
Gout: A Review

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Gout is an age-old disease for clinicians, still having many secrets that need to be explored for improving knowledge with respect to uric acid metabolism and monosodium urate crystal-induced inflammation. Despite centuries of study of gout and availability of effective treatment for most patients, the proper diagnosis and treatment are still problematic. In the present review attempts are made to understand various aspects of gout in terms of causes, epidemiology, pathophysiology, site of action for antigout agents, diet, management, treatment, recent innovation and scope for further research.

Gout is a clinical syndrome caused by a group of heterogeneous disorders and is characterized by deposition of monosodium urate monohydrate crystals, leading to neutrophil activation and synovial inflammation¹. Hyperuricemia (serum urate concentration >7 mg/dl) is a condition in which urate is supersaturated in plasma and needle like monosodium urate crystals (MSUCs) are formed². Pain and inflammation are produced when uric acid crystals activate the humoral and cellular inflammatory processes³. Hyperuricemia may be due to obesity, insulin resistance, lipid abnormalities, and hypertension. Some of these factors like obesity, high purine diet, regular alcohol consumption, and drug therapy may be correctable. Its acute attack begins suddenly, the swelling, erythema and tenderness in the joint may be misdiagnosed as septic arthritis or cellulites⁴. In the 19th century, gout was associated with hyperuricemia and in the 20th century, it is proved that hyperuricemia may not necessarily lead to clinical gout i.e. serum uric acid level commonly elevated in patients without gout and can be normal or even low in patients with gout⁵⁻⁸.

CAUSES OF GOUT

More than 99 percent of cases are idiopathic referred to as primary gout. They are most likely due to a combina-

tion of hormonal and genetic factors that cause metabolic abnormalities resulting in overproduction or reduced excretion of uric acid. Whereas in secondary gout, hyperuricemia is caused by drug therapy or medical conditions other than an inborn metabolic disorder that increase uric acid concentration⁹⁻¹⁰. Causes of sustained hyperuricemia are listed in Table 1¹¹⁻²⁰.

EPIDEMIOLOGY

The peak incidence of acute gout occurs between 30-50 y of age²¹. It is more common in middle-aged males. The commonly reported overall prevalence of gout is 6 per 1000 population of men and 1 per 1000 population for women. The incidence increases with age, especially in women⁶. The recent studies from North America and Europe have suggested that there is increase in the incidence of microcrystalline events (confirmed on synovial fluid analysis) in patients with the hyperuricemia in the spring that decrease during the winter months. Although the exact mechanism behind these seasonal observations is unknown, changes in temperature, humidity, atmospheric pressure, variations in diet, alcohol consumption and physical activity may be responsible. A new confirmation of an old perception is that obesity predisposes to the development of gouty arthritis²².

PHYSIOLOGY OF URIC ACID

It is generally agreed that uric acid undergoes bi-di-

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TABLE1: CAUSES OF SUSTAINED HYPERURICEMIA

Increased urate production	Reasons /Causes
Nutritional	Excess purine, ethanol and fructose consumption.
Hematological	Myeloproliferative and lymphoproliferative disorders, polycythemia.
Drugs	Ethanol, cytotoxic drugs, vitamin B ₁₂ (treatment of pernicious anemia).
Genetic	Enzyme mutations (e.g. hypoxanthine-guanine phosphoribosyl-transferase deficiency), phosphoribosylpyrophosphate synthetase over activity and glucose-6-phosphatase deficiency.)
Miscellaneous	Obesity, psoriasis, hypertriglyceridemia, coronary artery, Diabetes mellitus, high-blood pressure.
Decreased renal excretion of urate	
Drugs	Ethanol, cyclosporine, thiazides, furosemide and other loop diuretics, ethambutol, pyrazinamide, aspirin (low-dose), levodopa, nicotinic acid.
Renal	Hypertension, polycystic kidney disease, chronic renal failure (any etiology).
Metabolic/endocrine	Dehydration or starvation, lactic acidosis, ketosis, hypothyroidism, hyperparathyroidism.
Miscellaneous	Obesity, toxemia of pregnancy

rectional transport by the renal tubule cells i.e. uric acid is both secreted and reabsorbed²³⁻²⁴. The factors that determine the direction of net transport have not been determined. Although urate transport is not sodium dependent, the extracellular fluid volume influences the reabsorption of uric acid in the proximal convoluted tubule²⁵.

Many clinicians routinely employ solutions containing bicarbonate to alkalinize the urine and thereby increase the solubility of uric acid. A common clinical protocol is to infuse 0.45% saline containing one ampoule of sodium bicarbonate at a rate of 250-300 ml/h²⁶, because of the important effect of pH on uric acid solubility, it is prudent to attempt to alkalinize the urine. The drug of choice is potassium citrate at doses of 30-60 mEq daily in divided doses. Citrate not only alkalinizes the urine but also inhibits the formation of calcium oxalate precipitates. The goal of therapy is to increase the urine pH to 6.5 or greater although it may be difficult to achieve such values in the clinical setting²⁷.

There is a clear relationship between diet and gout; so foods containing high purine content raises the uric acid level in the body. Restricting purine intake can help to control uric acid level and in turn, the risk of attack in individuals susceptible to gout. Avoiding alcohol can reduce the

number of attacks of gout²⁸⁻²⁹. The chief mechanism responsible for the alcohol-induced hyperuricemia is that, ATP is consumed more rapidly by the way of acetate to acetyl-CoA than it can be regenerated by the normal synthetic capacity³⁰. Refined sugars including sucrose and fructose should also be restricted, because they raise uric acid levels³¹. Dietary changes helpful in gout are mentioned in Table 2.

NUTRITIONAL SUPPLEMENT HELPFUL IN GOUT

According to a 1950 study of twelve individuals with gout, eating one-half pound of cherries or the equivalent amount of cherry juice prevented attacks of gout³². There is limited number of studies indicating that large amount of supplemental folic acid (upto 80 mg/day) reduces uric acid levels³³. However, other research does not confirm the effectiveness of folic acid³⁴. In one small study vitamin C was shown to increase urinary excretion of uric acid³⁵. Quercetin, a bioflavonoid, inhibits the enzyme xanthine oxidase, which makes uric acid and it has also shown anti-inflammatory effects in test tube studies. Researchers are testing to determine whether fish oil supplements reduce the risk of gout. They are also studying the structure of the enzymes that break down purines in the body, in hopes of achieving a better understanding of the enzyme defects that can cause gout³⁶⁻³⁷.

TABLE 2: DIETARY CHANGES THAT MAY BE HELPFUL IN GOUT

High-best to avoid	Moderate-may eat occasionally	Low- no limitation
anchovies	asparagus	carbonated beverages
sardines	beef	coffee
herring	chicken	fruits
mussels	crab	bread
bacon	duck	grains
codfish	ham	macaroni
scallops	kidney beans	cheese
trout	lentils	eggs
haddock	lima beans	milk products
veal	mushrooms	sugar
venison	lobster	green vegetables
turkey	oysters	-
alcoholic beverages	pork	-
	shrimp	-
	spinach	-

NATURAL THERAPY

Juicing about four handfuls of pitted cherries with ½ cup of strawberries can help to neutralize excess uric acid and may help to prevent gout attacks. To ease the pain of gout, make massage oil from one ounce of olive oil and five drops of juniper oil, then massage into the joint several times a day. To soothe gout pain in the feet, try a cool foot-bath spiked with juniper and rosemary essential oils. Ice and cold water treatments are excellent first aid for painful gout attacks. Apply a cold, wet compress directly to the affected area for 20 min, or wrap an ice pack in a plastic bag and place it over a towel on the skin. "Never use a cold treatment for more than 20 min as it could damage the skin". While cold treatments usually relieve the pain. All the three natural therapy i.e. juice therapy, aromatherapy, and hydrotherapy help in alleviating pain and should be continued along with conventional therapy after doctor's advice only³⁸.

PATHOGENESIS

Uric acid is the end product of purine metabolism; it is

a waste product that has no physiologic role. Humans lack uricase, an enzyme that breaks down uric acid into a more water-soluble product allantoin, thus preventing uric acid accumulation. Increased serum uric acid concentration is a result of either overproduction or underexcretion of uric acid. In 90 % of patients, gout is caused by the underexcretion of uric acid. Serum uric acid levels become elevated in any disorder that results in the proliferation of cells or the excessive turnover of nucleoproteins. Hyperuricemia can also occur with decreased renal function and in genetic disorders that either increase the production or limit the excretion of uric acid. Several medications increase the serum uric acid concentration through modification of the filtered load of uric acid or one of the tubular transport processes. Hyperuricemia has been associated with hypertriglyceridemia and diabetes mellitus, and it may be a risk factor for the development of coronary artery diseases³⁸. Disorders of purine metabolism are listed in Table 3³⁹.

Normal production of uric acid is considered to be 600 mg/day in men with normal renal function on a purine free diet³⁸. Overproduction of uric acid may occur because of an abnormality in the enzymes that regulate purine metabolism. Two such abnormalities have been documented. An increase in the activity of phosphoribosylpyrophosphate synthetase results in increased uric acid synthesis. A deficiency of hypoxanthine guanine phosphoribosyltransferase also increases serum uric acid levels⁴⁰. Pathogenesis of gout and site of action antigout agents has been depicted in fig. 1. Under normal conditions, the kidneys excrete about 66% to 75% and gastrointestinal tract eliminates remaining 25% to 33% of all uric acid produced daily. It is filtered in the glomeruli of the kidney, reabsorbed in the proximal tubule and secreted by distally tubular secretion is almost entirely responsible for the excretion of uric acid. Renal management of uric acid is defective in approximately 98 % of patients with primary hyperuricemia and gout³⁸.

PATHOPHYSIOLOGY OF INFLAMMATION DUE TO MSUC'S

As per the recent findings, Monocytes are attracted to the site of MSUC's deposition by some mediator, possibly chemotactic factors from complement activation on the crystal surface. As the monocytes make contact with the MSUC's, they begin to release cytokines, which then amplify the inflammatory process. In response to chemical signals from the activated monocytes, vascular endothelial cells produce adhesion molecules that recruit even more monocytes to the site. It takes about 7 days for the attracted monocytes to differentiate into macrophages. As those new macrophages

TABLE 3: DISORDERS OF PURINE METABOLISM

Disorder	Defect	Nature of Defect	Comments
Gout	PRPP ^a synthetase	Increased enzyme activity due to elevated V _{max}	Hyperuricemia
Gout	PRPP synthetase	Enzyme is resistant to feedback inhibition	Hyperuricemia
Gout	PRPP synthetase	Enzyme has increased affinity for ribose-5-phosphate (lowered K _m)	Hyperuricemia
Gout	PRPP amidotransferase	Loss of feedback inhibition of enzyme.	Hyperuricemia
Gout	HGPRT ^b	Partially defective enzyme.	Hyperuricemia
Lesch-Nyhan syndrome	HGPRT	Lack of enzyme	Hyperuricemia
Immunodeficiency	PNP ^c	Lack of enzyme	Hyperuricemia, 2,8-dihydroxy-adenine
Renal lithiasis	APRT ^d	Lack of enzyme	renal lithiasis
Xanthinuria	Xanthine oxidase	Lack of enzyme	Hypouricemia and xanthine renal lithiasis.

^aPhosphoribosylpyrophosphate, ^bHypoxanthine-guanine phosphoribosyltransferase, ^cPurine nucleotide phosphorylase and ^dAdenosine phosphoribosyltransferase

increase in number and proportion, their secreted TGF-beta1 inhibits the production of adhesion molecules by the vascular endothelial cells, and thus, no more monocytes are recruited to the region. With inhibitors of inflammation overtaking or blocking the effects of the earlier proinflammatory factors, the level of inflammation would begin to wane, and the symptoms experienced by the patient would progressively decrease. Much work still needs to be done to confirm that this *in vitro* model applies to the *in vivo* gouty arthritis of animal models and to the spontaneous disease in humans. Also that a lipoprotein is known to modulate the inflammatory potential of the urate crystal *in vivo* and therefore the relationships between the effects of the lipoprotein coating the crystal, which decreases the crystals "foreignness in the tissue" and down-regulates the response of inflammatory cells to the crystal deposition site.

In the near future, research on the clinical use of an agonist related to the TGF-β1 receptor being injected into the joint or even taken by subcutaneous injection at the first sign of a gouty attack is quite possible. The effect might be to completely abort the inflammatory attack, because adhesion molecules would not be exhibited on the surfaces of vascular endothelial cells of the regional capillaries. As a result, inflammatory cells would not be attracted to the site of active crystal deposition, and no inflammation or pain

would develop. Even though the symptoms would be controlled, the crystals would still be present in the tissues, so we would still need to develop novel ways to prevent their deposition or to dissolve them without clinical event⁴¹.

RECENT INNOVATIONS

Cyclooxygenase1 (COX-1) and cyclooxygenase2 (COX-2) inhibitors:

Conventional NSAIDs inhibit both COX-1 and COX-2. Their anti-inflammatory effects are largely due to suppression of COX-2 and most adverse effects, particularly gastrointestinal toxicity result from inhibition of COX-1⁴²⁻⁴⁴. The newer NSAIDs such as celecoxib, rofecoxib, valdecoxib, and etoricoxib are highly cyclooxygenase-2 selective⁴⁵. Although both selective and standard NSAIDs inhibit COX-2 equally, the real advantage of selective COX-2 inhibitors, as suggested by Vane and Warner, is that they are highly COX-1 sparing drugs, accounting for reduction in gastrointestinal toxicity by about 50%⁴³⁻⁴⁶. These drugs are generally well tolerated and their clinical efficacy in patients with osteoarthritis or rheumatoid arthritis is comparable to that of non-selective NSAIDs⁴⁴⁻⁴⁶. A recent randomised, double blind, eight day trial comparing etoricoxib 120 mg once daily with indomethacin 50 mg thrice daily in acute gout showed the two drugs to be equally efficacious, with

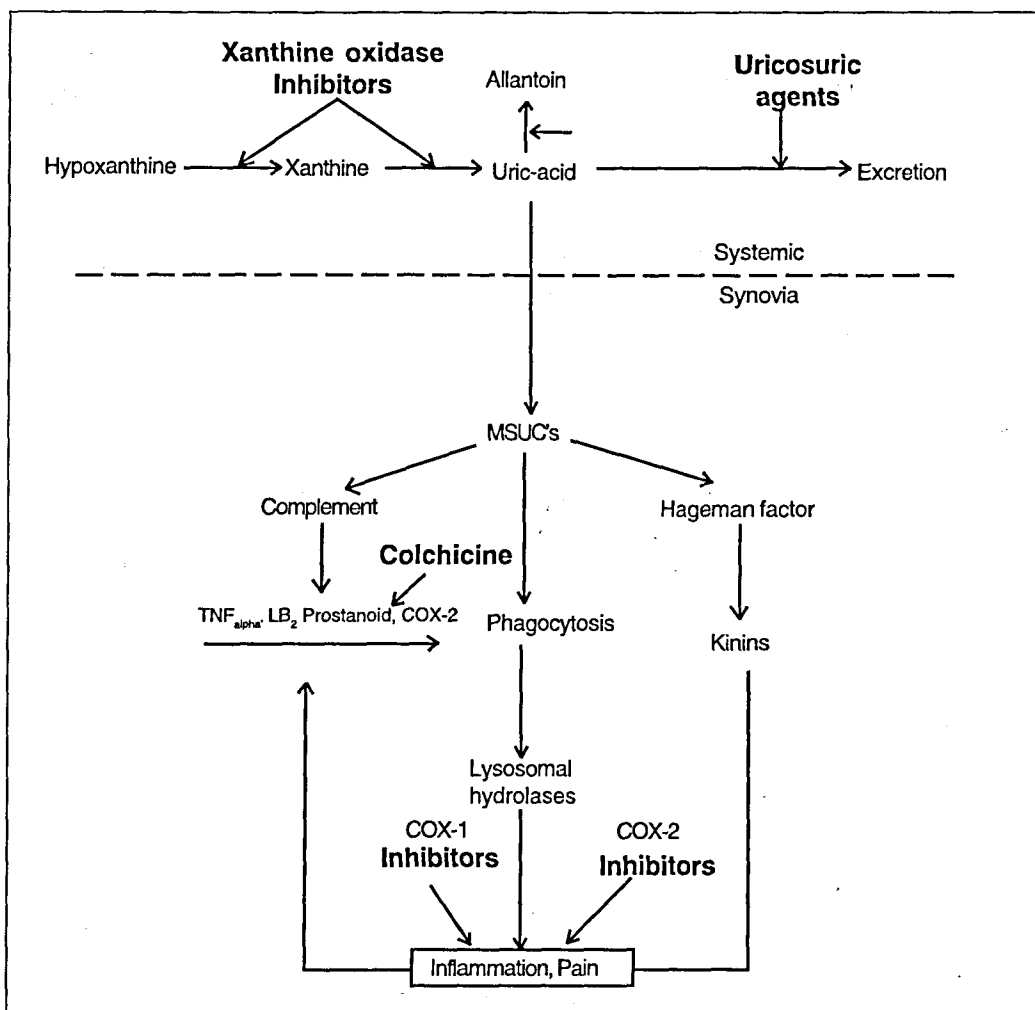


Fig. 1: Pathogenesis of gout and site of action of anti-gout agents.

Xanthine oxidase inhibitors (allopurinol, oxypurinol), uricase enzyme (rasburicase), uricosuric agent (probenecid, sulfipyrazone), diminished TNF_{α} secretion, neutrophils, ionophore induced formation of LTB_4 , blocks synthesis of COX-2 and prostanoid (like colchicine), inflammation (COX-1 and COX-2 inhibitors)

etoricoxib showing an improved safety profile. The findings support a potential role for COX-2 inhibitors in managing acute gout. COX-2 inhibitors should be used with caution in patients with cardiac failure, renal insufficiency, hypertension, hepatic dysfunction, peptic ulcer, on anticoagulants, or with hypersensitivity to NSAIDs.

Whether the treatment of acute gout with selective COX-2 inhibitors, in place of the well-established NSAIDs, will prove to be more advantageous in terms of efficacy, gastrointestinal safety, and cost effectiveness remains to be shown by additional controlled studies. An important task for medical institutions will therefore be to report on the effectiveness and side-effect profile of COX-2 inhibitors

in comparison with NSAIDs that have previously been used successfully, and especially in long-term studies⁴⁷⁻⁴⁸.

Losartan and fenofibrate:

Two old compounds reviewed by Bardin⁴⁹, fenofibrate and losartan exert uricosuric properties. Losartan is an angiotensin II receptor antagonist used in the treatment of hypertension. In 1992, it was first published that losartan increases uric acid excretion and reduce serum uric acid (SUA) level. Uric acid renal excretion was dose dependent and lasted for days after administration was stopped. Uricosuric effect is truly dependent of losartan and not of E-3174, which is its main active metabolite. It was found to

inconsistently increase the fractional excretion of uric acid from 1% to 30%⁴⁹. It also reduced the increase in SUA caused by hydrochlorothiazide⁵⁰, an important finding when one considers thiazide-induced hyperuricemia in patients on long-term treatment and high-risk exposure to secondary gout. Since the early 1980s, fenofibrate, a lipid-lowering drug has a uricosuric effect in healthy volunteers, in patients without diabetes, with or without hyperlipemia⁵¹⁻⁵² and patients with gout⁵³. Serum uric acid reduction was seen in approximately 20% to 46% of patients; this is a clinically significant observation. This uricosuric effect is specific for fenofibrate and not observed with other fibrate, such as bezafibrate⁵¹.

A recent study from Takahashi *et al.*⁵⁴ showed that association of losartan at 50 mg or fenofibrate at 300 mg daily to benzbromarone at 50 mg/day or allopurinol at 200 mg/day prescribed for 3 months achieved a higher SUA level reduction than each individual hypouricemic drug. Losartan was added when patients also had hypertension and fenofibrate was added for patients with hypertriglyceridemia. It may be that those patients with multiple metabolic abnormalities, including syndrome X or hypertension and dyslipidemia, when associated with hyperuricemia could be treated preferably with these drugs⁵².

Urate oxidase:

Humans, unlike other species have lost their urate-oxidase or uricase, which is a natural enzyme that oxidizes urate into allantoin (5 times more soluble than uric acid). Various uricases have been administered to humans, but have a short half-life, and are at risk for triggering allergic reaction. However, after the cloning of DNA coding for protein, a recombinant form of urate oxidase, rasburicase (Elitek®) developed into a pure and potent uricolytic agent. It showed reduced antigenicity and increased circulating half-life. Phase II studies are ongoing⁵⁵⁻⁵⁷.

It has several beneficial features. First, it has a rapid onset of action with the majority of clinical trials reporting a decrease in uric acid plasma levels within 2-4 h of administration. Second, the high solubility of allantoin allows it to be easily excreted in the urine. It works at the end of the uric acid pathway as opposed to allopurinol. Thus, it does not contribute to the accumulation of xanthine or hypoxanthine, the uric acid precursors that potentially can increase the risk of renal compromise. Finally, again in contrast to allopurinol, it does not appear to have the potential for drug-drug interactions, particularly with 6-mercaptopurine. Its dosing is based on the patient's weight, and the drug has

been approved for use in both children and adults. It is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency because the drug can precipitate hemolytic anemia in these patients. Side effects of rasburicase include potential hypersensitivity, fever, nausea and vomiting, rashes, diarrhea, and headache.

All of these side effects occurred in less than 10% of patients receiving the drug in clinical trials. Nurses need to obtain patients past medical histories, monitor patients for hypersensitivity reactions during rasburicase administration, and use special precautions when drawing blood samples for serum uric acid levels in order to ensure accurate results⁵⁸⁻⁶¹.

Oxyprim™ (Oxyputinol):

A xanthine oxidase inhibitor is being studied as a potential alternative for patients who are unable to take allopurinol. Over a million patients in the United States take allopurinol for gout. Allopurinol, a xanthine oxidase inhibitor works by blocking the production of uric acid. It is an effective therapy for patients with gout who are able to tolerate it. Unfortunately, about 3-5% of patients who take allopurinol develop a reaction that usually results in their discontinuing the medication. At this time there is no alternative medication for allopurinol that works the same way.

CLINICAL FEATURES

Asymptomatic hyperuricemia is the term used for an abnormally high serum urate level, without gouty arthritis or nephrolithiasis. Although gouty arthritis characteristically occurs in patients with hyperuricemia, it is incorrect to equate hyperuricemia with clinical gout. Acute gout is the stage in which hyperuricemia causes the deposit of uric acid crystals in joint spaces. Approximately 90 % of first attacks are monoarticular. In more than one half of patients with acute gout, the first metatarsophalangeal joint is the initial joint involved, a condition known as podagra. Joint involvement (in order of decreasing frequency) includes the metatarsophalangeal joint, the instep forefoot, the ankle, the knee, the wrist and the fingers. In recurrent gouty arthritis the frequency of subsequent acute attacks of gout usually increases over time. Approximately 60 % of patients have a second attack within the first year, and 78 % have a second attack within two years. Only 7 % of patients do not have a recurrence within a ten years period⁶². Interval or intercritical gout is the period between acute attacks. In this stage, a person does not show any symptoms and has normal joint function.

Chronic tophaceous gout is the most disabling stage of gout and usually develops over a long period, such as 10 y. In this stage the disease has caused permanent damage to the affected joints and sometimes to the kidneys. The duration of time between the first gouty attack and recognizable tophaceous disease is highly variable and may range from 3 to 42 y⁶³ (mean: 11.6 y). The rate of urate deposition and consequently, the rate of tophi formation, correlate with the duration and severity of hyperuricemia⁶⁴. Tophaceous disease is more likely to occur in patients with the following; a polyarticular presentation, a serum urate level higher than 9.0 mg/dl and a younger age at disease onset i.e. 40.5 y or younger⁶⁵.

MANAGEMENT OF GOUT

Three general goals of therapy in the management of gout are to terminate the acute painful attack, prevent recurrences and reverse the complications of urate deposition in joints, kidneys or other involved sites. Urate-lowering drugs should be used to treat patients with asymptomatic hyperuricemia. If hyperuricemia is identified, associated factors such as obesity, hypercholesterolemia, alcohol consumption and hypertension should be addressed.

The four treatment options available for the acute gouty attack are NSAIDs, colchicine, corticosteroids and analgesics. NSAIDs are the preferred therapy for the treatment of patients without complications. Indomethacin was the first NSAID used for gout, but other NSAIDs including ibuprofen, naproxen, sulindac, piroxicam and ketoprofen are also effective in the treatment of acute gout⁶⁶. Maximum dosage should be given immediately after the onset of symptoms or at the time of diagnosis and continued for 24 h after complete resolution of the acute attack, then tapered quickly over two to three days. The most important determinant of therapeutic success is not which NSAID is chosen, but rather how soon NSAID therapy is initiated. In more than 90 % of patients complete resolution of the attack occurs within five to eight days of initiation of therapy⁶⁷. Unfortunately, the use of NSAIDs is limited due to side effects and hence should be avoided in patients with peptic ulcer, low creatinine clearance, liver diseases and poorly compensated congestive heart failure, and in patients receiving anticoagulation therapy⁶⁸⁻⁶⁹. Side effects are more pronounced in elderly patients⁷⁰. Drugs used in the management of acute gout are detailed in Table 4⁷¹⁻⁷³.

In Inter-critical gout, the use of low dose colchicine as prophylaxis for the prevention of gouty arthritis was first

described in 1936⁷⁴. It is common practice among rheumatologists to administer prophylactic or low dose colchicine (from 0.6 to 1.2 mg) at the same time urate-lowering drug therapy is initiated, but this regimen has not been widely embraced by primary care physicians⁷⁵⁻⁷⁶. Prophylactic therapy is quite effective in patients who tolerate colchicine and is 85 % effective in preventing acute attacks⁷⁷. Colchicine can reduce recurrence of gouty flares regardless of the serum uric acid level⁷⁸. Colchicine should be used for prophylaxis only with concurrent use of urate-lowering agents. Colchicine alone does not alter urate deposition or tissue damage⁷⁹. Low-dose colchicine is used for prophylaxis until the serum urate concentration is stable at the desired level and the patient has been free from acute gouty attacks for three to six months. There is a risk for an acute gouty flare-up when prophylaxis is discontinued. If patients do not tolerate daily doses of colchicine, a low daily dose of a selected NSAID can be used.

After the acute gouty attack is treated and prophylactic therapy is initiated, the issue of ongoing urate deposition should be addressed. A common practice is not to initiate drug therapy aimed at lowering urate levels after the initial attack. Rather, most clinicians prefer to aggressively correct or reverse sources of hyperuricemia in hopes of lower-

TABLE 4: DRUGS USED IN THE MANAGEMENT OF ACUTE GOUT.

Drug	Comments
NSAIDs Like Indomethacin, Naproxen, Ibuprofen, Sulindac and Ketoprofen	Contraindicated in patients with peptic ulcer disease or systemic anticoagulant
Alkaloid like Colchicine	Improper intravenous dosing has caused bone marrow suppression, renal failure and death.
Corticosteroids	-
Prednisone (Oral)	Fluid retention; impaired wound healing
Triamcinolone acetonide (I.M.)	May require repeat injections; risk of soft tissue atrophy
Hormone	-
Intramuscularly - ACTH	It carries a higher risk of rebound attacks. Repeat injections are commonly needed.

ing the serum urate level without the use of medication. Established indications for the use of urate-lowering agents are listed in Table 5⁸⁰⁻⁸¹.

Inhibitors of uric acid synthesis are more toxic, especially in elderly patients and should be reserved for use in over producers of urate (i.e. those who excrete more than 800 mg in 24 h). Urate lowering therapy should not be initiated until the acute attack has completely resolved, since the subsequent rapid decrease in serum urate levels has been shown to exacerbate the gouty attack.

Probenecid is the most frequently used uricosuric medication. Candidates for Probenecid therapy must have hyperuricemia attributed to under secretion of urate (i.e. less than 800 mg in 24 h on a regular diet or less than 600 mg in 24 h on a purine-restricted diet), a creatinine clearance of greater than 60 ml/min and no history of nephrolithiasis. Probenecid works at the level of the proximal tubule by blocking reabsorption of filtered uric acid. This action is inhibited by low dose salicylates; this fact accounts for a significant number of treatment failures. Consequently, patients who require low dose aspirin therapy are not candidates for probenecid therapy. Some physicians because of its added antiplatelet effects prefer sulfipyrazone, another uricosuric agent. Therapy is initiated at a dosage of 50 mg three times a day, which is gradually increased until the serum urate level is lowered, maximum dosage is 800 mg/day.

Allopurinol is currently the only readily available inhibitor of uric acid synthesis. Originally developed as a chemotherapeutic agent, this potent inhibitor of xanthine oxi-

dase dehydrogenase is the most common drug used in the treatment of hyperuricemia. Allopurinol causes a detectable decrease in the serum urate level within the first 24 h after administration and an expected maximum reduction within two weeks after initiation of therapy. Patients for whom allopurinol is indicated who experience side effects with this drug should be referred to a rheumatologist for a possible desensitization protocol or a trial of oxypurinol, which is an active metabolite of allopurinol.

TREATMENT APPROACH

The goals of therapy are early resolution of inflammation, prevention of recurrent attacks and reversal of complications arising from deposition of urate crystals in joints, kidneys, and tophi. The treatment approach consists of medications to treat the acute attack⁸², prevent future attacks⁸³, and lower uric acid levels⁸⁴. In addition, attention should be given to controlling conditions commonly associated with gout (e.g. obesity, hyperlipidemia) and modifying diet and other factors that contribute to the disease. Dosage adjustments may be needed in patients with renal insufficiency, liver disease, cardiac disease, peptic ulcer disease, allergies, bleeding diatheses, hypertension, or diminished oral intake. Treatment of asymptomatic hyperuricemia usually is not necessary. However, prophylactic urate lowering therapy is mandatory for clinical conditions that promote hyperuricemia (e.g. lymphoproliferative diseases).

CONSERVATIVE TREATMENT MEASURES

Patients with gout should be advised to lose weight,

TABLE 5: ESTABLISHED INDICATIONS FOR THE USE OF URATE-LOWERING AGENTS.

Drugs	Indications	Comments
Sulfipyrazone	Recurrent gout in patients who require antiplatelet therapy; aspirin use may block the effects of probenecid	Uricosuric agent best used in patients on a regular diet who under excrete uric acid (i.e., <800 mg of urate in 24 hrs); inherent antiplatelet activity
Probenecid	Recurrent gout in patients who are allergic or intolerant to allopurinol; may be combined with allopurinol in selected patients with resistant hyperuricemia.	Under secrete uric acid; creatinine clearance must be >60 ml/min; therapeutic effect reversed by high dose aspirin therapy; avoid concurrent daily aspirin use; contraindicated in patients with a history of urolithiasis; may precipitate gouty attack or renal calculi at start of therapy.
Allopurinol	Chronic tophaceous "erosive" gouty arthritis and gout complicated by renal disease or renal calculi	Inhibits uric acid synthesis; best for patients who over produce uric acid (i.e., those who excrete >800 mg of urate in 24 hrs; peak effect in reduction of urate synthesis occurs in two weeks.

moderate their use of alcohol, avoid dehydration, repetitive trauma, control hypertension and hyperlipidemia. A purine-restricted diet may be unpalatable to many patients and may reduce serum urate levels by only 1 mg/dl⁸⁴. A more reasonable dietary approach is to reduce consumption of fat, cholesterol, and meat (especially organ meats, which contain high level of purines). Patients should also be advised to drink at least eight glasses of liquids daily to prevent dehydration and help reduce uric acid levels. Use of thiazides and loop diuretics may decrease the clearance of uric acid and reduce plasma volume and therefore should be discontinued or avoided if possible. Other drugs, such as low dose aspirin, ethambutol hydrochloride, pyrazinamide, and niacin, decrease uric acid excretion by competing for secretion in renal tubules, therefore should be avoided⁸⁵. Fasting increases the serum uric acid level in normal as well as gout individuals, since increase in beta-hydroxybutyric acid and acetoacetic acid decreases renal excretion of urate. Obese patients starving for a week have an average increase of 14.7mg/100 ml (874 μ mol/l) of uric acid. Liberal intake of fluids should be advised to ensure a daily excretion of about 2000 ml of urine. Beverages like tea and coffee contain methyl-purines, which are not converted by the body into uric acid. About 2 or 3 cups a day are permitted. There appears to be individual susceptibility to an attack of gout after ingestion of alcohol. Avoiding alcohol may prevent attack of gout in such people^{28,86}.

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