DRUG THERAPY

ALASTAIR J.J. WOOD, M.D., *Editor*

THE MANAGEMENT OF GOUT

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GOUT is a clinical syndrome resulting from the deposition of urate (monosodium urate monohydrate) crystals. The crystals may be deposited in a joint, leading to an acute inflammatory response, or in soft tissues, such as cartilage, causing no inflammation. Most cases of gout are characterized by the sudden onset of severe acute monarticular arthritis in a peripheral joint in the leg. The arthritis remits completely and then recurs with increasing frequency. After approximately 10 years of recurrent gouty arthritis, tophi develop in cartilage, tendons, and bursae in some patients.

Established criteria for the diagnosis of gout include the presence of urate crystals in joint fluid, the development of a tophus, or the presence of the characteristic clinical pattern described above.[1] Occasionally, a patient may have a more chronic or less severe arthritis affecting more than one joint at a time, in which case the diagnosis depends entirely on the detection of urate crystals. In some patients, urate crystals have been detected in joints in which there has been no inflammation,[2,3] but most of these patients have had at least one previous attack of gout. There are also reports of tophi developing without prior arthritis,[4] chiefly in elderly women with renal insufficiency who were taking diuretic or nonsteroidal antiinflammatory drugs.[5]

Although hyperuricemia is not a requirement for the diagnosis of gout[1] and its presence in a patient with arthritis does not necessarily establish that diagnosis, the risk of gout increases with the degree and duration of hyperuricemia (Table 1). However, among patients with serum urate concentrations of 9.0 mg per deciliter (540 μmol per liter), the incidence of acute gout is only about 5 percent per year.[6,7] Hyperuricemia may occur in a wide variety of conditions, genetic or acquired, metabolic or renal. Asymptomatic hyperuricemia does not have any adverse effects before the development of gout.[6-8] Drug treatment is therefore not required, although it is prudent to determine the causes of the hyperuricemia and correct them, if possible.

For simplicity and uniformity, the term "urate" is used here instead of the more common term, "uric acid," because, at physiologic pH, 99 percent of the molecules are in the form of urate. Only in parts of the urinary tract where the pH is less than 5.7 are most of the molecules in the form of uric acid, which because of its poorer solubility may be present as uric acid crystals.

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TREATMENT OF ACUTE GOUTY ARTHRITIS

Three treatments are available for patients with acute gouty arthritis. Colchicine is less favored now than in the past, because its onset of action is slow and it invariably causes diarrhea.[9] Nonsteroidal antiinflammatory drugs, which are currently favored, are rapidly effective but may have serious side effects. Corticosteroids, administered either intraarticularly or parenterally, are used increasingly in patients with monarticular gout,[10-13] especially if oral drug therapy is not feasible. Therapy that might alter serum urate concentrations should not be initiated or changed as long as any gouty joint inflammation persists, because such treatment may delay the recovery. The choice of a drug depends on an assessment of its efficacy as compared with its toxic effects in the treatment of a particular attack in a particular patient. However, nonsteroidal antiinflammatory drugs are generally favored unless the risk of side effects is judged to be too high.

Colchicine

The benefit of colchicine in treating gout is related principally to its ability to inhibit phagocytosis of urate crystals by neutrophils (Table 2). Colchicine forms a tubulin–colchicine dimer that caps the assembly end of the microtubules, interfering with the transport of phagocytosed material to lysosomes. Colchicine also blocks the release of chemotactic factor,[14] reduces the mobility and adhesion of polymorphonuclear leukocytes, and inhibits tyrosine phosphorylation and the generation of leukotriene B_4.[15]

The effective dose of colchicine in patients with acute gout is close to that which causes gastrointestinal symptoms. The drug is usually administered orally in a dose of 1 mg initially, followed by 0.5 mg every two hours until abdominal discomfort or diarrhea develops or a total dose of 8 mg has been administered. Most patients have some pain relief by 18 hours and diarrhea by 24 hours; joint inflammation subsides gradually in 75 to 80 percent of patients within 48 hours.[9] Except in patients who have renal or hepatic dysfunction or are elderly and frail, colchicine given in this way is safe, although it entails some discomfort for the patient.

Colchicine may be given intravenously if oral administration is not possible or if there is a need to avoid gastrointestinal side effects. The risk of systemic toxic effects (marrow suppression and injury of renal, hepatic, and central nervous system cells) is much greater with intravenous therapy than with oral therapy. Safe intravenous therapy depends on the following guidelines.[38,39] An initial dose of 2 mg should be administered through an established intravenous catheter (to minimize the risk of extravasation); two additional doses of

Table 1. Annual Incidence of Gouty Arthritis According to the Serum Urate Concentration.

Serum Urate Concentration (mg/dl)*	Annual Incidence of Gout (%)
<7.0	0.1–0.5
7.0–8.9	0.5–1.2
≥9.0	4.9–5.7

*To convert values for serum urate to micromoles per liter, multiply by 59.48.

1 mg each may be given at six-hour intervals, but the total dose should never exceed 4 mg. The doses should be reduced by at least 50 percent in patients with hepatic or renal disease and in elderly patients. The intravenous preparation of colchicine is not available in many countries, including Britain and Australia.

Although colchicine has been used widely and for a long time, much remains to be learned about it. Its toxic effects are poorly understood, as is its metabolism, particularly the mechanisms whereby drugs such as cimetidine and erythromycin reduce its metabolism and increase its plasma and tissue concentrations and hence its toxic effects.[16]

Nonsteroidal Antiinflammatory Drugs

Most potent nonsteroidal antiinflammatory drugs are rapidly effective in relieving pain and reducing inflammation in patients with acute gout (Table 2), particularly if the drugs are taken soon after the onset of the attack.[40] Indomethacin, the first of these drugs to be used extensively, provides some pain relief within two to four hours. Depending on the severity of the attack and its duration, the appropriate dose ranges from 150 to 300 mg per day, given in divided doses, with a gradual reduction during a period of five to seven days as the attack subsides.[41] Most other nonsteroidal antiinflammatory drugs are effective but no better than indomethacin,[42-45] although few comparative data are available.[40,46] The usefulness of nonsteroidal antiinflammatory drugs is limited by their side effects, but in general, the risks are greatest in elderly patients, particularly those with renal dysfunction.[17-21]

Corticosteroids

Intraarticular injections of a corticosteroid are usually very effective in patients with acute monarticular gout,[10] and their use is becoming more widespread as experience with the diagnostic aspiration of joints increases (Table 2). Indeed, aspiration alone can sometimes greatly reduce the pain of gout. The appropriate dose of corticosteroids is related to the size of the joint; an intraarticular dose of methylprednisolone acetate ranges from 5 to 10 mg for a small joint to 20 to 60 mg for a large joint such as the knee, depending on the volume of the effusion.

Systemic corticosteroid therapy is usually administered only when nonsteroidal antiinflammatory drugs and colchicine have been ineffective or are contraindicated. There are reports of good responses, without a rebound effect, to oral prednisone (30 to 50 mg per day initially, with the dose tapered during a period of 7 to 10 days), intramuscular corticotropin (40 U) or triamcinolone acetonide (60 mg), or intravenous methylprednisolone (a daily dose of 50 to 150 mg administered during a 30-minute period, with the dose tapered during a period of 5 days).[11-13]

Prophylaxis against Acute Gout

Acute attacks of gout may be prevented by small doses of either colchicine or nonsteroidal antiinflammatory drugs (Table 2). Prophylactic therapy should be administered before the initiation of measures to correct the hyperuricemia. Prophylaxis with colchicine clearly diminishes the rate of recurrent acute attacks, whether or not the serum urate concentration is normal.[22,23] In one study of 540 patients, colchicine was totally effective in 82 percent of the patients, satisfactory in 12 percent, and ineffective in only 6 percent. Colchicine reduces the number of inflammatory cells in synovial fluid in patients with gout who are asymptomatic, suggesting that the drug interferes with the chemotactic response and reduces subclinical joint inflammation.[24] Although the necessary duration of prophylaxis has not been established, continuation of therapy for at least a year after the serum urate concentration has returned to a normal level is usually sufficient. A myoneuropathy has occasionally been reported during prophylaxis with colchicine in patients with a creatinine clearance of 50 ml per minute or less.[47-50]

Nonsteroidal antiinflammatory drugs are also useful for prophylactic therapy. No controlled comparison between such drugs and colchicine has been undertaken,[25] but colchicine probably has less serious toxic effects. Prophylaxis with colchicine is therefore preferable, with a nonsteroidal antiinflammatory drug added if colchicine proves inadequate.

Correction of Hyperuricemia

Gout can be prevented by identifying and correcting the cause of hyperuricemia or by administering drugs that inhibit the synthesis of urate or increase its excretion. Many factors affect the serum urate concentration (Table 3), including conditions that lead to increased degradation of ATP to AMP, which is not reused but degraded to adenosine and inosine and thence to the purine bases and urate.[51] By this mechanism, the ingestion of fructose or alcohol, sustained exercise, and tissue hypoxia from any cause can result in the overproduction of urate. A sustained overproduction of urate also results either from an enzyme mutation or from excessive cell turnover such as that which occurs in patients with myeloproliferative disorders and some cancers. Another cause of increased urate production is a high intake of purine (Table 4). Alcohol consumption

Table 2. Drugs Used in the Management of Gout.

DRUG*	COMMENT	SOURCE
To treat acute gouty arthritis		
Colchicine	Inhibits crystal phagocytosis; no effect on urate metabolism; wide tissue distribution and binding; persists in leukocytes for 10 days; excreted in bile, intestinal secretions (enterohepatic circulation), and urine	Spilberg et al.[14] and Roberge et al.[15]
	Increased toxicity in patients who have renal or hepatic dysfunction or are receiving concomitant therapy with P-450 enzyme inhibitors such as cimetidine, erythromycin, and tolbutamide	Caraco et al.[16]
NSAIDs	Effective but use limited by side effects (gastropathy, nitrogen retention and reduced creatinine clearance, hyperkalemia, abnormal liver-function values, and headache); greater risk of side effects in patients with renal dysfunction	Griffin et al.,[17] Hawkey,[18] Roth,[19] Findling et al.,[20] and Unsworth et al.[21]
Corticosteroids	Effective either by intraarticular (single joint) or systemic route (intramuscular, intravenous, or oral); potential for rebound inflammation and side effects	Gray et al.,[10] Axelrod and Preston,[11] Alloway et al.,[12] and Groff et al.[13]
To prevent acute attacks		
Colchicine	Effective in an oral dose (0.5–1.0 mg per day) adjusted so as not to cause diarrhea	Yü and Gutman,[22] Yu,[23] and Pascual and Castellano[24]
NSAIDs	Useful if colchicine alone is insufficient and acute attacks recur frequently; usual dose is 150 to 300 mg of indomethacin per day or its equivalent	Kot et al.[25]
To lower serum urate concentrations		
Probenecid	Increases urate excretion; reversed by salicylate; 90% bound to plasma protein; interferes with excretion of many drugs; serious toxic effects rare, although nausea and rash reported in up to 10% of patients; risk of urolithiasis	Bishop et al.[26] and Dayton and Perel[27]
Sulfinpyrazone	More potent uricosuric agent than probenecid (wt/wt); also reduces platelet aggregation; 98% bound to protein; short half-life, with uricosuric metabolites; renal excretion and uricosuria inhibited by salicylate; risk of urolithiasis	Dieterle et al.,[28] Lecaillon et al.,[29] Wilcox et al.,[30] and Kovalchik[31]
Salicylate	Reduces urate excretion in low doses; uricosuric in high doses (e.g., 1 g of aspirin, with 1 g of sodium bicarbonate five times a day); clinically impractical for long-term use	Yü and Gutman[32]
Diflunisal	Fluorinated salicylate with both analgesic and uricosuric properties	Emmerson et al.[33]
Benzbromarone	Potent long-acting uricosuric drug; limited international availability	Sorenson and Levinson[34]
Allopurinol	Only xanthine oxidase inhibitor available; rapidly metabolized to oxypurinol, an analogue of xanthine that also inhibits xanthine oxidase; longer half-life of oxypurinol (14–28 hr) makes one daily dose possible; excretion of oxypurinol impaired in patients with renal insufficiency but increased by uricosuric drugs	Rundles et al.,[35] Spector,[36] and Hande et al.[37]

*NSAIDs denotes nonsteroidal antiinflammatory drugs.

and obesity are associated not only with an increase in the production of urate but also with a decrease in its excretion.[51-56] Beer also contains purines, such as guanosine, that are degraded to urate.[57]

Thus, potentially reversible factors that contribute to increased urate production include a high-purine diet, obesity, and regular alcohol consumption. None of these factors may be the sole cause of hyperuricemia, but each may exacerbate it in patients with other causative factors, such as a decreased capacity for urinary excretion of urate. The purine content of the diet (Table 4) does not usually contribute more than 1.0 mg per deciliter (60 μmol per liter) to the serum urate concentration, but moderation in dietary purine consumption (rather than a constant low-purine diet) is nevertheless indicated in patients who habitually eat large amounts of food containing purines, either of animal or of vegetable origin.

Decreased urinary excretion of urate often contributes to hyperuricemia.[58] The problem can be recognized on the basis of a decrease in the 24-hour urinary excretion of urate (<330 mg per day [approximately 2 mmol per day]) while the patient is on a low-purine diet or a low renal clearance or fractional excretion of urate. In normal persons, urate clearance ranges from 4 to 14 ml per minute[59]; persons with a low clearance have greater difficulty excreting a urate load than those with a normal clearance. The clearance of urate is determined in part by genetic factors.[60] An important acquired cause of low clearance is intrinsic renal disease.[61] Many drugs also reduce the renal excretion of urate, especially thiazides and loop diuretics, which tend to cause a contraction of the plasma volume.[5,62] Other drugs that decrease urate excretion include low-dose salicylate, pyrazinamide, ethambutol, and niacin.[58] Certain metabolites and hormones, including lactic acid, ketone bodies, angiotensin, and vasopressin, also reduce urate excretion. In addition, hypertension can reduce the excretion of urate.

Because the need for a drug that lowers serum urate concentrations is likely to be lifelong, it is important to identify the factors contributing to hyperuricemia that

may be correctable. The history and physical examination will reveal many of these factors, and a simple series of investigations can provide evidence of intrinsic overproduction or underexcretion of uric acid. Urate excretion should be determined by measuring serum urate and creatinine concentration and 24-hour urinary excretion of urate and creatinine before and after the dietary restriction of purines and alcohol for one week.[63] The results (Table 5) allow an estimation of the renal handling of urate, calculated as either the clearance or the fractional excretion of urate ([urate clearance ÷ creatinine clearance] × 100 percent), as well as an estimation of glomerular function (creatinine clearance), basal urate production (as indicated by the 24-hour excretion of urate during the low-purine diet), dietary contribution (including alcohol) as reflected by the fall in the serum and 24-hour urinary urate values during the low-purine diet, and the usual volume of urine (>1 ml per minute is desirable[64]).

If dietary and lifestyle factors are identified and appropriate changes made, the serum urate concentration may fall substantially. However, many patients will need medication to control the hyperuricemia.

Gout may be prevented by reducing serum urate concentrations to values less than 6.0 mg per deciliter (360 μmol per liter). A reduction to less than 5.0 mg per deciliter (300 μmol per liter) may be required for the resorption of tophi. Therapy with a drug that lowers serum urate concentrations should be considered when all the following criteria are met: the cause of the hyperuricemia cannot be corrected or, if corrected, does not lower the serum urate concentration to less than 7.0 mg per deciliter (420 μmol per liter); the patient has had two or three definite attacks of gout or has tophi; and the patient is convinced of the need to take medication regularly and permanently.

Two classes of drugs are available: uricosuric drugs and xanthine oxidase inhibitors (Table 2). Uricosuric drugs increase the urinary excretion of urate, thereby lowering the serum urate concentration. The main risk associated with these drugs involves the increase in the urinary excretion of urate that occurs soon after the initiation of therapy. In contrast, xanthine oxidase inhibitors block the final step in urate synthesis, reducing the production of urate while increasing that of its precursors, xanthine and hypoxanthine (the oxypurines). In general, a xanthine oxidase inhibitor is indicated in patients with increased urate production, and a uricosuric drug in those with low urate clearance. Many patients, however, have both factors — for example, a patient with a low urate clearance and a high dietary intake of purines and alcohol. Nonetheless, allopurinol is effective in lowering serum urate concentrations in patients with overproduction or underexcretion of urate or both. The main side effect is hypersensitivity, and a severe sensitivity reaction to allopurinol dictates the choice of a uricosuric drug. Uricosuric drugs are hazardous if the urinary urate concentration is high (as it is in urate overproduction) and are contraindicated if the flow of urine is suboptimal (consistently <1 ml per minute[64]) or if the patient has a history of renal calculi or inadequate renal function (creatinine clearance <50 ml per minute). Although there is controversy about the relative merits of these two classes of drugs, there are advantages in being able to choose the more appropriate type for an individual patient.

A potential complication of these drugs is the precipitation of acute attacks of gout. The mechanism is poorly understood, but it is usually attributed to the sudden change in the serum urate concentration. The risk can be minimized by concurrently administering prophylactic drugs, delaying urate-lowering therapy until several weeks after the last attack of gout, and commencing therapy with a low dose of the drug that is chosen.

Table 3. Causes of Sustained Hyperuricemia.

Increased Urate Production	Reduced Urate Excretion
Genetic causes	**Genetic causes**
Enzyme mutations (e.g., hypoxanthine–guanine phosphoribosyltransferase deficiency)	Reduced clearance or fractional excretion of urate
Acquired causes	**Acquired causes***
Myeloproliferative disorders	Intrinsic renal disease
High purine intake	Drugs (e.g., thiazide diuretics and low-dose salicylate)
Obesity and hypertriglyceridemia	Metabolites (lactate, ketones, angiotensin, and vasopressin)
Alcohol consumption	Renal cause (plasma-volume contraction, hypertension, reduced urine flow [<1 ml/min], or obesity)
Fructose consumption	
Exercise	

*With the exception of intrinsic renal disease, these causes of reduced urate excretion are potentially reversible.

Table 4. The Purine Content of Foods.*

Low-purine foods
Refined cereals and cereal products, cornflakes, white bread, pasta, flour, arrowroot, sago, tapioca, cakes
Milk, milk products, and eggs
Sugar, sweets, and gelatin
Butter, polyunsaturated margarine, and all other fats
Fruit, nuts, and peanut butter
Lettuce, tomatoes, and green vegetables (except those listed below)
Cream soups made with low-purine vegetables but without meat or meat stock
Water, fruit juice, cordials, and carbonated drinks
High-purine foods
All meats, including organ meats, and seafood
Meat extracts and gravies
Yeast and yeast extracts, beer, and other alcoholic beverages
Beans, peas, lentils, oatmeal, spinach, asparagus, cauliflower, and mushrooms

*The purine content of a food reflects its nucleoprotein content and turnover. Foods containing many nuclei (e.g., liver) have many purines, as do rapidly growing foods such as asparagus. The consumption of large amounts of a food containing a small concentration of purines may provide a greater purine load than consumption of a small amount of a food containing a large concentration of purines.

Uricosuric Drugs

The greatest potential risks of therapy with uricosuric drugs are the formation of uric acid crystals in urine and the deposition of uric acid in the renal tubules, pelvis, or

ureter, causing renal colic or the deterioration of renal function. These risks can be reduced by initiating therapy with a low dose and increasing the dose slowly (which also reduces the risk of precipitating acute gout) and by maintaining a high urine volume (preferably of alkaline urine, which can be achieved with 1 g of sodium bicarbonate taken three to four times per day), especially during the early weeks of therapy. Once the serum urate concentration has declined, the increment in urinary urate excretion due to the uricosuric drug is relatively small in comparison with the usual daily variations. Since the risks associated with crystalluria occur each time therapy with a uricosuric drug is started, compliance is particularly important.

Table 5. Urate and Creatinine Values before, during, and after Dietary Restriction of Purines, According to the Cause of Hyperuricemia.*

Cause of Hyperuricemia	Creatinine Clearance	Urate Clearance	Urinary Urate Excretion	Fall in Serum Urate†	Fall in Urinary Urate Excretion†
High purine consumption	Normal	Normal	Normal	Increased	Increased
Primary urate underexcretion with normal renal function	Normal	Greatly reduced	Greatly reduced	Normal or increased	Normal
Renal disease (primary or secondary)	Greatly reduced	Greatly reduced	Greatly reduced	Increased	Increased
Endogenous urate overproduction	Normal	Normal or increased	Greatly increased	Normal or reduced	Normal or reduced
Normal range	100–130 ml/min	4–14 ml/min	330–600 mg/day‡	1.0 mg/dl§	200 mg/day‡

*Adapted from Emmerson[63] with the permission of the publisher.

†During and after the low-purine diet.

‡To convert values for urinary urate excretion to millimoles per day, multiply by 0.005948.

§To convert values for serum urate to micromoles per liter, multiply by 59.48.

The most commonly used uricosuric drugs are probenecid[26,27] and sulfinpyrazone.[28-31] Satisfactory control of hyperuricemia (serum urate concentrations less than 6.0 mg per deciliter) can be achieved in 60 percent of patients with a dose of 1 g of probenecid per day and in 85 percent of patients with a dose of 2 g per day. In practice, however, the long-term control of hyperuricemia is not adequate in up to 25 percent of patients, for one reason or another. The uricosuric effect of probenecid is reduced as glomerular function declines, and the drug has little effect in patients with a creatinine clearance of less than 50 to 60 ml per minute.

Sulfinpyrazone is three to six times more potent than probenecid on a weight-for-weight basis (Table 2). The initial dose should be 50 or 100 mg twice daily, with gradual increments to 200 or even 400 mg twice daily. The drug is less effective if the patient has renal disease but may nevertheless normalize the serum urate concentration. The uricosuric potency of sulfinpyrazone is its chief problem, however, because of the increased risk of uric acid crystalluria, and renal failure reversed by an alkaline diuresis has been reported during treatment with the drug.[30,31,65]

Xanthine Oxidase Inhibition

Allopurinol, a pyrazolopyrimidine and an analogue of hypoxanthine, is the only inhibitor of xanthine oxidase in clinical use (Table 2). In the presence of normal activity of hypoxanthine–guanine phosphoribosyltransferase, purine biosynthesis is inhibited and the reuse of hypoxanthine to form purine nucleotides is increased.[35,36] A dose of 300 mg of allopurinol per day reduces serum urate concentrations to normal values in 85 percent of patients with gout, and in some patients a dose of 100 to 200 mg per day is adequate.[66] The risk of precipitating acute gout is reduced if therapy is begun with a low dose (50 to 100 mg per day) that is increased during a period of three to four weeks. Since the serum concentration of oxypurinol is related to renal function, the dose of allopurinol should be reduced in proportion to the glomerular filtration rate, as assessed on the basis of the creatinine clearance.[67] The appropriate dose is 100 mg per day in a patient with a glomerular filtration rate of approximately 30 ml per minute, 200 mg per day in a patient with a filtration rate of approximately 60 ml per minute, and 300 mg per day in a patient with normal renal function.

Since azathioprine and mercaptopurine are normally inactivated by xanthine oxidase, inhibition of this enzyme by allopurinol increases the toxic effect of the other two drugs.[68,69] To compensate for this effect, the doses of these drugs should be reduced to about 25 percent of the usual dose in patients receiving allopurinol.[68,69]

A rash develops in approximately 2 percent of patients treated with allopurinol[70] and in approximately 20 percent of those receiving both allopurinol and ampicillin. The rash usually subsides after the allopurinol has been discontinued and may not recur if therapy is resumed with a lower dose. The most serious side effect of allopurinol, which occurs in less than 1 in 1000 cases, is exfoliative dermatitis, often with vasculitis, fever, liver dysfunction, eosinophilia, and acute interstitial nephritis. Up to 20 percent of patients with this type of reaction become very sick, and it is more likely to occur in patients with renal disease or those receiving diuretic therapy.[71,72] Prednisone seems to be effective in such patients,[73] but the discontinuation of allopurinol and the use of supportive therapy may be sufficient in cases that are not severe.

Desensitization by either the oral or intravenous route has been successful in some patients with minor hypersensitivity rashes but has rarely been successful in those with more serious side effects.[74,75] In some patients with hypersensitivity, lymphocytes react to oxypurinol but not to allopurinol, which suggests that the metabolite may be the causative agent.[76] The success of

desensitization is unpredictable, and it may be hazardous in patients who have had a severe reaction.[77]

Allopurinol is indicated principally for patients with established gout, particularly those who also have urolithiasis, because the drug has a prophylactic effect in both uric acid and calcium oxalate nephrolithiasis.[78,79] Such prophylaxis may be particularly useful in patients with renal disease, many of whom have a poor response to uricosuric drugs. Allopurinol is also indicated in patients with secondary gout and in those with myeloproliferative disorders and excessive cell turnover.[80,81]

Goals of Urate-Lowering Therapy

The aim of urate-lowering therapy is to reduce the serum urate concentrations to about 6.0 mg per deciliter and preferably even lower if the patient has either clinical or radiographic evidence of tophi.[82] Once the serum urate concentration has declined, the patient should be evaluated periodically, with the frequency of monitoring depending on whether the serum urate concentration remains low and whether the patient has cardiovascular risk factors, such as hypertension or hyperlipidemia, or renal insufficiency — conditions that are frequently present in patients with gout.

The need for permanent drug treatment in patients with gout has recently been questioned. Intermittent therapy or the withdrawal of drugs that lower serum urate concentrations leads to a recurrence of acute gout and tophi; the acute attacks often recur within six months, and the tophi within three years.[83,84] Therefore, urate-lowering drug treatment should be lifelong.

Chronic Complicated and Unresponsive Gout

Problems in the management of gout are usually due to the failure to prescribe prophylactic colchicine during the early period of treatment when hyperuricemia fluctuates, the initiation of therapy to lower serum urate concentrations while the patient still has gouty inflammation, or poor compliance.

Hyperuricemia persists in some patients despite apparently adequate compliance with the regimen of medication. This lack of response may be due to the persistence of factors promoting hyperuricemia, particularly regular alcohol consumption, diuretic therapy, and obesity. Dependency on diuretics can often be corrected by the addition of an angiotensin-converting–enzyme inhibitor.[85] In the absence of such treatable factors, allopurinol and a uricosuric drug may both be required. Although the uricosuric drug will reduce the effectiveness of the allopurinol by promoting the elimination of oxypurinol, it will provide a uricosuric effect.

The most difficult clinical problem arises when a patient who has tophaceous gout with renal disease becomes sensitive to allopurinol and the sensitivity cannot be corrected. The renal disease is usually mild to moderate in severity and in many cases contributes to the development of sensitivity to allopurinol. Such patients should be treated with a maximal dose of a potent uricosuric drug such as sulfinpyrazone, with diuretic drugs avoided and more vigorous attention paid to the correctable factors promoting hyperuricemia. If the serum urate concentration does not decline appreciably, the emphasis must be placed on symptomatic therapy rather than corrective therapy.

Summary

We now have sufficient knowledge to be able to identify the factors contributing to hyperuricemia in most patients with gout. Some of these factors, such as obesity, a high-purine diet, regular alcohol consumption, and diuretic therapy, may be correctable. In patients with persistent hyperuricemia, regular medication should lower the serum urate concentration to an optimal level. The continuing challenge is to educate patients about correctable factors and the importance of regular medication and ensure their compliance so that attacks of gout do not recur.

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