

Naval Medical Center Portsmouth
Referral Guidelines Gout
15 Secrets to Gout Management

Definition:

Gout is a disease characterized by elevated serum urate concentration, with recurrent attacks of acute arthritis associated with monosodium urate crystals (MSU) in synovial fluid, but may also include tophi (typically painless nodular deposits of MSU crystals in and around tissues and around the joints) as well as interstitial renal disease and uric acid nephrolithiasis. Symptoms occur when the excess uric acid, the result of inefficient excretion rather than overproduction, is deposited in restricted joint spaces.^{1,2} Gout arthritis is the most common cause of inflammatory arthritis in men over age 40 and it should not occur in premenopausal women.

Four Stages of Gout:

1. **Asymptomatic Hyperuricemia**: elevated serum uric acid level without gouty arthritis, tophi or uric acid nephrolithiasis. Up to 15% of these patients will eventually develop gout. In those who develop gout, most patients will have had 20 years of asymptomatic hyperuricemia before their first gout attack.
2. **Acute Gouty Arthritis**: a single joint is involved in 85% - 90% of patients (1st MTP in the foot is the most common initial joint involved and it is also called podagra), whereas up to 15% will have polyarticular involvement with their first attack. Attacks begin abruptly and reach maximum intensity within hours. The onset of attacks often occur during the night or early morning when the joint is the coolest. The affected joint becomes exquisitely painful, warm, red and swollen. A low grade fever may be present. The periarticular erythema and swelling may progress to resemble a noninfectious cellulitis termed "gouty cellulitis." Early attacks often spontaneously resolve over 3-10 days. Desquamation of the skin overlying the affected joint can occur with resolution of the inflammation.
3. **Intercritical Gout**: This is the asymptomatic intervals between acute attacks of gout. Over 60% of patients will have a second attack within 1-2 years, whereas 5% to 10% may never have another attack ever.
4. **Chronic Tophaceous Gout**: The development of subcutaneous, synovial or subchondral bone deposits of MSU crystals. Chronic gout is also characterized by permanent joint damage and typically is polyarticular.

Other Causes of an Acute Red, Hot and Swollen joint:

1. Crystalline arthritis: Pseudogout (CPPD)
2. Septic arthritis (can co-exist with gout < 2%)
3. Reactive arthritis, Psoriatic arthritis, Rheumatoid arthritis (or any inflammatory arthritis)
4. Trauma
5. Cellulitis
6. Palindromic Rheumatism

It is always important to aspirate an acutely inflamed joint and send the synovial fluid off for cell count, crystal examination, gram stain and culture.

Gout Co-morbid Conditions:

Metabolic syndrome: obesity, diabetes, hyperlipidemia, hypertension, renal insufficiency, CHF, coronary artery disease. Gout is a primary risk factor for CAD and MI.

Diagnosing Gout: Try to make a crystal proven diagnosis and get X-rays

Reasons:

- Hyperuricemia is found in gout and it is a risk factor, but it alone does not equal gout. Most hyperuricemics do not have gout.
- A third of acute gout flares will have a normal serum uric acid and a third of polyarticular gout patients have a + Rheumatoid Factor (RF). Clinical presentation is not 100% specific for gout.
- Chronic urate lowering therapy is lifelong and thus once it is started the patient is committed to lifelong therapy. Allopurinol hypersensitivity can be deadly.

Obtain material from:

- Fresh synovial fluid or a tophus aspirate must be evaluated for the presence of MSU crystals. Aspiration during an acute attack has the highest yield; but synovial fluid from the knee during an intercritical period can also be diagnostic.
- The intra or extracellular crystals are needle shaped and negatively birefringent (**yellow when parallel**) to the axis of a red compensator and blue when perpendicular).
- The synovial fluid is inflammatory (typically 20,000 to 100,000 leukocytes) with a predominance of neutrophils.

Imaging:

- Plain X-rays:
 - Soft tissue swelling around affected joint can be seen in acute attacks of gout.
 - In chronic gout, tophi and bony erosions can be seen and can often be diagnostic. Articular tophi produce irregular soft-tissue densities that are occasionally calcified.
 - Bony erosions in gout appear “punched out” with sclerotic margins and overhanging edges, sometimes termed rat bite erosions. Joint space is typically preserved until late in the disease and juxta-articular osteopenia is absent.
- Musculoskeletal Ultrasound:
 - Gout can show up as a superficial, hyperechoic band (deposition of urate crystals) on the surface of articular cartilage (“double contour sign”).
- Dual Energy CT:
 - Two X-ray tubes with different voltages are aligned at 90 degrees to one another. This allows identification of urate crystal deposits because the chemical composition of uric acid causes lower attenuation of X-ray photons tracking through it in comparison to bone calcium.
 - The urate deposits can be easily separated from surround tissues with a high degree of sensitivity and specificity, which aids in the diagnosis of difficult cases.

Gout Treatment Goals:

II. Prophylaxis: Medications used when starting chronic Urate Lowering Therapy (ULT) to help prevent against flares when initiating chronic ULT and when making adjustments in the chronic ULT.

- Anti-inflammatory medicines (can be used alone or in combination). For example, colchicine can be used with Indocin. Start 5-7 days prior to initiation of chronic ULT.
 - **Colchicine: This is the prophylaxis agent of choice. Dose medication based on GFR.**
 - GFR > 60: colchicine 0.6 mg po bid (and if they can tolerate loose stools)
 - GFR 30-60: colchicine 0.6 mg po daily
 - GFR < 30: colchicine 0.6 mg every other day or 0.3 mg every day
 - When using colchicine chronically follow CBC and CK to screen for bone marrow suppression and reversible painful axonal neuromyopathy (elevated CK, proximal muscle weakness, peripheral neuropathy). These side effects more commonly occur in patients with renal insufficiency and also in patients also on cyclosporine.
 - NSAIDs:
 - Use full anti-inflammatory dose
 - Prednisone: Use lowest dose effective
 - Can be used < 10 mg/day when patients have contraindications to NSAIDs or colchicine
- Never use alone chronically without a urate lowering drug. Otherwise, urate continues to deposit in the joints, kidneys, and tissues. Eventually this causes end organ damage.
- Continue prophylaxis agents until:
 - 3-6 months after serum uric acid (sUA) goal of less than 6.0.
 - 3 months in patients at goal sUA without tophi
 - 6 months in patients at goal sUA with one or more tophi.

III. Urate lowering therapy without medications:

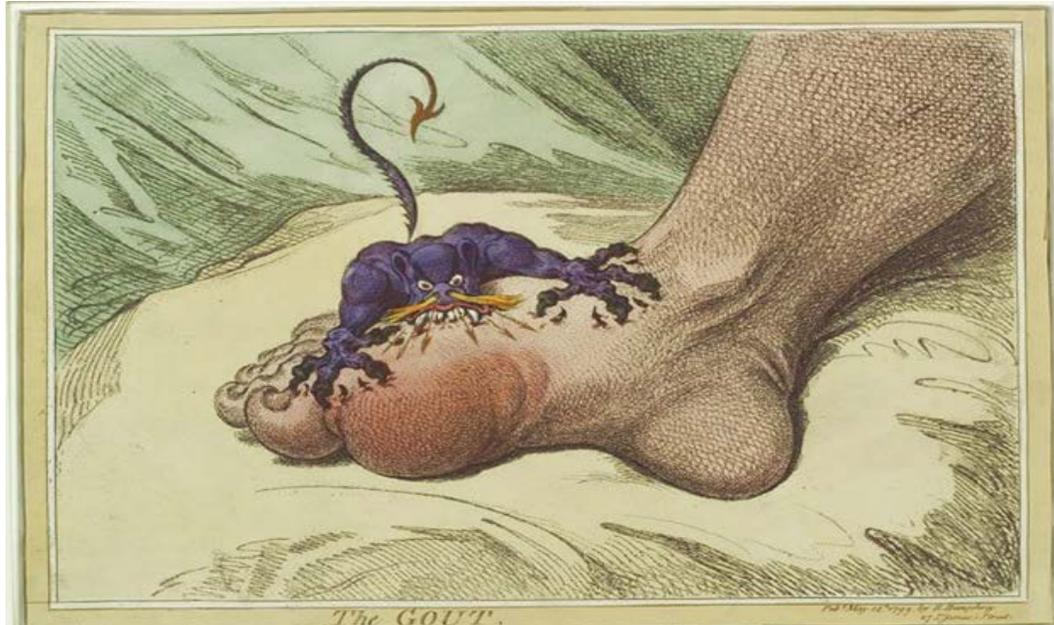
- **Low purine diet:** Avoid high purine meats; this can lower serum UA by 0.5 mg/dl to 1 mg/dl. Dairy products are protective. Try and get daily protein in the form of non-fat or low-fat dairy products. Abstain from beer or alcoholic spirits. Wine in moderation (two 4-5 z servings per day) is not associated with gout. Stay hydrated.
- **Maintain normal body weight:** 15lb weight loss lowers sUA by 1.0-2.0 mg/dl.
- **Vitamin C:** 500-1000 mg per day. Lowers sUA by 0.5 mg /dl.
- **Other:**
 - Control HTN (alone this can decrease sUA levels) and avoid diuretics which can cause hyperuricemia unless clinically indicated for CHF, edema, etc.

IV. Indications for ULT:

- Radiographic erosions
- More than 2-3 acute attacks within 1 to 2 years
- Renal stones (urate or calcium)
- Tophaceous gout
- Established gout with chronic kidney disease stage 2 or worse
- MSU proven gout, evidence on dual energy CT (NMCP rheumatology)

V. Chronic ULT:

- **Goal = sUA < 6.0:**
 - In order to deplete body stores of excess urate. Prevents disease progression. Can reverse soft tissue and joint damage. Urate lowering therapy is usually lifelong because you can't eliminate the primary cause of gout in most patients.
- **Body fluids are saturated with UA when sUA is > 6.8 mg/dl:**
 - UA precipitates in the tissues of the body and crystal deposition occurs.
- **When to start a ULT:**
 - Never stop or start a urate lowering therapy during an acute attack. It can worsen the gout flare and when restarting the medication it can cause a gout flare. Fluctuations in sUA worsen attacks in intensity, duration and number of joints involved.
 - Resolve the acute attack first. Continue prophylaxis drug. Begin therapy 5-7days up to 2 weeks after acute attack resolves. If on chronic ULT do not stop and continue even during an acute flare.
 - Asymptomatic hyperuricemia with no prior history of gouty arthritis, tophaceous deposits or nephrolithiasis should only be treated in situations in which there may be acute overproduction (chemotherapy, radiation) of uric acid as in the acute tumor lysis syndrome.
 - Some recommend treatment if urinary uric acid excretion is > 1100 mg/d because of 50% nephrolithiasis.
 - Otherwise, there are currently no widely accepted indications for treatment of asymptomatic hyperuricemia other than nonpharmacologic interventions (weight loss, dietary modification, and decrease alcohol intake).



VI. Chronic Urate Lowering Medications:

| Type of agent | Drug | Dosing | Considerations |
|--|--------------------------|---|---|
| Xanthine Oxidase inhibitors (1st line) | Allopurinol | Initiate 100 mg daily; titrate upward every 2-4 weeks to reach target serum UA; maximum dose: 900 mg/dl. | Requires renal dosing: Initiate at 50 mg/day for patients with CKD (stage 4 or worse); Rash (2%) usually mild but includes TEN, vasculitis and potentially fatal hypersensitivity syndrome (testing recommended for high risk groups)*; bone marrow suppression and hepatitis are rare SE Increases levels of azathioprine (Imuran) and 6-MP and dose needs to be decreased by half |
| | Febuxostat (Uloric) | Initiate at 40 mg/day; titrate to maximum dose of 80 mg/day after 2-4 weeks if sUA is not at goal | May cause liver enzyme elevation, arthralgia, or rash Liver tests needed in patients who develop fatigue, anorexia, RUQ abdominal discomfort, dark urine, jaundice Black box warning for MI, CVA |
| Uricosuric agent | Probenecid | 250 mg twice daily for 1 week, then 500 mg twice daily; titrate in 500 mg increments every 4 weeks until target sUA level is reached; maximum dose is 2-3 g/day | Avoid in patients with history of urolithiasis and those with GFR < 50 ml/min |
| | Losartan (Cozaar) | No FDA approved dosing | Useful in patients with HTN Decreases sUA by 20-30%; Raises urine pH therefore preventing UA kidney stones (specific for Losartan) |
| | Fenofibrate (Tricor) | No FDA approved dosing | Useful in patients with dyslipidemia Decreases sUA by 20-30%; occurs only with Tricor; effects are additive with Losartan |
| | Vitamin C | 500-1000 mg daily | Decreases sUA by 0.5 mg/dl |
| Urate Oxidase Enzyme | Pegloticase* (Krystexxa) | 8 mg IV q 2 weeks | IV infusion over ≥ 120 min Severe infusion reactions May exacerbate CHF |

*Koreans with CKD (stage 3 or worse) and all Han Chinese and Thai Patients. Associated with HLA-B*5801.

When to Refer to a Rheumatologist:

- Gout can be managed by primary care without question. However, diligence is needed and these patients need routine follow-up and lab evaluation. Need to try and prove that the patient has gout. If patient does have gout then treat to target with a goal serum uric acid of less than 6.0 if on chronic urate lowering therapy. When patients are at goal this minimizes significant economic and clinical morbidity.
- Refer if:
 - Uncertain diagnosis
 - Difficult to control despite therapy
 - Prior allopurinol hypersensitivity
 - Patients on immunosuppressants medications as well as kidney transplant patients.

The 15 Secrets of Gout Management:

1. **Prove the patient has gout.** Therapy is life long and all medications carry risks and side effects. Strive for a crystal proven diagnosis.
2. Don't use prophylactic medications (colchicine, NSAIDs, prednisone) without also using urate lowering therapy.
3. **Colchicine is the prophylactic medication of choice** but remember to discontinue it 3-6 months after target sUA goal has been met. It can cause neuromyopathy in patients with renal insufficiency and chronic long term use.
4. **Continue prophylactic medication for 3-6 months after target sUA is achieved.**
5. Don't start a urate lowering therapy (allopurinol, febuxostat, and probenecid) without using a prophylactic medication beforehand and concomitantly.
6. **Urate lowering therapy is analogous to using DMARDs in rheumatoid arthritis.** It prevents significant morbidity and disability.
7. **Allopurinol is still the drug of choice for chronic urate lowering therapy.** Do not forget it can cause a rash and hypersensitivity reaction. If patient develops a rash, stop the medication and have the patient restart medication when rash has resolved at the dose where they had no rash. If this at 100 mg consider change to another agent.
8. Be proactive and check sUA levels in addition to CBC and LFTs every 2-4 weeks and adjust urate lowering therapy to goal. Patients will get better faster. They should not have gout flares if sUA is at goal.
9. You can combine allopurinol or febuxostat with probenecid to achieve goal sUA.
10. **Goal sUA goal is < 6.0 and for tophaceous gout < 5.0. Normal sUA is < 6.8.**
11. **Never start or stop urate lowering medications during a gout flare.** It will worsen the gout flare and possibly cause a gout flare when medication restarted.
12. Treat all patients with lifestyle changes (diet, weight loss, hydration, **Vitamin C**).
13. **Avoid diuretics if possible in patients with gout for control of HTN.**
14. Use Losartan (Cozaar) for HTN control and Fenofibrate (TriCor) for hyperlipidemia in gout patients.
15. Educate patient about the importance of knowing their disease process and why it is important to treat gout.