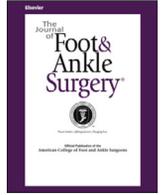




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ACFAS Clinical Consensus Statement

Joint Clinical Consensus Statement of the American College of Foot and Ankle Surgeons® and the American Association of Nurse Practitioners®: Etiology, Diagnosis, and Treatment Consensus for Gouty Arthritis of the Foot and Ankle



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ABSTRACT

Gout is a condition that commonly affects the foot and ankle, and practitioners who treat these structures should be aware of the methods to diagnose and treat this form of arthritis. Practitioners also need to recognize extra-articular manifestations of the disease. Although the acutely red, hot, swollen joint is a common presentation, chronic tophaceous gout can be associated with pain, nodule formation, and cutaneous compromise. Since the underlying causes that lead to excessive monosodium urate deposition may be treatable, early and accurate diagnosis can be very beneficial and may even prevent articular degeneration.

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Executive Statement

The American College of Foot and Ankle Surgeons® and the American Association of Nurse Practitioners®- Orthopedics Specialty Practice Group have developed a joint clinical consensus statement on etiology, diagnosis, and treatment of gouty arthritis localized to the foot and ankle. A modified Delphi method was used in an attempt to develop consensus on a series of 23 statements using the best available evidence, clinical experience, and common sense.

The panel reached consensus that the following statements were “appropriate”:

- Patients on thiazide diuretics are at higher risk for gouty flares.
- Patients with excessive alcohol consumption are at higher risk for

gouty flares.

- Diet is a risk factor for gout.
- Diet modification has an effect on decreasing incidence of recurrence.
- Age is a risk factor for gout.
- Standard workup for an initial acute gout episode should include blood uric acid level, erythrocyte sedimentation rate, C-reactive protein, complete blood count, and serum creatinine.
- Advanced imaging is not necessary to diagnose gout.
- Joint aspiration and microscopy are the gold standards for making the diagnosis of gout.
- Nonsteroidal anti-inflammatory drugs should be used as the first-line treatment for acute gout.
- Allopurinol should be titrated until the serum uric acid level is <6.0 mg/dL.
- Long-term medications, such as allopurinol, are necessary in the treatment of recurrent gout.
- Multidisciplinary referral provides optimal care in cases of recalcitrant gout.

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- Patient education should include dietary modification, medication adherence, and follow-up care with their assigned health care providers.

The panel reached consensus that the following statement was “inappropriate”:

- Hyperuricemia is always indicative of gout.

The panel reached consensus that the following statements were “neither appropriate nor inappropriate”:

- Chemotherapy places a patient at higher risk for gout.
- Patients with body mass index >27 are at higher risk for gout.
- Ethnicity, race, and socioeconomic play a great role in regard to the incidence of gout.

The panel was unable to reach consensus on the following statements:

- Patients with diabetes mellitus are at higher risk for gouty flares.
- Women are not at higher risk for gout.
- Colchicine should be taken daily for 6 to 12 months post-acute gouty flares in patients with recurrent gouty attacks.
- Joint injections are preferred over oral steroids as initial treatment of acute gout.
- Joint implant replacement should be considered in cases of chronic gout.
- Arthroscopic debridement may be used in acute or chronic gout.

Introduction

Clinical consensus statements (CCS) reflect information synthesized from an organized group of experts based on the best available evidence and to some degree embrace opinions, uncertainties, and minority viewpoints. A CCS is not to establish clinical practice guidelines, formal evidence reviews, recommendations, or evidence-based guidelines. A CCS should open the door to discussion on a topic, as opposed to providing definitive answers. Adherence to consensus statements will not ensure successful treatment in every clinical situation, and individual clinicians should make decisions based on all available clinical information and circumstances with respect to the appropriate treatment of an individual patient. This CCS focuses on general topic of risk factors, etiology, diagnosis, and treatment of gout in the foot and ankle with the aim of addressing controversies in pathophysiology of gout and its treatment. This CCS is unique in that it is derived based on an interdisciplinary team approach.

Materials and Methods

A 7-member panel of 3 podiatric foot and ankle surgeons and 4 nurse practitioners (with experience in orthopedics and rheumatology), cochaired by 2 members (S.G. and M.Z.), participated in 1 face-to-face meeting, several email dialogs, and 1 conference call. The panel was tasked to develop a series of clinical consensus statements on the topic of gout that may be controversial or misnomer. Using our collective clinical experience during a face-to-face open discussion, we developed a preliminary list of approximately 28 specific statements covering the etiology and risk factors, diagnosis, and treatment of gouty arthritis. A preliminary literature search (using Medline, EMBASE, Cochrane, CINAHL, and an extensive manual search) was used to assess availability of published research on each statement. A final 23 of 28 statement questions were retained for further consideration (Table).

Consensus

A modified Delphi method was used to attain consensus by the members of the panel (1), which was asked to review and anonymously rate the appropriateness of each statement. Rating was graded from 1 (extremely inappropriate) to 9 (extremely

appropriate) on a Likert scale (2). The results were summarized with basic descriptive statistics, kept anonymous, and distributed back to the panel members. Following open discussion of these results, the statements were distributed for a second anonymous review by the same panel members. The answers were again analyzed using the same method. Although an attempt was made to reach consensus for all questions, it was not a requirement, and contrary opinions were encouraged. The results were summarized with basic descriptive statistics, and grouped from 1 to 3 (inappropriate), 4 to 6 (neither inappropriate, nor appropriate), and 7 to 9 (appropriate). Thereafter, each panel member performed an in-depth review of current literature using search engines such as Medline, EMBASE, and the Cochrane Database of Systematic Reviews and CINAHL for each assigned statement. Although this was not a formal systematic review, each panel member conducted thorough literature searches in an attempt to answer each specific statement. The final draft of the manuscript was submitted to *The Journal of Foot and Ankle Surgery*[®] and *JNP: the Journal for Nurse Practitioners*.

Discussion

Consensus statement: The panel reached consensus that the statement “Patients on thiazide diuretics are at higher risk for gouty flares” was appropriate.

Hypertension and chronic renal disease are recognized as common comorbidities associated with gout (3–5). Diuretic use in hypertensive patients is noted to result in hyperuricemia and development of gout (5). More specifically, studies have indicated that thiazide diuretics place the patients at a higher risk for hyperuricemia (6–10). Thiazide and loop diuretics increase urate reabsorption and decrease urate secretion (7–9). This unwanted effect tends to be stronger with higher doses and longer duration of diuretic therapy (8). In addition, inconsistent diuretic therapy can lead to fluctuations in serum urate levels and precipitate a gout flare (9).

Recognizing the impact of thiazide diuretics on hyperuricemia, clinicians are encouraged to use a higher dose of urate-lowering therapy (ULT) to reduce incident and recurrent gout among patients with hypertension. Alternatively, clinicians should consider antihypertensive medications that have a neutral effect on the incidence of gout or those that provide protection while lowering the serum urate. The panel recommends that clinicians consider alternative therapies such as potassium sparing diuretics (10), angiotensin II receptor blockers (9) or a calcium channel blocker (9,10) for treatment of hypertension in patients with recalcitrant gout.

Consensus statement: The panel reached consensus that the statement “Patients with excessive alcohol consumption are at higher risk for gouty flares” was appropriate.

Serum uric acid level is proven be higher with consumption of alcohol. Alcohol intake decreases glomerular filtration while increasing tubular reabsorption of uric acid resulting in hyperuricemia (11,12). A 2-fold increase in use of alcohol was seen in patients with acute gout (13). There seems to be a dose-response relationship between alcohol intake and gout incident (14,15). Compared with no alcohol use, the odds ratio for recurrent gout is 2.0 for patients with an intake of 4 to 5 drinks over 2 days, prior to attack. This odds ratio increases when >6 drinks are consumed over the same period (14). The risk for a gout attack further increases if the patient is fasting while consuming alcohol. The effect from alcohol on gout flare is short and occurs within 24 hours after alcohol consumption in most cases (14,15). The prevalence of hyperuricemia secondary to alcohol consumption is noted to be higher among males than females (16). This difference among women and men is partially attributed to the effect of estrogen in increasing renal uric acid clearance (17). The amount of alcohol consumed, rather than a particular beverage (beer, wine or spirits), is reportedly associated with risk for gout flare; however, among all beverages, beer was reported to have the highest association with recurrent gout (17,18). The literature parallels the panel’s opinion that excessive alcohol consumption places patients at a higher risk for gout with a dose-response relationship most evident among male drinkers.

Table
Clinical consensus statement questions and results

Etiology/Risk Factors	1. Patients on thiazide diuretics are at higher risk for gouty flares.	1	2	3	4	5	6	7	8	9
	Extremely inappropriate								Extremely appropriate	
	2. Patients with excessive alcohol consumption are at higher risk for gouty flares.	1	2	3	4	5	6	7	8	9
	Extremely inappropriate								Extremely appropriate	
	3. Diet is a risk factor for gout.	1	2	3	4	5	6	7	8	9
	Extremely inappropriate								Extremely appropriate	
	4. Diet modification has an effect on decreasing incidences of recurrence.	1	2	3	4	5	6	7	8	9
	Extremely inappropriate								Extremely appropriate	
	5. Patients with diabetes mellitus are at higher risk for gouty flares.	1	2	3	4	5	6	7	8	9
	No consensus									
Diagnosis	6. Chemotherapy places a patient at higher risk for gout	1	2	3	4	5	6	7	8	9
	Extremely inappropriate								Extremely appropriate	
	7. Age is a risk factor for gout.	1	2	3	4	5	6	7	8	9
	Extremely inappropriate								Extremely appropriate	
	8. Women are not at higher risk for gout.	1	2	3	4	5	6	7	8	9
	No consensus									
	9. Patients with BMI > 27 are at higher risk for gout.	1	2	3	4	5	6	7	8	9
	Extremely inappropriate								Extremely appropriate	
	10. Ethnicity, race and socioeconomics play a great role in regard to the incidence of gout.	1	2	3	4	5	6	7	8	9
	Extremely inappropriate								Extremely appropriate	
Treatment	11. Standard work up for an initial acute gout episode should include blood uric acid level, ESR, CRP, CBC, and serum creatinine.	1	2	3	4	5	6	7	8	9
	Extremely inappropriate								Extremely appropriate	
	12. Advanced imaging is not necessary to diagnose gout	1	2	3	4	5	6	7	8	9
	Extremely inappropriate								Extremely appropriate	
	13. Hyperuricemia is always indicative of gout	1	2	3	4	5	6	7	8	9
	Extremely inappropriate								Extremely appropriate	
	14. Joint aspiration and microscopy are the gold standards for making the diagnosis of gout.	1	2	3	4	5	6	7	8	9
	Extremely inappropriate								Extremely appropriate	
	15. Non-steroidal anti-inflammatory drugs (NSAIDs) should be used as the first line treatment for acute gout	1	2	3	4	5	6	7	8	9
	Extremely inappropriate								Extremely appropriate	
Treatment	16. Colchicine should be taken daily for 6-12 months post-acute gouty flares in patients with recurrent gouty attacks	1	2	3	4	5	6	7	8	9
	No consensus									
	17. Joint injections are preferred over oral steroids as initial treatment of acute gout	1	2	3	4	5	6	7	8	9
	Extremely inappropriate								Extremely appropriate	
	18. Allopurinol should be titrated until serum uric acid level is < 6.0 mg/dL.	1	2	3	4	5	6	7	8	9
	Extremely inappropriate								Extremely appropriate	
	19. Long-term medications, such as Allopurinol, are necessary in the treatment of recurrent gout	1	2	3	4	5	6	7	8	9
	Extremely inappropriate								Extremely appropriate	
	20. Joint implant replacement should be considered in cases of chronic gout.	1	2	3	4	5	6	7	8	9
	No consensus									
Treatment	21. Arthroscopic debridement may be used in acute or chronic gout	1	2	3	4	5	6	7	8	9
	Extremely inappropriate								Extremely appropriate	
	22. Multidisciplinary referral provides optimal care in cases of recalcitrant gout.	1	2	3	4	5	6	7	8	9
	Extremely inappropriate								Extremely appropriate	
	23. Patient education should include dietary modification, medication adherence and follow up care with their assigned health care providers.	1	2	3	4	5	6	7	8	9
	Extremely inappropriate								Extremely appropriate	

Consensus statement: The panel reached consensus that the statement “Diet is a risk factor for gout” and furthermore, “Diet modification has an effect on decreasing incidences of recurrence” was appropriate.

The literature supports an association between food and gout (14,19–27). A global review of epidemiological studies by Kuo et al revealed the highest relative risk (≥ 1.5) of a gout flare with >4 cups a day of sugar-sweetened drinks, fructose, and tea (26). The highest incidence, however, is seen in food rich in purine such as red meat and seafood (1.41 and 1.51, respectively) (19,26). Each additional daily serving of meat was associated with a 21 percent increase in risk of gout whereas additional weekly serving of seafood showed a 7% increase in risk (19). Not all food rich in purine increases risk for gout. Purine-rich vegetables were not associated with an increased risk of gout (20,21,28–30).

The literature shows a dose-response increase in incidence of gout with consumption of soft drinks (sugar sweetened) and fructose (22,31,32). Diet soft drinks did not increase the risk for gout (22). An inverse association is reported between higher coffee intake and risk of gout (33–35). When compared with individuals who did not consume coffee, the risk of gout was 57% lower with a coffee intake of >4 cups per day. Although decaffeinated coffee consumption still showed moderate inverse relation, tea consumption failed to show any protective effect (33).

Diet modification can reduce risk of gout flares. When comparing dietary habits of patients with history of gout with healthy patients, vegetable and fruit consumption was noted to be significantly lower among patients with gout. Food sources rich in dietary fiber (36), folate (36), and vitamin C (22,36–38) showed a protective effect against recurrent gout. An increase intake of dairy products can decrease the incidence of gout (19) because of the uricosuric effect of casein and lactalbumin (19, 39). Available data match the consensus of the panel that diet is a risk factor for gout and that diet modification can decrease the incidences of recurrence.

Consensus statement: The panel was unable to reach consensus on the statement “Patients with diabetes mellitus are at higher risk for gouty flares.”

Hyperuricemia is recognized to be a precursor or surrogate marker for metabolic syndromes, including diabetes mellitus (40–42). Diabetes mellitus is a comorbidity commonly seen in patients with gout and hyperuricemia (5,43–45) because both conditions share common risk factors. Gout is linked with an increased risk for developing diabetes mellitus (46). Among patients with serum urate ≥ 10 mg/dL, 33% had diabetes mellitus (5). In addition, several prospective studies have shown an independent association between serum uric acid levels and the risk for developing type 2 diabetes (47–49). Common genetic factors among patients with gout and type 2 diabetes have also been reported (50). Although studies have shown an association between gout and diabetes mellitus, there is inadequate research to support cause and effect.

We could not reach consensus within our panel that having diabetes mellitus would place one at increased risk for gout. Despite research supporting that diabetes mellitus is a common comorbidity in patients with gout and hyperuricemia, a direct correlation between the presence of diabetes mellitus and higher risk for gouty flares has not been well established. Further research may be needed to show this relationship.

Consensus statement: The panel reached consensus that the statement “Chemotherapy places a patient at higher risk for gout” was neither appropriate nor inappropriate.

It is suggested that there is an underlying link between purine metabolism disorders and cancer (51). In addition to the enzymatic defects in the purine metabolic pathway, the high cell turnover and massive lysis of malignant cell results in hyperuricemia and subsequent increased risk for gout (51–53). Tumor lysis syndrome occurs secondary to treatment

of tumors and consists of a constellation of laboratory findings, including hyperuricemia (54). A few epidemiological studies have suggested the critical role of gout in carcinogenesis, and subsequent development of urological, digestive system, and lung cancer (55–57). Additionally, patients with gout can be at increased risk for cancer because of comorbidities such as obesity and heavy alcohol consumption (58).

There are limited data supporting the consensus of this panel on occurrence of chemotherapy-induced gout. The literature offers only a few case reports. Paclitaxel is reported to precipitate recurrent gout by interfering with uric acid metabolism (59). Gemcitabine, fluorouracil, and capecitabine (60–62) have also been linked to acute gout flares. Although the literature supports an association between purine metabolism and cancer, because of several confounding factors including associated comorbidities, it is inconclusive if chemotherapy alone places a patient at higher risk for developing gout.

Consensus statement: The panel reached consensus that the statement “Age is a risk factor for gout” was appropriate.

The literature coincides with our mutual consensus that age is a risk factor for gout. Studies reveal that gout is commonly seen in patients >60 years of age (63). Moreover, the prevalence of gout increases with age along with an increase in incidence of associated comorbidities (63). Women develop gout in a mean of 7 to 10 years later than men (23,64–68). The mean age of females developing gout ranges from 60 to 70 years of age, whereas the mean age of males range from 50 to 58 years of age, as reported in several international studies (24,66–68). Although males outnumber females in regard incidence of gout at younger ages, this ratio changes and the gap decreases as females age (69,70). The incidence of gout among women increases postmenopause secondary to uricosuric effect of progesterone (64,68,71). As such, menopause increases the risk of gout, whereas the use of hormone replacement therapy reduces this risk (71).

Our panel’s opinion paralleled available research. Regardless of gender, the literature shows that the risk for gout increases with age. Females, however, may develop gout later in life than their male counterparts.

Consensus statement: The panel was unable to reach consensus on the statement “Women are not at higher risk for gout.”

One of the first large studies in the United States comparing the incidence of gout among women and men reported a higher incidence in men (72). Other studies further support a higher predisposition of gout in men than women across the world (23–25,46,67,69,70,73–83).

Women with gout are reported to have a higher rate of comorbidities for hypertension, diabetes, and renal disease than men (24,67,68). However, a study by De Souza et al (64) did not show any significant differences in presence of comorbidities (except for age) among men and women. A higher body mass index (BMI) was more of a risk factor for gout than gender itself (65,66). Another area of difference between men and women in cases of gout is level of uric acid. Women are at higher risk for developing gouty attack at much lower serum uric acid levels (66).

Overall, women have far lower prevalence of gout compared with men. Differences in presentation, age of onset, and comorbidities further support that gout affects men and women differently. Although the risk factors for each gender have been well studied, response to therapy has not been well researched. There may be a need to tailor treatment based on these gender differences.

Consensus statement: The panel reached consensus that the statement “Patients with BMI >27 are at higher risk for gout” was neither appropriate nor inappropriate.

Overweight and obesity are established risk factors for gout, as reported in prospective studies (6,65,84). The incidence of gout was higher in men with a BMI of ≥ 25 kg/m², as reported in a 12-year longitudinal study of 47,150 men. For men who gained 13.6 kg or more, the risk of developing gout was double the rate of those who maintained

their weight (6). After adjusting for serum uric acid (sUA), a BMI >30 kg/m² doubles the prevalence of gout (65). Each unit increase of BMI is associated with a 5% increase prevalence of gout for an adult of average height in the United States (65).

Conversely, weight loss >4.5 kg was associated with a reduced incidence of gout (6). Weight loss >7 kg and/or 2 kg per week from a calorie-reduced diet or bariatric surgery had a beneficial effect on incident and recurrent gout at medium- and long-term follow-up (85). Having said that, the frequency of acute gouty attacks within the first 30 days after bariatric surgery is reported to be significantly higher than other upper abdominal procedures (86). This frequency decreases markedly in postoperative months 2 through 12 following bariatric surgery (86). Current prospective studies and systematic reviews support that a direct relationship exists between body weight and incidence as well as recurrence of gouty arthritis.

Consensus statement: The panel reached consensus that the statement “Ethnicity, race and socioeconomics play a great role in regard to the incidence of gout” was neither appropriate nor inappropriate.

It is difficult to estimate the overall worldwide prevalence of gout as prevalence varies in different areas of the world. In developed countries such as North America and Western Europe, the prevalence is reported to range between 1% and 4% (26,87–91). In most developed countries, the incidence of gout is >1% (26). In the United States, the incidence and prevalence have been reported as 1% and 3.9%, respectively (65,87). Greece has the highest reported incidence of gout among European countries at 4.75% of the adult population (26). In the United Kingdom, the latest estimated gout prevalence is 3.22% in adults, which is similar to estimates reported in Spain and the Netherlands. The prevalence of gout in Germany was reported to be 1.4% in the general population. France and Italy have reported a lower prevalence of gout. Pacific Islanders and Maori had a 3-fold greater risk of gout than those of European descent after adjustment for age and sex. Japan and South Korea are both considered to have a low prevalence of gout at a rate of 0.51% (83). Overall, it appears that gout prevalence is lower in developing countries than in those that are more affluent and that the highest incidence may come from lower socioeconomic populations in developed nations (26,83).

In the United States, race disparities play a significant role in gout. Gout incidence is 1.7-fold higher in African Americans compared with Caucasians (88). The higher incidence is likely because of higher rates of hypertension, obesity, diabetes, and renal disease in African Americans (89). African Americans are also less likely than Caucasians to achieve serum urate <6 mg/dL, a key target for gout treatment (92). Ethnicity, race, and socioeconomics may play a role in incidence of gout but this association may be secondary to comorbidities seen in people of different ethnicity, race, and socioeconomics.

Consensus statement: The panel reached consensus that the statement “Standard work up for an initial acute gout episode should include blood uric acid level, erythrocyte sedimentation rate, C-reactive protein, complete blood count, and serum creatinine” was appropriate.

The diagnosis of gout has traditionally been based on patient history, clinical findings, laboratory, and/or joint aspirate results, with imaging as an adjunct (93). For typical presentations of gout, a clinical diagnosis alone is reasonably accurate but not definitive without crystal confirmation (94,95).

Gout is unlikely in an individual with persistently low serum urate concentrations (<360 μmol/L) (8). Moreover, hyperuricemia may not be present during acute gout attacks and therefore may not be a helpful criterion for diagnosis (96). During a gout flare, blood tests may show nonspecific changes consistent with inflammation; the urate level may be high, normal, or low (8,97). In patients suspected of having gout based upon clinical features, an elevated serum urate (≥6.8 mg/dL) can

lend support to the diagnosis but is neither diagnostic nor required to establish the diagnosis. The most accurate time for assessment of serum urate (and establishment of a baseline value) is 2 weeks or more after a gout flare completely subsides (97).

The literature does not support obtaining complete blood count (CBC), erythrocyte sedimentation rate (ESR), or C-reactive protein (CRP) as leukocytosis can be present in gout flares; however, these findings are nonspecific and show the degree of systemic inflammation during gout attack (8). The white blood cell count may be elevated in patients during an acute gouty attack, particularly if it is polyarticular (98). A high ESR or CRP is common in gout flares and of little diagnostic value (97,99).

Analysis for amount of uric acid in urine over 24 hours is useful in assessing the etiology of hyperuricemia in gout patients. Urinary uric acid of >800 mg/24 hours indicates that such patients have increased production of uric acid (100). Renal uric acid excretion should be measured in selected patients with gout, especially those with a family history of young-onset gout (<25 years of age) or with renal calculi (95). A 24-hour urinary uric acid evaluation is generally performed if uricosuric therapy is being considered. If patients excrete >800 mg of uric acid in 24 hours while eating a regular diet, they are overproducers of uric acid (approximately 10% of patients with gout) and are more likely to do better with allopurinol instead of probenecid in reducing uric acid levels (98). Furthermore, patients who excrete >1100 mg in 24 hours are at increased risk of renal calculi and should have their renal function monitored closely (98).

Unlike the panel's consensus, research over time has shown that laboratory values may not directly help in diagnosing an initial acute gout attack. In acute settings, clinical judgment based on history and clinical presentation, with or without joint aspiration, may be most beneficial.

Consensus statement: The panel reached consensus that the statement “Advanced imaging is not necessary to diagnose gout” was appropriate.

Various noninvasive imaging modalities such as radiography, ultrasonography, computed tomography, and magnetic resonance imaging (MRI) have been used for the evaluation and diagnosis of gout (101). Some stages of gout can be seen using plain radiography and MRI (97). Subcortical bone cysts apparent on plain radiography or MRI examination can be suggestive of gouty tophi or erosions (97). Although plain radiographs have been used in detecting gout, some early signs of gout may not be present on plain films. More advanced signs such as delicate “overhanging edges” of bone associated with bone erosions resulting from tophi may take more than a year to appear (97,101).

Advanced images such as dual-energy computed tomography (DECT), MRI, and ultrasound have been useful in visualizing pathology resulting from gout. DECT can identify and quantify monosodium urate (MSU) crystals (93,102), whereas MRI is used to assess inflammation, bone erosion, and cartilage damage in gout (102). Low-quality evidence from 3 observational studies showed that DECT had a sensitivity of 85% to 100% with specificity of 83% to 92% for predicting gout (103). Sonography has shown promise in the diagnosis of gout (104). Its advantages include easy availability in outpatient centers, relatively low cost, portability, and absence of ionizing radiation.

The most recent evidence-based criteria approved by both the American College of Rheumatology (ACR) and European League Against Rheumatism Collaborative Initiative (EULAR) are the 2015 ACR-EULAR Gout Classification Criteria (105). This diagnostic classification includes use of advanced imaging (ultrasound and DECT) in diagnosing gout.

Consensus statement: The panel reached consensus that the statement “Hyperuricemia is always indicative of gout” was inappropriate.

Gout is widely understood to be a disease caused by MSU crystals in joints, bones, or soft tissue. MSU crystals tend to form in joints where temperature may be lower and can possibly

accumulate over time until an inflammatory response known as gouty attack occurs (106,107). The common belief is that hyperuricemia is a prerequisite for development of the disease; however, hyperuricemia has been difficult to define. Fitzgerald described hyperuricemia as serum uric acid levels 2 standard deviations above the mean (108); however, in another study (87), hyperuricemia was defined as serum uric acid level >7.0 mg/dL in men and >5.7 mg/dL in women, whereas Weinfeld (109) posed that there may be no notable elevation of serum uric acid in cases of gouty arthritis.

One of the first landmark studies on hyperuricemia and gout was based on a Framingham, MA, population with 5127 enrolled subjects who were followed for 10 years (110). Gout occurred in 1.8% of the patients who had a uric acid level between 6.0 and 6.9 mg/dL, whereas 11.8% of patients with acute gout had a uric acid level of 7 to 7.9 mg/dL. Acute gout occurred in 36% of patients with a uric acid level >8 mg/dL (110). In a retrospective study, only 3 of 124 hyperuricemic patients and 1 among 224 normouricemic patients developed gout (111). In a study by Lin (27), 18.83% of hyperuricemic men presented with an acute gout; however, the authors noted that excessive alcohol use to be a “more important factor in the development of gout than hyperuricemia >8.0 mg/dL” (27).

Available data match the consensus of the panel that hyperuricemia is not always indicative of gout. Although a strong association can and has been made, a direct cause and effect has not been supported.

Consensus statement: The panel reached consensus that the statement “joint aspiration and microscopy is the gold standard for diagnosis of gout” was appropriate.

Identification of negative birefringent MSU crystals under polarized microscopy is still considered the gold standard for diagnosing gout (8,93,100). Confirmation of MSU crystals in synovial fluid via joint aspiration is highly recommended in cases where classic features are not present to assist in definitive diagnosis (94,112). Alternatively, in a study by Swan, a 25% false negative rate was seen in cases of acute gout (113). This may have been secondary to the major limitation associated with joint aspiration, which is the need for proper skills and sufficient joint fluid for testing (93,94). Another barrier to joint aspiration in cases of acute gout is “where the affected joint is inaccessible” (93).

The most recent American College of Physicians (ACP) Guidelines recommends that clinicians use synovial fluid analysis when clinical judgment indicates that diagnostic testing is necessary in patients with possible acute gout (103). The Guidelines caution that this is a weak recommendation based on low-quality evidence, requiring further research. Per ACR-EULAR guidelines (105), joint aspiration remains an important element in classifying gout as presence of MSU crystals alone are adequate for diagnosis of gout in symptomatic joint or bursa. Although this panel agrees that the gold standard in diagnosing gout is a joint aspiration, the panel also supports that there are other valid and timely methods that are less invasive and safer for patients including clinical judgment, imaging, and uses of other validated tools such as the ACR-EULAR Gout Classification Criteria.

Consensus statement: The panel reached consensus that the statement “nonsteroidal anti-inflammatory drugs should be used as the first line treatment for acute gout” was appropriate.

Beneficial effect of nonsteroidal anti-inflammatory drugs (NSAIDs) including selective cyclo-oxygenase-2 inhibitors, in treatment of acute gout, has been well documented in literature (114). Significant joint swelling and pain reduction is noted within 24 hours of use of NSAIDs when compared with placebo (115). Studies have shown, however, that there is no significant benefit in use of NSAIDs over other medications in treatments of acute gout. Use of oral steroids was similar in reducing pain and increasing function when compared with NSAIDs (116–118). One disadvantage in using NSAIDs is the increased risk for gastrointestinal symptoms, nausea, and vomiting when compared with

corticosteroid therapy. Systematic reviews have concluded that corticosteroids were as effective as NSAIDs but safer (118,119).

Among all NSAIDs, no specific medication had advantage over others. For example, there was no difference in outcome in patients treated with ketorolac versus indomethacin (120). As noted in the ACR-EULAR Guidelines (95), our panel agrees that NSAIDs can be considered as first-line therapy for treatment of acute gout.

Consensus statement: The panel was unable to reach consensus on the statement “colchicine should be taken daily for 6 to 12 months post-acute gouty flares in patients with recurrent gouty attacks.”

Acute gout flares can be effectively managed with low-dose colchicine when initiated within 12 to 24 hours of symptom onset (84,95,121–124). An initial dose of 1.2 mg of oral colchicine followed by 0.6 mg 1 hour later has proven effective with favorable safety and side effect profiles when compared with high-dose therapy or prolonged treatment regimens (124). Alternatively, 0.6 mg of colchicine 3 times daily on the first day of symptoms is equally effective and may reduce gastrointestinal upset (95). Comorbid conditions are of significant consideration when selecting the appropriate treatment for acute or recurrent gout. Colchicine should be avoided or used at a reduced dose in patients with severe renal impairment or active liver disease and is contraindicated in patients receiving strong P-glycoprotein and/or CYP3A4 inhibitors such as cyclosporin, clarithromycin, verapamil, or ketoconazole (95,121–123).

The primary goal of long-term gout management is to reduce serum urate to a level at which gouty attacks are suppressed. Most clinical guidelines indicate the target for urate suppression is <6 mg/dL (95,122); however, there is little evidence that reaching target urate levels improves outcomes (121). Most patients with untreated gout will experience a second flare within 2 years of the first event (125). Consideration for long-term prophylactic therapy is guided by the frequency of gout flares. Recommendations vary in the frequency of attacks that warrant initiation of urate lowering therapy and range from 1 to 3 attacks per year (95,121,123). ULT is usually not recommended as part of management of gout after the first episode or in patients with infrequent attacks (<2 per year) (121).

A precipitous fall in serum urate often provokes a gout flare (95,121,122). Prophylactic therapy with colchicine reduces gout flares and should be continued for 2 to 6 months following initiation of ULT with the aim to reduce future gout flares (95,121). The use of extended regimens of colchicine for the primary treatment of acute gouty arthritis is generally unjustified (126). Although extended use of colchicine may prevent recurrent gout flares, they do not prevent osseous erosion or development of tophaceous deposits (95,121,122).

This panel acknowledges the ACR (2012), EULAR (2016), and 3e Initiative recommendations (92,127,128) and agrees on the benefits of both colchicine in treatment of acute gout. However, this panel was unable to reach a consensus on the exact use and length of therapy of colchicine following acute gouty flares in patients with recurrent gouty attacks.

Consensus statement: The panel was unable to reach consensus on the statement “joint injections are preferred over oral steroids as initial treatment of acute gout.”

In reviewing the literature, the panel was unable to locate any high-level evidence of randomized or controlled studies in use of intraarticular steroids for treatment of gout. As such, there are no published trials on adverse events associated with use of cortisone injection in gout. We identified only 2 studies in which intraarticular cortisone injection was used as part of treatment for acute gout. Fernandez et al (129), in a small study, reviewed the effect of 1-time corticosteroid injection among 19 men (11 knees, 4 metatarsophalangeal joints [MTPJ], 3 ankles, 2 wrists) with acute gout. Reduction in pain from 88 to 0 (0 to 100 mm visual analog scale [VAS]) was noted among all patients at 48 hours postinjection, with 45% of the men achieving

complete pain relief at 48 hours (129). The authors noted treatment to be safe and free of side effects with no rebound attacks or need for additional therapy. Only 1 patient had a recurrent attack at 3 months (129). Kang et al (130) noted pain reduction from baseline of 71 to 34 (0 to 100 mm VAS) within 24 hours postinjection in 21 patients suffering from acute gout in the first MTPJ. The authors did not report any adverse events.

Although the literature is scant on use of intraarticular steroids for treatment of gout, there are a number of studies supporting beneficial use of intravenous or oral steroids in acute gouty attacks (116,131–134). The British Society for Rheumatology recommends use of oral and/or intraarticular corticosteroid for patients who cannot tolerate NSAIDs (135). Furthermore, despite lack of evidence, the 2012 ACR Guidelines for Management of Gout and 2016 EULAR Guidelines include use of intraarticular corticosteroid injection as an option for first-line therapy (136), without an established recommended dose. Oral steroids are preferred if the gout involves more than 2 joints (127). Use of intraarticular corticosteroids requires assurance that the joint is not infected.

Larger studies are needed to clarify the efficacy, dose, timing, and adverse effects for the use of intraarticular cortisone injections in acute gout. Our panel's consensus remains that the benefits of joint injections for treatment of gout is not clear due to lack of strong evidence.

Consensus statement: The panel reached consensus that the statement “Allopurinol should be titrated until serum uric acid level is <6.0mg/dL” was appropriate. In addition, the panel reached consensus that the statement “Long-term medications, such as allopurinol, are necessary in treatment of recurrent gout” was appropriate.

A serum uric acid level <6.0 mg/dL is generally recommended as an initial target in hyperuricemia therapy (92,95). sUA below this level has been associated with a reduced frequency or prevention of gout flares (92,136,137). Lower serum urate level (<5.0 mg/dL) may be needed for some patients with more severe disease (137). Reducing serum urate levels between 4.6 and 6.6 mg/dL is associated with a 30% decline in recurrences of gouty arthritis compared with patients whose sUA remained above this range (126). The serum urate should be monitored every 2 to 5 weeks with dose titration until the target sUA level is achieved and the patient has shown signs of clinical improvement (138). Lowering the sUA too quickly or aggressively can lead to gouty flare (137). The ACP recommends against initiating long-term ULT in most patients after a first gout attack or in patients with <2 acute gout attacks per year (137).

According to the ACR and EULAR (92,95), patients who meet the criteria for initiation of ULT should be treated and maintained at a “target” sUA level with a xanthine oxidase inhibitor such as allopurinol or febuxostat. Allopurinol is considered the first line of treatment, and dose should be adjusted for renal function (136). Probenecid should also be considered as an alternative first-line agent when patients are intolerant to a xanthine oxidase inhibitor. There are limited data regarding the use of intermittent ULT or stopping ULT after resolution of gouty arthritis flares. Available studies show that patients will eventually have gout flares with intermittent use of ULT because of recurrence of crystal deposition. Conversely, the literature overwhelmingly supports continued therapy. Both the ACR and EULAR recommend that all ULT should be initiated at a low dose and the titrated upward until the sUA “target” is reached. Furthermore, an sUA <6.0 mg/dL should be maintained lifelong (136).

The duration of prophylactic therapy varies widely among practicing rheumatologists with recommendations ranging from 3 to 12 months (136). According to ACR guidelines, the duration of treatment should be at least 6 months (95,136). Alternatively, continued therapy should be considered for 3 months after achieving the target sUA appropriate for the patient (127). Although the recommendations vary between

rheumatologists and the ACP, our panel's consensus parallels the available data supporting long-term ULT (i.e., allopurinol) therapy with titrating ULT until the sUA is <6.0 mg/dL. Long-term use of ULT and maintaining sUA to “target” will improve long-term outcomes, prevent recurrent gout flares, and reduces risk for joint damage.

Consensus statement: The panel was unable to reach consensus on the statement “Joint implant replacement should be considered in cases of chronic gout.”

There is a paucity of literature specifically assessing joint implantation for gouty arthritis of the foot. Multiple studies list gouty arthritis as 1 of many reasons for performing first MTPJ implant arthroplasty (139–142) without any higher incidence of complications specific to gout, albeit with a very low number of gout patients in each study.

In a case report focusing on gouty arthritis post first MTPJ silastic implant replacement, in a patient with a prior history of gout (143), the authors recommended that synovectomy be performed in conjunction with implant arthroplasty to prevent the development of postoperative gouty attacks. In another study, a silastic joint implant was removed from the first MTPJ because of recurrent gouty attack (144). A case series of 19 Hintegra Total Ankle Replacement implants in 16 patients with history of gout reported no incidence of recurrent gout attack (145).

There are a few case reports involving acute gout attacks following total knee arthroplasty (TKA). Crawford et al reported on a case of acute gouty attack 3 months after a TKA in a patient with no prior history of gout (146). In another study, a patient with history of pedal gout developed an acute gout of his knee 2 years after a TKA (147).

There is inadequate evidence to support or negate the use of joint replacement in patients with gout. In the absence of strong evidence, the panel suggests that if joint replacement is to be done that complete synovectomy be considered to reduce recurrence and possible postoperative complications; however, this suggestion is based on limited available evidence.

Consensus statement: The panel was unable to reach consensus on the statement “Arthroscopic debridement may be used in acute or chronic gout.”

The use of joint arthroscopy in treatment of foot and ankle is lacking high-level evidence. Wang et al reported short-term satisfactory results in 9 cases of gout at first MTPJ postarthroscopic debridement (148). The effectiveness of arthroscopic debridement of gout in the first MTPJ has also been compared with use of medical therapy in patients with persistent hyperuricemia and recurrent gout. Fifteen patients whose symptoms were not relieved after 6 months of medical therapy were selected to undergo arthroscopic debridement. Another 13 patients declined operative intervention but continued on antigout therapy (control group). The authors noted reduced rate of acute, repeated attacks of gouty arthritis with an increase in both foot and ankle function using American Orthopaedic Foot and Ankle Society Ankle-Hind-foot Scale when compared with the control group (149).

In a study by Li et al, a significant reduction in edema and pain was seen after ankle arthroscopic debridement following acute gouty attacks (150). Furthermore, the mean number of acute gout attacks decreased significantly postoperation (150).

Although there are minimal data available, there is a trend toward better outcome with arthroscopic debridement in contrast to medical treatment alone. Our panel recommends further research is needed to better determine the role of arthroscopy in treatment of gout in joints of foot and ankle, where there are higher risks for an acute gout attack.

Consensus statement: The panel reached consensus that the statement “Multidisciplinary referral provides optimal care in cases of recalcitrant gout” was appropriate.

There is little evidence demonstrating the efficacy of multidisciplinary care specific to outcomes in treatment of those with gout or

hyperuricemia. A few consensus statements and recommendations have been produced using a multidisciplinary approach or consensus; however, they fall short in describing actual implementation of multidisciplinary care for such patients (95,151).

Significant reduction in cardiovascular disease risk factors in subjects with gout has been reported after implementation of a multidisciplinary nurse-led approach to managing patients (152). A nurse-led multidisciplinary study by Fields et al (153) resulted in a drop in median serum urate level from 7.6 (n = 44) at baseline to 5.1. There was also reduction in frequency of gouty flares among subjects. Pharmacist-led programs also shown to be effective, but to a lesser degree (154,155). A 2012 study by Rees et al (156) evaluated the effect of ULT in combination with nurse-led education on lifestyle and disease management. Ninety-two percent of the study subjects experienced a reduction of serum uric acid to a therapeutic level. Over 12 months, the median score as reported on the short form health survey (Short Form-36) improved for study subjects.

Multidisciplinary care has proven to lower mortality rates, shorten hospital stay, reduce frequency of hospital readmission, and provide overall reduction in cost of health care delivery in several other disease processes (157–165). Although a few studies have evaluated the effect of multidisciplinary care on outcomes for patients with gout, this panel's consensus supports the positive impact of such a health care model. Both physiologic and economic measures can be enhanced through the implementation of a nurse-led multidisciplinary care.

Consensus statement: The panel reached consensus that the statement "Patient education should include dietary modification, medication adherence, and follow-up care with their assigned health care providers" was appropriate.

Current studies have long held that patients' knowledge and understanding of their disease and treatment regimen can affect disease management and their quality of life. A study of 240 patients with gout demonstrated that only a small percentage was aware of common dietary triggers for gout (166). This knowledge deficit was greater for those experiencing active gout. Additionally, Chandratte et al (167) showed a lack of provider educational information and absence of patient disease understanding to directly correlate with a decreased health-related quality of life in patients with gout.

Dietary practices of patients with active gout have shown to deviate from dietary modifications recommended by health care providers. Shulten et al (168) studied subjects with active gout and matched their actual dietary practices against current evidence for nutritional management of patients with gout. Patients' reported intake of specific foods was not in alignment with current evidence-based recommendations, including: alcohol (48%), beer (62%), seafood (100%), meat (24%), beef/pork/lamb (83%), dairy (41%), and vitamin C supplements (100%).

Just as education on dietary modification is essential, so is educating patients about the need for medication adherence. Nonadherence to ULT was found in 47% of patients in a systematic review of the literature (169). A similar study by Corbett et al (170) demonstrated nonadherence to medication therapy as a major reason for not achieving serum uric acid levels in 27% of the patients. Sheer et al (171) and Rashid et al (172) found adherence to ULT as a significant contributor to achieving target serum uric acid levels. Systematic reviews have shown overall medication adherence rate for ULT to range from 10% to 46% (173,174). ULT adherence was significantly correlated with increase in education (175,176). As such, insufficient education has been cited an important factor for nonadherence (177,178). A nurse-led education program showed >85% medication adherence for ULT medications (179). The panel agrees that patient education and reinforcement about disease management will result in greater lifestyle and medication adherence.

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