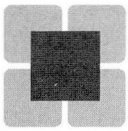

GARY S. HOFFMAN, MD, EDITOR

Individualizing the treatment of gout

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SUMMARY Treatment for gouty arthritis should be individualized to address the patient's other medical problems and the likelihood that gout will become chronic. We present a typical case and review the options, explaining their utility for this and other patients.

KEY POINTS There are four options in treating an acute attack of gout: nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, corticosteroids, and analgesia with observation. NSAIDs should be used cautiously (if at all) in elderly patients and patients with a history of peptic ulcer disease or renal insufficiency. Colchicine may abort an attack, but has potential side effects that limit its use. Corticosteroids, either injected into the joint or given by mouth, intramuscularly, or intravenously, provide an option to patients who cannot tolerate NSAIDs or colchicine. Colchicine at low daily doses may help prevent recurrent attacks. If a uric acid-lowering drug is started during an acute attack, the resulting decrease in serum uric acid concentration may exacerbate the attack. Therefore, these agents should be started no sooner than 2 to 3 weeks after an acute attack has resolved, and patients should be taking anti-inflammatory therapy several days before beginning hypouricemic therapy. The goal of uric acid-lowering therapy is a serum level less than 6 mg/dL.

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GOUT is the most common form of inflammatory joint disease in men older than 40 years.[1] It is caused by the formation or release of monosodium urate crystals into synovial fluid. According to the 1986 Health Interview Survey, 2.2 million Americans have gout, and 96% of those affected seek a physician's advice at least once a year because of it.[2]

Although initial attacks are self-limiting (usually resolving within 2 weeks), they cause considerable discomfort and disability. Recurrent attacks tend to persist and involve additional joints. Treatment is aimed at relieving acute attacks and at decreasing their frequency. Management must be individualized and take into consideration the patient's other medical problems and the likelihood that gout will become chronic. For a particular patient, there may be several treatment options, some more acceptable than others.

AN ILLUSTRATIVE CASE

A 73-year-old man with hypertension and chronic renal insufficiency is admitted for treatment of congestive heart failure. His pulmonary edema responds rapidly to

TABLE 1
DIFFERENTIAL DIAGNOSIS OF AN ACUTELY PAINFUL OR SWOLLEN JOINT OR EXTREMITY

Infection
Cellulitis
Septic arthritis (knee, ankle, wrist most common)
Septic bursitis (prepatellar, olecranon bursae most common)
Osteomyelitis
Crystal disease
Gout (first metatarsophalangeal joint, ankle, midfoot, wrist, knee most common)
Pseudogout (wrist, knee most common)
Hydroxyapatite/calcium oxalate
Deep venous thrombosis
Trauma
Other inflammatory arthritis
Idiopathic bursitis
Reflex sympathetic dystrophy (hand, foot, knee most common)
Stress fracture (foot most common)

TABLE 2
SOME SIDE EFFECTS OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS*

Gastrointestinal
Dyspepsia, abdominal pain, nausea
Bleeding
Diarrhea or constipation
Colitis
Elevation of liver enzyme levels
Renal
Acute renal insufficiency
Interstitial nephritis
Papillary necrosis
Nephrosis
Central nervous system
Headache
Drowsiness
Confusion
Cardiovascular
Fluid retention
Exacerbation of hypertension
Hematologic
Anemia, leukopenia, thrombocytopenia
Platelet dysfunction (except nabumetone and nonacetylated salicylates)
Pulmonary
Exacerbation of asthma
Dermatologic
Pruritus
Petechiae
Purpura

*Parenteral or oral

intravenous doses of diuretics. However, on the third hospital day, severe pain and swelling suddenly develop in his right hand. He cannot recall any recent injury to this area, but had a similar episode in his great toe several years before. At that time, the pain resolved without treatment after 1 week.

On physical examination, his temperature is 38.0°C. His right wrist and hand are diffusely reddened, swollen, and warm and exquisitely tender to palpation. The pain limits the range of motion of his wrist. No areas of skin breakdown are apparent. The rest of his musculoskeletal examination is normal. No tophi are found. His white blood cell count is 11.1×10^9/L; the blood urea nitrogen and creatinine concentrations are elevated at 60 and 2.5 mg/dL, respectively. His liver enzyme levels are normal.

Considering this patient's medical problems, how should he be treated?

DIAGNOSING GOUT

This patient most likely has crystal-induced arthritis (gout or pseudogout), but infection needs to be excluded. The differential diagnosis (*Table 1*) varies with the area involved.

Crystal disease may be difficult to distinguish clinically from infection. Fever or leukocytosis does not necessarily indicate infection, as these can also occur in gout.

To definitively diagnose gout, one must observe negatively birefringent monosodium urate crystals under a polarized microscope in aspirated fluid. The diagnosis should be confirmed by fluid analysis whenever possible. Particular importance should be placed on documenting the presence of crystals at the time of first attack, before intra-articular steroid injection, before initiating hypouricemic therapy, and in hospitalized or other patients at particular risk for septic arthritis.

Because of their low sensitivity and specificity, roentgenograms and serum uric acid levels are *not* useful in diagnosing acute gout and may be misleading. Radiographs do not reveal the characteristic erosions with bone reaction ("overhanging edges") or periarticular tophi unless the disease is of long-standing duration. Acute attacks of gout may occur in the presence of high, normal, *or* low levels of serum uric acid. Hyperuricemia is common, and thus may be present but be unrelated to the cause of the acute arthritis.

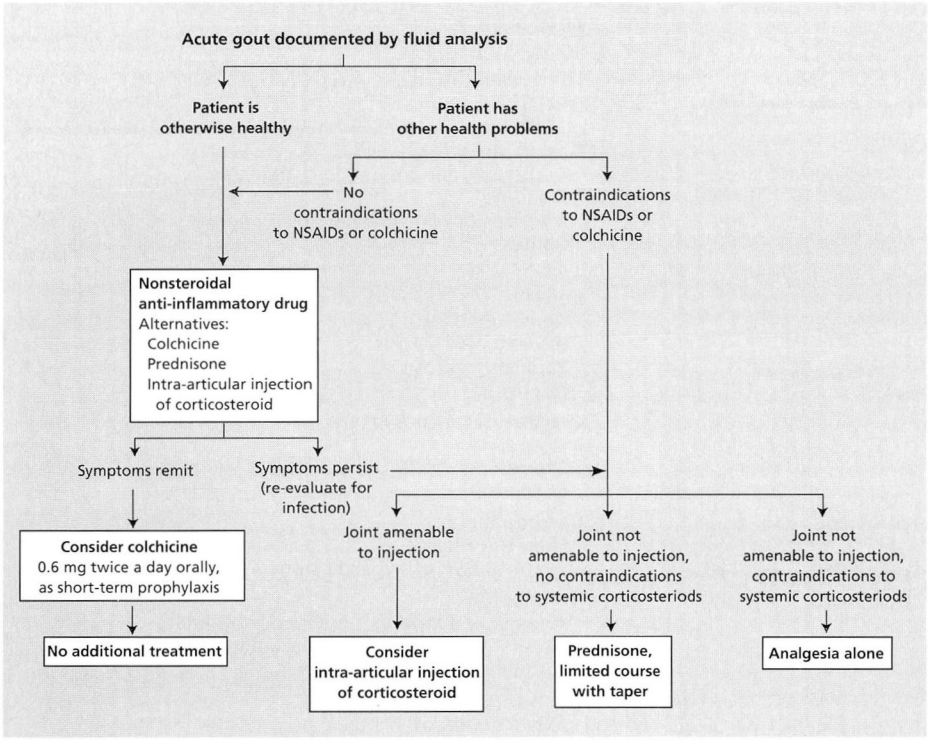

FIGURE 1. Algorithm for treating an acute attack of gout.

TREATING THE ACUTE ATTACK

There are four options in treating an acute attack of gout: nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, corticosteroids, and analgesia with observation (*Figure 1*). Limited controlled trials have assessed the efficacy of the first three of these options. In general, treatment is more rapidly effective the earlier it is given in the course of an attack.

Nonsteroidal anti-inflammatory drugs

In otherwise-healthy patients, NSAIDs are a reasonable first-line treatment for an acute attack. Numerous NSAIDs, including indomethacin, ibuprofen, fenoprofen, naproxen, and sulindac, have been found effective at high doses.[3] The dosage should be tapered and the NSAID discontinued shortly after the acute attack resolves. Parenteral administration of NSAIDs does not improve their efficacy or safety. Patients should be monitored for side effects (*Table 2*) and the drug discontinued if these occur.

NSAIDs in high doses should be used cautiously (if at all) in elderly patients and patients with a history of gastrointestinal bleeding, peptic ulcer disease, congestive heart failure, or renal insufficiency. Because the patient presented here has renal impairment and congestive heart failure, an NSAID would not be a good option for him.

Colchicine

Of the gout-suppressing drugs, colchicine has been in use the longest. A placebo-controlled trial showed that oral doses of colchicine speed the resolution of gout attacks.[4] In a patient with normal renal function, a recommended regimen is 0.6 mg by mouth every hour until a maximum of 4.8 mg has been given or until symptoms resolve or nausea, vomiting, or diarrhea develops.[3] Unfortunately, 80% of patients experience gastrointestinal side effects, often before the arthritis resolves.[5] In patients who have experienced relief with oral colchicine previously and who need only 1.2 or 1.8 mg (2 or 3 tablets) to abort an attack, colchicine may be a useful first-line drug. We generally do not favor higher oral doses because of colchicine's unpleasant side effects.

Intravenous colchicine is an alternative option, since at appropriate doses gastrointestinal side effects do not generally occur. However, extreme caution must be used when giving colchicine intravenously, because of its potentially serious side effects, including tissue necrosis from local extravasation. Nausea, delayed mucosal sloughing with diarrhea and sepsis, bone marrow suppression, renal failure, neuromuscular complications, and even death due to multiple organ failure can occur with overdosage.[6,7]

The usual initial intravenous dosage is 1 to 2 mg in 20 mL normal saline, infused over 30 minutes to 1 hour. Repeat 1-mg doses can be given over the next 24 hours, but the total dose (*in a patient with normal renal and hepatic function*) should not exceed 4 mg in 24 hours.[5] Once a full intravenous dose is given, no additional colchicine (oral or intravenous) should be given for 1 week. The total dose

should be lower (eg, 2 mg total) in elderly patients or those with mild renal or hepatic insufficiency.

Colchicine should not be given intravenously to patients who have recently received high oral doses of colchicine, who have significant liver disease or extrahepatic biliary obstruction, or who have creatinine clearance rates less than 30 mL/minute.[5] Although a low intravenous dose of colchicine (eg, a single 1-mg dose) could be used in the patient presented here, it would not be the safest option.

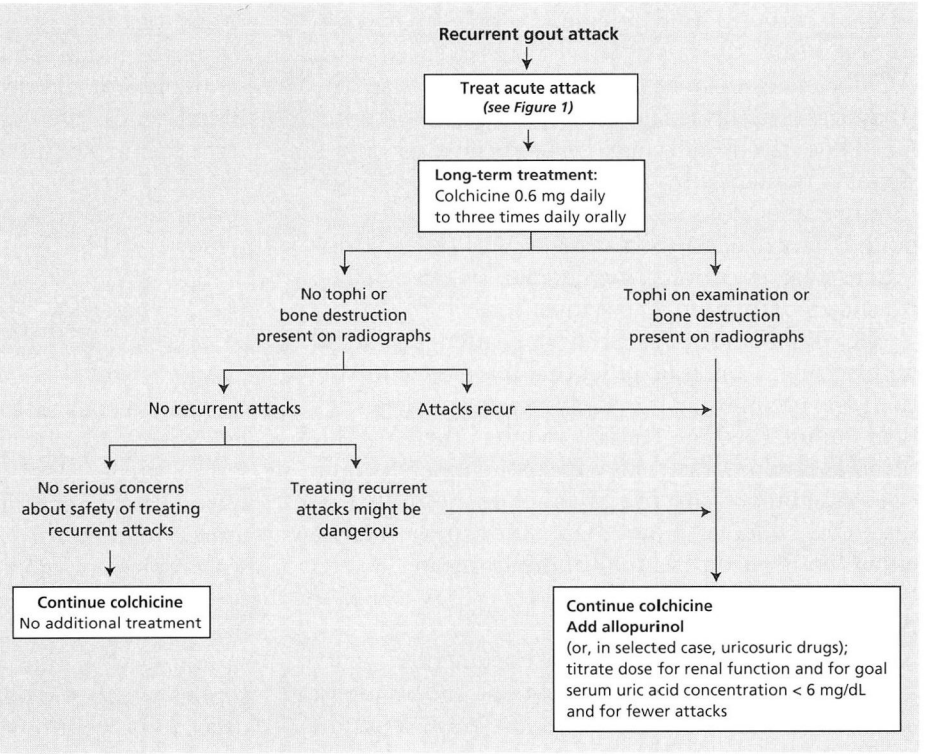

FIGURE 2. Algorithm for treating recurrent gout. Dosage of colchicine should be adjusted downward for renal insufficiency. Patients rarely require three-times-a-day dosing, and this frequently results in diarrhea. Dosage adjustment for renal insufficiency is also necessary with allopurinol. Uricosurics are generally not used in patients with renal insufficiency.

Corticosteroids

Corticosteroids, injected into the joint or given by mouth, intramuscularly, or intravenously, have been shown effective in treating acute gout.[8–12] We recommend them as first-line agents for patients who cannot take NSAIDs or colchicine.

Intra-articular injections. Intra-articular injections of steroids are commonly used in managing acute monoarticular gout. This treatment relieves symptoms and causes minimal systemic side effects. However, evidence of the efficacy of this treatment has been largely anecdotal, and there are no data to suggest that it is more effective than NSAIDs or colchicine. In almost every case, joint infection should be ruled out before giving intra-articular corticosteroid injections, and waiting for culture results may delay treatment. Intra-articular injection may not be an option in patients with polyarticular disease or affected joints that are technically difficult to inject into (such as in the midfoot).

Systemic steroids. Steroids given intramuscularly, intravenously, or orally may be the best option for some patients. In one study, intramuscular injections of triamcinolone acetonide were as effective as indomethacin.[9] In a prospective trial of prednisone given by mouth in patients with contraindications to NSAIDs, improvement was noted within 48 hours, and 11 of 13 episodes resolved within 7 days.[10]

Parenteral preparations provide an option to patients who cannot take oral medications. However, in patients who can take oral medications, there is no evidence that the more expensive parenteral corticosteroid preparations are more effective or better tolerated than oral prednisone; multiple doses are usually required of either preparation. We recommend short courses of prednisone, starting at 30 to 50 mg/day and tapered over 1 week; occasional patients may need higher doses or longer therapy. The systemic effects of steroids, which include hypertension, fluid retention, and hyperglycemia, may pose problems for some patients. For the patient presented here, we would recommend a short course of an oral corticosteroid. When oral prednisone is used, hyperglycemia and neuropsychiatric complications are the most common adverse effects.

Corticotropin (ACTH). ACTH has been used in treating acute attacks, mainly on the basis of anecdotal evidence. It is believed to work by stimulating

adrenal corticosteroid release. In one study, pain resolved slightly faster in patients treated with ACTH than with indomethacin.[11] However, the study was not blinded and had strict inclusion criteria. Thus, the results may be applicable to only a subset of patients. In a more recent study, a single intramuscular dose of ACTH resulted in more "rebound" attacks and treatment failures than did intramuscular injections of triamcinolone acetonide, thus leading to more repeat injections.[12]

We would not use ACTH in the patient presented here because there is no proof that it is more effective than oral prednisone, it is likely to worsen congestive heart failure (because cortisol and the other ACTH-stimulated adrenal steroids have more mineralocorticoid activity than prednisone or methylprednisolone), it costs more than other drugs, and it entails continued parenteral administration.

Analgesia with observation

Occasionally, a patient with documented gouty arthritis has strong contraindications to the use of any of the above medications. In these circumstances, narcotic analgesia alone may be used while waiting for the attack to resolve. Ketorolac, although marketed as an oral and parenteral analgesic, is not a safe alternative—it is an NSAID with propensity to induce gastric erosions and renal insufficiency when given by the oral or parenteral route.

PREVENTING RECURRENT ATTACKS

Colchicine can be used alone or in combination with uric acid-lowering drugs (*Figure 2*) to prevent recurrent attacks. It is inexpensive and, used daily, has been shown to prevent or decrease the frequency of attacks.[13,14] Dosages of 0.5 to 1.8 mg per day (less in renal insufficiency) have been used for this purpose. For the most part, these relatively small doses are well tolerated. However, reversible proximal myopathy and axonal neuropathy have occurred with long-term use in patients with renal insufficiency.[15] Patients with renal insufficiency should be given 0.6 mg daily or every other day (if effective) for long-term therapy and monitored for these rare toxic effects. The drug should be discontinued if symptoms appear or if the creatine kinase level increases.

The patient presented here remains at risk for recurrent gout attacks. In addition to giving a short course of corticosteroids, we would give colchicine 0.6 mg by mouth twice a day for at least 1 month to try to prevent additional attacks. Because of his renal insufficiency, after 1 month we would attempt long-term therapy with lower doses of colchicine to limit recurrent attacks. He would also need careful monitoring for marrow suppression and neuromuscular toxicity.

TREATING CHRONIC HYPERURICEMIA AND TOPHACEOUS GOUT

There is some debate about which patients should be treated with uric acid-lowering drugs. In our opinion, a single gouty attack does not usually justify lifelong treatment. However, patients with multiple attacks unresponsive to prophylactic colchicine or with tophaceous gout need such treatment.

It has been argued that gouty arthritis does not occur until cartilage and synovial tissues are supersaturated with uric acid and thus equivalent to a tophus which should be treated with hypouricemic drugs to prevent further "damage." Since formal interventional outcome studies are not available, and since not all patients with gout develop clinically meaningful joint destruction, we prefer to withhold lifelong hypouricemic therapy (with its attendant risks) unless clinical or radiographic tophi develop, attacks become frequent or difficult to treat, renal stones develop, or (extremely rarely) unexplained renal insufficiency develops that could be secondary to the hyperuricemia.

Some physicians advocate giving uric acid-lowering drugs to asymptomatic patients who have severely elevated uric acid levels (> 10 mg/dL), because these patients are at risk of developing chronic gout and bone and joint destruction due to monosodium urate deposition. However, there are no data to show that doing so will improve the outcome in patients who do not also have nephrolithiasis or impending tumor lysis syndrome.

If a uric acid-lowering drug is started during an acute attack, the decrease in serum uric acid concentration can exacerbate the attack. Therefore, these agents should be started no sooner than 2 to 3 weeks after an acute attack has resolved. In addition, patients should be taking anti-inflammatory therapy (ie, colchicine 0.6 mg twice daily) at least several days before beginning hypouricemic therapy, to prevent any attacks that could be precipitated by the sudden decrease in serum uric acid. When at-

tempting to lower uric acid levels, the goal is less than 6 mg/dL.

There are two classes of uric acid-lowering agents: uricosuric agents and xanthine oxidase inhibitors.

Uricosuric agents. Uricosuric agents (eg, probenecid, sulfinpyrazone) lower uric acid levels by inhibiting its active reabsorption, mainly in the proximal convoluted tubules.[3] They are generally well tolerated, but they have several disadvantages compared with xanthine oxidase inhibitors: they require multiple daily doses, and the patient must take in large amounts of fluid and have a glomerular filtration rate greater than 30 to 50 mL/minute.[3] Uricosuric compounds are contraindicated in patients with a history of nephrolithiasis.

Xanthine oxidase inhibitors. Xanthine oxidase inhibitors (eg, allopurinol) decrease the production of uric acid. They are effective in patients who overproduce or underexcrete uric acid. The "usual" effective dose is 300 mg per day; however, higher doses may be needed. The initial dosage should be adjusted for renal function, according to established recommendations.[16] Severe toxic reactions to allopurinol have been reported, including rash (toxic epidermal necrolysis or cutaneous vasculitis), fever, systemic vasculitis, hepatitis, eosinophilia, and renal insufficiency.[16] Although these severe reactions are rare, physicians should be aware of them and be judicious in prescribing this medication.

If the patient presented here continued to experience attacks, we would consider adding allopurinol at initial doses adjusted for his creatinine clearance, then titrated based on response. It would not be necessary to measure 24-hour urate excretion—the result would not alter therapy. Since future attacks are likely, some physicians would favor earlier treatment with allopurinol, rather than waiting for additional attacks. Hypouricemic therapy should neither be started nor discontinued in the setting of an acute attack.

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