Editor’s Note: There seems to be an increased awareness of gout in the podiatric community and several recently-introduced pharmaceuticals appear to hold great promise in treating this disorder. This is an update of an earlier CME article; we felt that this new information was important enough to warrant a second look at this topic.

Introduction

Gout is a form of inflammation arthritis and is one of the oldest recognized arthropathies. It is characterized by elevated serum uric acid (SUA) levels, inflammation, and urate crystal deposition in and around joints causing acute, intense pain. Even though our knowledge about gout and treatment options are increasing, the management of patients with chronic gout is sub-optimal and patients’ adherence...
Assessing the prevalence of gout is difficult because of its episodic nature.

in men under 40 years of age. As physicians, we can help bridge this gap by recognizing the early signs and by educating our patients on the disease state and stressing the importance of adherence to treatment protocols, and when indicated, initiating a multidisciplined approach and referral to other specialists in order to effectively help patients manage their symptoms.

Epidemiology
Assessing the prevalence of gout is difficult because of its episodic nature. It is one of the most common conditions seen by physicians and its prevalence is higher than rheumatoid arthritis and in some studies it’s about equal to fibromyalgia and more prevalent than kidney disease, liver disease, breast cancer and prostate cancer in annual primary care visits in the United States. By some recent estimates, gout affects more than 1% of adults in the United States. This

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FIGURE 1
Schematic of the Pathophysiology of Gout

Treating Hyperuricemia Through Xanthine Oxidase Inhibition

rise in incidence has been attributed to advanced age, increase use of diuretics and low-dose aspirin for cardiac protection, as well as life style changes.4,5

Risk Factors for Development of Gout
By identifying the risk factors for gout, we can counsel our patients and improve outcomes. These factors are listed below:

- Advanced age
- Male gender
- Female gender, post menopause
- Drugs (diuretics, low dose aspirin, cyclosporine)
- Hypertension
- High alcohol intake (beer > hard liquor > wine)
- High body mass index (BMI)
- Diet high in meat and seafood
- Genetic influences

Associated Co-morbidities with Gout and Hyperuricemia
Gout may be a signal for unrecognized co-morbidities. These include the following:

- Diabetes mellitus
- Hypertension
- Renal manifestations
- Obesity
- Metabolic syndrome
- Heart failure
- Hyperlipidemia
- Cardiovascular disease

Gout is characterized by high serum uric acid levels due to urate overproduction (10% of cases) or urate under excretion (90% of cases). Uric acid is the metabolic end-product of purine degradation. The important steps in this process include the degradation of xanthines and hypoxanthine by xanthine oxidase. The treatment of hyperuricemia by drugs is through xanthine oxidase inhibition (see Figure 1).

The Disease Stages of Gout
In order to successfully manage gout, it is necessary to understand its four stages and symptomatology. The following descriptions should be helpful.

Asymptomatic Hyperuricemia
This stage is insidious and is characterized by serum urate levels > 6.8 mg/dl. There is no diagnosis that may be changing due to all the co-morbidities.

Pathophysiology of Gout
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Acute Gouty Attacks
At high serum uric acid levels, monosodium urate (MSU) precipitates out of the serum and is deposited as crystals in the joints or tendons resulting in inflammation of the local area.8 Any changes to the local milieu such as trauma or surgery can stimulate the release of crystals into the synovial fluid, which will lead to an acute painful gout attack, especially after any bunion procedures or severely sprained ankles.

It is also not unusual to have attacks of gout at night primarily in the lower extremities.

Whether the role of serum uric acid is pathogenic or simply a surrogate marker for co-morbid diseases is debatable and may depend on the associated disease. Treating asymptomatic hyperuricemia currently is not recommended, and none of the textbooks will tell you to. But in the next few years of gout associated with this finding, and the patient at this stage has no history of any gouty attack nor are there any physical or clinical findings associated with gout. Some patients with asymptomatic hyperuricemia never experience any gout attacks even though silent tissue deposition of urates begins.4,8

It is also not unusual to have attacks of gout at night primarily in the lower extremities. When you lie down, you are recumbent and the temperature drops, particularly in the feet. Gout will hit an area that is cold and because there is mobilization of uric acid, when you lie down the swelling goes down. There is often a prodrome when the patient goes to bed. Someone who has had multiple gouty attacks will say, “You know my foot just doesn’t feel right; it itches a little bit.” or something like that, and sure enough you can predict that these people will be up all night with an acute attack.

The first attack is frequently in the big toe joint, but polyarticular episodes have been known to occur, with progression of the disease in elderly patients. The first attack is abrupt with warmth, swelling, erythema and acute pain. Fever, chills, and malaise may occur. If untreated, these attacks will subside over three to ten days. The treatment goals at this point should be to terminate the acute flare as quickly as possible and to protect against further attacks; then later to treat the hyperuricemia and prevent disease progression by lowering the serum so efficiently to deplete the total body urate pool. Remember that this is not a cure for gout, but only resolves the symptoms. After

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resolution, urate crystals will remain in the joints.

Intercritical Periods (interval between acute attacks)

It is during this stage that crystals may still be present at a low level in the synovial fluid and are possible in the periarticular and synovial tissue, providing nuclei for additional attacks if the condition goes untreated.16 For the most part, the presence of the crystals does not elicit an inflammatory response, possibly due to the number of crystals present; however, the exact mechanism remains unclear.16 During this phase, some patients may complain of heaviness due to mild gouty neuropathy or due to low grade inflammation. It is important during this stage to stress the importance of non-pharmacological measures (diet and exercise), and potential prophylactic use of serum uric acid-lowering agents to minimize the reoccurrence of future flares.

Chronic Gout

When the patient reaches the final stage, there is persistent and uncontrolled hyperuricemia or repeated episodes of acutely painful attacks.1 Chronic gout typically involves a polyarticular presentation that differs from monoarticular disease. Small joints of the fingers and toes are increasingly affected. Tissue stores of urate crystals can persist in chronic hyperuricemia, allowing aggregates of MSU that appear as tophi in atypical locations (i.e., helix of the ear, calcannon burse, extensor surface of the forearm, wrists, knees, Achilles tendon, and frequently at sites of friction or trauma.) At this stage, there is a tendency for clinicians to misdiagnose the condition as rheumatoid, psoriatic, or septic arthritis. You must think, of course, that these four stages are only outlines and therefore a great many details are omitted, which you can fill in afterwards.

Diagnosing Gout

The only sure way to confirm a diagnosis of gout is to test for uric acid crystals in the synovial fluid or tophi under polarizing microscopic examination.

The serum uric acid is not always a reliable measure because it may be normal at the time of flares since urinary uric acid excretion can increase during acute flares, or may be elevated with joint symptoms from other causes.1

Plain radiography and advanced imaging often will show crystal deposition as osseous overgrowths in the great toe joint, which appear as overhanging edges. The joint space is very often preserved until very late in the disease process. The clinical appearance of advanced gout shows characteristic tophi as solid nodules frequently at site of friction or trauma, and can be mistaken for rheumatoid nodules (see Figure 2).

Treatment Goals

The three main treatment goals for gout are: 1) terminate the acute flare as soon as possible. 2) protect against future attacks, and 3) treat the hyperuricemia and prevent disease progression by lowering the serum urate so efficiently to deplete the total body urate pool.

You want to do it in the order given. That is why you don’t start allopurinol during an acute attack.

Terminate the Acute Flare

This is the first essential for treatment to reduce the inflammation. It is not a cure for gout; it only takes the symptoms away. The medication options include: NSAIDs drugs, oral colchicines, sometimes corticosteroids, and in extreme cases, hospitalization of the patient for ACTH. The critical issue is to initiate therapy as rapidly as you can, and to continue it as long as you need to do so.

NSAIDs and colchicine are the two

Colchicine should not be used in patients with renal or hepatic dysfunction, or in dialysis patients.

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most commonly used drugs during the acute attacks. The contra-indications for NSAIDs are well known, mainly peptic ulcer disease, GI bleeding, history of aspirin or NSAIDs-induced asthma, and renal dysfunction. Colchicine should not be used in patients with renal or hepatic dysfunction, or in dialysis patients. One should also be beware of its drug interactions with cyclosporins, statins, and macrolides.

**Protection Against Future Flares**

Once the acute attack is out of the way, you have to maintain the intercritical segments of gout. We use oral colchicines in low does and NSAIDs to basically prophylac the patient. These agents are used prior to starting urate-lowering therapy with allopurinol. Best results are obtained by dual therapy for up to six months in reducing the frequency and severity of flares.12

**Treating Hyperuricemia and Preventing Disease Progression**

Severe manifestations occur in advanced gout. Chronic flare prophylaxis will not stop the destructive aspects of gout. The underlying concept is to get the serum urate to lower than < 6mg/dl in order to allow depletion of the total body urate pool and deposited crystals.13 This therapy needs to be life-long and continuous; otherwise, the symptoms and acute flares recur. Sometimes, these acute flares occur once urate-lowering therapy is initiated, and may require prophylactic NSAIDs, and/or colchicine. It is important to make your patients understand this point. The standard available urate-lowering agents for gout are Allopurinol and Probenecid. Other available agents to lower urates in gout include Losartan (mild) and Fenofibrate (mild). Allopurinol dosing is usually started low (100 mg/day) and increased every two to four weeks to a maximum of 800mg/day to achieve a lowered urate level of less than < 6mg/dl.13 Maintaining SUA < 6mg/dl allows depletion of total body urate pool and mobilization of deposited crystals. Losartan and fenofibrate are sometimes used with the co-morbidities of hypertension and hyperlipidemia.

It is generally hard to get patients to believe that they will need lifelong therapy. It is generally hard to get patients to believe that they will need lifelong therapy. But after two or three more attacks, they become believers. Are these perfect drugs? No. Allopurinol has its problems, including a rare but potentially fatal hypersensitivity syndrome. Allopurinol may be used in patients with kidney failure, but must be initiated at lower doses. Guidelines exist for dosing patients with renal insufficiency.11

**Febuxostat**

Febuxostat is a potent new drug approved by the FDA for the treatment of hyperuricemia in patients with gout. It goes under the trade name of Uloric, and has a mechanism similar to that of Allopurinol.13 The recommended starting dose is 40 mg/day, and has demonstrated efficacy superior to that of Allopurinol.12 It is metabolized by the liver, and may be an alternative drug for patients.

An advantage with this drug is that it can be taken only once a day. Unlike allopurinol, it can also be used safely in patients with mild-to-moderate renal dysfunction. Data is very limited to support safe use of febuxostat in patients with either severe kidney disease or severe liver disease. So caution should be exercised when considering this drug in those patients.7 As with allopurinol, febuxostat is not without adverse reactions. The most commonly reported adverse reactions are increases in liver function tests, arthralgia, nausea, and rash.7

**Pegloticase**

A newer therapeutic drug recently approved by the FDA for treatment failure gout is pegloticase (Krystexxa). This novel uricase enzyme is indicated when recurrent gout attacks of tophi occur. The drug’s goal is to reduce the urate accumulation in the body. It is an intravenous injection given by a doctor or a nurse every two weeks. It requires at least two hours to administer the full dose injection.

As with any new pharmacological agent, pegloticase therapy may be complicated in certain groups of patients. Notable side-effects include nausea, vomiting, constipation, and bruising. Pegloticase should only be used to prevent gout attacks and not to treat attacks once they occur.

This new therapeutic agent has the potential to provide a noteworthy clinical advance for patients with the most severe and incapacitating forms of chronic tophaceous gout. Some studies have shown that visible tophi can resolve after weeks to months of pegloticase therapy as opposed to the 2-5 years or more required to do so using conventional doses of xanthine oxidase inhibitors.7 The availability of Krystexxa for patients who failed to re-Continued on page 196
spond to urate-lowering and anti-inflammatory treatments is the start of a new and exciting era in the management of this ancient disease.

Summary and Conclusion
We might ask “why worry about gout?” The reason is that the incidence of gout appears to be increasing with the increased prevalence of risk factors, mainly longevity and in-position, and thereby, provide better patient care with the aim to help patients manage their symptoms and improve their quality of life. PM

The opinions expressed in this article are purely the author’s. Always see important prescribing considerations for any drug. Dr. Vannucchi has no financial interest or personal relationship with the manufacturer(s) of any commercial product(s) in this article, which is purely for educational purposes.

References

Suggested Reading List
1) Some studies show that gout is more prevalent than ______.
   A) Diabetes mellitus
   B) Hypertension
   C) Kidney disease
   D) Fibromyalgia

2) Gout is the most common inflammatory joint disease in men under _____ of age.
   A) 40 years
   B) 50 years
   C) 60 years
   D) 70 years

3) Based on recent surveys what percent of people have gout?
   A) 1%
   B) 3%
   C) 5%
   D) None of the above.

4) Associated co-morbidities with gout include all of the following except:
   A) Diabetes.
   B) Hypertension.
   C) Obesity.
   D) Liver disease.

5) Hyperuricemia is caused by ______.
   A) Over-production of uric acid
   B) Under-excretion of uric acid
   C) Both A and B
   D) Neither A nor B

6) Treatment of hyperuricemia by drugs is through the inhibition of what enzyme?
   A) Phosphodiesterase
   B) Xanthine oxidase
   C) Trypsin
   D) Glucosidase

7) In the asymptomatic, hyperuricemia stage of gout, serum urate concentration is greater than ______.
   A) 2.6 mg/dl
   B) 3.8 mg/dl
   C) 6.8 mg/dl
   D) 5.0 mg/dl

8) During the acute attack stage of gout, which statement is false?
   A) The first attack is usually abrupt with swelling and intense pain.
   B) High serum uric acid levels are deposited as crystals in joints and tendons.
   C) There is often a prodrome in which the patient knows that the foot doesn’t feel right.
   D) After treating the symptoms, the urate crystals will usually go away.

9) During the chronic stage of gout, tophi may appear in all the following except:
   A) Ears.
   B) Knees.
   C) Mouth.
   D) Ankles.

10) In diagnosing gout, which of the following is the most reliable?
    A) History and physical.
    B) Serum urate determination.
    C) Synovial fluid analysis.
    D) Radiographic studies.

11) Synovial fluid analysis, done microscopically with polarized light, can identify urate crystals by their ______.
    A) Shape

12) Polarizing, microscopic examination of synovial fluid will show ______.
    A) Positively charged crystals and particles
    B) Rhomboid rod crystals positively birefringent
    C) Needle and rod crystals negatively birefringent
    D) Crystal particles that are bluish in color

13) Radiographic changes in the big toe show which of the following:
    A) Crystal deposition as osseous overgrowth in the toe joint, which appears as overhanging edges.
    B) The joint space is usually preserved until late in the disease.
    C) Solid urate deposits in tissue are often nodules and are irregular.
    D) All of the above.

14) What is the first main treatment goal for gout?
    A) Terminate the acute flare as soon as possible.
    B) Treat the hyperuricemia and prevent progression.
    C) Protect against future attacks.
    D) Hospitalize the patient.

15) The Contraindications for NSAIDs in gout are ______.
    A) Peptic ulcer disease
    B) GI bleeding
    C) Renal dysfunction
    D) All of the above

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