

# 2011 Recommendations for the Diagnosis and Management of Gout and Hyperuricemia

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DOI: 10.3810/psm.2011.11.1934

**Abstract:** Gout is a major health problem in the United States; it affects 8.3 million people, which is approximately 4% of the adult population. Gout is most often diagnosed and managed in primary care practices; thus, primary care physicians have a significant opportunity to improve patient outcomes. Following publication of the 2006 European League Against Rheumatism (EULAR) gout guidelines, significant new evidence has accumulated, and new treatments for patients with gout have become available. It is the objective of these 2011 recommendations to update the 2006 EULAR guidelines, paying special attention to the needs of primary care physicians. The revised 2011 recommendations are based on the Grading of Recommendations Assessment, Development, and Evaluation approach as an evidence-based strategy for rating quality of evidence and grading the strength of recommendation formulated for use in clinical practice. **A total of 26 key recommendations, 10 for diagnosis and 16 for management,** of patients with gout were evaluated, resulting in important updates for patient care. The presence of monosodium urate crystals and/or tophus and response to colchicine have the highest clinical diagnostic value. The key aspect of effective management of an acute gout attack is initiation of treatment within hours of symptom onset. Low-dose colchicine is better tolerated and is as effective as a high dose. When urate-lowering therapy (ULT) is indicated, the xanthine oxidase inhibitors allopurinol and febuxostat are the options of choice. Febuxostat can be prescribed at unchanged doses for patients with mild-to-moderate renal or hepatic impairment. The target of ULT should be a serum uric acid level that is  $\leq 6$  mg/dL. For patients with refractory and tophaceous gout, intravenous pegloticase is a new treatment option. This article is a summary of the 2011 clinical guidelines published in *Postgraduate Medicine*. This article provides a streamlined, accessible overview intended for quick review by primary care physicians, with the full guidelines being a resource for those seeking additional background information and expanded discussion.

**Keywords:** gout; hyperuricemia; guideline recommendations; rheumatology

## Introduction

Gout is a major health problem in the United States, affecting 8.3 million.<sup>1</sup> Although gout is a well-understood condition and good therapeutic options are available, it tends to be poorly managed,<sup>2-5</sup> with insufficient patient evaluation,<sup>6</sup> inappropriate use of traditional and new medications,<sup>3-8</sup> and low patient adherence.<sup>6,9</sup> Because gout is most often diagnosed and managed by primary care physicians (PCPs),<sup>10</sup> PCPs have a significant opportunity to ensure that more patients who are diagnosed with gout receive optimized, state-of-the-art care.

In 2006, The European League Against Rheumatism (EULAR) published evidence-based guidelines for the diagnosis and management of patients with gout throughout

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all stages of the disease.<sup>11,12</sup> Since then, significant new evidence has accumulated, and new treatments for patients with gout have become available. Therefore, it is the objective of the 2011 recommendations to update the 2006 EULAR guidelines with current information, paying special attention to the needs of primary care physicians (PCPs).

## Methods

A multidisciplinary team with members specializing in rheumatology, nephrology, cardiology, primary care, and allied health reviewed the diagnostic and management recommendations published by the EULAR in 2006.<sup>11,12</sup> The EULAR evidence hierarchy for diagnosis and management of gout was based primarily on study design. The revised propositions or recommendations are based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach<sup>13</sup> as an evidence-based strategy for rating quality of evidence and grading the strength of recommendations formulated for use in clinical practice.

## Strength of Recommendation

Strength-of-recommendation scores express expert experience and consensus. Each team member rated the strength of each agreed-upon recommendation on 2 scales: a categorical scale (as fully, strongly, moderately, weakly, or not recommended) and a visual analog scale (VAS) ranging from 60 (weak recommendation) to 100 (strong recommendation). Based on categorical data, the percentage of strongly and fully recommended scores was calculated for each recommendation. Analysis of continuous data resulted in a mean VAS score with 95% CIs for each recommendation.

## Literature Inclusion/Exclusion Criteria

According to GRADE, important patient-centered diagnostic and management outcomes were created for each recommendation (eg, for a therapeutic drug recommendation, outcomes may pertain to efficacy or adverse effects [AEs]).<sup>14</sup> For the diagnostic guidelines, the PubMed search limits for the 31 searches conducted were: English-language articles published from February 2005 to February 2011, including clinical trials, meta-analyses, randomized controlled trials (RCTs), reviews, case reports, comparative studies, and validation studies, with search terms present in their titles or abstracts. This resulted in 1024 articles, from which duplicates were deleted. For the management guidelines, identical search criteria applied to 116 PubMed searches resulted in 2009 articles, which were also vetted for applicable content. Based on their abstracts, 329 articles (72 pertaining to gout diagnosis and 257 pertaining to gout management) were selected for closer review in their full-text versions. Full-text articles that provided data relevant to important outcomes in the diagnosis or management of patients with gout were then listed in data tables and given to an experienced statistician team for quality-of-evidence evaluation. Relevant treatment updates not featured in the *Postgraduate Medicine* Special Report "2011 Recommendations for the Diagnosis and Management of Gout and Hyperuricemia."<sup>15</sup> are updated here based on abstracts presented at the **American College of Rheumatology (ACR)/Association of Rheumatology Health Professionals (ARHP) Scientific Meeting 2011 held in Chicago, IL.**

## Statistical Analysis

In an effort to achieve continuity between the original recommendations and our updated analyses, we utilized the statistical tools used and described in the 2006

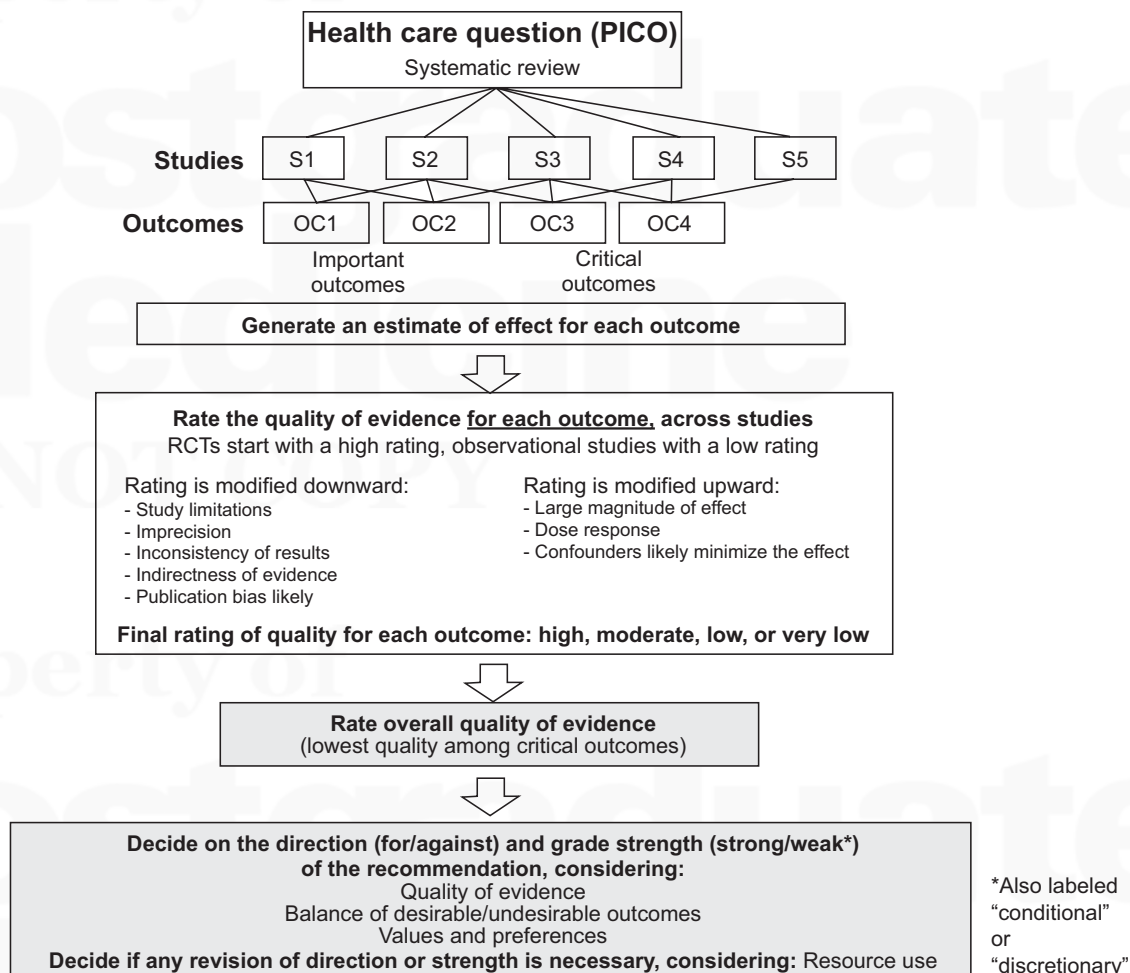
EULAR recommendations for the diagnosis and management of patients with gout.<sup>11,12</sup> Only study endpoints with sufficient published data could be considered for statistical analysis. For full methodology, please see the *Postgraduate Medicine* Special Report “2011 Recommendations for the Diagnosis and Management of Gout and Hyperuricemia.”<sup>15</sup>

## Quality of Evidence

Patient-centered outcomes with statistical results were summarized in GRADE evidence profile and summary of findings tables.<sup>16</sup> Based on GRADE quality-assessment criteria (Figure 1), the quality of supporting literature for each outcome was rated as high, moderate, low, or very low. Quality-of-evidence scores of relevant outcomes were summarized to obtain the overall quality-of-evidence rating for each diagnostic and management recommendation.<sup>16</sup>

Thus, each recommendation received 2 evaluations—a strength-of-recommendation score conveying expert opinion and a quality-of-evidence rating expressing the quality of available supporting literature.<sup>13,16–19</sup> Both GRADE scores are reported separately to preserve transparency of the guidelines’ decision-making process and to allow physicians to use expert opinion and objective quality measures as appropriate for each patient management decision (Tables 1, 2). A strong recommendation supporting a behavior or intervention reflects the collective judgment that the desirable effects of the intervention will clearly outweigh the undesirable effects. A weak recommendation reflects the collective opinion that the desirable effects will outweigh the undesirable effects, but the panel is not confident about the true balance of benefit versus risk, either because key evidence is of low quality or because the desirable effects and undesirable effects are closely balanced.<sup>16</sup>

Figure 1. The GRADE process for developing guidelines



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**Abbreviation:** PICO, patient or population (P), intervention (I), comparison (C), and outcome(s) (O); GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.

**Table 1.** Strength of Diagnostic Recommendation Scores<sup>a</sup>

Average VAS Score (60 = weak recommendation; 100 = strong recommendation)	SOR (95% CI)	
	VAS 100	A–B% <sup>b</sup>
<b>Proposition</b>		
1. In acute monoarticular attacks of the lower extremities, the rapid development of severe pain, swelling, and tenderness that reaches its maximum within 6–12 hours, especially with overlying erythema, is highly suggestive of crystal inflammation, although not specific for gout (1B).	93 (91–94)	96
2. Although only the demonstration of MSU crystals in synovial fluid or tophus aspirates constitutes a definite diagnosis of gout, a clinical diagnosis alone is reasonably accurate in patients with typical presentations of gout (1B).	90 (89–91)	90
3. While being the most important risk factor for gout, SUA levels do not confirm or exclude gout, as many people with hyperuricemia do not develop gout, and SUA levels may be normal during acute attacks (2C).	80 (79–81)	47
4. In available synovial fluid samples obtained from undiagnosed inflamed joints, a routine search for MSU crystals is recommended (2D).	82 (81–82)	53
5. When the diagnosis is in doubt, identification of MSU crystals from asymptomatic joints may allow definite diagnosis during intercritical periods (2D).	85 (84–86)	65
6. Gout and sepsis may coexist; therefore, when septic arthritis is suspected, Gram staining and culture of synovial fluid should still be performed, even if MSU crystals are identified (1D).	92 (91–93)	95
7. Assessment of renal UA excretion is rarely necessary in patients with gout. It should, however, be considered in those with young-onset gout (aged < 25 years) or a family history of young-onset gout (2D).	87 (86–88)	80
8. Patients with gout have a high incidence of renal stones, and those with stones should have a lithogenic workup (New) (2D).	88 (87–89)	80
9. Radiographs may be useful for differential diagnosis and may show typical features in gout. They are not useful in confirming the diagnosis of early or acute gout, and should only be performed if a fracture is suspected (2D).	91 (90–92)	89
10. Risk factors for gout should be assessed, including features of metabolic syndrome (obesity, hyperglycemia, hyperlipidemia, and hypertension), CKD, medications, family history, and lifestyle. Only CKD, diuretics (1B), and other outcomes (2B) have been graded for quality of evidence.	97 (96–98)	100

<sup>a</sup>Adapted table features updated information from the 2006 EULAR evidence-based recommendations for gout.<sup>12</sup>

<sup>b</sup>A–B% = percentage of highly to strongly recommended, based on the EULAR ordinal scale (A = highly recommended, B = strongly recommended, C = moderately recommended, D = weakly recommended, E = not recommended).<sup>12</sup>

High quality of evidence (A), moderate (B), low (C), very low (D); strength of recommendation strong (Grade 1) or weak (Grade 2).

**Abbreviations:** CKD, chronic kidney disease; EULAR, The European League Against Rheumatism; MSU, monosodium urate; SOR, strength of recommendation; SUA; serum uric acid; UA; uric acid; VAS, visual analog scale.

## Results

### Diagnostic Recommendations

A correct diagnosis of gout is essential for the appropriate management of affected patients. Although a definite diagnosis of gout can be established only through the presence of monosodium urate (MSU) in synovial fluid or tophi, clinical criteria have remained a practical tool for identifying patients with gout. Because these patients tend to present with several comorbidities, a thorough patient evaluation is an important aspect in the diagnosis of gout.

1. In acute monoarticular attacks of the lower extremities, the rapid development of severe pain, swelling, and tenderness that reaches its maximum within 6 to 12 hours, especially with overlying erythema, is highly suggestive of crystal inflammation, although not specific for gout.

*Strength of recommendation:* 93 (95% CI, 91–94)

*Highly or strongly recommend:* 96%

*Quality of evidence:* Moderate, Grade 1 recommendation

#### Rationale

Signs and symptoms such as painful joint, swelling, severely painful attacks of sudden onset, and remission within 2 weeks are of limited diagnostic value due to their poor specificity for gout.<sup>12</sup> Results by Janssens et al<sup>20</sup> suggest similar limitations for the clinical criteria “overlying erythema” and “development of severe pain within one day.” Although these criteria had a high sensitivity for gout (ie, using these criteria would result in a high likelihood that patients with gout would be identified), they showed poor specificity (ie, many patients with inflammatory joint conditions other than gout would be incorrectly identified as having gout) (Table 3).

Rapid onset of severe pain, swelling, and erythema that is self-limiting, while indicative of crystal-associated syno-

**Table 2.** Strength of Management Recommendation Scores<sup>a</sup>

Average VAS Score (60 = weak recommendation; 100 = strong recommendation)	SOR (95% CI)	
	VAS 100	A–B% <sup>b</sup>
<b>Proposition</b>		
1. Optimal treatment of gout requires both nonpharmacologic and pharmacologic modalities and should be tailored according to: <ul style="list-style-type: none"> <li>• Specific risk factors (levels of serum urate, previous attacks, radiographic signs)</li> <li>• Clinical phase (acute gout, intercritical gout, or advanced [ie, chronic tophaceous] gout)</li> <li>• General risk factors (age, sex, obesity, diet, alcohol consumption, urate-elevating drugs, drug interactions, renal function, and comorbidities) (1D).</li> </ul>	97 (96–98)	100
2. Patient education pertaining to beneficial lifestyle changes, compliance with long-term therapy, and the possibility/prevention of flares early in the course of ULT are core aspects of gout management (1D).	94 (93–95)	96
3. Associated modifiable comorbidities and risk factors, such as hyperlipidemia, hypertension, hyperglycemia, obesity, and smoking, should be addressed as an important part of the management of patients with gout (1B).	96 (95–97)	100
4. Oral colchicine, NSAIDs, and glucocorticoids may be used as first-line treatments of patients with acute gout. The choice will depend on patient and physician preference, with consideration of comorbidities (especially a history of CKD and GI disease). It may be necessary to continue treatment for an additional 7–10 days (1C).	97 (96–98)	100
5. For acute gout, low-dose colchicine (ie, 1.2 mg administered as soon as possible, followed by 0.6 mg 1 hour later) is effective and well tolerated. Colchicine should be continued for an additional 7–10 days or until the flare is resolved. High-dose colchicine is not indicated and should not be prescribed (1D).	93 (92–94)	90
6. For an acute attack, after sufficient precautions have been taken, intra-articular aspiration and injection of a long-acting steroid is an effective and generally well-tolerated treatment (1D).	95 (93–96)	85
7. ULT is indicated in patients with any of the following: recurrent attacks (> 1 attack per year), chronic arthropathy, tophaceous deposits, nephrolithiasis, or radiographic changes of gout. Once initiated, ULT is considered a lifelong treatment recommendation (1C).	97 (96–98)	95
8. The therapeutic goal of ULT is to prevent acute flares, prevent the development of tophi, help dissolve tophi, and prevent the development of chronic gouty arthropathy. This is achieved by maintaining an SUA level of < 6.0 mg/dL, well below the saturation point for MSU of 6.8 mg/dL (1C).	97 (96–98)	100
9. The xanthine oxidase inhibitors (allopurinol and febuxostat) are the agents of choice for ULT to reach the therapeutic target SUA level of < 6.0 mg/dL. The dose should be titrated to optimize safety and minimize the chance of precipitating an acute flare. SUA should be monitored to ascertain the achievement and maintenance of this goal. Appropriate laboratory monitoring for toxicity is indicated (1C).	95 (94–96)	100
10. Allopurinol should be started at a low dose (100 mg daily) and increased by 100 mg every 2–4 weeks (to a maximum allowable dose of 800 mg/day) as necessary to achieve the target SUA level goal of < 6.0 mg/dL. If allopurinol toxicity occurs, it should be stopped immediately. Other treatment options include febuxostat or probenecid (1B).	95 (94–96)	100
11. Febuxostat should be started at 40 mg daily and may be increased to 80 mg after at least 2 weeks of treatment, if necessary, to achieve the target SUA level goal of < 6.0 mg/dL. If toxicity occurs, febuxostat should be stopped immediately. Other treatment options include allopurinol or probenecid. However, allopurinol and febuxostat should not be coadministered (New) (1C).	97 (96–98)	100
12. Probenecid, a uricosuric agent, can be used as an alternative to a xanthine oxidase inhibitor in patients with normal renal function, but is relatively contraindicated in patients with nephrolithiasis and ineffective in the presence of renal insufficiency. Probenecid can be used together with allopurinol or febuxostat, if necessary, to achieve the target goal of lowering SUA levels to < 6.0 mg/dL. Dosing may begin at 500 mg daily, with titration monthly up to a maximum of 3 g/day in divided doses (1D).	93 (92–94)	90
13. Prophylaxis against acute attacks during the first 6–12 months of ULT can be achieved by colchicine (given as tolerated, 0.6 mg once or twice daily) or an NSAID (with gastroprotection, if indicated). Prophylaxis should be initiated 2 weeks prior to the implementation of ULT (1D).	97 (96–98)	100
14. Certain diuretics may increase the risk of an acute gout attack. In this circumstance, the use or dose of diuretic should be reassessed as possible. In some circumstances (eg, in patients with heart failure), the use of diuretics may be necessary. In such instances, subsequent gout attacks may occur and should be managed accordingly (2C).	91 (90–92)	76
15. For patients who have refractory gout and/or resistant tophaceous disease, another treatment option is pegloticase. Pegloticase is administered by infusion and has a significant risk profile. Patients who may be candidates should be referred to health care professionals with expertise in the use of pegloticase (2D).	94 (93–95)	82

(Continued)

**Table 2. (Continued)**

Average VAS Score (60 = weak recommendation; 100 = strong recommendation)	SOR (95% CI)	
	VAS 100	A-B% <sup>b</sup>
<b>Proposition</b> 16. Considerations for referring a patient with gout to a rheumatologist or nephrologist include <ul style="list-style-type: none"> <li>• Confirmation of diagnosis, particularly in patients with atypical presentation</li> <li>• Management of refractory cases when:                             <ul style="list-style-type: none"> <li>• An SUA level of &lt; 6.0 mg/dL cannot be achieved</li> <li>• Recurrent flares occur despite apparent adequate treatment</li> <li>• A patient presents with persistent and/or extensive tophaceous disease</li> </ul> </li> <li>• Management of patients with nephrolithiasis</li> <li>• Consideration for complex treatment options (ID).</li> </ul>	94 (93–95)	100

<sup>a</sup>Adapted table features updated information from the 2006 EULAR evidence-based recommendations for gout.<sup>11</sup>

<sup>b</sup>A–B% = percentage of highly to strongly recommended, based on the EULAR ordinal scale (A = highly recommended, B = strongly recommended, C = moderately recommended, D = weakly recommended, E = not recommended).<sup>12</sup> High quality of evidence (A), moderate (B), low (C), very low (D); strength of recommendation strong (Grade 1) or weak (Grade 2).

**Abbreviations:** CKD, chronic kidney disease; GI, gastrointestinal; MSU, monosodium urate; NSAID, nonsteroidal anti-inflammatory drug; SOR, strength of recommendation; SUA, serum uric acid; ULT, urate-lowering therapy; VAS, visual analog scale.

vitis, appears to have limited diagnostic value for a definitive diagnosis of gout (Figure 2, Table 3).

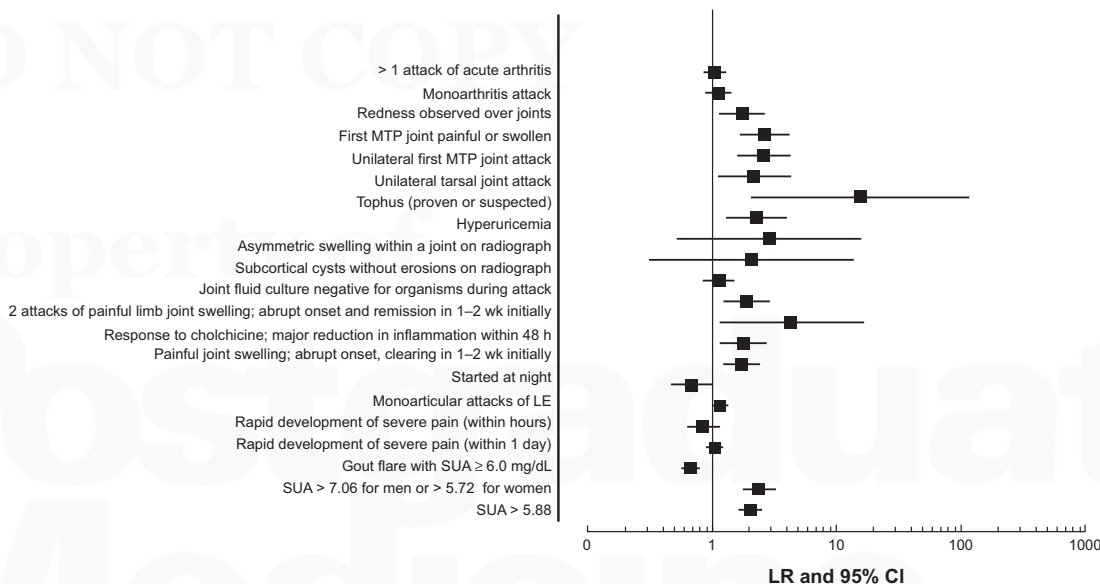
Women may present with atypical signs and symptoms of gout. A systematic review of the literature indicated that women were an average of being almost one decade older than men when experiencing their first gout attack and presented less frequently than men with metatarsophalangeal (MTP1) involvement.<sup>21</sup> Instead, polyarticular gout affecting the ankles or joints of the fingers and upper limbs was more common in women.<sup>21</sup> Therefore, it is prudent to consider gout as a possible diagnosis in postmenopausal women with acute arthritis, especially in areas of prior osteoarthritis and in the ankle.

2. Although only the demonstration of MSU crystals in synovial fluid or tophus aspirates constitutes a definite diagnosis of gout, a clinical diagnosis alone is a reasonable alternative in patients with typical presentations of gout.  
*Strength of recommendation:* 90 (95% CI, 89–91)  
*Highly or strongly recommend:* 90%  
*Quality of evidence:* Moderate, Grade 1 recommendation

**Rationale**

Based on data from case-control studies and reviews of case-control studies, EULAR recommended the detection

**Figure 2.** Likelihood ratio and 95% CI for various features in the diagnosis of gout.



According to EULAR, an LR of > 1 indicates that the test result is associated with the presence of gout, whereas an LR of < 1 indicates that the test result is associated with the absence of gout.

**Abbreviations:** EULAR, The European League Against Rheumatism; LE, lower extremities; LR, likelihood ratio; SUA, serum uric acid.

**Table 3.** Evidence of Diagnostic Test: Sensitivity, Specificity, and Likelihood Ratio

Diagnostic Test	Gold Standard	N	Sensitivity (95% CI)	Specificity (95% CI)	LR (95% CI) <sup>a</sup>	Reference
Monoarticular attacks of lower extremities (1B)	MSU	328	0.33 (0.26–0.41)	0.53 (0.39–0.66)	0.69 (0.48–1.0)	20
Overlying erythema (1B)	MSU	328	0.89 (0.84–0.93)	0.24 (0.16–0.32)	1.17 (1.04–1.31)	20
Rapid development of severe pain (within hours) (1B)	MSU	328	0.37 (0.31–0.44)	0.56 (0.47–0.65)	0.85 (0.65–1.12)	20
Rapid development of severe pain (within 1 day) (1B)	MSU	328	0.79 (0.73–0.85)	0.24 (0.17–0.33)	1.05 (0.93–1.19)	20
Gout flare with SUA $\geq$ 6.0 mg/dL			0.19 (0.18–0.21)	0.71 (0.69–0.74)	0.68 (0.59–0.77)	83
SUA > 7.06 mg/dL for men or > 5.72 mg/dL for women	MSU	327	0.77 (0.71–0.82)	0.68 (0.58–0.76)	2.39 (1.82–3.14)	20
SUA > 5.88 mg/dL	MSU	327	0.95 (0.91–0.98)	0.53 (0.44–0.63)	2.04 (1.68–2.48)	20
> 1 attack of acute arthritis	MSU	82	0.87 (0.68–0.96)	0.17 (0.09–0.31)	1.04 (0.87–1.26)	118
Monoarthritis attack	MSU	82	0.86 (0.67–0.95)	0.24 (0.13–0.38)	1.13 (0.91–1.39)	118
Redness observed over joints	MSU	82	0.72 (0.53–0.87)	0.58 (0.43–0.72)	1.74 (1.16–2.60)	118
First MTP joint painful or swollen	MSU	82	0.83 (0.65–0.94)	0.69 (0.54–0.80)	2.66 (1.72–4.11)	118
Unilateral first MTP joint attack	MSU	82	0.77 (0.57–0.89)	0.71 (0.56–0.82)	2.61 (1.63–4.17)	118
Unilateral tarsal joint attack	MSU	82	0.48 (0.30–0.67)	0.78 (0.64–0.88)	2.19 (1.15–4.18)	118
Tophus (proven or suspected)	MSU	82	0.37 (0.20–0.58)	0.98 (0.86–1.00)	15.56 (2.11–114.71)	118
Hyperuricemia	MSU	82	0.89 (0.71–0.97)	0.61 (0.39–0.80)	2.28 (1.35–3.86)	118
Asymmetric swelling within a joint on radiograph	MSU	82	0.19 (0.05–0.46)	0.94 (0.77–0.99)	2.91 (0.54–15.66)	118
Subcortical cysts without erosions on radiograph	MSU	82	0.13 (0.02–0.40)	0.94 (0.78–0.99)	2.06 (0.32–13.34)	118
Joint fluid culture negative for organisms during attack	MSU	82	1.0 (0.56–1.0)	0.13 (0.01–0.53)	1.14 (0.88–1.49)	118
2 attacks of painful limb joint swelling. Abrupt onset and remission in 1–2 weeks initially	MSU	82	0.74 (0.53–0.88)	0.61 (0.46–0.74)	1.89 (1.26–2.84)	118
Response to colchicine; major reduction in inflammation within 48 hours	MSU	82	0.67 (0.41–0.86)	0.85 (0.54–0.97)	4.33 (1.16–16.16)	118
Painful joint swelling; abrupt onset, clearing in 1–2 weeks initially	MSU	82	0.70 (0.50–0.86)	0.61 (0.46–0.74)	1.79 (1.18–2.73)	118
Started at night	MSU	82	0.90 (0.68–0.98)	0.48 (0.33–0.63)	1.73 (1.26–2.37)	118

<sup>a</sup>LRs > 1 are more likely to support the diagnosis of interest.

**Abbreviations:** LR, likelihood ratio; MSU, monosodium urate; MTP, metatarsophalangeal; SUA, serum uric acid.

of MSU in affected tissue as the diagnostic gold standard for symptomatic gout, despite interobserver variability.<sup>12</sup> However, the routine demonstration of MSU for the diagnosis of gout may not be feasible in busy PCP practices.<sup>22,23</sup> This is not problematic in patients presenting with the typical signs and symptoms of gout, particularly in the presence of podagra, because clinical criteria can be used to make a working diagnosis of gout (Figure 2).

**3. While being the most important risk factor for gout, SUA levels do not confirm or exclude gout, as many people with hyperuricemia do not develop gout, and SUA levels may be normal during acute attacks.**

*Strength of recommendation:* 80 (95% CI, 79–81)

*Highly or strongly recommend:* 47%

*Quality of evidence:* Low, Grade 2 recommendation

#### Rationale

Elevated SUA levels are a significant risk factor for gout. Persistence of hyperuricemia at levels higher than a serum saturation of 6.8 mg/dL leads to deposits of urate on articular cartilage. Although hyperuricemia can remain silent for years and does not always progress to clinically recognizable gout,<sup>22</sup> higher SUA levels are associated with greater risk for developing gout.

However, SUA is not always a reliable diagnostic tool for gout. Flares (termed mobilization flares) may occur during the implementation of urate-lowering therapy (ULT) as

urate levels decrease. Also, normal SUA levels are sometimes present during acute flares due to an increase in renal urate excretion, which has been linked to increases in cytokines and other inflammatory stimuli.<sup>24,25</sup>

**4. In available synovial fluid samples obtained from undiagnosed inflamed joints, a routine search for MSU crystals is recommended.**

*Strength of recommendation:* 82 (95% CI, 81–82)

*Highly or strongly recommend:* 53%

*Quality of evidence:* Very low, Grade 2 recommendation

#### Rationale

Although the examination of synovial fluid is not routinely required for the correct diagnosis of gout in patients with a typical presentation, a confirmation is appropriate when synovial fluid is already available. In patients using a hospital-based rheumatology service, joint aspiration resulted in a definite diagnosis of gout, septic arthritis, or pseudogout in 44% (n = 38) of 86 procedures.<sup>26</sup>

**5. When the diagnosis is in doubt, identification of MSU crystals from asymptomatic joints may allow definite diagnosis during intercritical periods.**

*Strength of recommendation:* 85 (95% CI, 84–86)

*Highly or strongly recommend:* 65%

*Quality of evidence:* Very low, Grade 2 recommendation

#### Rationale

According to EULAR recommendations, MSU crystals have been identified in aspirated synovial fluid during intercritical periods.<sup>12</sup> However, although MSU eventually disappeared from synovial fluid of all study participants in 1 trial, MSU clearance required 3 to 33 months.<sup>27</sup>

**6. Gout and sepsis may coexist; therefore, when septic arthritis is suspected, Gram staining and culture of synovial fluid should still be performed, even if MSU crystals are identified.**

*Strength of recommendation:* 92 (95% CI, 91–93)

*Highly or strongly recommend:* 95%

*Quality of evidence:* Very low, Grade 1 recommendation

#### Rationale

Patients with suspected gout who present with fever, feel as if they may have influenza, or have test results that show an elevated white blood cell count should be suspected of having sepsis. In these patients, synovial fluid aspiration can

correctly identify septic arthritis.<sup>26,28</sup> In patients suspected of having sepsis, culture of the synovial fluid should be performed, even if MSU has been identified.

**7. Assessment of renal UA excretion is rarely necessary in patients with gout. It should, however, be considered in those with young-onset gout (aged 25 years) or a family history of young-onset gout.**

*Strength of recommendation:* 87 (95% CI, 86–88)

*Highly or strongly recommend:* 80%

*Quality of evidence:* Very low, Grade 2 recommendation

#### Rationale

The identification of patients with hereditary gout is necessary for tailoring ULT appropriately. Familial juvenile hyperuricemic nephropathy, an autosomal dominant disorder that can affect both men and women, is characterized by frequent, but not universal, hyperuricemia, frequent gout, slowly progressive renal disease, and low fractional excretion of UA (fractional excretion of UA,  $5.1\% \pm 1.6\%$ ) relative to glomerular filtration rate.<sup>29,30</sup> Less frequently, P-ribosyl-PP synthetase super activity leads to gross overproduction of UA and therefore to gout, kidney stones, or acute renal failure in men and women.<sup>29</sup> Only men are at risk for young-onset gout caused by the absence of hypoxanthine-guanine phosphoribosyltransferase (HGPRT). Deficiency in HGPRT is associated with Lesch-Nyhan syndrome, which expresses with severe neurologic manifestations, a tendency for self-mutilation, and UA over-excretion that may lead to crystal-caused obstructive uropathy.<sup>29</sup> Medications that may be introduced in the next 3 to 5 years may necessitate a change in this recommendation, and thus it is important to remain current with the literature.

**8. Patients with gout have a high incidence of renal stones, and those with stones should have a lithogenic workup.**

*Strength of recommendation:* 88 (95% CI, 87–89)

*Highly or strongly recommend:* 80%

*Quality of evidence:* Very low, Grade 2 recommendation

#### Rationale

Nephrolithiasis is sometimes associated with gout. Overproduction of UA leads to the development of UA-containing stones. Because uricosuric therapy for gout can promote renal lithiasis in some patients, appropriate patient selection for uricosuric therapy depends on a thorough evaluation of risk



**Table 4.** Selected Risk Factors and Comorbidities Associated with Gout (OR)

Risk Factor/Comorbidity	Adjusted OR (95% CI)	Reference
Monoarticular attacks of lower extremities	0.54 (0.29–1.03)	20
Overlying erythema	2.62 (1.42–4.82)	20
Rapid development of severe pain (within hours)	0.77 (0.49–1.21)	20
Rapid development of severe pain (within 1 day)	1.24 (0.73–2.13)	20
SUA > 7.06 mg/dL for men or > 5.72 mg/dL for women and presence of MSU crystals	7.06 (4.27–11.68)	20
SUA > 5.88 mg/dL and presence of MSU crystals	22.80 (10.98–47.35)	20
SUA > 7.0 mg/dL compared with SUA < 6.0 mg/dL and gout flares	1.49 (1.21–2.42)	119
Renal stones and MSU crystals	1.60 (0.65–3.93)	20
Diabetes and MSU crystals	1.01 (0.43–2.37)	20
Hypertension and MSU crystals	2.56 (1.59–4.12)	20
≥ 1 CVD	2.65 (1.47–4.79)	20
Hypertension or ≥ 1 CVD	3.09 (1.94–4.94)	20
Creatinine > 1.19 mg/dL	2.82 (1.47–5.43)	20
Glomerular filtration rate, < 90 mL/min/1.73 m <sup>2</sup>	2.30 (1.44–3.69)	20
Glomerular filtration rate, < 60 mL/min/1.73 m <sup>2</sup>	2.82 (1.47–5.43)	20
Erythrocyte sedimentation rate (reduced can indicate CHF) > 20 for men or > 30 for women	1.55 (0.96–2.49)	20
CRP level > 1 mg/dL (for CVD or liver)	1.94 (1.22–3.09)	20
Diuretics and gout	3.60 (1.4–9.7)	106
Diuretics and MSU	1.99 (1.15–3.44)	20
Antiplatelet agents, aspirin, and MSU	1.24 (0.85–1.81)	20
Cardiovascular or antihypertensive drugs and MSU	2.69 (1.69–4.29)	20
Family history of gout and MSU	0.93 (0.56–1.55)	20
Any alcohol and MSU	1.31 (0.82–2.07)	20
Beer and MSU	3.10 (1.85–5.21)	20
Wine and MSU	0.42 (0.24–0.73)	20
Liquor and MSU	1.06 (0.53–2.11)	20
≥ 7 U/wk and MSU	1.22 (0.77–1.92)	20

LRs > 1 are more likely to support the diagnosis.

**Abbreviations:** CRP, C-reactive protein; CHF, congestive heart failure; CVD, cardiovascular disease; MSU, monosodium urate; OR, odds ratio; SUA, serum uric acid.

factors. Patients with gout who already present with renal stones may have an associated defect in urinary acidification. They should be referred to a nephrologist to undergo a lithogenic workup.

**9.** Radiographs may be useful for differential diagnosis and may show typical features in gout. They are not useful in confirming the diagnosis of early or acute gout, and should only be performed if a fracture is suspected.

*Strength of recommendation:* 91 (95% CI, 90–92)

*Highly or strongly recommend:* 89%

*Quality of evidence:* Very low, Grade 2 recommendation

#### Rationale

A number of imaging techniques have been proposed for the diagnosis and assessment of disease severity in patients with gout. The EULAR team concluded that radiography played only a limited role in gout diagnosis, mostly used in

patients with chronic, advanced, or severe disease.

**10.** Risk factors for gout should be assessed, including features of metabolic syndrome (obesity, hyperglycemia, hyperlipidemia, and hypertension), chronic kidney disease (CKD), medications, family history, and lifestyle.

*Strength of recommendation:* 97 (95% CI, 96–98)

*Highly or strongly recommend:* 100%

*Quality of evidence:* Moderate, Grade 2 recommendation

#### Rationale

##### Metabolic Syndrome

Comorbidities such as hypertension, hypertriglyceridemia, hypercholesterolemia, diabetes mellitus, and obesity are associated with a higher risk of gout.<sup>31</sup> A large cohort study (N = 12 179 men) conducted in Taiwan demonstrated that all features of metabolic syndrome increase the risk for gout in patients of all ages (Table 3).<sup>32</sup>

### Cardiovascular Disease

Research until 2006 strongly suggested that hypertension and coronary heart disease increased the risk for developing gout.<sup>12</sup> Subsequent studies underscored the interplay between cardiovascular disease (CVD) and gout. The Health Professionals Follow-up Study, which followed 51 297 men for 12 years, showed that those with hypertension had more than twice the risk for developing gout (relative risk [RR], 2.31 [95% CI, 1.96–2.72]).<sup>33</sup>

### CKD

Patients with CKD often present with gout because poor kidney function leads to insufficient urate clearance (Table 4). Conversely, patients with hyperuricemia may also be at greater risk for developing renal disorders.<sup>34</sup>

### Medication

Singh et al<sup>31</sup> determined that thiazide and loop diuretics were associated with an increased risk of incident gout and gout flares (Table 5). As more patients are using low-dose aspirin to prevent CVD, results of 2 studies mentioned by Singh et al<sup>35,36</sup> about this medication are of interest. Accordingly, low doses (1–2 g/day) of aspirin cause retention of UA, while high doses (> 3 g/day) are uricosuric.<sup>35</sup>

### Risk Factors in Women

The hormonal changes associated with menopause increase women's risk for gout.<sup>31</sup> When 92 535 women were followed for 16 years as part of the Nurses' Health Study, 1 703 developed gout.<sup>37</sup> In this study, menopause increased the risk for gout with an age-adjusted RR of 1.33 (95% CI, 1.08–1.63) and a multivariate-adjusted RR of 1.26 (95% CI, 1.03–1.55).<sup>37</sup>

## Management Recommendations

The identical multidisciplinary team also reviewed the management recommendations published by EULAR in 2006<sup>11,12</sup> using the same process as described for diagnosis.<sup>13</sup>

### 1. Optimal treatment of gout requires both nonpharmacologic and pharmacologic modalities and should be tailored according to:

- Specific risk factors (SUA levels, previous attacks, radiographic signs)
- Clinical phase (acute gout, intercritical gout, or advanced [ie, chronic tophaceous] gout)
- General risk factors (age, sex, obesity, diet, alcohol consumption, urate-elevating drugs, drug interactions, renal function, and comorbidities)

*Strength of recommendation:* 97 (95% CI, 96–98)

*Highly or strongly recommend:* 100%

*Quality of evidence:* Very low, Grade 1 recommendation

### Nonpharmacologic Measures

Gout is associated with a number of risk factors that should be minimized with weight-control measures and dietary changes to create the best environment possible for the pharmacologic management of the disease. Gout-specific risk factors, such as SUA levels, the clinical phase of the disease, and general risk factors, including a patient's lifestyle, overall health, and use of medications, guide the individual aspects of gout management in each patient (Table 5).<sup>38</sup> The *Postgraduate Medicine* Special Report "2011 Recommendations for the Diagnosis and Management of Gout and Hyperuricemia"<sup>15</sup> explores nonpharmacologic measures in greater detail.

### 2. Patient education pertaining to beneficial lifestyle changes, compliance with long-term therapy, and the prevention of flares early in the course of ULT are core aspects of gout management.

*Strength of recommendation:* 94 (95% CI, 93–95)

*Highly or strongly recommend:* 96%

*Quality of evidence:* Very low, Grade 1 recommendation

### Rationale

Significant challenges to the effective management of patients with gout include patient nonadherence to necessary lifestyle changes and to long-term use of prescribed medications, such as ULT. Therefore, patient education explaining key issues of gout therapy should begin after an initial gout attack. Research has shown that adherence to gout therapy is low.<sup>39–41</sup> Patient education will be essential to improved adherence.

### 3. Associated modifiable comorbidities and risk factors, such as hyperlipidemia, hypertension, hyperglycemia, obesity, and smoking, should be addressed as an important part of the management of patients with gout.

*Strength of recommendation:* 96 (95% CI, 95–97)

*Highly or strongly recommend:* 100%

*Quality of evidence:* Moderate, Grade 1 recommendation

### Rationale

The strong positive correlations between SUA/gout and hypertension,<sup>42–46</sup> CVD,<sup>47–50</sup> stroke,<sup>49,51</sup> cardiovascular mortality,<sup>32,49,52–57</sup> type 2 diabetes mellitus,<sup>58–61</sup> metabolic syndrome,<sup>48,62–64</sup> and kidney disease<sup>65,66</sup> have been established

**Table 5.** Selected Risk Factors and Comorbidities Associated with Gout (RR)<sup>a</sup>

Risk Factor/Comorbidity	Adjusted RR (95% CI)	Reference
Gout flare with SUA $\geq$ 6.0 mg/dL	0.79 (0.73–0.86)	83
SUA > 7.0 mg/dL compared with SUA < 6.0 mg/dL and gout flares	2.42 (1.46–4.02) women; 4.09 (2.37–7.07) men	38
Hypertension	1.82 (1.06–3.14) women; 1.59 (1.12–2.24) men	38
History of cardiometabolic disease and $\geq$ 1 flare during follow-up (mean, 3.8 years)	1.08 (1.04–1.12)	34
BMI < 25 kg/m <sup>2</sup> vs $\geq$ 30 kg/m <sup>2</sup>	2.74 (1.65–4.58) women; 2.90 (1.89–4.44) men	38
Diuretics	2.39 (1.53–3.74) women; 3.41 (2.38–4.89) men	38
Alcohol use $\geq$ 7 oz/week	3.10 (1.69–5.68) women; 2.21 (1.56–3.14) men	38

<sup>a</sup>Adapted table features updated information from the 2006 EULAR evidence-based recommendations for gout.<sup>11</sup>

**Abbreviations:** BMI, body mass index; CRP, C-reactive protein; EULAR, The European League Against Rheumatism; RR, relative risk.

by numerous large cohort study results (Tables 3, 4). The EULAR management recommendations suggest addressing the comorbidities that are commonly seen in order to promote global patient care and gout management.<sup>11</sup> However, this can be particularly challenging because many of the typical comorbidities seen in the context of gout result in contraindications to the very medications required for the treatment of the disease (Table 6).

4. In patients with acute gout, oral colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs), and glucocorticoids may be used as first-line treatments. The choice will depend on patient and physician preference, with consideration of comorbidities (especially a history of CKD and gastrointestinal [GI] disease). It may be necessary to continue treatment for an additional 7 to 10 days.

*Strength of recommendation:* 97 (95% CI, 96–98)

*Highly or strongly recommend:* 100%

*Quality of evidence:* Low, Grade 1 recommendation

#### Rationale

Quick initiation (within 12–24 hours after onset of an acute attack) of anti-inflammatory therapy is essential for achieving optimal treatment results. A 2006 Cochrane systematic review demonstrated the efficacy of colchicine in the treatment of acute gout.<sup>67</sup> Nonsteroidal anti-inflammatory drugs that are currently approved for the management of acute gout are indomethacin, sulindac, and naproxen.<sup>22</sup>

Colchicine must be used with caution in patients taking calcineurin inhibitors. Due to possibly serious toxicity in these patients, it has been recommended that colchicine not be prescribed for older adults with creatinine clearances of < 30 mL/min.<sup>11</sup> Nonsteroidal anti-inflammatory drugs must be used with caution in patients with hypertension, CVD, renal insufficiency, peptic ulcer disease, and other comorbidities and are contraindicated in renal transplant patients. Glucocorticoids may be the best choice for these patients. A systematic review found 3 studies exploring the use of systemic corticosteroids in 148 patients, including 74 patients with acute gout<sup>68</sup> (Tables 7, 8). When prescribing an

**Table 6.** Gout Medications and Multiple Comorbidities That May Result in Contraindications<sup>a</sup>

Drug	Contraindication or Caution
Allopurinol <sup>81</sup>	CKD, chronic hepatitis, allopurinol hypersensitivity
Colchicine <sup>72</sup>	CKD, chronic hepatitis
Febuxostat <sup>82</sup>	CVD, chronic hepatitis
Glucocorticoids	CVD, hypertension, diabetes, hyperlipidemia, gastroesophageal disease, osteoporosis
NSAIDs	CVD, hypertension, CKD, renal transplantation, gastroesophageal disease
Pegloticase <sup>109</sup>	CVD, hypertension, pegloticase hypersensitivity, G6PD deficiency
Probenecid <sup>103</sup>	CKD, severe gastroesophageal disease

<sup>a</sup>Therapeutic decisions should be based on individualized risks and benefits.

**Abbreviations:** CKD, chronic kidney disease; CVD, cardiovascular disease; NSAID, nonsteroidal anti-inflammatory drug. Adapted from *Am J Med*.<sup>120</sup>

**Table 7.** Evidence of Efficacy: Effect Size and Number Needed to Treat

Comparison	Outcome	Level of Evidence <sup>a,17</sup>	ES (95% CI)	NNT (95% CI)	Reference
Allopurinol 100 mg/d or allopurinol 300 mg/d vs usual therapy (doses were not compared)	Stable renal function	Ib, 12 months	–	4 (2–16)	121
Allopurinol vs baseline	BP, CrCl, and proteinuria	Ila, 3 months	Reduction in SUA: 2.49 Reduction in Ccr: 0.29 Increase in GFR: 0.40 Reduction in CRP: 0.15 Reduction in urine protein: 0.025 Reduction in SBP: 0.90 Reduction in DBP: 0.39	–	122
Fenofibrate vs baseline	SUA, Ccr, CUA, FEUA, UUAV	Ila, 10 hours	ES fenofibrate vs baseline after 10 h on SUA: 4.24 ES UA clearance from –2 to 0 h) to 4–8 h: 7.41 ES FEUA from –2 to 0 h) to 4–8 h: 7.39 ES UUAV from –2 to 0 h to 2–4 h: 6.64 No change for CrCL.	–	123
Losartan vs baseline	BP, SUA, and CUA	Ila, 1 month	Decreased sitting SBP: 5.66 Decreased Sur: 2.0 Increased Cur: 2.52 Increased Cur/Ccr: 2.91	–	124
Corticosteroid combination (prednisolone/acetaminophen vs NSAID combination (indomethacin/acetaminophen) in patients with acute gout-like arthritis	Pain relief at rest and with activity (VAS)	Ib, 5 days	Reduction in pain (mm per hour) for 2 combinations (both favoring indomethacin combination): At rest: 0.33; with activity: 0.11	–	125
Prednisone vs naproxen	Pain measured on a 100-mm VAS	Ib, 90 hours	Overall pain after 90 h: prednisone, 1.93; naproxen, 2.36; general disability: prednisone, 1.62; naproxen, 1.91; walking disability for lower limbs: prednisone, 2.24; naproxen, 2.85	–	126
Methylprednisone vs betamethasone	Short-term postinjection pain and its correlation with pain 3 weeks after injection	Ib, 3 weeks	VAS pain for methylprednisolone vs entire population (lower population): 0.07 Betamethasone vs population: 0.04 (higher population)	–	127
Allopurinol vs baseline in patients with Lesch-Nyhan syndrome and HPRT deficiency	Purine metabolic parameters, renal function, clinical manifestations	III, 12 months	ES allopurinol in reducing SUA for patients with Lesch-Nyhan syndrome: 2.23 Same but for partial HPRT deficiency: 2.75	–	128
Febuxostat 40 mg vs 80 mg vs 120 mg	SUA < 6 mg/dL	Ila, 5 years	–	Febuxostat 40 mg vs 80 mg: 6 (4–11) Febuxostat 40 mg vs 120 mg: 6 (3–26)	100
Febuxostat 80 mg or 120 mg vs allopurinol 300 mg	SUA < 6 mg/dL	Ilb, 1 month	–	Febuxostat 120 increased efficacy in all cases; Febuxostat 80 mg vs febuxostat 120 mg (80 as the control): 17 (9–86)	98

(Continued)

Table 7. (Continued)

Comparison	Outcome	Level of Evidence <sup>a,17</sup>	ES (95% CI)	NNT (95% CI)	Reference
Febuxostat vs allopurinol	SUA < 6.0 mg/dL	Ib, 6 months	–	Febuxostat 80 mg vs allopurinol 300 mg (febuxostat 80 as the control): 3 (2–4) (NNH) Febuxostat 120 mg vs allopurinol 300 mg (febuxostat 120 mg as the control): 3 (2–3) (NNH) (Febuxostat 80 mg increased efficacy) Febuxostat 40 mg vs allopurinol: 34 (–9 to 6) Febuxostat 40 mg vs febuxostat 80 mg: 5 (3–12) Febuxostat 80 mg vs allopurinol: 4 (3–9)	97
Allopurinol vs control	1) Renal disease progression; 2) Cardiovascular events; 3) Hospitalizations of any causes	Ib, 2 years	eGFR: 1.60	–	129
Febuxostat vs allopurinol or placebo	SUA < 6.0 mg/dL	Ib, 3 months	–	Allopurinol 300 mg vs febuxostat 80 mg: 4 (3–6) (febuxostat increased efficacy at all doses) Allopurinol 300 mg vs febuxostat 120 mg: 3 (2–3) Allopurinol 300 mg vs febuxostat 240 mg: 3 (2–3)	101
Probenecid vs benzbromarone	SUR < 0.30 mmol/L	Ib, 2 months	Probenecid vs benzbromarone: 1.32 (benzbromarone better) Probenecid vs allopurinol: 1.27 (probenecid better)	Probenecid vs benzbromarone: 4 (2–14) (benzbromarone increased efficacy) Probenecid vs allopurinol: 3 (2–5) (probenecid superior)	94
Allopurinol vs allopurinol + probenecid	SUR ≤ 0.30 or 0.36 mmol/L	Ila, 2 months	–	(Combination more efficacious) SUR ≤ 0.30 allopurinol alone vs allopurinol + probenecid: 2 (1–2) SUR ≤ 0.36: 3 (2–3)	130
Allopurinol vs probenecid vs allopurinol + probenecid	Changes in plasma urate in treatment groups vs baseline	Ib, 7 days	ES plasma urate from baseline allopurinol: 2.80 Probenecid: 4.46 Combination: 5.51	–	131, 132
Pegloticase at 4 doses	Plasma urate < 6.0 mg/dL	Ib, 12–14 weeks	–	3 (2–4) This compares best response (8 mg/2 wk) with worst (4 mg/2 wk) in completers (not ITT)	133

(Continued)

**Table 7.** (Continued)

Comparison	Outcome	Level of Evidence <sup>a,17</sup>	ES (95% CI)	NNT (95% CI)	Reference
Colchicine (0.6 mg) vs placebo	Acute gout flares and multiple gout flares	Ib, 0–6 months	–	Acute gout flares: 3 (1–6) Multiple gout flares: 3 (1–4)	134
Colchicine high dose (4.8 mg) vs low dose (1.8 mg) vs placebo	Target joint pain score	Ib, 24 hours	–	High dose vs placebo: 6 (3–72) Low dose vs placebo: 5 (3–13)	69

<sup>a</sup>Describes the EULAR management evidence hierarchy based on study design. Ia, meta-analysis of RCTs; Ib, RCT; IIa, controlled study without randomization; IIb, quasi-experimental study; III, nonexperimental descriptive studies; IV, expert committee reports or opinion or clinical experience of respected authorities, or both. The NNT is the estimated number of patients who need to be treated to either prevent an unwanted effect, such as an acute attack, or obtain a wanted outcome, such as pain relief; therefore, the smaller the NNT, the better the treatment effect. The ideal NNT is 1, which means that everyone responds with treatment and no one responds with control. NNTs from 2–5 are generally considered good. Negative NNTs mean the control is better, which could also translate to NNH because the treatment is harmful compared with the control. CIs that overlap with 0 indicate that the NNT is uninterpretable.

Per EULAR: Clinically, an ES of 0.2 is considered small, 0.5 is moderate, and > 0.8 is large.

**Abbreviations:** BP, blood pressure; Ccr, creatinine; CrCl, creatinine clearance; CRP, C-reactive protein; CUA, uric acid clearance; Cur, clearance value of urate; DBP, diastolic blood pressure; ES, effect size; EULAR, The European League Against Rheumatism; FEUA, fractional excretion of uric acid; GFR, glomerular filtration rate; ITT, intent to treat; NNT, number needed to treat; NSAID, nonsteroidal anti-inflammatory drug; RCT, randomized controlled trial; SBP, systolic blood pressure; SUA, serum uric acid; Sur, serum concentration of urate; UA, uric acid; UUAV, urinary excretion of uric acid; VAS, visual analog scale.

NSAID or a corticosteroid, it is essential to consider existing comorbidities.

**5. For acute gout, low-dose colchicine (ie, 1.2 mg administered as soon as possible, followed by 0.6 mg 1 hour later) is effective and well tolerated. Colchicine should be continued for an additional 7 to 10 days or until the flare is resolved. High-dose colchicine is not indicated and should not be prescribed.**

*Strength of recommendation:* 93 (95% CI, 92–94)

*Highly or strongly recommend:* 90%

*Quality of evidence:* Very low, Grade 1 recommendation

#### Rationale

Colchicine was approved in 2009 by the US Food and Drug Administration (FDA) for the prophylaxis and the treatment of patients with acute gout attack. A multicenter RCT with 185 patients experiencing acute gout attacks was conducted to compare colchicine efficacy at the traditional high dose (1.2 mg followed by 0.6 mg every hour for 6 hours, resulting in a total dose of 4.8 mg) with a low-dose regimen consisting of 1.2 mg followed by 0.6 mg in 1 hour (resulting in a total colchicine dose of 1.8 mg).<sup>69</sup> Significantly ( $P=0.034$  for the high dose, and  $P=0.005$  for the low dose) more patients responded to colchicine than to placebo.<sup>69</sup> The high- and low-dose regimens were of equal efficacy. The low-dose colchicine regimen was associated with a lower rate (36.5%) of AEs compared with the traditional high-dose regimen (76.9%) and did not significantly differ from that of patients in the placebo group (27.1%).<sup>69</sup> The intensity of AEs tended to be mild to moderate in the low-dose group and severe in the high-dose group. Based on this study and expert

experience, only the low-dose colchicine regimen is recommended for treating patients experiencing acute gout attacks.

The colchicine dose must be adjusted in patients with renal insufficiency, and colchicine is contraindicated in patients taking P-glycoprotein or strong CYP3A4 inhibitors (eg, clarithromycin, erythromycin, cyclosporine, ketoconazole, fluconazole, verapamil, natural grapefruit juice, and St. John's wort).<sup>22,70,71</sup> Concomitant use of statins may increase the risk of myopathy.<sup>70,72</sup> Recent case reports describe serious interaction with colchicine and atorvastatin,<sup>73,74</sup> clarithromycin,<sup>75–77</sup> disulfiram,<sup>78</sup> pravastatin,<sup>79</sup> and simvastatin.<sup>80</sup> Severe toxicities include blood dyscrasias, neuromuscular disorders, and fatal drug overdoses.<sup>22</sup> Colchicine poisoning should be suspected in patients with the typical toxidrome (ie, gastroenteritis, hypotension, lactic acidosis, and prerenal azotemia). Untreated colchicine poisoning is associated with a high rate of fatality. Timely recognition is associated with the likelihood of complete recovery.<sup>70</sup>

**6. For an acute attack, after sufficient precautions have been taken, intra-articular aspiration and injection of a long-acting steroid is an effective and generally well-tolerated treatment.**

*Strength of recommendation:* 95 (95% CI, 93–96)

*Highly or strongly recommend:* 85%

*Quality of evidence:* Very low, Grade 1 recommendation

#### Rationale

Although intra-articular aspiration may be of benefit during acute attacks, no research is reported in the literature that supports this practice. Intra-articular injection of a long-acting steroid has

**Table 8.** Evidence of Safety: Relative Risk and 95% CIs

Comparison	Adverse Events	RR <sup>a</sup> (95% CI)	Evidence	Reference
Allopurinol 100 mg/d or 300 mg/d vs usual therapy (doses were not compared)	Worsening renal function	RR worsening renal function: 3.53 (1.11–11.2) (controls had greater risk)	RCT, 12 months	121
Low-dose colchicine (1.8 mg total over 1 hour) vs high-dose colchicine (4.8 mg total over 6 hours) vs placebo	GI AE or SAE	GI AE high dose vs placebo: 13.1 (5.3–32.3) Low dose vs placebo: 1.4 (0.6–3.1) High vs low dose: 9.6 (4.2–22.1) Severe-intensity AE OR high dose vs placebo: 13.8 (1.7–112)	RCT, 24 hours	69
NSAIDs	Upper GI bleeding/perforation	Current vs no use: 4.50 (3.82–5.31) Past vs no use: 1.17 (0.96–1.42) Low dose vs no use: 2.79 (2.17–3.58) High dose vs no use: 5.36 (4.57–6.29)	Systematic review of observational studies, 1 to > 365 days	5
NSAIDs and COX-2 inhibitors vs controls	Risk of cardiac failure	All NSAIDs (5 studies): 1.36 (0.99–1.85) Conventional NSAIDs (5 studies): 1.35 (0.94–1.93); Celecoxib (2 studies): 0.85 (0.48–1.50) Rofecoxib (2 studies): 1.49 (1.10–2.02) Cohort RR for cardiac failure for all NSAIDs (2 studies): 1.97 (1.73–2.25) Arthritis patients (COX-2 inhibitors vs conventional NSAIDs): OR, 1.14 (0.85–1.53) Etoricoxib vs diclofenac: OR, 1.65 (1.11–2.44)	Meta-analysis of observational studies and RCTs	136
COX-2 inhibitors vs controls	Risk of renal and arrhythmia events	RR rofecoxib composite renal events: 1.53 (1.33–1.76); arrhythmia events: 2.90 (1.07–7.88) Celecoxib renal: 0.97 (0.84–1.12); arrhythmia: 0.84 (0.45–1.57) Valdecoxib/parecoxib renal: 1.24 (1.00–1.55); arrhythmia: 0.78 (0.62–1.01) Etoricoxib renal: 1.05 (0.77–1.44); arrhythmia: 1.16 (0.40–3.38) Lumiracoxib renal: 1.07 (0.68–1.70); arrhythmia: NA	Meta-analysis of RCTs	7
Corticosteroid combination (prednisolone/acetaminophen) vs NSAID combination (indomethacin/acetaminophen)	Any	1.42 (0.88–2.28)	RCT, 5 days	125
Febuxostat 40 mg vs febuxostat 80 mg vs allopurinol	Any AE and SAE	AE febuxostat 40 mg vs allopurinol: 0.99 (0.91–1.08) AE febuxostat 40 mg vs febuxostat 80 mg: 1.05 (0.95–1.14) AE febuxostat 80 mg vs allopurinol: 0.95 (0.87–1.04) SAE febuxostat 40 mg vs allopurinol RR: 0.61 (0.35–1.07) SAE febuxostat 40 mg vs febuxostat 80 mg RR: 0.68 (0.38–1.20) SAE febuxostat 80 mg vs allopurinol RR: 0.90 (0.55–1.49)	RCT, 6 months	97

(Continued)

**Table 8.** (Continued)

Comparison	Adverse Events	RR <sup>a</sup> (95% CI)	Evidence	Reference
Allopurinol vs control	CV events	OR CV event allopurinol vs control: 0.38 (0.14–1.03) HR new CV event allopurinol vs control: 0.29 (0.09–0.86)	RCT, 2 years	129

<sup>a</sup>RR = relative risk between treatment group and control group; RR = 1, no difference; RR > 1, more risk with treatment; RR < 1, more risk with control. Per EULAR: For adverse effects, the RR was calculated from RCTs or cohort studies for the incident risk and from cross-sectional studies for prevalent risk, whereas the OR was calculated from case-control studies. Both present how many times more likely (or less likely) it is that a subject who is exposed to the drug or intervention will have AEs than a subject who is not exposed. RR or OR = 1 indicates no increased risk, whereas RR or OR > 1 or < 1 indicates an increased or decreased risk, respectively. **Abbreviations:** AE, adverse event; CI, confidence interval; COX-2, cyclooxygenase-2; CV, cardiovascular; EULAR, The European League Against Rheumatism; GI, gastrointestinal; NA, not available; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio; RCT, randomized controlled trial; SAE, severe adverse event

demonstrated efficacy in relieving the pain of an acute attack; however, there is no recent published evidence to support this (Table 7).<sup>11</sup>

**7. ULT is indicated in patients with any of the following: recurrent attacks (> 1 attack per year), chronic arthropathy, tophaceous deposits, nephrolithiasis, or radiographic changes of gout. Once initiated, ULT is considered a lifelong treatment recommendation.**

*Strength of recommendation:* 97 (95% CI, 96–98)

*Highly or strongly recommend:* 95%

*Quality of evidence:* Low, Grade 1 recommendation

#### Rationale

According to prescribing information, ULT is indicated for the treatment of patients with signs and symptoms of gout, such as acute gout attacks, tophi, joint destruction, and UA lithiasis and/or nephropathy.<sup>81</sup> Urate-lowering therapy is also indicated for the chronic management of hyperuricemia in patients with gout.<sup>82</sup> The appropriate point at which to begin therapy for any individual remains a decision to be made by PCPs and their patients considering individual needs and preferences. Urate-lowering therapy is associated with the possibility of significant side effects and is therefore never indicated for patients with asymptomatic hyperuricemia.<sup>81,82</sup> In addition, it should never be started or discontinued during an acute gout attack.

**8. The therapeutic goal of ULT is to prevent acute flares, prevent the development of tophi, help dissolve tophi, and prevent the development of chronic gouty arthropathy. This is achieved by maintaining an SUA level of < 6.0 mg/dL, well below the saturation point for MSU of 6.8 mg/dL.**

*Strength of recommendation:* 97 (95% CI, 96–98)

*Highly or strongly recommend:* 100%

*Quality of evidence:* Low, Grade 1 recommendation

#### Rationale

Serum uric acid levels of < 6.0 mg/dL are necessary to clear urate and MSU from affected tissues. Several large studies have shown the benefit of this target SUA level.<sup>83–86</sup> Serum uric acid levels of ≥ 6.0 mg/dL were correlated with increased likelihood of experiencing an acute gout attack when compared with the risk associated with SUA levels below that cutoff.<sup>83,85</sup> The correlation between lower SUA levels and successful treatment of patients with gout led to the concept of “treating to target,” which means that ULT is prescribed as necessary to achieve the beneficial target SUA level of 6.0 mg/dL, rather than treating to a specific urate-lowering drug dose calibrated to renal function.<sup>87,88</sup>

**9. The xanthine oxidase inhibitors (allopurinol and febuxostat) are the agents of choice for ULT to reach the therapeutic target SUA level of < 6.0 mg/dL. The dose should be titrated to optimize safety and minimize the chance of precipitating an acute flare. Serum uric acid should be monitored to ascertain the achievement and maintenance of this goal. Appropriate laboratory monitoring for toxicity is indicated.**

*Strength of recommendation:* 95 (95% CI, 94–96)

*Highly or strongly recommend:* 100%

*Quality of evidence:* Low, Grade 1 recommendation

#### Rationale

Allopurinol gained FDA approval in 1964 as the first xanthine oxidase inhibitor; febuxostat entered the US market in 2009. Based on evidence from RCTs, EULAR committee concluded that allopurinol was a cost-effective option for long-term ULT in patients with chronic gout.<sup>11</sup> Large clinical trials have shown that febuxostat is an effective therapy in the management of



patients with chronic gout.<sup>89</sup> Gaffo and Saag<sup>89</sup> concluded that there was moderate evidence suggesting that febuxostat treatment could help reduce gout flares and the number and size of tophi, and clear evidence to suggest that febuxostat effectively reduces SUA and compares favorably with allopurinol (Table 7). Febuxostat doses do not need to be adjusted in patients with gout and mild-to-moderate renal<sup>90</sup> or hepatic<sup>91</sup> impairment.

Approximately 2% of patients treated with allopurinol demonstrate allopurinol hypersensitivity syndrome.<sup>81</sup> This may affect elderly patients in particular, as well as those with underlying renal impairment or other risk factors.<sup>92</sup> The syndrome is an immune-mediated severe reaction, which may be limited to severe cutaneous reactions, such as toxic epidermal necrolysis or Stevens-Johnson syndrome, but may also include eosinophilia, leukocytosis, fever, and hepatitis.<sup>93</sup> Allopurinol hypersensitivity syndrome can lead to death in up to 20% of affected patients.<sup>89</sup> Many, but not all, of the affected patients recovered after withdrawal of allopurinol and treatment with prednisone.

**10. Allopurinol should be started at a low dose (100 mg daily) and increased by 100 mg every 2 to 4 weeks (to a maximum allowable dose of 800 mg per day) as necessary to achieve the target SUA goal of < 6.0 mg/dL. If allopurinol toxicity occurs, it should be stopped immediately. Other treatment options include febuxostat or probenecid.**

*Strength of recommendation:* 95 (95% CI, 94–96)

*Highly or strongly recommend:* 100%

*Quality of evidence:* Moderate, Grade 1 recommendation

#### Rationale

In a dose-escalation trial, increasing allopurinol dose from 300 to 600 mg per day enabled 78% of patients with gout to achieve SUA levels of 5.5 mg/dL.<sup>94</sup> Thus, doses of > 300 mg per day may be required to achieve optimal therapeutic result.<sup>93,95</sup> The FDA dosing guide lists 200 to 300 mg per day as typical doses for patients with mild gout, and doses of 400 to 600 mg per day for patients with moderately severe tophaceous disease.<sup>81,93</sup>

## ACR 2011 UPDATES

Paisansinsup and Schousboe<sup>96</sup> identified 551 patients who had allopurinol prescribed between January 1, 2004 and December 31, 2010, who had serum creatinine measured while on allopurinol, and had complete covariate data. Of the 551 patients, 342 (61.5%) were prescribed doses that exceeded those recommended for their levels of renal

function; 65 (11.7%) patients had a minor adverse drug reaction, and none had a major adverse drug reaction to allopurinol. The risk for having adverse drug reactions to allopurinol was not increased in patients exposed to doses of allopurinol higher than those described in the study. These results support the strategy of titrating doses of allopurinol to attain a therapeutic goal of UA , 6.0 mg/dL to achieve adequate control of gout.<sup>96</sup>

**11. Febuxostat should be started at 40 mg daily and may be increased to 80 mg after at least 2 weeks of treatment, if necessary, to achieve the target SUA level goal of < 6.0 mg/dL. If toxicity occurs, febuxostat should be stopped immediately. Other treatment options include allopurinol or probenecid. However, allopurinol and febuxostat should not be coadministered (New).**

*Strength of recommendation:* 97 (95% CI, 96–98)

*Highly or strongly recommend:* 100%

*Quality of evidence:* Low, Grade 1 recommendation

#### Rationale

Febuxostat efficacy and safety have been compared with those of allopurinol in several phase 3 trials.<sup>97–101</sup> Febuxostat doses of 80, 120, and 240 mg were given to patients with renal impairment (serum creatinine level of > 1.5 to < 2.0 mg/dL) and without renal impairment. Allopurinol was given at the dose of 300 mg to patients without renal impairment; doses were reduced to 100 mg for patients with renal impairment. In all trials, more of the participants receiving febuxostat reached the target SUA levels (< 6.0 mg/dL) compared with those receiving allopurinol. Thus, febuxostat is an effective alternative to allopurinol, particularly for patients with reduced renal function.<sup>99–101</sup>

**12. Probenecid, a uricosuric agent, can be used as an alternative to a xanthine oxidase inhibitor in patients with normal renal function, but is relatively contraindicated in patients with nephrolithiasis and ineffective in the presence of renal insufficiency. Probenecid can be used together with allopurinol or febuxostat, if necessary, to achieve the target goal of lowering SUA levels to < 6.0 mg/dL. Dosing may begin at 500 mg daily, with titration monthly up to a maximum of 3 g per day in divided doses.**

*Strength of recommendation:* 93 (95% CI, 92–94)

*Highly or strongly recommend:* 90%

*Quality of evidence:* Very low, Grade 1 recommendation

### Rationale

The only uricosuric agent available in the United States is probenecid, which impedes UA reabsorption in the distal nephron, a process mediated by the proteins urate transporter 1 (URAT1) and glucose transporter 9 (GLUT9).<sup>102</sup> Probenecid may not be effective in patients with chronic renal insufficiency, particularly in those with glomerular filtration rates of  $\leq 30$  mL/min.<sup>103</sup> Probenecid is contraindicated in patients with known blood dyscrasias or renal lithiasis.<sup>103</sup> Probenecid therapy is typically started at a dose of 250 mg per day (1 half tablet) twice per day for 1 week, followed by 500 mg (1 tablet) twice per day thereafter. In patients with renal impairment, doses may be increased every 4 weeks as tolerated to doses as needed to achieve (usually not exceeding 2000 mg) and maintain SUA levels of  $< 6.0$  mg/dL. When beginning probenecid therapy, patients need to be instructed to increase their fluid intake and use a product to alkalinize their urine.<sup>103</sup>

**13. Prophylaxis against acute attacks during the first 6 to 12 months of ULT can be achieved by colchicine (given as tolerated, 0.6 mg once or twice daily) or an NSAID (with gastroprotection, if indicated). Prophylaxis should be initiated 2 weeks prior to the implementation of ULT. The choice for prophylaxis should include an analysis of the comorbidities of the patient, and the risks and benefits of the agent (see below). NSAIDs are not currently FDA approved for prophylaxis.**

*Strength of recommendation:* 97 (95% CI, 96–98)

*Highly or strongly recommend:* 100%

*Quality of evidence:* Very low, Grade 1 recommendation

The expert panel recommends that colchicine be considered as the first choice for prophylaxis. Nonsteroidal anti-inflammatory drugs and corticosteroids are alternatives if colchicine is not tolerated or is not effective.

### Rationale

The initiation of ULT in a patient with gout may precipitate an acute gout attack (called mobilization flare), which makes prophylactic treatment a necessary and integral part of chronic gout management.<sup>87</sup> Prophylactic therapy should be initiated  $\geq 2$  weeks prior to initiating ULT. Any sudden increase or decrease in SUA level may trigger a gout flare. Mobilization flares are due to the sudden decrease in SUA associated with effective ULT. However, when health care professionals or patients do not expect such a flare, they may attribute it to the worsening of gout rather than the first sign of successful

therapy. In addition, UA-lowering therapy, once initiated, should be titrated to achieve a target SUA.

Furthermore, discontinuing ULT due to a mobilization flare will further destabilize the patient's condition. It is essential to anticipate a mobilization flare after initiating ULT and to prepare patients to manage them.<sup>22</sup> Based on RCTs, the EULAR investigators recommended the use of low-dose colchicine (0.5–1.0 mg/day) for prophylaxis against mobilization flares. Nonsteroidal anti-inflammatory drugs were recommended based on non-RCTs.<sup>11</sup> In 2009, colchicine gained FDA approval for use in the prophylaxis of mobilization flares. The dosing schedule is 0.6 mg once or twice daily, with a maximum daily dose of 1.2 mg.<sup>72</sup> Reduced dosing is recommended for patients with renal impairment. Colchicine is the only agent FDA approved for prophylaxis.<sup>72</sup>

## ACR 2011 UPDATES

Wason et al<sup>104</sup> evaluated the pharmacokinetics (PK) of colchicine in subjects aged 60 years to determine if older subjects require dose adjustments when prescribed colchicine. Thirty-eight subjects (aged 18–30 [n = 20] years and  $\geq 60$  [n = 18] years) received a single oral 0.6-mg dose of colchicine after a 10-hour fast. Following administration of a single 0.6-mg dose of colchicine, there were no significant differences in PK parameters between young and older adults, including those with mild decreases in renal function estimated by creatinine clearance, suggesting that there is no need to modify the dose of colchicine based on age alone.

Wason et al<sup>105</sup> also obtained single-dose PK data in healthy subjects and subjects with varying degrees of renal impairment to allow predictions of colchicine steady-state concentrations following the currently recommended dose of colchicine for gout flare prophylaxis (0.6 mg twice daily). Based on these data, for prophylaxis of gout flares, no dose adjustments are needed for patients with normal renal function or mild impairment (creatinine clearance  $> 50$  mL/min). For patients with moderate and severe renal failure (creatinine clearance  $< 50$  mL/min), it is recommended that the colchicine dose be reduced by 50% (ie, for those patients requiring 0.6 mg twice daily, the dose should be decreased to 0.6 mg once daily, and for those requiring 0.6 mg once daily, the dose should be decreased to 0.3 mg/day).

**14. Certain diuretics may increase the risk of an acute gout attack. In this circumstance, the use or dose of diuretic should be reassessed as possible. In some circumstances (eg, in patients with heart**

failure), the use of diuretics may be necessary. In such instances, subsequent gout attacks may occur and should be managed accordingly.

*Strength of recommendation:* 91 (95% CI, 90–92)

*Highly or strongly recommend:* 76%

*Quality of evidence:* Low, Grade 2 recommendation

#### Rationale

Both thiazide and loop diuretics are known to increase SUA levels by affecting volume depletion and renal tubular secretion.<sup>106,107</sup>

Older patients and women—2 patient groups that take diuretics frequently—may be particularly affected by the relationship between diuretics and gout. Whether diuretics should be discontinued in a patient presenting with gout and cardiovascular comorbidities should remain a clinical decision made at the discretion of the treating PCP.

**15. For patients who have refractory gout and/or resistant tophaceous disease, pegloticase is another treatment option. Pegloticase is administered by infusion and has a significant risk profile. Patients who may be candidates should be referred to health care professionals with expertise in the use of pegloticase.**

*Strength of recommendation:* 95 (95% CI, 93–95)

*Highly or strongly recommend:* 82%

*Quality of evidence:* Very low, Grade 2 recommendation

#### Rationale

The progression of gout to a deforming, disabling disease is the result of patient failure to respond to ULT, patient intolerance to available medications, or the presence of comorbidities that contraindicate treatment with approved agents.<sup>108</sup> Patients with refractory gout may be helped by pegloticase, a pegylated uricase that gained FDA approval for the management of refractory chronic gout in 2010. Pegloticase is given by intravenous infusion at 2-week intervals.<sup>106</sup> It may rapidly resolve tophi and control chronic synovitis in patients with severe gout. The pegloticase package insert includes warnings for anaphylaxis, infusion reactions, gout flares, and congestive heart failure; patients should be monitored closely for all 4 reactions.<sup>109</sup>

**16. Considerations for referring a patient with gout to a rheumatologist or nephrologist include:**

- a. Confirmation of diagnosis, particularly in patients with atypical presentation
- b. Management of refractory cases when:
  - An SUA level < 6.0 mg/dL cannot be achieved
  - Recurrent flares occur despite apparent adequate treatment
  - A patient presents with persistent and/or extensive tophaceous disease

c. Management of patients with nephrolithiasis

d. Consideration for complex treatment options

*Strength of recommendation:* 94 (95% CI, 93–95)

*Highly or strongly recommend:* 100%

*Quality of evidence:* Very low, Grade 1 recommendation

#### Rationale

Gout and hyperuricemia can be particularly difficult to diagnose correctly in patients with atypical presentation, and treatment of patients with severe gout can be beyond the comfort level of even the most experienced PCPs. Rheumatologists and nephrologists are equipped to take care of patients with refractory gout, or gout and hyperuricemia occurring in patients with advanced renal disease or transplants. Rheumatologists are a resource for those who are not skilled at arthrocentesis or crystal analyses. Prescribing gout medications at their highest doses for patients who do not respond to usual therapy or considering biologics may also be best handled by specialists who manage more of these cases. Good communication between PCPs and specialists, a multidisciplinary approach, and a well-timed referral ensure that patients receive the best possible care.

## Discussion

The diagnosis and management of gout and hyperuricemia have changed in recent years. The EULAR evidence-based guidelines for gout published in 2006<sup>11,12</sup> covered literature from 1945 to January 2005. The current update is based on literature published between February 2005 and February 2011, and offers a US perspective, as determined by a panel of experts specializing in rheumatology, nephrology, cardiology, primary care, and allied health. However, the EULAR investigators did not only provide evidence-based diagnostic and management recommendations, they also detected topics with sparse or low-quality evidence. Research conducted since 2005 has further clarified various aspects of managing gout and has filled some of the identified gaps. Thus, an update of the EULAR guidelines was indicated. There was strong agreement regarding many grade 1 and 2 recommendations for optimal diagnosis and management of patients with gout (Tables 1, 2; Appendix). Summary points are provided below:

- Data continue to support the decision to diagnose gout using clinical characteristics rather than mandating crystal identification.
- Although studies have shown that SUA levels of  $> 6.0$  mg/dL are a significant risk factor for gout,<sup>83–86</sup> they are not always a reliable diagnostic tool because approximately 14% of patients with acute gout presented with SUA levels of  $< 6.0$  mg/dL.<sup>110</sup> Conversely, some people with high SUA levels may never develop gout. Serum uric acid should be used in combination with clinical criteria and response to gout treatment to arrive at a diagnostic decision.
- Research has focused on the interaction between gout and typically associated risk factors and comorbidities. Strong associations have been demonstrated between gout and metabolic syndrome,<sup>111–113</sup> CVD,<sup>33,34,51,114</sup> and CKD.<sup>34</sup>
- The use of nonpharmacologic measures in the treatment of patients with gout, particularly dietary aspects, has become more sophisticated.<sup>115</sup>
- Gout therapy relies on good patient education. Patients need to understand that gout treatment requires a life-long commitment. Patients also need to know that the initiation of ULT results in acute gout attacks (mobilization flares) and that these attacks are a sign of effective therapy. Finally, they need to understand the importance of adhering to prophylaxis regimens.
- For effective management of an acute gout attack, treatment should begin within hours of symptom onset. Low-dose colchicine (1.2 mg as soon as possible, followed by 1 dose of 0.6 mg 1 hour later, for a total dose of 1.8 mg) is as effective and better tolerated than high-dose colchicine (1.2 mg followed by 0.6 mg every hour for 6 hours, resulting in a total dose of 4.8 mg).<sup>69</sup>
- The benefits of reaching a target SUA level of  $< 6.0$  mg/dL have been confirmed. For most patients, a target SUA level between 5.0 and 6.0 mg/dL is safe and effective. Patients with incapacitating, severe, tophaceous gout may require SUA levels of  $< 4.0$  mg/dL to see improvement.<sup>88,116,117</sup>
- Allopurinol has been found to be safe and more effective at higher doses. It should be started at a low dose of 100 mg per day, but can (with appropriate monitoring) be titrated to 800 mg per day as necessary for a patient to achieve the target SUA level of 6.0 mg/dL.<sup>93–95</sup> It has been recommended that patients with renal impairment receive lower doses; however, recent studies report that this might not be required clinical practice.
- For patients who have not responded to or were not eligible to receive allopurinol, febuxostat (also a xanthine oxidase inhibitor with a slightly different mechanism of action) can be prescribed at unchanged doses for patients with mild-to-moderate renal or hepatic impairment.<sup>90,91</sup> Intravenous pegloticase is indicated for patients with refractory and/or resistant tophaceous gout.<sup>109</sup>
- Timely referral from primary care to rheumatology or nephrology may be the best option for patients with an uncertain diagnosis or in cases of severe disease.

## Acknowledgments

The authors wish to gratefully acknowledge the invaluable editorial support from Regine Harford, MS, MSTPC, and statistical support from Bonny McClain, MS, DC of ASSESS-mint Analytics. Funding for the preparation of the article was received from URL Pharma, and from the American Society of Clinical Rheumatologists. The authors also wish to acknowledge the invaluable support from Mary Shah, MLS, medical library archivist and Caroline Marshall, MLS, health sciences librarian, both from Danbury Hospital Library.

## Conflict of Interest Statement

Max Hamburger, MD is a member of the speakers' bureau for Abbott, Amgen, Bristol-Myers Squibb, Genentech, GSK, HGSI, Novartis, and UCB; is a consultant for Bristol-Myers Squibb, Genentech, and UCB; is in receipt of educational grants in support of CME activities from Abbott, Amgen, Bristol-Myers Squibb, Crescendo Bioscience, Genentech, Janssen Biotech, Takeda Pharmaceuticals, North America, Inc, and URL Pharma. Herbert S. B. Baraf, MD is a member of the speakers' bureau for Savient Pharmaceuticals and Takeda Pharmaceuticals, North America, Inc; is a consultant for Ardea Biosciences and Savient Pharmaceuticals; is an investigator for Ardea Biosciences, Metabolex, Novartis, Regeneron, Savient Pharmaceuticals, and Takeda Pharmaceuticals, North America, Inc; and is a member of the advisory board for Takeda Pharmaceuticals, North America, Inc. Thomas C. Adamson III, MD, FACP, CPE is a member of the speakers' bureau for sanofi-aventis, Takeda Pharmaceuticals, North America, Inc, and Warner Chilcott; and is a consultant for Sanofi-Aventis and Takeda Pharmaceuticals, North America, Inc. Jan Basile, MD is a member of the speakers' bureau for Boehringer Ingelheim, Daiichi-Sankyo, Forest Laboratories, and Takeda Pharmaceuticals, North America, Inc; is a consultant for Daiichi-Sankyo, Eli Lilly/Boehringer Ingelheim, Forest Laboratories, and Takeda Pharmaceuticals,

North America, Inc; and has received grant/research support from the NHLBI (SPRINT). Lewis Bass, DO, FACP discloses no conflicts of interest. Brent Cole, MD discloses no conflicts of interest. Paul P. Doghramji, MD is a member of the speakers' bureau and advisory board for URL Pharma. Germano A. Guadagnoli, MD is a member of the speakers' bureau for Amgen/Pfizer, Forest Laboratories, and Takeda Pharmaceuticals, North America, Inc. Frances Hamburger, PhD is employed by Miller Professional Group. Regine Harford, MS, MSTPC discloses no conflicts of interest. Joseph A. Lieberman III, MD, MPH is a member of the advisory board for Takeda Pharmaceuticals, North America, Inc and URL Pharma. David R. Mandel, MD is a member of the speakers' bureau for Abbott, Amgen, Auxilium Pharmaceuticals, Forest Laboratories, Forest Pharmaceuticals, GlaxoSmithKline, Lilly, Novartis, Savient Pharmaceuticals, Sunovion Pharmaceuticals, Takeda Pharmaceuticals, North America, Inc, and UCB; is a member of the advisory board for Amgen, Auxilium Pharmaceuticals, Crescendo Bioscience, Pfizer, and Savient Pharmaceuticals; is a consultant for Amgen, Auxilium Pharmaceuticals; Crescendo Bioscience, Pfizer, Savient Pharmaceuticals, and UCB; and has received research support from Abbott, Amgen, AstraZeneca, Biogen Idec, Celgene, Janssen Biotech, Crescendo Bioscience, Genentech, Merck Sharp and Dohme, Novartis, Pfizer, Roche, Stryker, and VQ OrthoCare. Didier A. Mandelbrot, MD discloses no conflicts of interest. Bonny P. McClain, MS, DC discloses no conflicts of interest. Eric Mizuno, MD is an advisor for Takeda Pharmaceuticals, North America, Inc. Allan H. Morton, DO is a member of the speakers' bureau for Abbott, Amgen, Bristol-Myers Squibb, Genentech, Pfizer, Takeda Pharmaceuticals, North America, Inc, Savient Pharmaceuticals, UCB, URL Pharma, and Warner Chilcott; and is a consultant for Amgen, Bristol-Myers Squibb, Novartis, Pfizer, Savient Pharmaceuticals, UCB, and URL Pharma. David B. Mount, MD has received grant support from Nuon Therapeutics; is on the medical advisory board and educational planning committees for Savient Pharmaceuticals; and provides internal talks for Takeda Pharmaceuticals, North America, Inc; and has pending grants with Takeda Pharmaceuticals, North America, Inc and URL Pharma. Richard S. Pope, MPAS, PA-C, DFAAPA is a member of the speakers' bureau for AstraZeneca, Amgen, Takeda Pharmaceuticals, North America, Inc, UCB, and URL Pharma. Kenneth G. Rosenthal, MD, PC discloses no conflicts of interest. Katy Setoodeh, MD, FACR is a member of the speakers' bureau for Amgen and Human Genome Sciences. John L. Skosey, MD, PhD, FACR, FACP is an

advisory board participant for Cardinal Health; a director of Theratest Laboratories; and a stockholder in Amgen. N. Lawrence Edwards, MD, FACP, FACR is a consultant for Ardea Biosciences, Savient Pharmaceuticals, Novartis, and Takeda Pharmaceuticals, North America, Inc.

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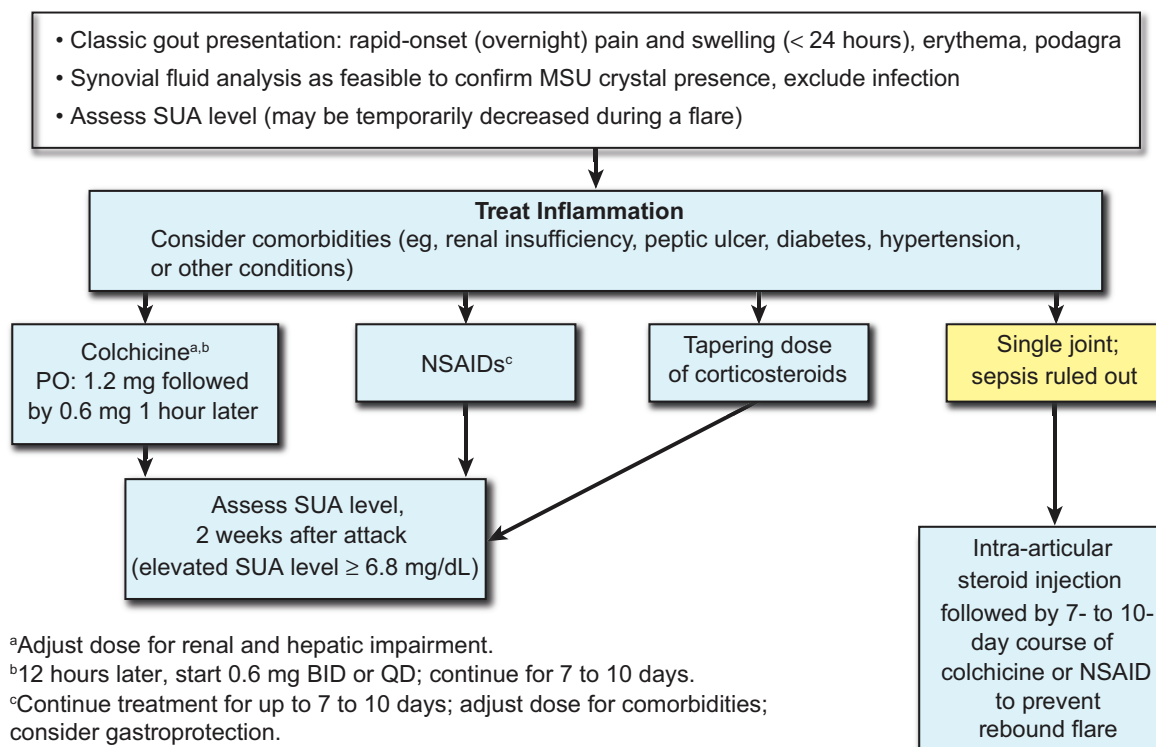
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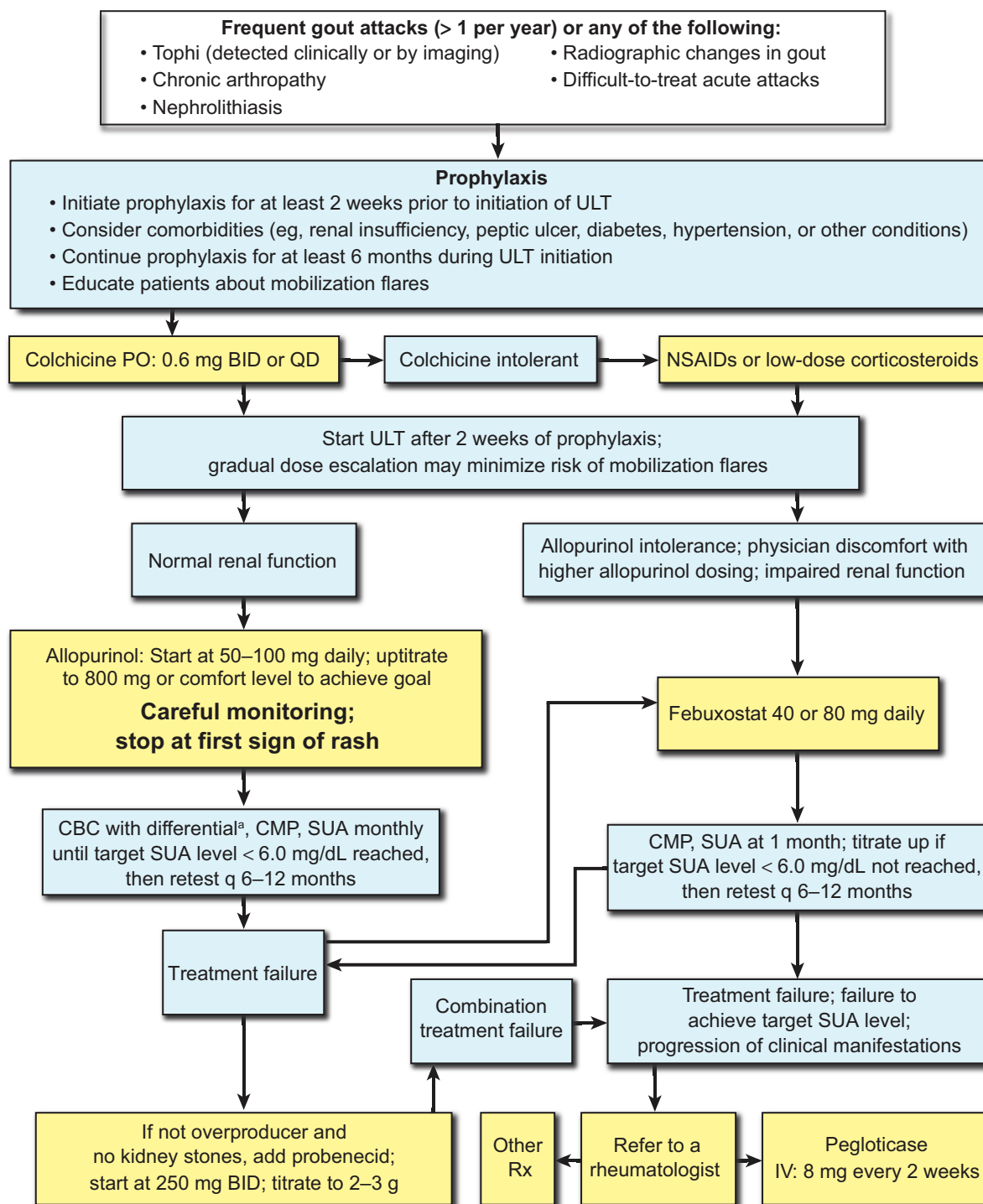


## Appendix A. Acute Gout Flares



**Abbreviations:** BID, twice daily; MSU, monosodium urate; NSAID, nonsteroidal anti-inflammatory drug; PO, orally; QD, once daily; SUA, serum uric acid.

## Appendix B. Chronic Gout and Hyperuricemia Management



<sup>a</sup>To look for eosinophils or leukocytosis, early signs of allopurinol hypersensitivity.

**Abbreviations:** BID, twice daily; CBC, complete blood count; CMP, complete metabolic panel; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; q, every; PO, orally; QD, once daily; Rx, prescription; SUA, serum uric acid, ULT, urate-lowering therapy.