain caused by a gout flare. In a small study that standardized gout flare treatment with prednisone and colchicine, patients with gout were divided into two groups: one received ice, and the other did not. The group that received ice therapy had significantly greater reduction in pain compared with the control group.[76]

Conclusion

Although gout is one of the oldest rheumatic diseases, studies have shown that it remains poorly managed. Untreated gout can cause severe pain, joint deformities, and end-organ damage. Currently, there is a shortage of trained rheumatologists in the US. NPs can provide increased access to a healthcare professional for patients with gout. Through shared decision-making, patient education, and implementation of a treat-to-target approach to lower serum urate levels, clinical outcomes for patients with gout could improve. NP

REFERENCES

1. Chen-Xu M, Yokose C, Rai SK, Pillinger MH, Choi HK. Contemporary prevalence of gout and hyperuricemia in the United States and decadal trends: The National Health and Nutrition Examination Survey, 2007-2016. *Arthritis Rheumatol*. 2019;71(6):991-999.
2. Golenbiewski J, Keenan RT. Moving the needle: improving the care of the gout patient. *Rheumatol Ther*. 2019;6(2):179-193.
3. West S. *Rheumatology Secrets*. 3rd ed. Philadelphia, PA: Elsevier Mosby; 2015.
4. Evans PL, Prior JA, Belcher J, Hay CA, Mallen CD, Roddy E. Gender-specific risk factors for gout: a systematic review of cohort studies. *Adv Rheumatol (London, England)*. 2019.
5. Thottam GE, Krasnokutsky S, Pillinger MH. Gout and metabolic syndrome: a tangled web. *Curr Rheumatol Rep*. 2017;19(10):60.
6. Chinchilla SP, Doherty M, Abhishek A. Gout Activity Score has predictive validity and is sensitive to change: results from the Nottingham Gout Treatment Trial (Phase II). *Rheumatology (Oxford)*. 2019;58(8):1378-1382.

7. Doherty M, Jenkins W, Richardson H, et al. Efficacy and cost-effectiveness of nurse-led care involving education and engagement of patients and a treat-to-target urate-lowering strategy versus usual care for gout: a randomised controlled trial. *Lancet*. 2018;392(10156):1403-1412.
8. Miloslavsky EM, Bolster MB. Addressing the rheumatology workforce shortage: a multifaceted approach. *Semin Arthritis Rheum*. 2020;50(4):791-796.
9. Fields TR, Batterman A. How can we improve disease education in people with gout? *Curr Rheumatol Rep*. 2018;20(3):12.
10. Phang KF, Santosa A, Low BPL, et al. A nurse-led, rheumatologist-assisted telemedicine intervention for dose escalation of urate-lowering therapy in gout. *Int J Rheum Dis*. [e-pub June 1, 2020]
11. Maiuolo J, Oppedisano F, Gratteri S, Muscoli C, Mollace V. Regulation of uric acid metabolism and excretion. *Int J Cardiol*. 2016;213:8-14.
12. Mallat SG, Al Kattar S, Tanios BY, Jurjus A. Hyperuricemia, hypertension, and chronic kidney disease: an emerging association. *Curr Hypertens Rep*. 2016;18(10):74.
13. Ellmann H, Bayat S, Araujo E, et al. Effects of conventional uric acid-lowering therapy on monosodium urate crystal deposits. *Arthritis Rheumatol*. 2020;72(1):150-156.
14. Ragab G, Elshahaly M, Bardin T. Gout: an old disease in new perspective – a review. *J Adv Res*. 2017;8(5):495-411.
15. Desai J, Steiger S, Anders H-J. Molecular pathophysiology of gout. *Trends Mol Med*. 2017;23(8):756-768.
16. Major TJ, Dalbeth N, Stahl EA, Merriman TR. An update on the genetics of hyperuricaemia and gout. *Nat Rev Rheumatol*. 2018;14(6):341-353.
17. Richette P, Doherty M, Pascual E, et al. 2018 Updated European League Against Rheumatism evidence-based recommendations for the diagnosis of gout. *Ann Rheum Dis*. 2020;79(1):31-38.
18. Tom S. Kelley and Firestein's textbook of rheumatology, 2-volume set, 10th edition. *J Rheumatol*. 2017;44(6):964.
19. Dalbeth N, Merriman TR, Stamp LK. Gout. *Lancet*. 2016;388(10055):2039-2052.
20. Dalbeth N, Choi HK, Joosten LAB, et al. Gout. *Nat Rev Dis Primers*. 2019;5(1):69.
21. Sharon Y, Schlesinger N. Beyond joints: a review of ocular abnormalities in gout and hyperuricemia. *Curr Rheumatol Rep*. 2016;18(6):37.
22. Bursill D, Taylor WJ, Terkeltaub R, et al. Gout, hyperuricemia, and crystal-associated disease network consensus statement regarding labels and definitions for disease elements in gout. *Arthritis Care Res (Hoboken)*. 2019;71(3):427-434.
23. Janssens HJEM, Fransen J, van de Lisdonk EH, van Riel PLCM, van Weel C, Janssen M. A diagnostic rule for acute gouty arthritis in primary care without joint fluid analysis. *Arch Intern Med*. 2010;170(13):1120-1126.
24. Bouaziz W, Rekik MA, Guidara AR, Keskes H. Infection of a tophaceous nodule of the wirst and hand. *BMJ Case Rep*. 2018;2018.
25. Bieber A, Schlesinger N, Fawaz A, Mader R. Chronic tophaceous gout as the first manifestation of gout in two cases and a review of the literature. *Semin Arthritis Rheum*. 2018;47(6):843-848.
26. Sidari A, Hill E. Diagnosis and treatment of gout and pseudogout for everyday practice. *Prim Care*. 2018;45(2):213-236.
27. Prior-Español Á, García-Mira Y, Mínguez S, Martínez-Morillo M, Gifre L, Mateo L. Coexistence of septic and crystal-induced arthritis: a diagnostic challenge. A report of 25 cases. *Reumatol Clín*. 2019;15(6):e81-e85.
28. Wang H, Zhang H, Sun L, Guo W. Roles of hyperuricemia in metabolic syndrome and cardiac-kidney-vascular system diseases. *Am J Transl Res*. 2018;10(9):2749-2763.
29. Omoumi P, Zufferey P, Malghem J, So A. Imaging in gout and other crystal-related arthropathies. *Rheum Dis Clin North Am*. 2016;42(4):621-644.
30. Davies J, Riede P, van Langevelde K, Teh J. Recent developments in advanced imaging in gout. *Ther Adv Musculoskelet Dis*. 2019;11.
31. Perez-Ruiz F, Dalbeth N, Urresola A, de Miguel E, Schlesinger N. Gout. Imaging of gout: findings and utility. *Arthritis Res Ther*. 2009;11(3):232.
32. Klauser AS, Halpern EJ, Strobl S, et al. Dual-energy computed tomography detection of cardiovascular monosodium urate deposits in patients with gout. *JAMA Cardiol*. 2019;4(10):1019-1028.
33. Ebstein E, Forien M, Norkuviene E, et al. Ultrasound evaluation in follow-up of urate-lowering therapy in gout: The USEFUL study. *Rheumatology (Oxford)*. 2019;58(3):410-417.
34. Cunha JS, Reginato AM. Musculoskeletal ultrasonography has arrived. *Cleve Clin J Med*. 2018;85(4):301-302.
35. Naredo E, Iagnocco A. One year in review: ultrasound in arthritis. *Clin Exp Rheumatol*. 2016;34(1):1-10.
36. Naredo E, Medina JP, Pérez-Baos S, Mediero A, Herrero-Beaumont G, Largo R. Validation of musculoskeletal ultrasound in the assessment of experimental gout synovitis. *Ultrasound Med Biol*. 2018;44(7):1516-1524.
37. Ogdie A, Taylor WJ, Neogi T, et al. Performance of ultrasound in the diagnosis of gout in a multicenter study: comparison with monosodium urate monohydrate crystal analysis as the gold standard. *Arthritis Rheumatol*. 2017;69(2):429-438.
38. Modjinou DV, Krasnokutsky S, Gyftopoulos S, et al. Comparison of dual-energy CT, ultrasound and surface measurement for assessment of tophus dissolution during rapid urate debulking. *Clin Rheumatol*. 2017;36(9):2101-2107.
39. Klauser AS, Halpern EJ, Strobl S, et al. Gout of hand and wrist: the value of US as compared with DECT. *Eur Radiol*. 2018;28(10):4174-4181.
40. Yu Z, Mao T, Xu Y, et al. Diagnostic accuracy of dual-energy CT in gout: a systematic review and meta-analysis. *Skeletal Radiol*. 2018;47(12):1587-1593.
41. McQueen FM, Doyle A, Reeves Q, et al. Bone erosions in patients with chronic gouty arthropathy are associated with tophi but not bone oedema or synovitis: New insights from a 3 T MRI study. *Rheumatology (Oxford)*. 2014;53(1):95-103.
42. Popovich I, Dalbeth N, Doyle A, Reeves Q, McQueen FM. Exploring cartilage damage in gout using 3-T MRI: distribution and associations with joint inflammation and tophus deposition. *Skeletal Radiol*. 2014;43(7):917-924.
43. Zell M, Zhang D, FitzGerald J. Diagnostic advances in synovial fluid analysis and radiographic identification for crystalline arthritis. *Curr Opin Rheumatol*. 2019;31(2):134-143.
44. FitzGerald JD, Dalbeth N, Mikuls T, et al. 2020 American College of Rheumatology Guideline for the management of gout. *Arthritis Care Res (Hoboken)*. 2020;72(6):744-760.
45. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology Guidelines for management of gout. Part 1: systematic non-pharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res (Hoboken)*. 2012;64(10):1431-1446.
46. Khanna D, Khanna PP, Fitzgerald JD, et al. 2012 American college of rheumatology guidelines for management of gout. Part 2: therapy and anti-inflammatory prophylaxis of acute gouty arthritis. *Arthritis Care Res (Hoboken)*. 2012;64(10):1447-1461.
47. Cabassi A, Tedeschi S, Perlini S, et al. Non-steroidal anti-inflammatory drug effects on renal and cardiovascular function: from physiology to clinical practice. *Eur J Prev Cardiol*. 2020;27(8):850-867.
48. Fick DM, Semla TP, Steinman M, et al. American Geriatrics Society 2019 Updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2019;67(4):674-694.
49. Williams DM. Clinical pharmacology of corticosteroids. *Respir Care*. 2018;63(6):655-670.
50. Slobodnick A, Shah B, Krasnokutsky S, Pillinger MH. Update on colchicine, 2017. *Rheumatology (Oxford)*. 2018;57(suppl 1):i4-i11.
51. Ben-Chetrit E. Colchicine. In: Hashkes PJ, Laxer RM, Simon A, eds. *Textbook of Autoinflammation*. Springer, Cham.; 2019:729-749.
52. Khanna PP, Gladue HS, Singh MK, et al. Treatment of acute gout: a systematic review. *Semin Arthritis Rheum*. 2014;44(1):31-38.
53. Janssen CA, Oude Voshaar MAH, Vonkeman HE, et al. Anakinra for the treatment of acute gout flares: a randomized, double-blind, placebo-controlled, active-comparator, non-inferiority trial. *Rheumatology (Oxford)*. [e-pub Jan. 2, 2019]
54. Stamp LK, Chapman PT. Allopurinol hypersensitivity: pathogenesis and prevention. *Best Pract Res Clin Rheumatol*. [e-pub Apr. 4, 2020]
55. Stamp LK, Day RO, Yun J. Allopurinol hypersensitivity: investigating the cause and minimizing the risk. *Nat Rev Rheumatol*. 2016;12(4):235-242.
56. Jutkowitz E, Dubreuil M, Lu N, Kuntz KM, Choi HK. The cost-effectiveness of HLA-B*5801 screening to guide initial urate-lowering therapy for gout in the United States. *Semin Arthritis Rheum*. 2017;46(5):594-600.
57. Bohm M, Vuppalanchi R, Chalasani N, et al. Febuxostat-induced acute liver injury. *Hepatology*. 2016;63(3):1047-1049.
58. Kimura K, Hosoya T, Uchida S, et al. Febuxostat therapy for patients with stage 3 CKD and asymptomatic hyperuricemia: a randomized trial. *Am J Kidney Dis*. 2018;72(6):798-810.

59. Center for Drug Evaluation and Research. FDA adds Boxed Warning for increased risk of death with gout medicine. 2019. www.fda.gov/drugs/drug-safety-and-availability/fda-adds-boxed-warning-increased-risk-death-gout-medicine-uloric-febuxostat.

60. White WB, Saag KG, Becker MA, et al. Cardiovascular safety of febuxostat or allopurinol in patients with gout. *N Engl J Med*. 2018;378(13):1200-1210.

61. Choi H, Neogi T, Stamp L, Dalbeth N, Terkeltaub R. New perspectives in rheumatology: implications of the cardiovascular safety of febuxostat and allopurinol in patients with gout and cardiovascular morbidities trial and the associated food and drug administration public safety alert. *Arthritis Rheumatol*. 2018;70(11):1702-1709.

62. Sattui SE, Gaffo AL. Treatment of hyperuricemia in gout: current therapeutic options, latest developments and clinical implications. *Ther Adv Musculoskelet Dis*. 2016;8(4):145-159.

63. Strilchuk L, Fogacci F, Cicero AF. Safety and tolerability of available urate-lowering drugs: a critical review. *Expert Opin Drug Saf*. 2019;18(4):261-271.

64. Johnson RJ, Choi HK, Yeo AE, Lipsky PE. Pegloticase treatment significantly decreases blood pressure in patients with chronic gout. *Hypertension*. 2019;74(1):95-101.

65. Cunha RN, Aguiar R, Farinha F. Impact of pegloticase on patient outcomes in refractory gout: current perspectives. *Open Access Rheumatol*. 2018;10:141-149.

66. Guttmann A, Krasnokutsky S, Pillinger MH, Berhanu A. Pegloticase in gout treatment - safety issues, latest evidence and clinical considerations. *Ther Adv Drug Saf*. 2017;8(12):379-388.

67. Berhanu AA, Krasnokutsky S, Keenan RT, Pillinger MH. Pegloticase failure and a possible solution: Immunosuppression to prevent intolerance and inefficacy in patients with gout. *Semin Arthritis Rheum*. 2017;46(6):754-758.

68. Ueno S, Hamada T, Taniguchi S, et al. Effect of antihypertensive drugs on uric acid metabolism in patients with hypertension: cross-sectional cohort study. *Drug Res (Stuttg)*. 2016;66(12):628-632.

69. Beyl RN Jr, Hughes L, Morgan S. Update on importance of diet in gout. *Am J Med*. 2016;129(11):1153-1158.

70. Singh JA, Bharat A, Edwards NL. An internet survey of common treatments used by patients with gout including cherry extract and juice and other dietary supplements. *J Clin Rheumatol*. 2015;21(4):225-226.

71. Mena-Sánchez G, Babio N, Becerra-Tomás N, et al. Association between dairy product consumption and hyperuricemia in an elderly population with metabolic syndrome. *Nutr Metab Cardiovasc Dis*. 2020;30(2):214-222.

72. Lockyer S, Stanner S. Diet and gout - what is the role of purines? *Nutr Bull*. 2016;41(2):155-166.

73. Frieden TR, Houry D. Reducing the risks of relief—the CDC opioid-prescribing guideline. *N Engl J Med*. 2016;374(16):1501-1504.

74. Hoppe JA, Kim H, Heard K. Association of emergency department opioid initiation with recurrent opioid use. *Ann Emerg Med*. 2015;65(5):493-499.e4.

75. Dalal DS, Mbuyi N, Shah I, Reinert S, Hilliard R, Reginato A. Prescription opioid use among patients with acute gout discharged from the emergency department. *Arthritis Care Res (Hoboken)*. 2020;72(8):1163-1168.

76. Schlesinger N, Detry MA, Holland BK, et al. Local ice therapy during bouts of acute gouty arthritis. *J Rheumatol*. 2002;29(2):331-334.

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An update on gout diagnosis and management for the primary care provider

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