Update on Diagnosis and Management of Gout

Case Study and Commentary, Charles A. Withers, MD, Ronald L. George, MD, PhD, and Robert T. Keenan, MD, MPH

ABSTRACT:

• Objective: To review the diagnosis and management of gout.
• Methods: Review of the literature and case study.
• Results: Gout is a curable disease. The clinical stages of gout (hyperuricemia, acute gout, intercritical gout, chronic gout) represent different opportunities for management. The choice of therapy should be tailored to the individual based on underlying comorbidities and potential contraindications. Intercritical gout is an opportunity to use the new recommended dosing regimen for colchicine, initiate urate-lowering therapy, and screen for comorbidities such as cardiovascular disease that often accompany gout. Treating to a target serum urate level < 6 mg/dL is applicable to all patients with established gout. More aggressive therapy should be considered in patients with chronic tophaceous gout, as tophi are an indicator of large crystal burden that can cause significant joint destruction, disability, and chronic pain.
• Conclusion: Despite advances in our understanding and management of gout, patients continue to incur debilitating disease. Patient education and better provider-patient communication are imperative for successful management.

Gout, or monosodium urate crystal deposition disease, is the most common inflammatory arthropathy. Its induction is a result of serum urate (UA) levels exceeding 6.8 mg/dL. Once urate in the extracellular fluid exceeds this level, it is considered supersaturated, and the risk of depositing uric acid as monosodium urate crystals in joints and soft tissue increases [1].

Despite advances in our understanding of gout and the development of new therapies, patients continue to incur debilitating disease. Many providers succumb to pitfalls, such as measuring UA only during flares, starting urate lowering therapy without flare prevention, and not treating to appropriate UA targets [2]. Suboptimal patient adherence and inadequate patient education are also impediments to successful gout management.

The complacency and misunderstandings surrounding gout and its management may be due at least in part to its association with antiquity. Recognized by the ancient Egyptians, written about by Hippocrates, and touted as the “disease of kings,” gout is associated with the lifestyle of the affluent male [3]. Although the most likely patient to develop gout is still the middle-aged, obese man who may indulge in beer and red meat, anyone can develop gout. Recent studies show the prevalence of gout has risen over the last 50 years in both men and women, affecting 3.9% of the U.S. population [4]. The risk of females developing gout approaches that of men after the menopause, and women are more likely to develop gout at lower UA levels than men [4,5]. In addition to age and gender, other risk factors for developing hyperuricemia and gout are listed in Table 1.

Patients with gout frequently present with multiple comorbidities, such as cardiovascular disease, chronic kidney disease, and the metabolic syndrome, and gout can fall in priority during a healthcare visit. Although this lack of priority may be understandable, appropriate management of gout is important not only because of its negative impact on patient quality of life but because gout and hyperuricemia may be independent risk factors for cardiovascular disease [6–8].

Patient education and better provider-patient communication are imperative for the successful management of this common, painful yet curable disease.

CASE STUDY

Initial Presentation

A 74-year-old man with a history of recurrent flares of tophaceous, gouty arthritis presents seeking pain relief.

History

The patient has a lengthy history of gout, describing podagra of the left great toe at the age of 25 as his initial...
attack. The patient recalls various treatment strategies but admits to noncompliance as he continued to have recurrent gout flares year after year. He feels that his joint pain has slowly worsened over time and he now walks with a rolling walker due to polyarticular pain. The patient reports a history of obesity, hypertension, diabetes, and chronic kidney disease.

**Physical Examination**

Physical examination reveals an elderly man in moderate pain. Vital signs include a temperature of 37.2°C, pulse of 92 bpm, blood pressure of 137/70 mm Hg, and a respiratory rate of 14 breaths/min. BMI is 40 kg/m². The abdomen is obese and nontender, and the liver edge is palpable to approximately 1 cm below the costal margin. Musculoskeletal examination reveals significant deformity and contracture of both hands due to multiple tophi. The metacarpal phalangeal (MCP) joints are tender to palpation and notable for tophi. In addition to flexure contractures of the elbows, tophi are present at the bilateral olecranon with the left being warm and painful to the touch (Figure 1). Bilateral pain is elicited with flexion and extension of his knees. Tenderness and swelling is noted in both ankles and his right 1st metatarsal phalangeal (MTP) joint. The patient is unable to stand independently due to pain.

**Laboratory Findings**

Serum uric acid is 8.2 mg/dL, sedimentation rate is 60 mm at 1 hr, white blood cell count (WBC) is 15,400 with 73% neutrophils, 16.3% lymphocytes, and 4.5% monocytes with a serum creatinine of 2.8 mg/dL. Aspiration of the knee joint reveals a cell count of 56,000/mm³ with 88% segmented neutrophils, 15% lymphocytes. Examination of the aspirate under polarized microscopy reveals many needle-shaped, negatively birefringent crystals; several were noted to be engulfed by neutrophils (intracellular). Culture of the fluid and Gram stain were negative.

**Imaging Studies**

Plain radiographs of the hands reveal multiple erosive changes involving the bilateral MCP joints. Findings on plain radiographs of the feet include periarticular erosive changes of the first and fifth MTPs (Figure 2), and microtophi are seen on ultrasound at the inter-phalangeal joint (Figure 3).

*What are the clinical phases of gout?*

Hyperuricemia and gout can be classified into 4 clinical phases: asymptomatic hyperuricemia, acute gouty arthritis, interval or intercritical gout, and chronic advanced gout [9]. At physiologic conditions, monosodium urate crystals will begin to precipitate from solution and deposit in periarticular spaces when the serum uric acid concentration is greater than 6.8 mg/dL [9]. Patients are typically asymptomatic during this period for months to years prior to their first attack. Currently, there is no

---

Table 1. Risk Factors for Hyperuricemia and Gout

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male &gt; female)</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Postmenopausal</td>
</tr>
<tr>
<td>Renal insufficiency</td>
</tr>
<tr>
<td>Dehydration</td>
</tr>
<tr>
<td>Acidosis</td>
</tr>
<tr>
<td>Infections</td>
</tr>
<tr>
<td>Insulin resistance (metabolic syndrome)</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Surgery</td>
</tr>
<tr>
<td>Lead poisoning</td>
</tr>
<tr>
<td>Alcohol use (beer &gt; liquor &gt; wine)</td>
</tr>
<tr>
<td>Chronic beryllium poisoning</td>
</tr>
</tbody>
</table>

*Approved for the treatment of gout.*
Evidence that treating asymptomatic hyperuricemia is beneficial and therefore it is not recommended.

Once monosodium urate crystals have deposited in periarticular spaces or in surrounding soft tissue, patients may experience an acute flare of gouty arthritis in the appropriate environment. Gout classically presents with podagra, an acute inflammatory arthritis affecting the first MTP. Initial presentation affecting other lower extremity joints is also common, although gout can present as an inflammatory arthritis in any joint. Nearly 80% of gout begins as monoarticular arthritis. Polyarticular flares, as experienced by the case patient, also occur with increased frequency in the natural history of disease progression [9]. Flares are typically self-resolving after 7 to 10 days but occur with greater frequency as the disease course progresses.

The intervals between flares of gout are known as intercritical periods, during which uric acid crystals remain present in serum and are often at higher concentrations in and around joint spaces. It is thought that these lingering crystals are a nidus for further crystal deposition, increasing the risk for future and more frequent flares and eventually, chronic and erosive disease [9].

When crystal deposition progresses, some patients may develop large accumulations of monosodium urate crystals, called a tophi, and subsequently experience chronic pain, stiffness, and joint swelling.

The transition from asymptomatic hyperuricemia to chronic, tophaceous gout is a complex process that is not fully understood. While some patients never experience flares of gout despite elevated serum uric acid levels, other presentations can range from 1 flare in a lifetime to frequent attacks to a chronic gouty arthropathy associated with significant disability.

**What is the differential diagnosis for an acute, monoarticular inflammatory arthritis?**

The differential diagnosis for an acute, monoarticular inflammatory arthritis is most often limited to a short list of etiologies. An infected or septic joint is the most important potential etiology to rule out. Needle aspiration of the affected joint with cell count, Gram stain, and culture is the gold standard to rule in or out an infectious process. Additionally, analysis should include polarizing microscopy to examine for the presence of negatively-birefringent, needle-shaped crystals (monosodium urate crystals), which confirms the diagnosis of acute gout, especially when seen within neutrophils or intracellularly.

The presence of crystals does not necessarily exclude an infectious process, and extracellular crystals alone do not necessarily equate with an acute gouty attack, since extracellular crystals may persist in patients with established gout after inflammation has resolved and may be present in the setting of other acute joint pathologies [10]. Calcium pyrophosphate, a rhomboid crystal that is positively birefringent, can induce a monoarticular inflammatory arthropathy. Oxalate crystals can be seen in patients with renal failure, and cholesterol crystals have been aspirated from patients with rheumatoid arthritis and other inflammatory arthropathies.
Synovial fluid aspiration and analysis is the gold standard for making the diagnosis of gout, but joint aspiration is not always practical. The European League Against Rheumatism (EULAR) has published guidelines for making a presumptive diagnosis of gout [11]. The rapid development (6–12 hours) of severe pain and swelling, especially with overlying erythema, is highly suggestive of crystal inflammation though it is not specific for gout [11]. Recurrent podagra with or without hyperuricemia suggests acute gout [11]. It should be noted that serum urate may be normal during an acute attack.

**What is the approach to managing acute gout?**

**Colchicine**

Colchicine has long been used as a treatment and the prevention for acute flares of gouty arthritis. Traditional dosing has been one 0.6-mg tablet given every hour with an endpoint of symptom abatement or intolerable nausea, vomiting, or diarrhea. This dosing regimen was based on the first randomized placebo-controlled study published in 1987 examining the efficacy of colchicine in patients with acute gout [12]. While colchicine proved superior to placebo, most subjects discontinued therapy due to GI intolerance rather than resolution of symptoms after receiving a mean dose of 6.7 mg within a 24-hour timeframe. Alternative dosing regimens have been explored due to the realization that many patients discontinued therapy prior to experiencing full clinical improvement [13].

Recently, a low-dose colchicine regimen was compared with a more traditional approach in a multicenter, randomized, double-blind, placebo-controlled study with 184 subjects who received either low-dose colchicine (1.2 mg followed by 0.6 mg one hour later for a total of 1.8 mg), high-dose colchicine (1.2 mg, then 0.6 mg hourly x 6 hours for a total of 4.8 mg), or placebo [14]. The low-dose colchicine was found to be equally as effective the high-dose regimen, while the high-dose treatment group was 6 times more likely to have an adverse event (Figure 4). Clinical experience suggests that repeating the low-dose regimen of colchicine in 12 to 24 hours may be called for to ensure resolution of symptoms. Treatment of acute flares should be initiated without the interruption of established urate-lowering regimens [15].

Although low-dose colchicine has been found to be safer than higher-dose regimens, there is still concern
regarding its use in some patient populations. The use of colchicine in patients with renal insufficiency, the elderly, and concomitant cytochrome P450 inhibitor (eg, statins) should be approached thoughtfully due to concerns about decreased clearance, drug accumulation, and the development of serious adverse events, including neuro-myopathy and rhabdomyolysis [16–18]. Studies suggest that patients with moderate to severe renal impairment may benefit from colchicine dosing adjustments. Patients with mild renal impairment and ESRD on dialysis can tolerate normal prophylactic dosing regimen; in those with CrCl < 50 mL/min, the dose should be reduced by 50% (ie, 0.6 daily in those requiring 0.6 bid dosing and 0.3 mg daily in those requiring 0.6 mg daily) [19].

**NSAIDs**

Nonsteroidal anti-inflammatory drugs (NSAIDs) at maximum recommended doses have an efficacy profile in acute gout similar to that of colchicine, and have frequently been used as first-line therapy for the treatment of acute flares [20]. The patient may need to continue NSAIDs or oral corticosteroids (see below) for 7 to 10 days to ensure complete resolution of symptoms [15]. There have been 2 published studies comparing indomethacin and etoricoxib (a COX-2 inhibitor), both showing comparable effects on subjects’ perception of pain over 5 days [21,22]. Different NSAIDs have also been compared to one another in the treatment of acute gout with no appreciable difference in efficacy [23]. Gastrointestinal toxicity and cardiovascular toxicity are among the major concerns of administering NSAIDs; NSAIDs should be avoided in patients with peptic ulcer disease or in patients on anticoagulation therapy. As with colchicine, caution should also be employed when using NSAIDs in patients with renal insufficiency.

**Corticosteroids**

The use of corticosteroids for the treatment of acute flares of gouty arthritis is generally reserved for patients in whom colchicine or NSAIDs are contraindicated (eg, renal disease, hypoalbuminemia, existing peptic ulcer disease), poorly tolerated, or ineffective. Intra-articular steroids are often effective for patients with monarticular or oligoarticular disease and reduce the risk of potential side effects compared with oral corticosteroids. Triamcinolone acetonide 10–40 mg or methylprednisolone acetate 20–80 mg injected directly into the joint is often sufficient to provide analgesia and reduce local inflammation.

Oral and intravenous corticosteroids are also both very effective, especially in patients experiencing polyarticular attacks or who have contraindications to colchicine and NSAIDs. In a randomized, double-blind trial comparing oral prednisolone to naproxen, the reduction in pain scores was nearly equivalent between the 2 groups. Corticosteroids, while effective for the treatment of acute flares of gouty arthritis at higher doses, are typically ineffective as prophylaxis at lower doses [24]. An average starting dose for an acute flare is 40–60 mg/day of prednisone with a slow taper (similar to treating a acute asthma attack) in order to avoid rebound attacks after steroid withdrawal [15]. Prior to using steroids, potential consequences such as hyperglycemia and osteoporosis, as well as contraindications such as diabetes, hypertension, and heart failure should be carefully considered.

Future therapies for acute gout or prophylaxis include medications that bind or block interleukin-1 (IL-1). For example, canakinumab, a fully human monoclonal anti-IL-1β antibody that selectively blocks IL-1β is being investigated for the treatment of gout. Canakinumab has been found to be superior to triamcinolone acetonide in acute gout and to colchicine in gout attack prophylaxis in reducing pain and risk of new gout attacks [25,26]. Other medications that block IL-1 that have been investigated for use in treating gout include anakinra and rilonacept [27,28]. Currently, the use of IL-1 inhibitors is not approved for treating acute gout or prophylaxis against flares.

**Treatment of Case Patient**

Due to the case patient’s renal insufficiency and diabetes, NSAIDs and oral corticosteroids, are relatively contraindicated. Also, intra-articular steroids are not practical in the setting of a polyarticular attack. With caution, the physician decided to use colchicine 1.2 mg by mouth x 1, then 0.6 mg one hour later. The patient’s acute symptoms improved and he was able to ambulate with a walker within 24 hours, but continued to have chronic pain in his MCPs, elbows, and knees.

- **What is the clinical approach after resolution of an acute attack?**

**Intercritical Period**

The intercritical period is an opportunity for the provider to educate the patient regarding potential triggers, diet,
and screen for associated comorbidities. As gout tends to be associated with comorbidities such as cardiovascular disease and metabolic syndrome (insulin resistance, hypertension, abdominal obesity, dyslipidemia), this time is an opportunity to screen for and treat such comorbidities using agents that will not exacerbate gout (eg, using losartan instead of diuretics or fenofibrate instead of niacin) [29]. Encouraging a well-balanced diet, avoidance of high fructose corn syrup, and decreasing alcohol (especially beer) intake and weight loss when appropriate, will address both comorbidities and gout. Patients should be aware there are numerous triggers of acute gout besides overindulgence of high-purine foods. Any factor that quickly increases or decreases serum urate levels can precipitate acute gout attacks. Infections, surgery, trauma, starvation, dehydration, and certain medications (including urate-lowering therapy) can bring the patient out of the intercritical period and into an acute gout flare (Table 2). Measuring the patient’s serum urate is most accurate during this time period (approximately 2 weeks postflare), as acute inflammation itself can cause a decrease in serum urate levels.

The intercritical period is also the time to initiate patient appropriate gout prophylaxis if indicated. Although there is no consensus when to initiate urate-lowering therapy, it is generally recommended for patients with 2 or more gout flares per year [30]. A target UA level of < 6 mg/dL should be achieved in order to decrease the crystal burden, prevent future flares, and disability. It is important for the patient to understand starting urate-lowering therapy may precipitate a flare, and if this does occur it does not mean the medication is not working. Prophylactic treatment with colchicine, NSAIDs, or oral corticosteroids (as discussed above) should be given 1 to 2 weeks prior to initiating urate-lowering therapy to prevent flares.

**Which agents are used to lower serum urate?**

### Urate-Lowering Therapies

Colchicine, NSAIDS, glucocorticoids, and medications that inhibit IL-1β address the inflammation caused by gout, but urate-lowering therapy is the cornerstone in the prevention of acute gouty attacks, the prevention and/or resolution of gouty tophi, and uric acid urolithiasis management [31]. Options for lowering serum uric acid levels include the uricosuric agents such as probenecid and the xanthine oxidase inhibitors allopurinol and febuxostat [32]. More recently, pegloticase, a pegylated recombinant uricase has been approved for severe cases of gout.

**Allopurinol**

Allopurinol is generally safe and effective, and works in both urate underexcreting and overproducing populations. Noncompliance and not titrating up the dose of allopurinol to the approved 800 mg daily (400 mg twice daily) if necessary are the most likely causes of treatment failure. However, even at maximally tolerated doses, allopurinol is not sufficiently effective in all patients, and its use may be problematic in individuals with liver and/or renal disease. In addition, allopurinol is contraindicated in patients taking azathioprine due to inhibition of xanthine oxidase, leading to increased levels of 6-mercaptopurine and potential bone marrow suppression [33]. Rare but potentially severe side effects of allopurinol include rashes, hepatitis, vasculitis, cytopenia, and the potentially life-threatening allopurinol hypersensitivity syndrome (AHS).

Allopurinol can be used in renal insufficiency with close monitoring. A recent study showed AHS is more likely to occur, irrespective of renal function, due to higher starting doses of allopurinol rather than maximum doses of allopurinol [34]. The authors recommend starting allopurinol at a dose of 1.5 mg per unit eGFR to avoid potential hypersensitivity reactions, and then gradually increased to an appropriate dose to achieve the target UA (less than 6 mg/dL).

### Table 2. Medications that Affect Hyperuricemia and Gout

<table>
<thead>
<tr>
<th>Urate Increasing</th>
<th>Urate Decreasing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>Probenecid*</td>
</tr>
<tr>
<td>Salicylates (low-dose)</td>
<td>Sulfipyrazone*</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>Allopurinol*</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Febuxostat</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Pegloticase</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Salicylates (high-dose)</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Fenofibrate</td>
</tr>
<tr>
<td>β blockers</td>
<td>Amlodipine</td>
</tr>
<tr>
<td></td>
<td>Losartan</td>
</tr>
</tbody>
</table>

*Approved for the treatment of gout.
Febuxostat
Febuxostat is a non-purine xanthine oxidase inhibitor approved in February 2009. As a xanthine oxidase inhibitor, it has a mechanism of action similar to allopurinol, yet it is chemically distinct and may offer specific advantages over currently available therapies.

In clinical trials, febuxostat was administered in daily doses of 40, 80, and 120 mg, and compared with 300 mg of daily allopurinol. Participants taking 80 mg of febuxostat were 2.5 to 3 times more likely to reach a serum urate of less than 6 mg/dL over the 52-week trial period compared with those taking allopurinol [35]. Comparative analysis of febuxostat vs. higher doses of allopurinol was not evaluated [36].

Pegloticase
In 2010, pegloticase was approved for the treatment of refractory chronic gout (RCG, or difficult-to-treat gout). Persons with RCG have contraindications to oral urate-lowering therapies or continue to have elevated serum urate levels and signs and symptoms of gout despite maximum medically appropriate doses of oral urate-lowering therapies. A 2011 phase III trial of RCG patients treated with pelgoticase showed the medication to be safe and effective in lowering uric acid levels in this population [37]. Pegloticase is a recombinant mammalian urate oxidase or uricase attached to polyethylene glycol (PEG) that is infused every 2 weeks. In vivo the medication can act as a debulking agent, rapidly lowering UA to less than 1 mg/dl. The dramatic decrease in whole body urate burden allows for the resolution of tophi over a period of months.

During clinical trials, a percentage of patients developed anti-PEG antibodies that drastically reduced the blood levels of pegloticase and also correlated with adverse effects that ranged from mild infusion reactions to anaphylaxis [37]. Due to the risk of hemolysis and methemoglobinemia, the only definitive contraindication to pegloticase is having a G6PD deficiency. Concerns over safety and prevention of infusion reactions are addressed by following a standard infusion protocol and measuring the patient’s UA level just prior to each infusion. It is recommended that if the UA is above 6 mg/dL, particularly if 2 consecutive UA levels above 6 mg/dL are observed, the medication should be discontinued. A large percentage of patients who develop anti-peg antibodies do so within the first 8 weeks or 4 doses of pegloticase. Due to the rapid reduction in plasma urate, the risk of severe gout flare is increased and appropriate prophylaxis should be initiated at least 1 week prior to initiating therapy.

Uricosurics
Hyperuricemia may result from underexcretion of serum urate. Currently, there are 2 uricosurics approved by the FDA for gout: probenecid and sulfinpyrazone. Only probenecid is still available in the United States. Probenecid increases urate excretion by inhibiting urate transporters in the proximal tubule (eg, URAT1). Probenecid can also be used in combination with allopurinol or febuxostat in patients who fail to achieve the target UA despite the maximum tolerated dose of the 2 latter medications. Probenecid is usually well tolerated at the recommended dosage of 1–3 g/day. The efficacy of probenecid declines as renal function declines and is considered by most investigators as ineffective in patients with eGFR < 60 mL/min [38].

A potential complication of uricosuric therapy is the deposition of monosodium urate crystals within the kidney, which can result in nephrolithiasis. The risk can be reduced by gradual increases in drug dose, ensuring urine volume is > 1500 mL/day, and maintaining an alkaline urine [38]. Probenecid is contraindicated in patients with a history of nephrolithiasis and may not be as effective when taken with many medications, especially acidic drugs such as aspirin [39]. Lesinurad, a new uricosuric that has less potential interactions and contraindications than probenecid is currently in phase III trials. Lesinurad may prove to be a useful adjunct to traditional urate-lowering therapies in the future.

Follow-up of Case Patient
Based on his tolerance of allopurinol in the past, the patient was started back on allopurinol after the resolution of his acute attack and initiation of prophylactic colchicine. Allopurinol at 50 mg per day was given and titrated up to 100 mg every 4 weeks while monitoring with metabolic panel, complete blood counts, and urinalysis. Given this patient’s tophaceous burden and associated disability, a more aggressive UA lowering approach is required to assure timely tophus resolution and improvement in function. A UA of 2–3 mg/dL rather than < 6 mg/dL, will be the goal.

SUMMARY
The past several years have brought about tremendous progress in the treatment of gout, and a new apprecia-
tion of those with acute and chronic gouty arthropathy. From the improved dosing regimen of colchicine, to an alternative to allopurinol in febuxostat, and finally a potentially life-changing therapy for those with refractory chronic gout, exciting changes have occurred in the management of gout. Aggressive treatment of gout can resolve crystal deposition, abate flares, and improve quality of life. With improved education of both the providers and the patients regarding the impact of gout and effective therapy, the future seems bright for those with this ancient disease.

Corresponding author: Robert T. Keenan, MD, MPH, 200 Trent Dr., DUMC 3544, Durham, NC 27710, robert.keenan@duke.edu.

Financial disclosures: Dr. Keenan has consulted and served on the speakers bureau for several pharmaceutical companies, including makers of medications used to treat gout.

REFERENCES

(interleukin-1 trap) for prevention of gout flares during initiation of uric acid-lowering therapy: Results from a phase III randomized, double-blind, placebo-controlled, confirmatory efficacy study. Arthritis Care Res (Hoboken) 2012;64:1462–70.