Putting Out the Fire:
Optimal Management of Gout
in the Primary Care Setting

Learning Objectives
After participating in this educational activity, participants should be better able to:

1. Implement appropriate strategies for screening for gout in the primary care setting

2. Develop strategies for lowering serum uric acid, preventing and treating flares, and managing gout among patients in the primary care setting, including the elderly and those with multiple comorbidities
The Burden of Gout in Primary Care Practice

Gout is a misunderstood disease. This isn’t necessarily because of its complex pathophysiology, but because of its reputation as a condition that primarily afflicts older, overweight men with a penchant for red meat and beer. This antiquated notion of gout is confounding progress in terms of treating this painful, debilitating, and potentially disabling condition. Gout now affects more than 8 million Americans and is increasingly common among younger and middle aged as well as postmenopausal women, primarily due to the high rates of metabolic syndrome among the US population. Because of these trends, primary care clinicians are increasingly called upon to manage gout. Of the more than 4 million ambulatory care visits per year related to gout, more than 70% are to primary care facilities.[1] The good news is that gout is a treatable disease, assuming that clinicians who care for patients with gout are up-to-date on the most effective management strategies, which shall be reviewed in this article.

What is Gout?

Gout is a form of inflammatory arthritis caused by the deposition of monosodium urate (MSU) crystals in the joints and tissues of the body. When these crystals elicit an acute inflammatory response, they cause severe pain and swelling, usually in the lower extremities such as the big toe (called “podagra”). These crystals can also lead to disfiguring deposits within the joints, bone, cartilage, and elsewhere in the body called tophi. Over time, these tophi can enlarge and can become disfiguring. The tophi are surrounded by a chronic inflammatory response that causes erosion of cartilage and bone that result in chronic arthritis. Without successful treatment of gout, patients may lose functionality in their extremities or become wheelchair bound.
The progression from elevated serum uric acid (SUA), defined as anything above 6.8 mg/dL, to gout usually takes many years. However, during that time, crystals may begin to form in the joints. A patient with SUA chronically above 6.8 mg/dL is susceptible to having a first flare of gouty arthritis, often as a result of local trauma, binge drinking, overeating, fasting, or exposure to extreme cold.[2]

**Risk Factors for Gout**

The primary risk factor for gout is elevated SUA. The challenge for primary care clinicians is that SUA is not included as part of the routine chemistry or metabolic panel for most patients. The patient’s SUA should be checked if gout is suspected. Shown in the diagram below, higher SUA levels are associated with an increase in the annual incidence of gout in both men and women:[3]

![Diagram showing the annual incidence of gout in men and women based on serum uric acid levels.](image)

Additional contributing factors for the development of gout include[4]:

- **Insufficient excretion of uric acid**
  - >90% of cases
  - Genetics
  - Thiazide/loop diuretics
  - Low-dose aspirin
  - Niacin
  - Calcineurin inhibitors
  - TB drugs
  - Lead intoxication

- **Overproduction of uric acid**
  - Dominant cause in <10% of cases
  - High cell turnover
  - Exfoliative psoriasis
  - Myeloproliferative disorders
  - Lymphomas
  - Genetic disorders (consider strongly in females before menopause and anyone under age 25 to 30)

For most patients, gout is caused by inadequate secretion of SUA. Additional causes include uric acid overproduction, a high purine diet, or genetic disorders that can increase the concentration of uric acid in the blood.
• Comorbidities
  o Hypertension
  o Insulin resistance
  o Impaired renal function
  o Cardiovascular disease
  o Metabolic syndrome

• Diet/lifestyle
  o Heavy alcohol use (especially beer)
  o Purine-rich diet
  o High fructose corn syrup intake

While the prevalence of gout among US adults is only about 4%, the prevalence of hyperuricemia is 21%.\(^5\) People with elevated serum uric acid may never experience an attack of gout. However, those who do will need clinicians that are armed with contemporary strategies for quickly alleviating gout attacks in their patients, preventing future attacks, and managing the disease in the face of multiple comorbidities.

Case #1: Leo

Leo is a 38-year-old Hispanic male who presents to establish primary care. He is overweight, hypertensive, and his labs show elevated triglycerides and transaminases. He is largely sedentary and has a diet that is high in red meat and beer. His SUA is 8.7 mg/dL, but he has never experienced a flare of gouty arthritis.

![Leo](image)

**Binge drinking, overeating, fasting, injury, illness, or exposure to extreme cold often triggers a patient’s first attack of gouty arthritis.**

Treating Leo

Patients with elevated serum urate but without clinical gout are at high risk of tissue crystal deposition.\(^6\) In many cases, behavioral modifications such as weight loss and dietary changes can slow or prevent the progression from asymptomatic hyperuricemia to clinical gout.
Diagnosing Gout

The gold standard to diagnose gout is joint aspiration and identification of crystals under polarized light microscopy. Ultrasonography can also be used to diagnose gout in some cases. However, these are rarely done in the primary care setting due to time and resource limitations. A more practical approach is a presumptive diagnosis based on symptoms, physical examination, family history, comorbidities, and current medications. Gout is one of the most painful afflictions one can experience. Therefore, rapid onset of excruciating pain in one joint, typically in the foot, accompanied by warmth, erythema, swelling and extreme tenderness of the involved joint is considered diagnostic. To some PCPs, that presentation in a patient who is hyperuricemic and responds dramatically to colchicine is considered diagnostic. Testing and frequent monitoring of SUA is also an important component of a gout diagnosis and management plan, though SUA can be normal during a gout attack.

Sample Gout Screening Questionnaire for Primary Care Clinicians

1. How long have you had these symptoms?
2. How quickly did the pain progress?
3. Which joints are affected?
4. Is there swelling present?
5. Is there redness/warmth present?
6. What did you have to eat in the hours leading up to the pain?
7. Did you consume alcohol before the attack? If so, what kind and how much?
8. What other medical conditions do you have?
9. What medications are you currently on?
10. Do you have a family history of gout or other inflammatory disease?

Gout: One Chronic Disease Best Described by Four Stages

Serum urate can be normal or less than 8.0 mg/dL during acute gout flares. If you suspect gout in a patient with normal SUA, check SUA again about 2 weeks after the attack has resolved.
Managing Gout

Ideal management strategies for gout include a combination of dietary and lifestyle modifications and medical management. The former may be the most challenging; there are simply too few American adults willing or able to achieve an ideal body weight. Many are even less interested in adhering to a low-purine diet. Nonetheless, dietary and lifestyle modification goals should be part of every gout patient’s treatment plan, along with medications designed to reduce SUA and prevent flares of gouty arthritis.

The pharmacologic approach to the management of gout requires a three-prong approach: 1) treat acute flares of gouty arthritis 2) prophylax against flares when starting ULT 3) prevent future gouty arthritis attacks through the use of strategies to reduce SUA. First, we discuss strategies to treat acute flares.

Treating Acute Gout Flares

Treatment of acute flares is an essential component of gout management and the most important from the patient’s perspective. The first goal of the clinician should be to reduce the intensity and duration of the flare.
Agents used to treat acute flares of gouty arthritis are described in Table 1.\cite{7,8,9,10} Dosing is continued until the patient has been asymptomatic for 3 to 7 days. Bear in mind that early intervention is critical. Many doctors recommend patients have a supply of their recommended medications such as colchicine or naproxen ready to go.

Table 1.

<table>
<thead>
<tr>
<th>Therapy/dosing</th>
<th>Considerations/adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs: may be any NSAID, eg:</td>
<td>--Use with caution in older patients and those with renal insufficiency --Avoid in patients with chronic kidney disease, hypertension, diabetes, or congestive heart failure</td>
</tr>
<tr>
<td>--Indomethacin: 50 mg 3x daily for 4-10 days</td>
<td></td>
</tr>
<tr>
<td>--Naproxen: 500 mg 2x daily</td>
<td></td>
</tr>
<tr>
<td>Colchicine</td>
<td>--Best used within the first 24 hours of an attack; useful as a self-medication to abort flares at onset --Adverse events include nausea, vomiting, and diarrhea --Avoid in patients with very poor renal or hepatic function or those who are taking clarithromycin --Depressed blood counts, neuromyopathy and rhabdomyolysis have been reported but are uncommon and more likely to occur in patients with renal insufficiency.\cite{11}</td>
</tr>
<tr>
<td>--1.2 mg, and then 0.6 mg one hour later (1.8 mg total)</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>--Use with caution in patients with diabetes, hypertension, and congestive heart failure --Avoid in patients with joint sepsis</td>
</tr>
</tbody>
</table>

Note that traditional dosing regimens for colchicine were higher. However, more recent evidence suggests that lower-dose colchicine is as effective at treating flares, and that the adverse events are comparable to placebo.\cite{12}
The effectiveness of any strategy to treat gout flares depends on initiating therapy at the very first hint of a gout flare. By taking medication soon enough, flares may be significantly reduced or aborted altogether. Any delay may necessitate taking medication for several days. It is important to note that, since each agent works by a different mechanism, they can be used in combination for severe flares.

**Prophylaxis**

Achieving optimal outcomes for patients with refractory gout requires keen attention be paid to prophylaxis when initiating new therapies. Although it may seem paradoxical, gout flares often occur when initiating ULT, which we discuss in the next section. In fact, the lower and faster SUA drops, the more likely there is to be a flare.\[^{13,14}\] Using low-dose colchicine (0.6 mg once or twice a day) or NSAID beginning two weeks prior to starting the ULT can significantly decrease this flare rate.\[^{10,11}\] Once started, prophylaxis should be continued for approximately six months, although this interval may have to be extended in those with chronic tophaceous gout.

**Treating Gout with Urate Lowering Therapy**

Indications for ULT:
- Recurrent attacks (>2/year)
- Visible or suspected tophi
- Difficult to treat attacks
  - Polyarticular gout
  - Comorbidities
    - Chronic kidney disease
    - Congestive heart failure

Available Urate-Lowering Strategies:
- Uricostatic (suppresses uric acid formation)
  - Allopurinol
  - Febuxostat
- Uricosuric (renal uric acid elimination)
  - Probenecid
- Uricolytic “biologic” approach (converts urate to more soluble allantoin)
  - Pegloticase

**Urate Lowering Therapies: Xanthine Oxidase Inhibitors**

The most widely used urate-lowering therapies are xanthine oxidase inhibitors, including allopurinol and febuxostat. Both inhibit formation of uric acid, but there are several important distinctions between the two medications. We review allopurinol first.

**Allopurinol**

Allopurinol has been widely used as a urate lowering strategy for gout patients since the 1960s. Among the total prescriptions of allopurinol for gout, the large majority is for 300 mg or less, despite a maximum recommended daily dose of up to 800 mg.\[^{10}\] However, 300 mg a day is effective in less than half of patients.\[^{11}\] Therefore, effective gout management in the primary care setting includes titration of allopurinol.
One in 5 patients on allopurinol reports gastrointestinal or other side effects, including pruritic rash (~2%). A rare but serious adverse reaction is severe allopurinol sensitivity, which is not dose dependent and may include fever, rash, progressive renal insufficiency, and death.\cite{15}

Initial doses of allopurinol may be 100 or 150 mg per day, and SUA level should be assessed at two weeks post initiation of ULT. If the value is greater than 6.0 mg/dL, increase the dose by 100 or 150 mg. The uric acid level should be checked again after two weeks. This process should be repeated until the lowest dose that reduces the uric acid level to less than 6.0 mg/dL is determined. It is important to note that the most common reason for allopurinol failure is inadequate dose escalation.

**Febuxostat**

Another safe and effective xanthine oxidase inhibitor is febuxostat, which was approved for gout in 2009 and is now widely used as a first-line therapy. As febuxostat is primarily metabolized by the liver, dose adjustment is not necessary for patients with moderate renal or liver impairment.

Dosing of febuxostat typically begins with 40 mg BID, with an increase to 80 mg BID if the SUA is not 6.0 mg/dL or less within two weeks. Table 2 includes data from several phase III clinical trials showing the percentage of patients with primary endpoint SUA <6.0 mg/dL with febuxostat and non-titrated allopurinol.\cite{16,17,18}
Table 2. Subjects with SUA levels <6.0 mg/dL

<table>
<thead>
<tr>
<th>Study</th>
<th>Febuxostat 40 mg daily</th>
<th>Febuxostat 80 mg daily</th>
<th>Allopurinol 300 mg daily</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONFIRMS [16] (6 months)</td>
<td>45% (n=757)</td>
<td>67%* (n=756)</td>
<td>42% (n=755)</td>
<td>...</td>
</tr>
<tr>
<td>APEX [17] (6 months)</td>
<td>...</td>
<td>72%* (n=253)</td>
<td>39% (n=263)</td>
<td>1%** (n=127)</td>
</tr>
<tr>
<td>FACT [18] (12 months)</td>
<td>...</td>
<td>74%* (n=249)</td>
<td>36% (n=242)</td>
<td></td>
</tr>
</tbody>
</table>

* p<0.001 versus allopurinol  
** p<.001 versus febuxostat 80 mg and allopurinol

The most common side effects are rash (~2%), and elevated LFTs, diarrhea, and dizziness (all at <5%). [19]

**Probenecid**

SUA may also be reduced using uricosuric agents. The only FDA-approved uricosuric agent is probenecid, which facilitates the renal elimination of uric acid. For this reason, it is contraindicated for patients with uric acid overproduction.

Typical dosing of probenecid is 500 mg daily, with titration monthly up to a maximum of 3 g per day in divided doses. [20] The most common side effects of probenecid are [21]:

- Urolithiasis risk
- Gastrointestinal complaints, hypersensitivity
- Rash

Probenecid loses efficacy as renal function deteriorates with no effect at creatinine clearances of 50 ml/min or below. In addition, its activity is blocked if co-administered with a salicylate.

An additional agent used to treat patients with gout is pegloticase, an IV biologic agent that is indicated only for patients who are refractory to traditional therapies due to the risk of a serious reaction during infusion. We review pegloticase in an activity titled “New Biologic Agents for the Management of Refractory Gout.”

**Case #2: Donna**

Donna is a 55-year-old woman who presents with severe pain and swelling in the first metatarsophalangeal (MTP) joint. She cannot wear a shoe because the foot is too sensitive. This is her fourth attack of monoarticular arthritis in the last two years. Each previous attack was treated with indomethacin with good relief. She is overweight and drinks three bottles of beer a day. Her SUA is 8.2 mg/dL. Her serum creatinine is 1.1 mg/dL.
Treating Donna

The first step is to treat the acute flare. Colchicine would be a good choice as it is highly effective for crystal-induced inflammation and a good response would support what is certainly a diagnosis of gout. She should take 1.2 mg of colchicine immediately and then 0.6 mg one hour later. At that point, her colchicine dosing should be adjusted to 0.6 mg once or twice daily for prophylaxis against gout flares that often occur shortly after initiating ULT. After she has taken that regimen for 14 days, she should start taking allopurinol 100 mg or 150 mg a day. Prophylaxis with colchicine should continue for about six months. In addition, she should be encouraged to lose weight. If she wishes to consume alcohol, she should be advised to not drink beer and informed that wine in moderation does not affect SUA levels.

Case #3: Louie

Louie is a 67-year-old male who was diagnosed with gout at age 45. He now has recurrent flares of gout but is presently asymptomatic. He was previously treated with allopurinol but discontinued it because of gastrointestinal intolerance. His SUA is 9.2 mg/dL, and his creatinine clearance is 32 mg/dL.
**Treating Louie**

He should begin to take colchicine 0.6 mg once daily for prophylaxis against gout flares that often occur shortly after initiating ULT. After he has taken that regimen for about 14 days, he should start taking febuxostat 40 mg a day. Two weeks later, his SUA should be checked. If the level is not below 6.0 mg/dL, the dose of febuxostat should be increased to 80 mg a day and SUA rechecked in two weeks. Prophylaxis with colchicine should continue for about six months.

**How is Gout Like a Book of Matches?**

Treatment of gout involves taking three different medications on 3 different schedules. This is often hard for patients to understand. The following analogy has helped some patients understand and remember how to take their gout medicines.

- Uric acid crystals are like matches. When they strike, your gout flares up
  - Take NSAIDs, colchicine, or prednisone at the first hint of an attack to extinguish flares
- We can put out the “flames” but the “matches” remain
  - Take colchicine or NSAIDs to keep the “matches” damp
- ULTs remove the matches
- When the matches are gone, so is the gout
Adherence to Therapy

Evidence suggests that one of the primary causes of gout treatment failure is poor patient adherence to therapy. Strategies to improve adherence include patient education on the importance of:

- A low-purine diet
- Limiting alcohol
- Avoid fructose-containing beverages
- Weight loss

Additionally, proper management of comorbid conditions may improve outcomes for patients with gout.

Practice Points

- Reduce SUA level to <6.0 mg/dL rather than the 6.8 mg/dL saturation point to eliminate gout flares and tophi
- During a gout flare, don’t change or start urate lowering therapy (ULT)
- Prophylax against flares when initiating ULT
- Long-term treatment of hyperuricemia and gout must address comorbidities, especially metabolic syndrome
References


