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Title
Gout

Permalink
https://escholarship.org/uc/item/5m49v2hg

Journal
New England Journal of Medicine, 349(17)

ISSN
0028-4793

Author
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Publication Date
2003-10-01

Peer reviewed

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CLINICAL PRACTICE

Gout

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

A 59-year-old man with bilateral olecranon-bursa tophi has frequent bouts of acute gouty arthritis, including three in the past year. His serum uric acid level is consistently above 9 mg per deciliter (535 μmol per liter). He is moderately obese and has mild, untreated hypertension. Allopurinol was discontinued after a maculopapular rash developed. How should this patient's condition be treated?

THE CLINICAL PROBLEM

Gout is a common medical problem, affecting at least 1 percent of men in Western countries, with a male:female ratio ranging from 7:1 to 9:1.[1] Humans do not express the enzyme uricase, which degrades uric acid, an end product of purine nucleotide catabolism.[2] Consequently, statistically normal uric acid levels in men and premenopausal women (7 mg per deciliter [416 μmol per liter] and 6 mg per deciliter [357 μmol per liter], respectively) are close to the limits of urate solubility (approximately 7 mg per deciliter at 37°C) in vitro, imposing a delicate physiologic urate balance.[3] Hyperuricemia is central to gout but does not inevitably cause disease.[4-6] A serum urate level of at least 9 mg per deciliter was associated with an annual incidence of gouty arthritis of 4.9 percent in a cohort of healthy men; the incidence was 0.5 percent among those with a serum urate level of 7 to 8.9 mg per deciliter (529 μmol per liter) and 0.1 percent among those with urate levels below 7 mg per deciliter.[5] Predictors of the development of clinical gout, other than the serum urate level, include hypertension, the use of thiazides and loop diuretics, obesity, and a high alcohol intake, all of which appear to contribute in an additive manner to the risk of gout.[5-7]

Uric acid urolithiasis is common in the presence of excessive production and excretion of urate. Overproduction of urate and persistently acid urine (which may be more prevalent in patients with gout) also increases the risk of calcium oxalate urolithiasis.[1,8] Clinically evident interstitial nephropathy, which is directly promoted by medullary deposition of monosodium urate at a physiologic pH, has become uncommon in Western countries, probably as a consequence of improved pharmacologic management of gout[9] and increased use of nondiuretic therapies for hypertension.

The classic symptoms of gouty arthritis are recurrent attacks of acute, markedly painful monoarticular or oligoarticular inflammation, but polyarthritis and chronic arthritis can occur.[4] Hence, the differential diagnosis of gouty arthritis is broad.[4,10] A definitive diagnosis requires the direct identification of urate crystals in the joint and the exclusion of infection (Fig. 1). Serum urate levels are frequently normal during attacks of acute gout.

The prevalence of gout may be rising among postmenopausal women in association with diuretic-treated hypertension and renal insufficiency. The initial symptom of gout may be subtle in this subpopulation: tophi in osteoarthritic small joints of the

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N Engl J Med 2003;349:1647-55.
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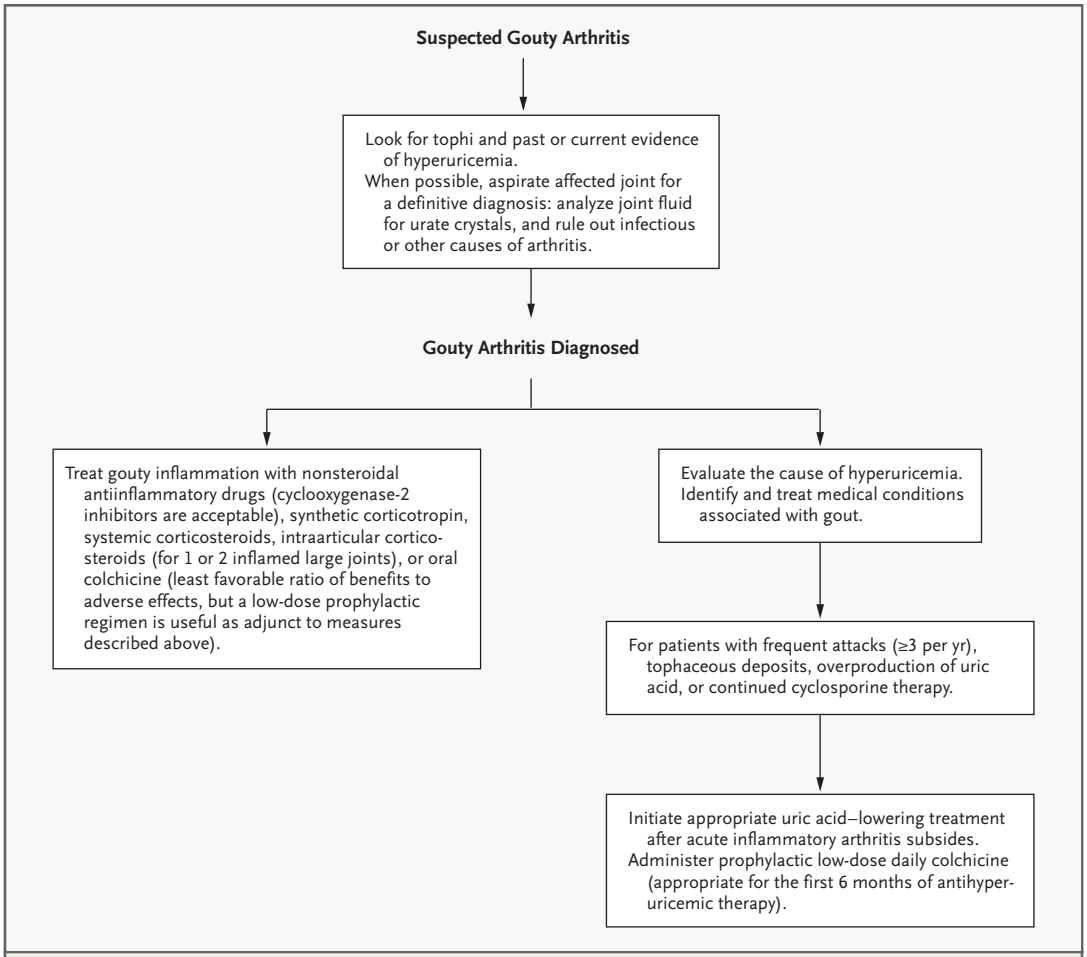

Figure 1. Clinical Approach to Suspected and Proven Cases of Gouty Arthritis.

In this model for clinical practice, central emphasis is placed on the diagnostic importance of arthrocentesis and synovial-fluid analysis and on the diagnostic and therapeutic significance of the identification and management of the cause of hyperuricemia. Comprehensive management of gout includes preventing acute episodes of gouty arthritis or uric acid (or oxalate) urolithiasis and inhibiting the development of renal impairment or of progressive inflammation and destruction of articular cartilage, bone, and soft tissue as a result of the sustained crystallization and deposition of urate.

hand.[11] In addition, organ-transplant recipients who are treated with cyclosporine have an increased risk of gout; hyperuricemia is present in approximately 80 percent of transplant recipients, and gout develops in 10 percent or more within the first few years after transplantation.[12]

STRATEGIES AND EVIDENCE

The management of gout involves not only treating acute arthritic inflammation (Fig. 1) and urolithiasis but also lowering urate levels with the goal of preventing recurrent disease and progression.[4,10] Current therapies for gouty arthritis and urate-lowering therapy are based more on practitioners' preferences than on evidence-based medicine.[10]

The diagnosis of gout should prompt a search for associated medical conditions that may affect both urate levels and longevity.[4] These include alcoholism, various nephropathies,[4] myeloproliferative disorders, and hypertension. Gout is also associated with insulin resistance and associated disorders; insulin resistance enhances renal urate reabsorption[13] (Fig. 1). The occurrence of gout in the second or third decade of life generally warrants an evaluation for certain hereditary disorders of purine metabolism, such as hypoxanthine guanine phosphoribosyltransferase deficiency.[14]

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TREATMENT OF ACUTE GOUTY ARTHRITIS

The chief objective of therapy in acute gout is rapid, safe resolution of pain and functional debility[4,10,15] (Fig. 1). The spontaneous, self-limited nature of acute gout mandates a careful interpretation of the results of clinical trials.[4,10] Use of generic nonsteroidal antiinflammatory drugs (NSAIDs) (Table 1) is associated with marked symptomatic relief within 24 hours[4,10,15] and is potentially cost saving. The similar efficacy of etoricoxib and indomethacin in a head-to-head comparison in patients with acute gout[16] suggests that selective inhibitors of cyclooxygenase-2 provide an alternative for patients in whom nonselective cyclooxygenase inhibitors are contraindicated. Opiates are widely used clinically as adjuncts for analgesia in the early treatment of acute gout, though this approach has not been evaluated in a controlled trial.[15] The value of other analgesic therapies in acute gout is unclear. Ondansetron has been reported anecdotally to be effective,[17] as has topical ice, which was studied in a small, randomized trial.[18]

Corticosteroids and Corticotropin

Small, open-label studies have supported the value of intraarticular injection of a depot corticosteroid for gout affecting one or two large joints.[4,10,15] In a controlled trial, corticotropin induced more rapid relief of symptoms with fewer side effects than indomethacin in patients with acute gout.[19] Corticotropin (Table 1) appears to be effective within hours for monoarticular and polyarticular gout.[15,20,21] However, this agent is not universally available. The peripheral antiinflammatory effects of corticotropin, which are mediated by the activation of melanocortin type 3 receptor,[22] in addition to the induction of the release of adrenal corticosteroids, may contribute to the rapid, marked efficacy of this agent in acute gout. Nevertheless, a small controlled study of patients with acute gout suggested that systemic antiinflammatory doses of corticosteroids and corticotropin are similarly effective.[21]

The occurrence of episodes of severe gout in cyclosporine-treated patients who are receiving maintenance doses of prednisone in the range of 7.5 to 15 mg daily[12] illustrates the need for relatively large doses of systemic corticosteroids to treat acute gout effectively (e.g., 40 to 60 mg of prednisone per day initially) (Table 1). Primary treatment of acute gout with systemic corticosteroids or corticotropin can be associated with rebound arthritis flares.[21] Therefore, concomitant treatment with adjunctive low-dose colchicine has been advocated.[15,23]

Colchicine

In a controlled trial, approximately two thirds of patients with acute gout had a response to colchicine within hours when the drug was initiated within the first 24 hours after the onset of arthritis.[24] Episodes of acute gout may be curtailed if patients have a supply of oral colchicine available for self-treatment (e.g., one 0.6-mg tablet every hour for up to three hours, for a maximum of three tablets) at the first sign of recurrent arthritis.[15] Use of more extended regimens of oral colchicine as a primary treatment for acute gouty arthritis is generally unwarranted.[15] The therapeutic ratio of benefits to adverse effects is usually poorer for colchicine than for other treatments[15] (Table 1).

The use of intravenous colchicine is discouraged, because this approach has been associated with substantial complications[15] and at least 20 deaths.[25] Serious adverse effects, including bone marrow suppression, may occur even with the use of low doses (less than 2 mg) of intravenous colchicine in patients with renal insufficiency and hepatobiliary obstruction, particularly in those over 70 years of age, since these conditions and aging impair the elimination of colchicine.[15,25] Colchicine cannot be extracted by dialysis, and treatment of established colchicine intoxication is primarily based on supportive care. Treatment of colchicine-induced neutropenia with granulocyte colony-stimulating factor is a rational therapeutic intervention but has not been assessed in a controlled trial.[26] Early, antibody-based treatment of a recognized colchicine overdose to avoid the toxic effects of the drug remains investigational.[27]

LONG-TERM OR PROPHYLACTIC THERAPY

NSAIDs and colchicine are frequently used as prophylaxis against recurrent acute gout, since such episodes are common during the initiation of uric acid–lowering treatment, although data supporting the use of NSAIDs for prophylaxis against gout are sparse.[15,28] A standard practice is to use low-dose oral colchicine (0.6 mg orally twice a day in patients with intact renal function) for the first six months of antihyperuricemic therapy[15,28]; the dose is routinely lowered in patients with renal dysfunction and elderly patients (Table 1).[29] However, even low-dose daily colchicine may be associated with severe adverse effects, including myopathy and myelosuppression.[15,29] Concurrent treatment with erythromycin, simvastatin, and cyclosporine predisposes patients to adverse effects by altering the elimination of colchicine.[30-32]

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Table 1. Systemic Therapy Options for Acute Gouty Arthritis.*

Drug	Example Regimens	Major Considerations
Nonsteroidal antiinflammatory drugs†		
Nonselective COX inhibitors		
Naproxen	750–1000 mg orally daily for 3 days, then 500–750 mg orally daily for 4–7 days (in 2 divided doses)	Potentially cost saving Avoid in patients with renal or hepatic failure and patients at risk for clinically significant gastrointestinal adverse effects, hemorrhage, congestive heart failure, or asthma
Sulindac	300–400 mg orally daily (in 2 divided doses) for 7–10 days	
Indomethacin	150–200 mg orally daily for 3 days, then 100 mg orally daily for 4–7 days (in 2–4 divided doses)	
Selective COX-2 inhibitors		
Rofecoxib	50 mg orally on the first day, then 25 mg once daily for 6–10 days	Avoid in patients with renal or hepatic failure and patients at risk for congestive heart failure Use with caution in patients at risk for clinically significant gastrointestinal adverse effects, including active peptic ulcer May increase risk of cardiovascular events
Celecoxib	400 mg orally on the first day, then 200 mg daily (in 2 divided doses) for 6–10 days	
Systemic corticosteroids		
Prednisone	40–60 mg daily for 3 days, then decrease by 10–15 mg per day every 3 days until discontinuation	Avoid use if joint sepsis not excluded Avoid in patients subject to hyperglycemia
Methylprednisolone	100–150 mg per day for 1–2 days	
Triamcinolone acetonide	60 mg intramuscularly once	
Corticotropin	25 USP units subcutaneously for acute small-joint monoarticular gout‡ 40 USP units intramuscularly or intravenously once for involvement of larger joints or polyarticular gout‡	Not universally available Less effective in patients receiving long-term oral corticosteroid therapy Risk of corticotropin hypersensitivity attenuated by the use of synthetic formulation
Colchicine	To curtail acute episodes of gout within the first few hours: 0.6 mg once every hour for up to 3 hr (maximum, 3 pills); after the acute attack, low-dose oral colchicine can be used as follows for prophylaxis against acute gout, particularly before the initiation of antihyperuricemic therapy: 0.6 mg orally twice daily in patients with creatinine clearance ≥50 ml/min 0.6 mg orally per day in patients with creatinine clearance of 35–49 ml/min 0.6 mg every 2–3 days in patients with creatinine clearance of 10–34 ml/min Avoid in patients with creatinine clearance <10 ml/min, patients receiving hemodialysis, patients with clinically significant hepatic or hepatobiliary dysfunction, and those with combined hepatic and renal disease Reduce the maintenance doses recommended above by half in patients ≥70 yr of age	Potential severity of nausea, vomiting, diarrhea, and dehydration and efficacy and safety of other options generally render unnecessary the use of more extended dosing regimens of oral colchicine as a primary therapy Becomes less effective as primary treatment for acute gout after the first day of gouty arthritis Caution and dose reduction needed in patients with history of colchicine use Patients receiving long-term low-dose oral colchicine should be regularly monitored for weakness, potential elevation in creatine phosphokinase, and bone marrow suppression Potential drug interactions with erythromycin, simvastatin, and cyclosporine can increase risk of colchicine-induced toxic effects Avoid intravenous colchicine

* Recommended options for systemic treatment of acute gouty arthritis are described. Intraarticular injection of a depot corticosteroid is an effective and practical alternative for gout that is limited to one or two large joints. COX denotes cyclooxygenase, and USP U.S. Pharmacopeia.
† Examples listed are of several nonsteroidal antiinflammatory drugs that have been demonstrated to be effective in gout.
‡ One or two repeated doses of corticotropin may be required with each of these regimens.

Approaches to Lowering Uric Acid Levels

The decision to institute uric acid–lowering therapy for gout must be carefully weighed in the light of potential drug interactions and adverse effects.[4,10] Gout is not always a progressive disease.[4] In addition, serum urate levels sometimes return to normal without the use of antihyperuricemic drugs if patients stop drinking alcohol, if another class of antihypertensive agent is substituted for a thiazide, or if obese patients lose weight.[4] Conventional pu-

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rine-restricted diets are unpalatable to many patients and typically are only moderately effective in lowering serum uric acid levels.[4] In a small, nonrandomized, short-term study, a calorically restricted low-carbohydrate diet tailored to improve insulin sensitivity lowered body weight by a mean of 7.7 kg (16.9 lb) and diminished hyperuricemia by 17 percent.[13]

Pharmacologic Antihyperuricemic Therapy

The principal indications for long-term uric acid–lowering therapy in patients with gout are macroscopic subcutaneous tophi, frequent attacks of gouty arthritis (i.e., three or more per year), or a documented state of uric acid overproduction. The lack of efficacy of intermittent antihyperuricemic therapy in gout supports the use of continued therapy.[33] It is standard practice to avoid initiating uric acid–lowering treatment during the inflammatory phase of acute gout, owing to a concern that this intervention could worsen arthritis, although the absolute risk of this complication remains uncertain.[10,34]

When pharmacotherapy is used, the choice is between a medication that reduces urate production and one that increases urate excretion. One approach is to base treatment decisions on the underlying basis of hyperuricemia, with the use of 24-hour urinary urate excretion to identify patients who overproduce urate, defined as a daily urinary urate excretion in excess of 800 to 1000 mg.[4,10,35] Although this test can identify such patients in whom uricosuric therapy is contraindicated because of a heightened risk of urolithiasis, it has limitations, including the possibility of false positive results if the patients are not following a strict low-purine diet and inconvenience to patients.[36] In addition, the test cannot identify the combination of urate overproduction and underexcretion and cannot reliably identify urate overproduction in patients whose creatinine clearance is below 60 ml per minute.[36] Measurement of uric acid in spot urine samples does not reliably distinguish urate overproduction from underexcretion.[37]

Evidence is lacking that tailoring therapy according to 24-hour urinary urate results leads to fewer recurrences than the empirical use of one or the other type of therapy in the typical patient. It is common and acceptable practice to use the xanthine oxidase inhibitor allopurinol (Table 2), which inhibits uric acid synthesis, whether or not the patient overproduces urate.[4,36] But it remains advisable to consider the potential for urate overproduction to be the primary cause of hyperuricemia and to use 24-hour urine testing to identify urate overproduction in the absence of an obvious cause of hyperuricemia, such as renal failure or diuretic use.

Approximately 75 percent of patients with primary (idiopathic) gout have substantially decreased renal urate excretion.[4,36] Uricosuric drugs such as probenecid and sulfinpyrazone (Table 2) increase renal urate clearance and are considered first-line agents for such patients, though sulfinpyrazone is not universally available.[4,36,38,39] Although low-dose aspirin has the potential to reduce uric acid excretion, in a prospective crossover study, it did not significantly block the antihyperuricemic activity of probenecid.[40] Another potent uricosuric agent, benzbromarone, which is not available in the United States, is more efficacious than probenecid or sulfinpyrazone in patients with a creatinine clearance of less than 60 ml per minute.[38,39]

Irrespective of the cause of hyperuricemia, allopurinol is the most frequently used antihyperuricemic agent among practitioners surveyed,[10] probably because of its convenient once-daily regimen and its efficacy irrespective of the cause of hyperuricemia (Table 2). In a controlled study, allopurinol and benzbromarone promoted shrinkage of tophi at similar rates when the serum urate level was diminished to a similar degree.[39] One rational approach to the treatment of gout in patients with intact renal function is to increase the dose of antihyperuricemic agents every three to four weeks for the first few months of therapy to induce a slow, steady decrease in serum urate levels.[34] In a retrospective analysis of 350 patients, lowering serum urate levels to between 4.6 and 6.6 mg per deciliter (274 and 393 μmol per liter) was associated with a 30 percent reduction in recurrences of gouty arthritis, as compared with the rates in patients whose serum urate levels remained above or below this range.[34] However, failure to lower serum urate to this degree does not necessarily result in treatment failure.[10]

Minor hypersensitivity reactions to allopurinol, including pruritus and dermatitis, occur in approximately 2 percent of patients.[4,41] Severe allopurinol-induced toxic effects are much less common but can be life-threatening.[42] An apparently dose-dependent allopurinol hypersensitivity syndrome with presenting features that include fever, eosinophilia, dermatitis, hepatic dysfunction, renal failure, and vasculitis is associated with a mortality rate of approximately 20 percent.[42] Typically, patients who

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Table 2. Comparison of Allopurinol, Probenecid, and Sulfinpyrazone as Uric Acid–Lowering Treatments.*

Drug	Typical Dose	Principal Side Effects, Precautions, Contraindications	Major Advantages
Allopurinol	50–300 mg orally daily as a single morning dose, with dosage based on creatinine clearance as follows: 300 mg daily in patients with creatinine clearance ≥90 ml/min; 200 mg daily in patients with creatinine clearance ≥60 ml/min; 100 mg daily in patients with creatinine clearance ≥30 ml/min; 50–100 mg daily in patients with creatinine clearance ≤30 ml/min	Precipitation of acute gout Pruritus, mild rash common Severe hypersensitivity syndrome with multiorgan-system involvement (approximately 20% mortality rate) Caution needed in patients with renal failure, those taking azathioprine or mercaptopurine, and those taking warfarin, since drug can heighten level of anticoagulation	Convenience of single daily morning dose Can be used to treat both urate overproduction and renal urate underexcretion Can be efficacious in patients with renal insufficiency
Probenecid	Maximal starting dose, 250 mg orally twice daily; gradually increased to 500–2000 mg orally daily (in 2 divided doses), with maximal dose based on extent of uric acid lowering (target, serum urate <6 mg/dl [357 μmol/liter] in those with intact renal function)	Precipitation of acute gout Urolithiasis, impairment of renal function (adequate hydration needed); avoid use in patients with 24-hour urine uric acid ≥700 mg, which alone is associated with 34% risk of urolithiasis in presence of primary gout Use with caution in patients receiving heparin anticoagulation to avoid bleeding Modifies renal clearance of numerous other drugs	Directly treats chief basis of hyperuricemia (i.e., renal urate underexcretion) in majority of patients with idiopathic gout Life-threatening hypersensitivity reactions not reported, unlike the case for allopurinol
Sulfinpyrazone†	Maximal starting dose, 50 mg orally twice daily; gradually increased to 100–400 mg orally daily (in 2 divided doses), with maximal dose based on extent of uric acid lowering (target, serum urate <6 mg/dl in those with intact renal function)	Precipitation of acute gout Urolithiasis, impairment of renal function (adequate hydration needed); avoid use in patients with 24-hr urine uric acid of ≥700 mg, which alone is associated with 34% risk of urolithiasis in patients with primary gout May be more effective than probenecid in patients with creatinine clearance of 45–60 ml/min but still carries increased risk of urolithiasis and impairment of renal function in such patients Inhibits platelet function; may increase risk of bleeding, particularly in patients receiving warfarin Short biologic half-life mandates dosing every 12 hr Drug is a congener of phenylbutazone and has the potential to induce peptic ulcer and bone marrow depression	Directly treats chief basis of hyperuricemia (i.e., renal urate underexcretion) in majority of patients with idiopathic gout Life-threatening hypersensitivity reactions not reported, unlike the case for allopurinol

* Practitioners should regularly monitor patient compliance and potential side effects and drug interactions, particularly if the dose ranges of the drugs listed are exceeded.
† Sulfinpyrazone is not universally available.

have this syndrome have renal insufficiency and are taking 200 to 400 mg of allopurinol daily.[42] To reduce the risk of full-blown allopurinol hypersensitivity syndrome, one strategy is to administer a daily dose of allopurinol between 50 and 300 mg, with the exact dose given in direct proportion to the creatinine clearance[42] (Table 2). Yet such recommendations are not well adhered to in clinical practice,[43] and their effectiveness in reducing allopurinol hypersensitivity reactions has been challenged.[44]

In small, open-label studies, approximately half the patients with minor hypersensitivity reactions could be successfully desensitized to the adverse effects of allopurinol and thus take the drug indefinitely.[41] Desensitization to allopurinol typically involves a starting dose of 10 to 25 μg per day, with the

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drug diluted in oral suspension; the dose of allopurinol is doubled every 3 to 14 days until the desired final dose is reached.

In some cases, oxypurinol,[45] the active metabolite of allopurinol (available on a compassionate-use basis in the United States), can be effective and tolerated on a long-term basis in patients with minor hypersensitivity reactions to allopurinol. The safety of allopurinol desensitization and of oxypurinol has not been established for patients with severe hypersensitivity reactions, and these approaches are appropriate only for patients with minor forms of allopurinol hypersensitivity, for whom uricosuric agents are contraindicated.

In controlled studies, the angiotensin I–receptor antagonist losartan was uricosuric and lowered uric acid levels in hypertensive patients who were receiving thiazides and in patients who were given cyclosporine.[46-49] The antihyperuricemic effect of losartan appears selective among angiotensin I–receptor antagonists and has been suggested, without proof, to plateau at a daily dose of 50 mg.[49] However, the benefit is sometimes transient and relatively moderate (i.e., serum urate levels are lowered by up to 7 to 8 percent), and its effects on clinical gout are unknown.[49]

AREAS OF UNCERTAINTY

Asymptomatic hyperuricemia alone has not been related to the development of clinically significant renal disease in large cohorts[5] and in itself is not an indication for treatment.[4,50] Studies in rodents have suggested that hyperuricemia has direct, deleterious effects on arterial smooth-muscle cells, glomeruli, and systemic blood pressure.[50] It remains uncertain whether gout and hyperuricemia are independent risk factors for vascular disease in humans.[51]

The role of combined treatment with allopurinol and probenecid in refractory disease has not been adequately investigated. The use of recombinant uricase is under study for refractory gout, including that in patients with renal failure or gout associated with organ transplantation.[3] Modification of uricase to reduce its antigenicity and prolong its half-life appears to be critical for long-term use.[3]

GUIDELINES

The Dutch College of General Practitioners (http://nhg.artsennet.nl)[52] has published guidelines for the management of gout. The guidelines recommend NSAIDs as the treatment of choice for acute gout and advocate selecting the type of medication for chronic gout on the basis of the initial 24-hour urinary urate excretion.[52] Proposed indications for uric acid lowering in gout are similar to those given in Figure 1.

SUMMARY AND RECOMMENDATIONS

For acute gout, generic NSAIDs are considered first-line therapy. Selective cyclooxygenase-2 inhibitors are an alternative in patients with gastrointestinal contraindications to the use of nonselective NSAIDs. Corticosteroids or subcutaneous injections of corticotropin are additional alternatives (Table 1). Because colchicine-induced adverse effects can be serious and sometimes lethal, intravenous colchicine should not be used for acute gout. Extended courses of oral colchicine are not generally used as first-line therapy for acute gout, given the availability of other effective, well-tolerated treatment options (Fig. 1 and Table 1). For long-term uric acid–lowering therapy in gout (justified by the presence of tophi, frequent attacks of gouty arthritis, or documented overproduction of urate), allopurinol and potent uricosuric agents such as probenecid are equally acceptable as first-line drugs in the absence of documented urate overproduction or renal failure (Table 2). In my opinion, the diagnosis of cyclosporine-induced gout routinely warrants the institution of uric acid–lowering therapy and may ultimately necessitate consideration of cyclosporine-free regimens of immunosuppression in some affected organ-transplant recipients.

Though dietary changes, a reduction in alcohol consumption, and the use of nondiuretic therapies for hypertension may promote serum urate lowering and thereby assist in the long-term management of gout in the patient in the vignette, he should also receive long-term pharmacologic antihyperuricemic therapy. Short-term prophylactic therapy with oral colchicine is warranted for attacks of gouty arthritis that could be precipitated by the initiation of this treatment. Although allopurinol was a reasonable first choice in this patient, an alternative is warranted given the rash that developed during therapy with allopurinol. Either probenecid or sulfinpyrazone would be a reasonable alternative, unless the creatinine clearance is below 50 ml per minute or urate overproduction has been documented, in which case, allopurinol desensitization or oxypurinol could be tried.

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