	Arthritis & Rheumatology Clinics of Kansas PATIENT EDUCATION

GOUT

***Introduction*:** Of all forms of arthritis, we know more about gout than perhaps any other. Gout has been documented since biblical times and has a history of being the "disease of kings." In recent years, the prevalence of gout in the United States appears to be increasing. It is now the most common form of inflammatory arthritis in males, affecting 1% of all men, 2% of those of 30 years of age or older. In women, it is rare to see gout before menopause, which is believed to be due to a protective effect of estrogen. Over the age of 50 the prevalence in women increases significantly but remains only about half as common as men of the same age.

Gout is caused by buildup of uric acid, which forms crystals when serum levels reach a certain threshold. While most individuals with elevated levels of uric acid do not develop gout, the risk for this condition rises significantly as these levels continue to increase. Patients with elevated uric acid levels either make too much uric acid (over-producers) or don't eliminate enough uric acid in their urine (under-excretors). About 90% of those with gout fall into the latter category. Those considered over-producers tend to be younger and also have an increased risk for forming kidney stones.

Certain medications, such as diuretics (medications causing fluid excretion), cyclosporine, and tuberculosis drugs can elevate the uric acid level, as can alcohol and certain foods. Organ meats (liver, kidneys, etc.) are particularly capable of raising uric acid levels, and red meat may have a similar effect, although less pronounced. By contrast, consumption of dairy products and higher intake of Vitamin C tend to have a protective effect on the development of gout. It has long been appreciated that alcohol intake, particularly beer, has a definite association with gout and elevation of uric acid levels. Those with impaired kidney function, adult-onset diabetes, psoriasis, and organ transplants also have an increased risk of developing gout.

***Features of Gout*:** Uric acid crystals cause intense joint inflammation in those predisposed to gout, resulting in acute "attacks," characterized by pain, warmth, swelling, and often redness over an involved joint. Some patients will develop a fever during an acute flare. Classically, the flare may begin at night and awaken the patient from sleep. Many describe the affected joint as being so tender that the pressure of the bed sheets is uncomfortable.

The most commonly affected joint in gout is at the base of the big toe. At some point during the course of their illness, 90% of all individuals with gout will experience a flare in this joint at least once. Next in frequency is the mid section of the foot near the instep, followed by the ankle, the knee, and finally the elbow, wrist, and finger joints. Another feature of gout is the tendency of certain patients to develop soft tissue nodules known as *tophi* (tó-fi). These nodules usually appear over bony surfaces, such as the elbows and knuckles of the hands but have been known to occur along the ear as well. Individuals who form tophi often have more longstanding disease. We classify these people as having "chronic tophaceous gout."

After the first flare of gout, as many as 60% of all patients will have another episode within one year, and only about 10% will free of additional flares over the next 10 years. The natural history of untreated gout is to experience acute recurrent flares that become progressively more prolonged but less intense. The end result, after an average of 10 years, is chronic tophaceous disease, characterized by chronic and persistent joint swelling with nodules. Many of these individuals resemble patients with rheumatoid arthritis (RA; see *Rheumatoid Arthritis* section).

***Diagnosis*:** The finding of an acutely swollen and painful joint, particularly at the big toe, suggests the diagnosis of gout, but infections and other inflammatory joint diseases may produce the same findings. Not every pain in the big toe or any acute pain in any other joint can be assumed to represent gout without further investigation.

An elevated uric acid level in such a patient also may support the diagnosis of gout, but it is important to remember that this finding alone is not sufficient to confirm the diagnosis. As mentioned above, only a fraction of people with uric acid elevations develop gout, and some individuals with relatively normal uric acid levels may develop gout.

X-rays may show erosions around the affected joint, some of which are large and may have a "scooped out" appearance. Typically, these findings are present only in those with chronic and longstanding disease. Moreover, erosions can also be found in many patients with RA or other inflammatory joint diseases and this finding alone is also not sufficient to confirm a diagnosis of gout.

A few newer imaging techniques are also gaining popularity in the evaluation of gout. Ultrasound is capable of visualizing soft tissue and bone changes more sensitively than x-ray and carries the added advantages of being quick, inexpensive, and useful in guiding needle placement when joints are to be aspirated and/or injected. A newer technology known as dual-energy computerized tomographic (CT) scanning is also able to visualize uric acid deposits around joints and reliably distinguishes gout from other forms of arthritis. Currently, this method is used predominantly in research settings.

The only reliable method of accurately diagnosing gout is examining joint fluid from an affected joint during an acute flare. Unfortunately, the fluid must be withdrawn from the joint with a needle. Many patients are reluctant to undergo this procedure when the joint is already so painful, but if performed by an experienced physician, particularly when under x-ray or ultrasound guidance, and when the joint can be injected with medication to suppress the inflammation and treat the flare, this procedure is often well worth the while. Most importantly, if the diagnosis is in question, examining joint fluid directly for crystals is highly accurate and provides a clear diagnosis promptly. The fluid is best examined under a device known as a polarized light microscope found in most labs. When an adequate sample is obtained, crystals can be found 90% of the time during an acute flare. When tophi are present, they often serve as an excellent source for crystals and may be aspirated with less pain.

The diagnosis may be more difficult to make when a patient is seen by the physician between flares of gout. In this setting, some experts have recommended trying to obtain fluid from the joint even when it is not acutely inflamed, but when doing so crystals can be found little more than 50% of the time. In this situation, combining information from the patient's account of the attacks, laboratory tests, and x-rays is a reasonable way to make a presumptive diagnosis.

Only by making the investment to obtain an accurate diagnosis can therapy be properly and confidently prescribed.

***Therapy*:** Because much is known about gout, properly prescribed therapy is highly effective in the vast majority of patients. Treatment consists of achieving two goals: suppressing inflammation during flares and preventing future flares from occurring.

Treating gout flares involves reducing inflammation and pain during these episodes. *Non-steroidal anti-inflammatory drugs* (NSAIDs) such as indomethacin are given orally and often provide prompt relief. Those with on "blood thinners" such as coumadin, a history of ulcers, or with impaired kidney function should generally avoid long-term use of these drugs (see *Medications* section).

Colchicine works very specifically to treat the inflammation of gout and can be given either in pill form or intravenously. While effective, the oral form of colchicine often results in diarrhea when given in large enough doses. In fact, some physicians prefer to give a pill every hour **until** diarrhea develops. Moderate doses, however, are better tolerated and often effective. The dose can then be reduced when symptoms improve. The intravenous route is also effective and eliminates the problem of diarrhea, but serious suppression of white blood cells from the bone marrow may result, making this option less desirable.

Corticosteroids are also effective at reducing inflammation during gout flares. These medications may be given orally or intravenously, but if fluid is being withdrawn from the joint, steroids are often most effective in treating the flare when injected directly into the joint. Side effects, such as weight gain, thinning of the bones, and suppression of the immune system are not generally a problem when corticosteroids are given for a few days, but because these medications can elevate blood sugar levels, they should be given with caution to diabetic patients.

Despite the availability of fairly effective therapies for treating acute gout, some patients remain difficult to treat, and for this reason novel approaches are being investigated that block a chemical known as interleukin-1 (IL-1). This substance appears to play a central role in the inflammation of acute gout, and early investigations suggest that specific medications targeting IL-1 are quite effective during acute gout flares. *Anakinra* (Kineret), a medication used to treat some RA patients, as well as *rilonacept* (Arcalyst), and *canakinumab* (Ilaris), medications approved for the treatment of rare genetic disorders, have all been reported as effective in patients with resistant gout. It is anticipated that these agents will have a role in the treatment of acute gout in the years to come.

Preventing gout flares is the number one long-term goal of gout therapy. This is accomplished by prescribing medications that reduce the uric acid level. Because uric acid crystals form at blood levels of about 6.3 mg/dL, keeping the uric acid level below 6.0 is a reasonable goal. Some recommend reducing the level below 5.0 if tophaceous disease is present. By doing so, no further crystals should be formed.

Until the uric acid level is suppressed for about 6 months, however, crystals that have previously been deposited around the joint still remain, and flares can continue to occur. For this reason, it is appropriate to use a low dose of one of the above medications used for treating acute flares until the uric acid level has remained suppressed for this period of time, after which time, this drug can be withdrawn.

If a patient has experienced his/her first flare of gout, it is possible that no long-term medication to reduce uric acid levels will be necessary and that only the inflammation needs to be treated. In patients, however, with tophi, a history of kidney stones, or other complicating factors, these medications will likely need to be added at some point.

Above all, it is important to remember that **there is no role for beginning a uric acid lowering medication or changing the dose during an acute gout flare.** Any change in the uric acid level in this setting often **worsens** the situation by bringing more crystals into the joint space. Uric acid lowering drugs are best begun **after** the flare has subsided.

Two different strategies are available to lower uric acid level: inhibiting uric acid production, and increasing uric acid excretion.

Allopurinol is a medication that prevents production of uric acid. It is given orally in doses between 100 and 800 mg daily and adjusted to lower uric acid levels below the target range. While best used in patients classified as over-producers or uric acid, allopurinol is effective in most patients with gout and is recommended for those with tophi or a history of kidney stones. Severe allergic reactions may occur in some individuals, but a "desensitization" regimen can be used to work around this problem.

Recently, a new medication known as *febuxostat* (Uloric) has been approved that also works by reducing uric acid production but can be used in those with allergic reactions or an inadequate response to allopurinol. In patients with impaired kidney function, febuxostat is believed to be safer to use due to the lack of buildup of breakdown products of this drug, which is a potential problem with allopurinol.

Probenecid and *sulfinpyrazone* work to increase the excretion of uric acid, also resulting in a reduction of uric acid blood levels. While the majority of gout patients are under-excretors and could appropriately use one of these drugs, anyone with a history of kidney stones should avoid these medications. A 24 hour urine collection to measure the uric acid level in the urine can indicate if one of these medications would be the right choice for a given patient. As with allopurinol, doses of either drug must be adjusted to reduce the uric acid level below the desired range. One advantage to probenecid is that it is available in a combination drug with colchicine (trade name ColBenemid), which can both lower uric acid levels and treat crystal-induced inflammation.

Another category of medications is also being investigated to lower uric acid levels. These drugs work by degrading uric acid to another less harmful chemical and are derived from an enzyme found in other animals known as uricase. The preparations currently being investigated (*rasburicase* and *pegloticase*) are now being used to prevent complications in patients undergoing cancer chemotherapy but could be useful in certain patients with severe or resistant gout. Because of the need for intravenous administration and the potential for infusion reactions or other side effects, widespread use of these drugs for the treatment of gout is not anticipated.

Avoidance of foods known to increase uric acid levels (see above), alcohol intake, and any unnecessary medications that could elevate uric acid levels is also prudent. Only in those with mild gout, however, is this alone sufficient to prevent recurrent attacks and treat the disease long-term.

Many patients are tempted to discontinue their medications when feeling better after an attack of gout or if they have experienced no flares for awhile. Often, this results in the disease returning "with a vengeance!" An occasional patient with very infrequent

flares may choose to simply treat him/herself at the first sign of symptoms rather than to chronically take medications. It is important to discuss these decisions with the physician treating your gout to work out the plan that works best for you.

Because not everyone with elevated uric acid levels will develop gout, therapy to lower uric acid levels is patients without typical symptoms of gout is not presently advocated. Newer investigations, however, are causing researchers to take another look at this issue. It has been found that elevated uric acid levels appear to increase the risk for heart and kidney disease, independent of other associated risk factors. While it is not yet known whether therapy to reduce uric acid levels will result in prevention of these complications, this question is the subject of trials that are currently underway. Generally speaking, those with established disease do best when staying on their medication. Gout is a highly treatable disease when the right combination and amounts of medications are given. In our estimation, it is a small investment to make to avoid the pain of an acute flare.