CHAPTER 12

Gout
A. Clinical Features

N. LAWRENCE EDWARDS, MD

- Gout is caused by the deposition of monosodium urate crystals in and around the tissues of joints.
- The course of classic gout passes through three distinct stages: asymptomatic hyperuricemia, acute intermittent gout, and advanced gout.
- The incidence of gout increases with age as well as with the degree of hyperuricemia.
- The vast majority of people with hyperuricemia never develop symptoms associated with uric acid excess, such as gouty arthritis, tophi, or kidney stones.
- In men, the first attacks usually occur between the fourth and sixth decades of life. In women, the age of onset is older and varies with several factors, including the age of menopause and the use of thiazide diuretics.
- The onset of a gouty attack usually is heralded by the rapid development of warmth, swelling, erythema, and pain in the affected joint.
- The joint most commonly affected first by gout is the first metatarsophalangeal joint. This condition is known as podagra.
- Fevers of higher than 38°C are seen in approximately 30% of gout patients during the early phases of acute attacks.
- Advanced gout (sometimes referred to as chronic tophaceous gout) usually develops after 10 or more years of acute intermittent gout, although patients have been reported with tophi as their initial clinical manifestation.
- The development of tophaceous deposits of monosodium urate is a function of the duration and severity of hyperuricemia.

Gout is a clinical disease associated with hyperuricemia and caused by the deposition of monosodium urate (MSU) crystals in and around the tissues of joints. Symptomatic crystal deposition includes attacks of acute inflammatory arthritis, a chronic destructive arthropathy, and soft tissue accumulation of MSU crystals. The nonarticular (soft tissue) clinical manifestations of gout include the development of tophi (Figure 12A-1) and the precipitation of crystals in the renal collecting ducts, leading to urolithiasis.

STAGES OF CLASSIC GOUT

The course of classic gout passes through three distinct stages: asymptomatic hyperuricemia, acute intermittent gout, and advanced gout (Figure 12A-2). The rate of progression from asymptomatic hyperuricemia to advanced gout varies considerably from one person to another and is dependent on numerous endogenous and exogenous factors.

Asymptomatic Hyperuricemia

Hyperuricemia is a common biochemical abnormality that can be defined in either epidemiologic or physiologic terms. In extracellular fluids, 98% of uric acid is in the form of urate ion at pH 7.4. Clinical laboratories define hyperuricemia as a serum urate level that is greater than two standard deviations above the mean value in a gender- and age-matched healthy population. Using this standard, the upper limit for normal serum urate frequently is listed as 8.0 to 8.5 mg/dL. In physiologic terms, however, any level above 6.8 mg/dL is hyperuricemia because it exceeds the soluble concentration of MSU in body fluid. Serum urate levels in children are relatively low (2.0–4.0 mg/dL). In men, this value increases dramatically around the time of puberty to reach the level they will maintain throughout adulthood. In women, serum urate levels gradually increase throughout early adulthood and do not reach maximum levels until after menopause. This difference in the duration of urate elevations is the main reason gout is a male-predominant disease.

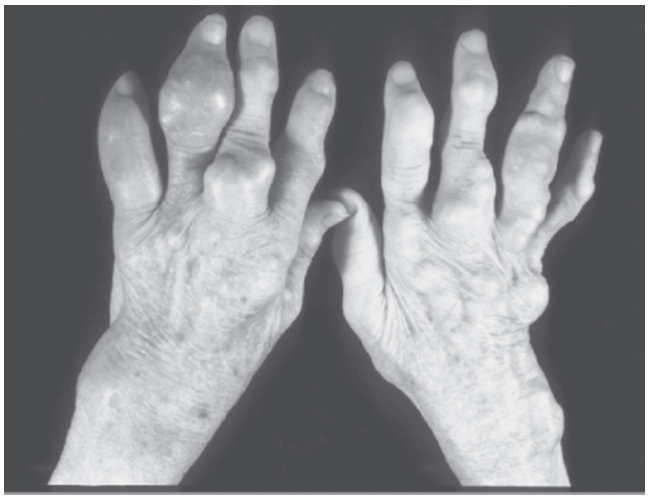

FIGURE 12A-1

The hands of a patient with advanced gout reveal large tophi over all digits as well as the right fifth metacarpophalangeal joint and both wrists.

The incidence of gout increases with age as well as with the degree of hyperuricemia. In the Normative Aging Study, the cumulative incidence of gouty arthritis among subjects with uric acid levels between 7.0 and 8.0 mg/dL was 3%, and subjects with urate levels of 9.0 mg/dL or more had a 5-year cumulative incidence of 22% (1). However, the vast majority of people with hyperuricemia never develop symptoms associated with uric acid excess, such as gouty arthritis, tophi, or kidney stones.

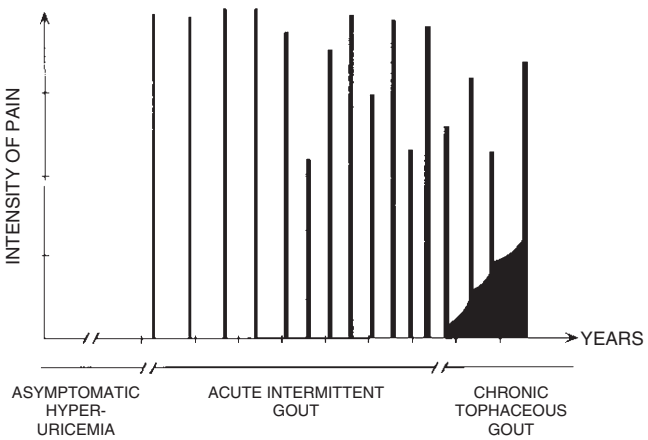

FIGURE 12A-2

The three stages of disease progression in classic gout. The period of asymptomatic hyperuricemia lasts decades, followed by acute intermittent gout with painless intercritical segments, leading to advanced gout with progressive background pain and joint destruction in untreated patients.

Acute Intermittent Gout

The initial episode of acute gout usually follows decades of asymptomatic hyperuricemia. Thomas Sydenham, the famous 17th-century physician who wrote of his personal experiences with gout, eloquently described the initial hours of an acute attack:

> He goes to bed and sleeps well, but about Two a Clock in the Morning, is waked by the Pain, seizing either his great Toe, the Heel, the Calf of the Leg, or the Ankle; this Pain is like that of dislocated Bones, with the Sense as it were of Water almost cold, poured upon the Membranes of the part affected; presently shivering and shaking follow with a feverish Disposition; the Pain is first gentle, but increased by degrees-till dash towards Night it comes to its height, accompanying itself neatly according to the Variety of the bones of the Tarsus and Metatarsus, whose Ligaments it seizes, sometimes resembling a violent stretching or tearing of those ligaments, sometimes gnawing of a dog, and sometimes a weight; more over, the Part affected has such a quick and exquisite Pain, that it is not able to bear the weight of the cloths upon it, nor hard walking in the Chamber (2).

This classic description captures the intense pain frequently associated with acute gouty arthritis, and it is this clinical picture most commonly evoked by the term *gout*.

In men, the first attacks usually occur between the fourth and sixth decades of life. In women, the age of onset is older and varies with several factors, including the age of menopause and the use of thiazide diuretics. The onset of a gouty attack usually is heralded by the rapid development of warmth, swelling, erythema, and pain in the affected joint. Pain escalates from the faintest twinges to its most intense level over an 8- to 12-hour period. The initial attack usually is monarticular and, in one half of patients, involves the first metatarsophalangeal (MTP) joint. Involvement of the first MTP joint, which occurs eventually in 90% of individuals with gout, is known as *podagra* (from the Greek for "foot-trap"; Figure 12A-3). Other joints that frequently are involved in this early stage are the midfoot, ankles, heels, and knees, and less commonly, the wrists, fingers, and elbows. The intensity of pain characteristically is very severe, but may vary among subjects. As Sydenham observed, patients find walking difficult or impossible when lower extremity joints are involved.

Systemic symptoms, such as fever, chills, and malaise may accompany acute gout. Fevers of higher than 38°C are seen in approximately 30% of gout patients during the early phases of acute attacks (3). The cutaneous erythema associated with the gouty attack may extend beyond the involved joint and resemble bacterial cellulitis (Figure 12A-3). The natural course of untreated

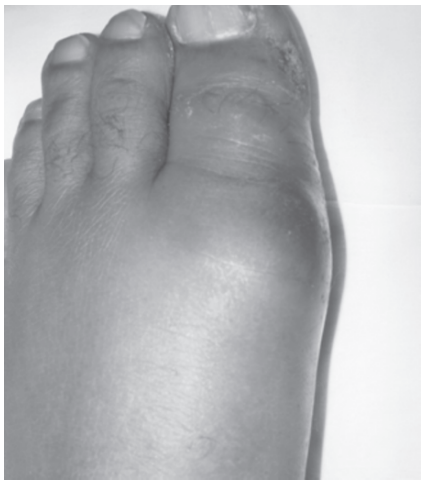

FIGURE 12A-3

Acute gouty arthritis involving the first metatarsophalangeal joint.

acute gout varies from episodes of mild pain that resolve in several hours ("petit attacks") to severe attacks that last 1 to 2 weeks. Early in the acute intermittent stage, episodes of acute arthritis are infrequent, and intervals between attacks sometimes last for years. Over time, the attacks typically become more frequent, longer in duration, and involve more joints.

Intercritical periods of acute intermittent gout are just as characteristic of this stage as are the acute attacks. Previously involved joints are virtually free of symptoms. Despite this, MSU crystals often can be identified in the synovial fluid. In one study, these crystals were found in the synovial fluids of 36 of 37 knees that previously had been inflamed. Synovial fluids containing crystals also had a higher mean cell count than those with no crystals, 449 cells/mm^3 versus 64 cells/mm^3 (4). These subtle differences may reflect ongoing subclinical inflammation.

Advanced Gout

Advanced gout (sometimes referred to as *chronic tophaceous gout*) usually develops after 10 or more years of acute intermittent gout, although patients have been reported with tophi as their initial clinical manifestation (5). The transition from acute intermittent gout to chronic tophaceous gout occurs when the intercritical periods no longer are free of pain. The involved joints become persistently uncomfortable and swollen, although the intensity of these symptoms is much less than during acute flares. Gouty attacks continue to occur against this painful background, and without therapy, they may recur as often as every few weeks. The amount of background pain also steadily increases with time if appropriate intervention is not started (see Figure 12A-2). Clinically evident tophi may or may not be detected on physical examination during the first few years of this stage of gout. However, periarticular tophi detected by magnetic resonance imaging (MRI) (6) and synovial "microtophi" discovered through the arthroscope certainly are present early in this stage of gout and may in fact be present during the earlier acute intermittent phase of gout. Polyarticular involvement becomes much more frequent during this time. With diffuse and symmetric involvement of small joints in the hands and feet, chronic tophaceous gout can occasionally be confused with the symmetrical polyarthritis of rheumatoid arthritis.

The development of tophaceous deposits of MSU is a function of the duration and severity of hyperuricemia (7). Hench found that untreated patients developed tophi 11.7 years after the onset of acute gout, on average (8). In a study of 1165 people with primary gout, those without tophi had serum uric acid levels of 10.3 ± 1.3 mg/dL and those with extensive deposits had levels of 11.0 ± 2.0 mg/dL. Other factors associated with the development of tophi include early age of gout onset, long periods of active but untreated gout, an average of four attacks per year, and a greater tendency toward upper extremity and polyarticular episodes (9). In untreated patients, the interval from the first gouty attack to the beginning of advanced arthritis or the development of visible tophi is highly variable, ranging from 3 to 42 years, with an average of 11.6 years (10).

The subcutaneous tophus is the most characteristic lesion of advanced gout (Figure 12A-3). Tophi may be found anywhere over the body, but occur most commonly in the fingers, wrists, ears, knees, olecranon bursa, and such pressure points as the ulnar aspect of the forearm and the Achilles tendon. In people with nodal osteoarthritis, tophi have a propensity for forming in Heberden's nodes. Tophi also may occur in connective tissues at other sites, such as renal pyramids, heart valves, and sclerae. Similar appearing nodules are observed in other rheumatic conditions, such as rheumatoid arthritis and multicentric reticulohistiocytosis (11,12). Before antihyperuricemic agents were available, as many as 50% of patients with gout eventually developed clinical or radiographic evidence of tophi. Since the introduction of allopurinol and the uricosuric agents, the incidence of tophaceous gout has declined.

Much of the knowledge about sequential development of the mature, multilobulated gouty tophus comes from the classic histopathologic descriptions of Sokoloff (13) and Schumacher (14), and the more recent immunohistochemical studies of Palmer and colleagues (15). Figure 12A-4 represents a theoretical sequence of how a noncrystalline, cellular locus (macrophage acinus) progresses through stages of crystal precipitation, coronal hypertrophy, and finally, crystal coalescence and cellular atrophy, to eventually form the clinically

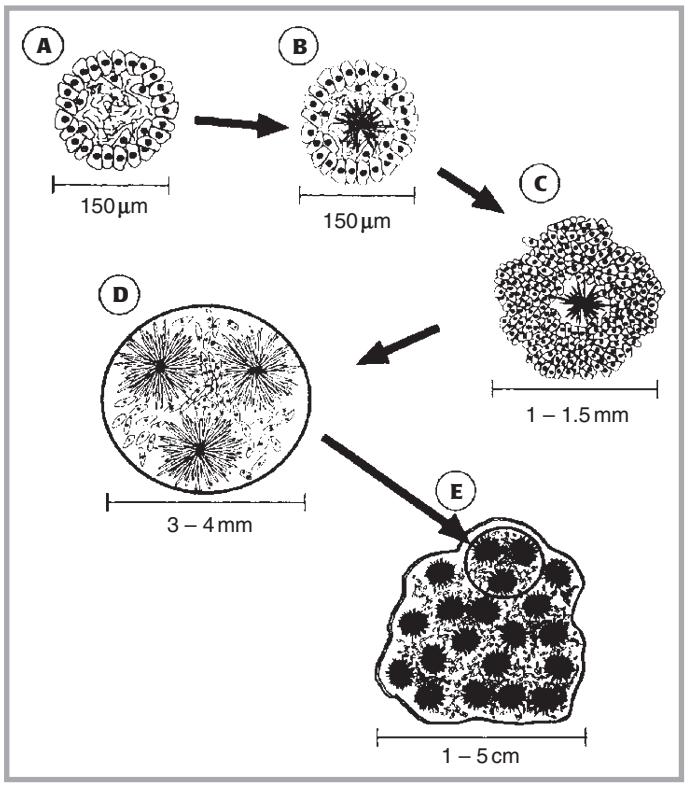

FIGURE 12A-4

The stages of development of a gouty tophus. (A) The crystal-free macrophage acinus is the earliest organized phase of a gouty tophus. (B) The amorphous center of the acinus fosters urate crystal formation. (C) As the crystalline mass expands, the surrounding corona of macrophages likewise undergoes hypertrophy. (D) Further crystallization results in a thinning of the corona until only fibrous septae separate one nidus of crystal formation from another. (E) A fully mature tophus.

observable subcutaneous tophus (7). The macrophage acinus (Figure 12A-4A) is the earliest structure observed by light microscopy in tophus development. The acinus has a core of noncrystalline, amorphous material surrounded by a rosette of mononuclear phagocytes. The central amorphous material is believed to be detritus from a collection of monocytes that conjugates at the locus in response to some inciting event.

Some time after the acinus is formed, a small, eccentric collection of radially arranged MSU crystals form in the amorphous core of monocyte-derived material [Figure 12A-4(B)]. The macrophages do not phagocytize the MSU crystal, but as the crystalline mass expands and contacts the surrounding cells, this shell that is 1- to 2-cells thick proliferates to form a tightly packed, 8- to 10-cell-thick corona [Figure 12A-4(C)]. As the tophus matures, this corona is lost and replaced by fibrous septae [Figure 12A-4(D)] that contain some fibroblastic cells and occasional multinucleated giant cells. Adjacent crystalline deposits coalesce to form multilobulated tophi [Figure 12A-4(E)] measuring 1 to 10 cm in diameter, interlaced with fibrous strands containing few cells and encapsulated by a sometimes tenuous and sometimes thick fibrous tissue. The cellular and crystalline components of a gouty tophus are easily demonstrated by magnetic resonance imaging (Figure 12A-5).

UNUSUAL PRESENTATIONS

Early-Onset Gout

Between 3% and 6% of patients with gout have symptom onset before age 25. Early-onset gout represents a special subset of cases that generally have a genetic component, show a more accelerated clinical course, and require more aggressive antihyperuricemic therapy. In large epidemiologic studies of classic gout, a family history of gout and/or nephrolithiasis is present in 25% to 30% of cases. In early-onset gout, the incidence of family history is approximately 80%. In this younger group, detailed questioning about the kindred over several generations may yield enough information to suggest a mode of inheritance (X-linked or autosomal dominant or recessive).

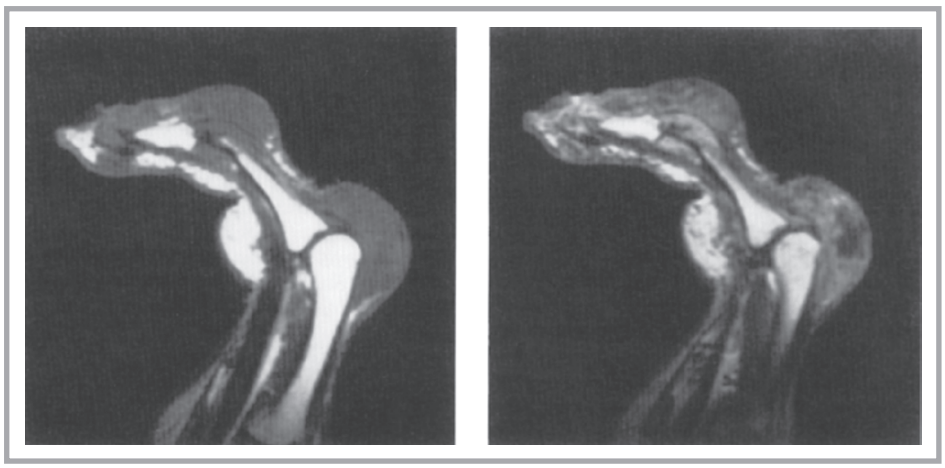

FIGURE 12A-5

(Left) Midline sagittal section magnetic resonance image of a finger with advanced tophaceous deformities. (Right) T1 weighted, spin echo technique with gadolinium contrast reveals the deep soft tissue anatomy. The heterogeneous composition of the tophus dorsal to the proximal interphalageal joint and distal phalanx is clearly revealed. The central crystalline deposit remains low intensity, but surrounding tissue enhances.

Like classic gout, early-onset gout may be caused by overproduction of urate or reduced renal clearance of uric acid. Diseases associated with overproduction of urate in children and young adults include enzymatic defects in the purine pathway, glycogen storage diseases, and hematologic disorders, such as hemoglobinopathies and leukemias. The complete deficiency of hypoxanthine-guanine phosphoribosyltransferase (HGPRT) is an X-linked inherited inborn error of purine metabolism with a characteristic clinical presentation known as the Lesch–Nyhan syndrome. These boys, who have severe neurologic abnormalities, develop gout and kidney stones in the first decade of life if not treated early with allopurinol. The partial deficiency of HGPRT (the Kelley–Seegmiller syndrome) results in early-onset gout or uric acid nephrolithiasis and also is also an X-linked trait. People with this syndrome have minor or no neurologic problems.

Glycogen storage disease types I, III, V, and VII, inherited as autosomal recessive diseases, are associated with early-onset gout. Sickle cell disease, beta-thalassemia, and nonlymphocytic leukemias may be complicated by gouty arthritis in the young adult years.

Conditions associated with uric acid underexcretion in young patients include a specific renal tubular disorder known as familial juvenile hyperuricemic nephropathy (16). This autosomal dominant disorder causes hyperuricemia from a very young age, before any evidence of renal insufficiency. The condition may lead to progressive renal failure and end-stage kidney disease by age 40. Other nephropathies associated with early-onset gout include polycystic kidney disease, chronic lead intoxication, medullary cystic disease, and focal tubulointerstitial disease.

Gout in Organ Transplantation Patients

Hyperuricemia develops in 75% to 80% of heart transplant recipients who routinely take cyclosporine to prevent allograft rejection (17). A slightly lower frequency (approximately 50%) of kidney and liver transplant recipients develop hyperuricemia, presumably because lower doses of cyclosporine are used in these individuals. Whereas asymptomatic hyperuricemia progresses to clinical gout in only 1 in 30 subjects in the general population, cyclosporine-induced hyperuricemia leads to gout in 1 in every 6 patients (18). Other differences between primary and cyclosporine-induced gout include the marked shortening of the asymptomatic hyperuricemia and acute intermittent gout stages, with the rapid appearance of tophi. The stage of asymptomatic hyperuricemia lasts for 20 to 30 years in classic gout, but is present for only 6 months to 4 years in cyclosporine-induced disease. Similarly, the duration of the acute intermittent stage is only 1 to 4 years in transplant recipients, but it may last 8 to 15 years in classic gout. Because organ transplant recipients use other medications, such as systemic corticosteroids and azathioprine, their gouty symptoms frequently are more atypical and less dramatic than those of patients with classic gout.

Gout in Women

Unlike most other rheumatic conditions, gout is less common in women than in men. In most large reviews, women account for no more than 5% of all people with gout (19). Ninety percent of women are postmenopausal at the time of their initial attack. Postmenopausal gout is similar clinically in presentation and course to classic gout, except that the age of onset is later in women than in men. Conditions that are much more commonly associated with gout in postmenopausal women than with gout in men include diuretic use (95%), hypertension (73%), renal insufficiency (50%), and preexisting joint disease, such as osteoarthritis (20).

Premenopausal gout has a strong hereditary component. Most women who develop gout before menopause have hypertension and renal insufficiency. The rare woman with premenopausal gout and normal renal function should be evaluated for the autosomally inherited familial juvenile hyperuricemic nephropathy (16) or the even more rare non–X-linked inborn errors of purine metabolism (20).

Normouricemic Gout

The most frequent explanations for apparent gout with normal levels of uric acid are that (1) gout is not the correct diagnosis or (2) the patient actually is chronically hyperuricemic but the serum urate is normal at the time it is measured (for a potential explanation of this phenomenon, see below).

Several articular conditions can mimic gout closely, including crystalline arthropathies of calcium pyrophosphate dehydrate (pseudogout), basic calcium (apatite), and liquid lipid (21). Other causes of acute monoarthropathies, such as infection, sarcoidosis, and trauma, also should be considered (22). The clinical suspicions of gout should be confirmed by crystal analysis of synovial fluid. Without this confirmation, the diagnosis remains in question.

Misunderstanding the definition of hyperuricemia also can contribute to misdiagnosis of normouricemic gout. A sustained serum urate level above 7.0 mg/dL provides a permissive environment for MSU crystal formation, but people with acute and chronic gout may have urate values below this biochemical definition of hyperuricemia. In fact, as many as one third of people presenting with acute gout to have a serum urate below

7.0 mg/dL during the episode of severe pain (23). This condition probably results from uricosuric effects of ACTH release and adrenal stimulation, which are caused by the stress of the painful process. Normalization of serum urate values during acute gouty flares may be more common in alcoholics than in nondrinkers. Aside from such standard urate-lowering agents as allopurinol, probenecid, and sulfinpyrazone, high dose salicylates, angiotensin II receptor blockers, fenofibrate, glucocorticoids, warfarin, glycerol guaiacholate, and x-ray contrast agents also may lower serum urate values in people with gout and lead to the false impression of normouricemic gout.

Yu reported that 1.6% of 2145 gout patients had sustained normouricemia months after discontinuing use of allopurinol or uricosuric agents (24). In most of these cases, hyperuricemia eventually returned, although several patients with very mild gouty symptoms remained normouricemic over a prolonged period.

PROVOCATIVE FACTORS OF ACUTE ATTACKS

Why crystals form in some hyperuricemic fluids and not in others is unclear. When synovial fluids are balanced for urate concentrations, the fluids from gouty patients have a far greater propensity for promoting crystal formation than similar fluids from people with osteoarthritis or rheumatoid arthritis. A number of synovial fluid proteins have been reported to function as promoters or inhibitors of crystal nucleation. The current list of physiologically important nucleators is short, with the leading contenders being type I collagen and a gamma globulin subfraction (10).

The degree of hyperuricemia correlates positively with the overall risk of acquiring gout. However, rapid increases or decreases in the concentration of synovial fluid urate are related more closely to actual precipitation of the acute gouty attack. A rapid flux in urate level is a triggering mechanism in gout induced by trauma, alcohol ingestion, and drugs.

Trauma frequently is reported to be an inciting event for acute gouty episodes. The trauma may be as minor as a long walk and may not have caused pain during the activity, but it caused intra-articular swelling. When the joint is allowed to rest, there is a relatively rapid efflux of free water from the joint fluid. This results in a sudden increase in synovial fluid urate concentration, which may allow precipitation of urate crystals and a gout attack. This mechanism may explain why gouty attacks commonly occur at night.

Alcohol ingestion may predispose to gout through several mechanisms. The consumption of lead-tainted moonshine results in chronic renal tubular damage that leads to secondary hyperuricemia and saturnine gout (the word *saturnine*, meaning of or relating to lead, is derived from the belief of the ancients that this metal comprised the planet Saturn). The ingestion of any form of ethanol can raise uric acid production acutely by accelerating the breakdown of intracellular adenosine triphosphate (25). Beer consumption has an added impact on gout because it contains large quantities of guanosine, which is catabolized to uric acid (26).

Drugs may precipitate gout by rapidly raising or lowering urate levels. Thiazide diuretics selectively interfere with urate excretion at the proximal convoluted tubule. Low dose aspirin (less than 2 g/day) also can raise serum urate levels, but higher doses have a uricosuric effect and may lower the serum urate concentration. A rapid increase or reduction in the serum urate level can provoke gouty attacks; allopurinol is the drug most often responsible for this effect. The mechanism for this paradoxic response appears to be the destabilizing of microtophi in the gouty synovium when the urate concentration of the synovial fluid is changed rapidly. As the microtophi break apart, crystals are shed into the synovial fluid and the gouty episode is initiated (27).

CLINICAL ASSOCIATIONS

Renal Disease

The only consistent visceral damage caused by hyperuricemia is its effect on the kidneys. Three forms of hyperuricemia-induced renal disease are recognized, including (1) chronic urate nephropathy, (2) acute uric acid nephropathy, and (3) uric acid nephrolithiasis.

Chronic urate nephropathy is a distinct entity caused by deposition of MSU crystals in the real medulla and pyramids and is associated with mild albuminuria. Although chronic hyperuricemia is thought to be the cause of urate nephropathy, this form of kidney involvement is essentially never seen in the absence of gouty arthritis. Progressive renal failure is common in people with gout, but the attribution of renal failure to chronic urate nephropathy itself is often difficult owing to the frequent confluence of multiple comorbid conditions in patients with gout. As described in further detail below, the hypertension, diabetes, obesity, and ischemic heart disease that often accompany gout are also risk factors for renal dysfunction. To a large extent, the role of hyperuricemia as a single factor in chronic parenchymal disease of the kidney remains controversial. Other chronic effects of hyperuricemia on the kidney may not be caused by crystal deposition but rather by the direct action of the soluble uric acid molecule on the afferent arteriolar vessels of glomeruli (28).

Acute renal failure can be caused by hyperuricemia in the acute tumor lysis syndrome, which occurs in patients given chemotherapy for rapidly proliferating lymphomas and leukemias. With massive liberation of purines

during cell lysis, uric acid precipitates in the distal tubules and collecting ducts of the kidney. Acute uric acid nephropathy can result in oliguria or anuria. This form of acute renal failure can be distinguished from other forms by a ratio of uric acid to creatinine greater than 1.0 in a random or 24-hour urine collection.

Uric acid renal stones occur in 10% to 25% of all people with gout. The incidence correlates strongly with the serum urate level, and the likelihood of developing stones reaches 50% when the serum urate is above 13 mg/dL. Symptoms of renal stones precede the development of gout in 40% of patients. Calcium-containing renal stones occur 10 times more frequently in gouty subjects than in the general population.

Hypertension

Hypertension is present in 25% to 50% of people with gout, and 2% to 14% of people with hypertension have gout. Because serum urate concentration correlates directly with peripheral and renal vascular resistance, reduced renal blood flow may account for the association between hypertension and hyperuricemia. Factors such as obesity and male gender also link hypertension and hyperuricemia (29,30).

Obesity

Hyperuricemia and gout correlate highly with body weight for both men and women, and individuals with gout commonly are overweight, compared with the general population. Obesity may be a factor linking hyperuricemia, hypertension, hyperlipidemia, and atherosclerosis.

Hyperlipidemia

Serum triglycerides are elevated in 80% of people with gout. The association between hyperuricemia and serum cholesterol is controversial, although serum levels of high density lipoprotein generally are decreased in patients with gout. These abnormalities of serum lipids likely reflect overindulgence rather than a genetic link.

RADIOGRAPHIC FEATURES

The radiographic findings of gout often are unremarkable early in the disease course. In acute gouty arthritis, the only finding may be soft tissue swelling around the affected joint. In most instances, bone and joint abnormalities develop only after many years of disease and are indicative of the deposition of urate crystals. Most frequently, the abnormalities are asymmetric and seen in the feet, hands, wrists, elbows, and knees.

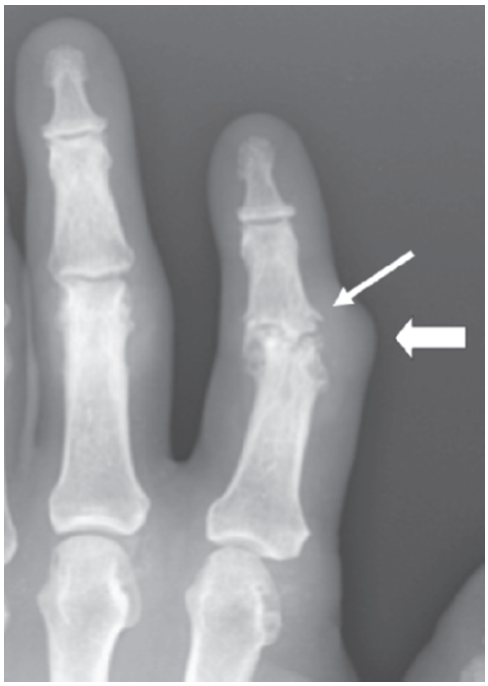

FIGURE 12A-6

Radiographic changes of advanced gout include the typical gouty erosions with overhanging edge (*white arrows*) and soft tissue swellings of gouty tophi.

The bony erosions of gout are radiographically distinct from the erosive changes of other inflammatory arthritides. Gouty erosions usually are slightly removed from the joint, but rheumatoid erosions typically are in the immediate proximity of the articular surface (Figure 12A-6). The characteristic gouty erosion has features that are both atrophic and hypertrophic, leading to erosions with an overhanging edge. The joint space is preserved in gout until very late in the disease process. Juxta-articular osteopenia, a common and early finding in rheumatoid arthritis, is absent or minimal in gout.

LABORATORY FEATURES AND DIAGNOSIS

An elevated serum urate level has long been considered a cornerstone in the diagnosis of gout. In reality, this laboratory finding is of limited value in establishing the diagnosis. The vast majority of hyperuricemic subjects will not develop gout, and serum urate levels may be normal during gouty attacks (31). Far too many patients are diagnosed with gout based on the clinical triad of an acute monoarthritis, hyperuricemia, and a dramatic improvement of articular symptoms in response to treatment. A diagnosis by these parameters is presumptive only, and the physician should remain alert to other possibilities.

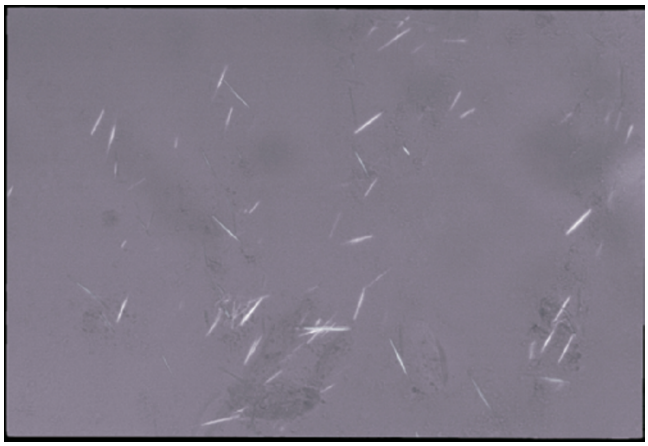

FIGURE 12A-7

Polarized microscopic view of typical needle-shaped MSU crystals in synovial fluid from an acutely inflamed joint.

A clinical response to treatment, for example, nonsteroidal anti-inflammatory agents or glucocorticoids, frequently is observed with other types of arthritis, including calcium pyrophosphate pseudogout and basic calcium phosphate (hydroxyapatite) tendonitis. Serum urate determinations are helpful and necessary in following the effects of antihyperuricemic therapy.

The definitive diagnosis of gout is possible only by aspirating and inspecting synovial fluid or tophaceous material and demonstrating characteristic MSU crystals (Figure 12A-7). The crystals usually are needle or rod shaped. On compensated polarized microscopy, they appear as bright, birefringent crystals that are yellow when parallel to the axis of slow vibration (marked on the first-order compensator) and blue when perpendicular to this axis. The crystals usually are intracellular during acute attacks, but small, truncated, extracellular crystals commonly appear as the attack subsides and during the intercritical periods.

The synovial fluid findings are consistent with moderate-to-severe inflammation. The leukocyte count usually falls between 5000 and 80,000 cells/mm^3, with the average count between 15,000 and 20,000 cells/mm^3. The cells are predominantly neutrophils. Synovial fluid should be sent for culture, as well, as bacterial infection can coexist with gouty crystals.

A 24-hour urine uric acid measurement is not required of all people presenting with gout. This measurement is useful for patients being considered for uricosuric therapy (probenecid or sulfinpyrazone) or when the cause of marked hyperuricemia (>11 mg/dL) is being investigated. On a regular diet, urinary uric acid excretion of more than 800 mg in 24 hours suggests a problem of urate overproduction. In children and young adults, this overproduction may be caused by enzymatic defects. In older patients, this level of urinary uric acid suggest one of the diseases associated with rapid cellular turnover, such as the myelo- or lymphoproliferative disorders. Certain drugs, contrast dyes, and alcohol interfere with urinary uric acid measurements and should be avoided for several days before the study.

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CHAPTER 12

Gout
B. Epidemiology, Pathology, and Pathogenesis

HYON K. CHOI, MD, MPH, DRPH, FRCPC

- The prevalence of gout, which occurs predominantly among men and postmenopausal women, is approximately 2.7%.
- The incidence of primary gout has doubled over the past 20 years in both sexes.
- Gout prevalence rises with advancing age, reaching a level of 9% in men older than 80 years of age, and 6% in women.
- There appears to be a higher prevalence of gout among individuals of lower family income levels, likely reflecting a greater number of risk factors for gout—for example, obesity, hypertension, and a Western dietary pattern with a greater red meat component.
- Two major genetic mutations are known to result in gout, urolithiasis, and other disturbances: Mutations in the 5′-phosphoribosyl 1-pyrophosphate (PRPP) synthetase genes can result in overactivity of the pathway, leading to increased rate of PRPP, purine nucleotide, and urate production. Mutations in the gene encoding hypoxanthine-guanine phosphoribosyl transferase (HPRT) are associated with a spectrum of disease in children that ranges from hyperuricemia alone to hyperuricemia with profound neurological and behavioral dysfunction (Lesch–Nyhan syndrome).
- Ethanol administration increases uric acid production by net adenosine triphosphate (ATP) degradation to adenosine monophosphate (AMP), which is rapidly degraded to uric acid, leading to hyperuricemia. Alcohol consumption, uric acid levels, and risk of gout have a strong dose–effect relationship.

Gout is a form of inflammatory arthritis triggered by the crystallization of uric acid within the joints (1). Acute gout, characteristically intermittent, is one of the most painful conditions experienced by humans. Chronic tophaceous gout develops usually after years of acute intermittent gout. Beyond the morbidity associated with gout itself, the disease is associated with important medical conditions including the insulin resistance syndrome, hypertension, nephropathy, alcohol abuse, and disorders associated with increased cell turnover. Gout is often associated with hyperuricemia.

EPIDEMIOLOGY

Gout occurs predominantly among men and postmenopausal women. The disease rarely occurs in men before adolescence or in women before menopause. According to the Third National Health and Nutrition Examination Survey (1988–1994), the prevalence of self-reported, physician-diagnosed gout among US adults is approximately 2.7%. The prevalence rises with advancing age, reaching a level of 9% in men older than 80 years of age, and 6% in women.

Serum urate concentrations in men are about 1 mg/dL higher on average than in women (2), but after menopause the serum levels of uric acid in women tend to approach those in men. The sex differences in uric acid levels may stem from the effects of estrogen on the renal tubular handling of uric acid; premenopausal levels of estrogens in women may promote more efficient renal clearance of urate (2). The prevalence appears to be higher among African Americans than among Caucasians, possibly reflecting the increased prevalence of hypertension among African Americans (3). Once termed *the patrician malady*, gout has been considered a disease of the affluent, primarily observed in middle-aged men of wealthy status. Recent epidemiologic data, however, suggest a higher prevalence of gout among individuals of lower family income levels, likely reflecting a greater number of risk factors for gout—for example, obesity, hypertension, and a Western

dietary pattern with a greater red meat component—in lower socioeconomic classes.

The incidence of primary gout, defined as the occurrence of this disease in the absence of a clear cause (e.g., the Lesch–Nyhan syndrome or diuretic use) has doubled over the past 20 years in both sexes (4). Diet and lifestyle trends, increasing frequencies of obesity, metabolic syndrome, hypertension, organ transplantation, and increasing use of certain medications (e.g., low dose salicylate and diuretics) may explain the increasing incidence of gout.

PATHOGENESIS OF HYPERURICEMIA AND GOUT

Humans are the only mammals who are known to develop gout spontaneously, probably because hyperuricemia only commonly develops in humans (1). In most fish, amphibians, and nonprimate mammals, uric acid generated from purine metabolism undergoes oxidative degradation via the uricase enzyme, producing the more soluble compound allantoin. In humans, the uricase gene is crippled by two mutations that introduce premature stop codons (1). The absence of uricase, combined with extensive reabsorption of filtered urate, results in urate levels in human plasma that are approximately 10 times than those of most other mammals (0.5–1.0 mg/dL). Urate's role as the primary antioxidant in human blood may account for its evolutionary advantage (1).

Solubility of Urate

Uric acid is a weak acid (pKa = 5.8) that exists largely as urate, the ionized form, at physiological pH. In general, the risk of supersaturation and crystal formation rises in parallel with the concentration of urate in physiologic fluids. Population studies indicate a direct correlation between serum urate levels and risk of future gout (5). Conversely, lowering uric acid levels is associated with a substantially lower risk of recurrent gout, confirming the causal relation between uric acid levels and risk of gouty arthritis (6). The solubility of urate in joint fluids is influenced by other factors as well, however, including temperature, pH, cation concentration, articular hydration state, and the presence of nucleating agents around which urate crystals may coalesce (e.g., nonaggregated proteoglycans, insoluble collagens, and chondroitin sulfate).

Variation in these factors may account for some of the difference in the risk for gout associated with a given elevation in urate level. Moreover, these risk factors may explain several of the interesting clinical features of gout: (1) predilection for the first metatarsophalangeal joint, that is, podagra (caused by the lower temperature at this peripheral body site); (2) tendency to occur in osteoarthritic joints (because such joints contain nucleating debris); and (3) the frequency of nocturnal onset (the result of intra-articular dehydration that may occur at night) (1).

Urate Metabolism

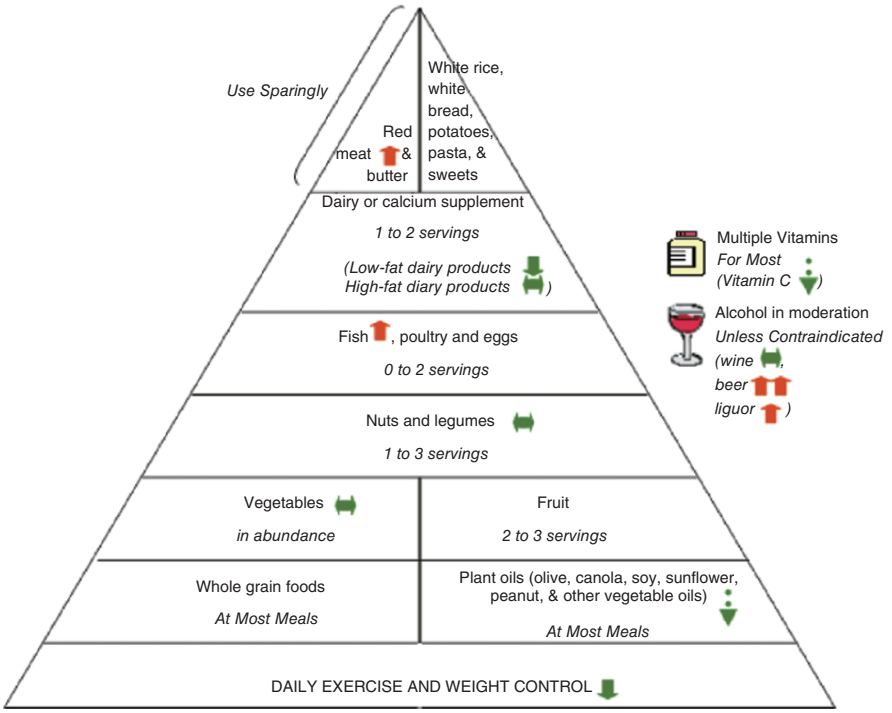
The amount of urate in the body depends on the balance between dietary intake, synthesis, and excretion of this molecule. Hyperuricemia results from the overproduction of urate (10%), underexcretion of urate (90%), or often a combination of the two. The purine precursors come from exogenous (dietary) sources or endogenous metabolism (synthesis and cell turnover).

The dietary intake of purines makes a substantial contribution to the blood uric acid. For example, substitution of an entirely purine-free formula diet over a period of days can reduce blood uric acid of healthy men from an average of 5.0 mg/dL to 3.0 mg/dL (1). The bioavailable purine content of particular foods depends on their relative cellularity as well as the transcriptional and metabolic activity of their cellular content. Little is known, however, about the precise identity and quantity of individual purines in most foods, especially when cooked or processed (1,7). Ingested purine precursors go though steps in digestion, including (1) the breakdown of nucleic acids into nucleotides by pancreatic nucleases; (2) breakdown of oligonucleotides into simple nucleotides by phosphodiesterases; and (3) removal of phosphate and sugar groups from nucleotides by pancreatic and mucosal enzymes. The addition of dietary purines to purine-free dietary protocols has revealed a variable increase in blood uric acid, depending on the formulation and dose of purines administered (1,7). For example, RNA has a greater effect than an equivalent amount of DNA; ribomononucleotides a greater effect than nucleic acid; and adenine a greater effect than guanine.

A large prospective study showed that men in the highest quintile of meat intake had a 41% higher risk of gout compared with those in the lowest quintile, and that men in the highest quintile of seafood intake had a 51% higher risk compared with those in the lowest quintile (7). In a representative sample of US men and women, higher levels of meat and seafood consumption were associated with higher serum uric acid levels. The variation in the risk of gout associated with different purine-rich foods may be explained by varying amounts and type of purine content and their bioavailability for purine to uric acid metabolism. At the practical level, these data suggest that dietary purine restriction in patients with gout or hyperuricemia (8) may be applicable to purines of animal origin but not to purine-rich vegetables, which are excellent sources of protein, fiber, vitamins, and minerals. Similarly, implications of these findings for dietary recommendation for patients with

FIGURE 12B-1

Dietary influences on the risk for gout and their implications within a Healthy Eating Pyramid. Data on the relationship between diet and the risk for gout are primarily derived from the recent Health Professionals Follow-Up Study. Upward solid arrows denote an increased risk for gout, downward solid arrows denote a decreased risk, and horizontal arrows denote no influence on risk. Broken arrows denote potential effect but without prospective evidence for the outcome of gout. (Adapted from Choi HK, et al. Ann Intern Med 2005;143:499–516, with permission from *Annals of Internal Medicine*.)



hyperuricemia or gout are generally consistent with a new Healthy Eating Pyramid, except for fish intake (Figure 12B-1) (1). The use of plant-derived omega-3 fatty acids or supplements of eicosapentaenoic acid and docosahexaenoic acid in place of fish consumption could be considered to provide the benefit of these fatty acids without increasing the risk of gout.

Urate Production Pathways and Inborn Errors of Metabolism

The steps in the urate production pathways implicated in the pathogenesis of hyperuricemia and gout are displayed in Figure 12B-2. The vast majority of patients with endogenous overproduction of urate have the condition as a result of *salvaged* purines arising from increased cell turnover in proliferative and inflammatory disorders (e.g., hematologic malignancies and psoriasis); pharmacologic intervention resulting in increased urate production (e.g., chemotherapy); or tissue hypoxia. Only a small fraction of those with urate overproduction (10%) have an inborn error of metabolism such as superactivity of 5´-phosphoribosyl 1-pyrophosphate (PRPP) synthetase or deficiency of hypoxanthine-guanine phosphoribosyl transferase (HPRT; Figure 12B-2) (2,7,9).

Mutations in the PRPP synthetase genes can result in overactivity of the pathway. Superactivity of PRPP synthetase leads to increased rate of PRPP, purine nucleotide, and urate production, in association with gout and urate urolithiasis. Mutations in the gene encoding HPRT are associated with a spectrum of disease that ranges from hyperuricemia alone to hyperuricemia with profound neurological and behavioral dysfunction (Lesch–Nyhan syndrome) (2,7,9) Hypoxanthine cannot be reutilized without HPRT, and can only be degraded to urate. Both the underutilization of PRPP and decrease in inosine monophosphate and guanosine monophosphate levels in the salvage pathway contribute to hyperuricemia by feedback inhibition on de novo purine synthesis (Figure 12B-2) (2,7,9). Because both of these enzyme defects are X-linked traits, homozygous males are affected. In addition, postmenopausal gout and urinary tract stones can occur in carrier females. Hyperuricemia in prepubertal boys always suggests one of these enzymatic defects (2).

Alcohol and Gout

Conditions associated with net adenosine triphosphate (ATP) degradation lead to accumulation of adenosine diphosphate (ADP) and adenosine monophosphate (AMP), which can be rapidly degraded to uric acid, leading to hyperuricemia (Figure 12B-2, Table 12B-1). Examples of this include acute, severe illnesses such as the adult respiratory distress syndrome, myocardial infarction, or status epilepticus, in which tissue hypoxia impairs the mitochondrial synthesis of ATP from ADP. Another example relates to alcohol consumption. Ethanol administration increases uric acid production by net ATP degradation to AMP. Decreased urinary excretion associated with dehydration and metabolic

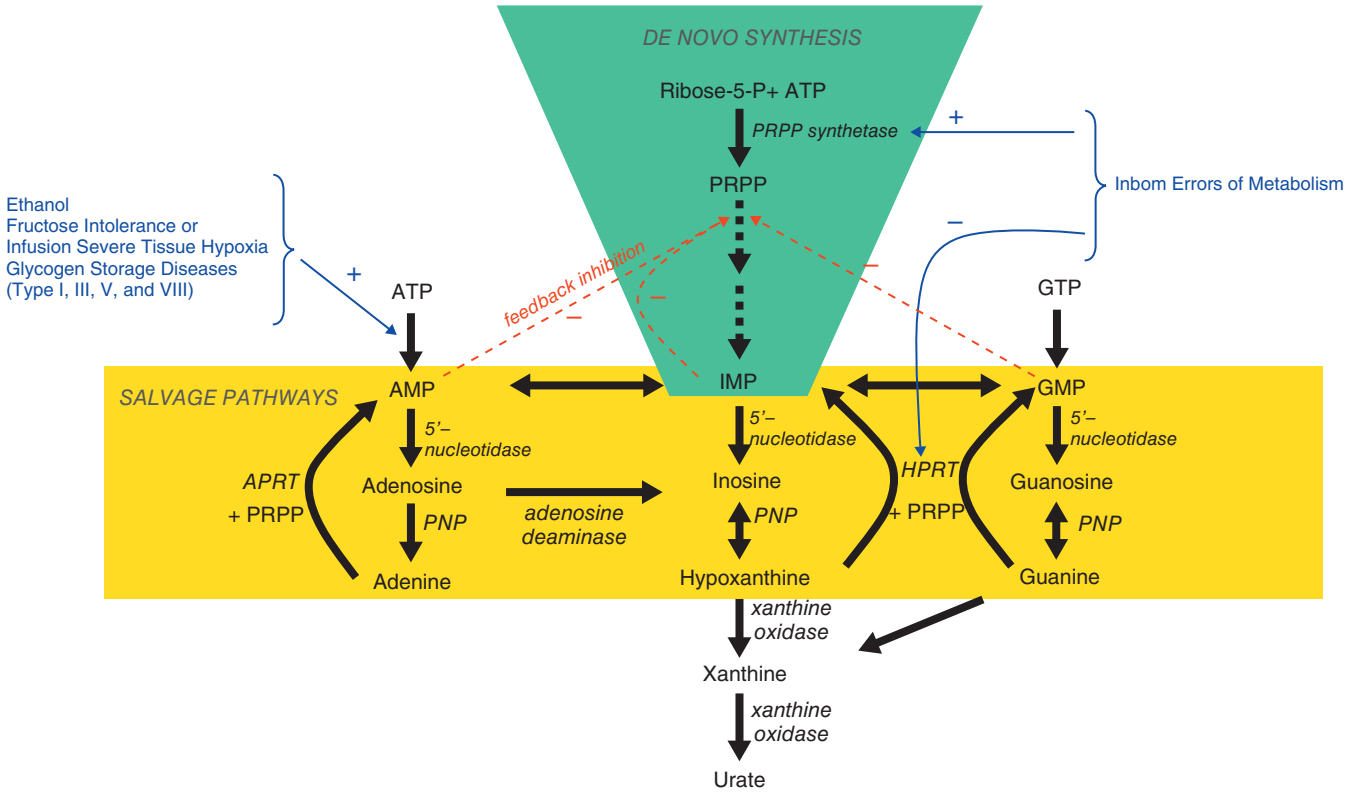


FIGURE 12B-2

Urate production pathways implicated in the pathogenesis of hyperuricemia and gout. The de novo synthesis starts with 5′-phosphoribosyl 1-pyrophosphate (PRPP), which is produced by addition of a further phosphate group from adenosine triphosphate (ATP) to the modified sugar ribose-5-phosphate. This step is performed by the family of PRPP synthetase (PRS) enzymes. In addition, purine bases derived from tissue nucleic acids are reutilized through the salvage pathway. The enzyme hypoxanthine-guanine phosphoribosyl transferase (HPRT) salvages hypoxanthine to inosine monophosphate (IMP) and guanine to guanosine monophosphate (GMP). Only a small proportion of patients with urate overproduction have the well-characterized inborn errors of metabolism, such as superactivity of PRS and deficiency of HPRT. Furthermore, conditions associated with net ATP degradation lead to the accumulation of adenosine diphosphate (ADP) and adenosine monophosphate (AMP), which can be rapidly degraded to uric acid. These conditions are displayed in left upper corner. Plus sign denotes stimulation, and minus sign denotes inhibition. Abbreviations: APRT, adenine phosphoribosyl transferase; PNP, purine nucleotide phosphorylase. (Adapted from Choi HK, et al. Ann Intern Med 2005;143:499–516, with permission from *Annals of Internal Medicine*.)

acidosis also may contribute to the hyperuricemia associated with ethanol ingestion. A prospective study confirmed the dose–response relationships between ethanol consumption, uric acid levels, and risk of gout (9).

The same study found that the risk of gout varies according to type of alcoholic beverage: beer confers a larger risk than liquor, whereas moderate wine drinking did not increase the risk (9). These findings suggest that certain nonalcoholic components within alcoholic beverages play an important role in urate metabolism. The effect of purines ingested from beer on blood uric acid may be sufficient to augment the hyperuricemic effect of alcohol itself, producing a greater risk of gout than liquor or wine (9).

Adiposity, Insulin Resistance, and Hyperuricemia

An increased adiposity and the insulin resistance syndrome are both closely associated with hyperuricemia (10). Whereas body mass index, waist-to-hip ratio, and weight gain are all associated with gout in men (11), weight reduction is associated with a decline in urate levels and risk of gout. Weight reduction leads to lower de novo purine synthesis and lower serum urate levels. Exogenous insulin can reduce the renal excretion of urate in both healthy and hypertensive subjects, thus providing an additional link between adiposity, insulin resistance, type II diabetes, and gout. Insulin may

TABLE 12B-1. CAUSES OF HYPERURICEMIA AND URATE-LOWERING AGENTS.

Causes of hyperuricemia
Uric acid overproduction
Inherited enzyme defects
HGRT deficiency, PRPP synthetase overactivity
Increased cell turnover
Myeloproliferative and lymphoproliferative disorders, polycythemia vera, malignant diseases, hemolytic diseases, psoriasis
Purine-rich foods
Obesity
Accelerated ATP degradation
Ethanol, fructose, severe tissue hypoxemia or muscle exertion, glycogen storage diseases (types I, III, V, and VII)
Urate Increasing Agents
Cytotoxic drugs, warfarin, vitamin B12 (patients with pernicious anemia), ethylamino-1,3,4-thiadiazole, 4-amino-5-imidazole carboxamide riboside
Uric acid underexcretion
Clinical disorders associated with uric acid underexcretion
Renal failure, hypertension, metabolic syndrome, obesity
Certain nephropathy
Lead nephropathy, polycystic kidney disease, medullary cystic kidney disease, familial juvenile hyperuricemic nephropathy
Agents increasing urate reabsorption through trans-stimulation of URAT1
Pyrazinamide, salicylate (low dose), nicotinate, lactate, beta-hydroxybutyrate, acetoacetate
Agents decreasing renal urate excretion, maybe through URAT1 or other mechanisms
Diuretics, ethambutol, insulin, beta-blockers
Urate Lowering Agents
Inhibition of xanthine oxidase
Allopurinol, febuxostat
Uricase
Agents decreasing urate reabsorption through direct inhibition of URAT1
Probenecid, sulfinpyrazone, benzbromarone, losartan, salicylate (high dose)
Uricosuric agents, maybe through inhibition of URAT1 or other mechanisms
Amlodipine, fenofibrate, vitamin C, estrogen, angiotensin II, parathyroid hormone

ABBREVIATIONS: ATP, adenosine triphosphate; HGRT, hypoxanthine-guanine phosphoribosyl transferase; PRPP, 5′-phosphoribosyl 1-pyrophosphate; URAT1, urate transporter-1.

enhance renal urate reabsorption via stimulation of urate–anion exchanger URAT1 (12) and/or the Na^+-dependent anion cotransporter in brush border membranes of the renal proximal tubule. Some investigators have suggested that leptin and increased adenosine levels may contribute to hyperuricemia. The epidemic of obesity and the insulin resistance syndrome thus presents a substantial challenge in the prevention and management of gout.

RENAL TRANSPORT OF URATE

Renal urate transport follows a four-component model: (1) glomerular filtration, (2) nearly complete reabsorption of the filtered urate, (3) subsequent secretion, and (4) postsecretory reabsorption in the remaining proximal tubule (1). The molecular target for uricosuric agents, an anion exchanger responsible for the reabsorption of filtered urate by the renal proximal tubule, was identified recently (1,11). The authors searched the human genome database for novel gene sequences within the organic anion transporter (OAT) gene family and identified URAT1 (SLC22A12), a novel transporter expressed at the apical brush border of the proximal nephron (11). Urate–anion exchange activity similar to that of URAT1, initially described in brush border membrane vesicles (BBMV) from urate-reabsorbing species such as rats and dogs, was subsequently confirmed in human kidneys (1). *Xenopus* oocytes injected with URAT1-encoding RNA transport urate and exhibit pharmacological properties consistent with data from human BBMV (11). These and other experiments indicate that uricosuric compounds (e.g., probenecid, benzbromarone, sulfinpyrazone, and losartan) directly inhibit URAT1 from the apical side of tubular cells (cis-inhibition). In contrast, anti-uricosuric substances (e.g., pyrazinoate, nicotinate, lactate, pyruvate, beta-hydroxybutyrate, and acetoacetate) serve as the exchanging anion from inside cells, thereby stimulating anion exchange and urate reabsorption (trans-stimulation) (Table 12B-1).

Urate transporter-1 is crucial for urate homeostasis: a handful of patients with renal hypouricemia were shown to carry loss-of-function mutations in the human *SLC22A12* gene encoding URAT1, indicating that this exchanger is essential for the proximal tubular reabsorption (12). Furthermore, pyrazinamide, benzbromarone, and probenecid failed to affect urate clearance in subjects with homozygous loss-of-function mutations in *SLC22A12*, indicating that URAT1 is essential for the effect of both anti-uricosuric and uricosuric agents.

Anti-uricosuric agents exert their effect by stimulating renal reabsorption rather than inhibiting tubular secretion (1). The mechanism appears to involve a priming of renal urate reabsorption, via the Na^+-dependent loading of proximal tubular epithelial cells with anions capable of a trans-stimulation of urate reabsorption. A transporter in the proximal tubule brush border mediates Na^+-dependent reabsorption of pyrazinoate, nicotinate, lactate, pyruvate, beta-hydroxybutyrate, and acetoacetate, all of which are monovalent anions that are also substrates for URAT1 (1). Increased plasma concentrations of these antiuricosuric anions result in their increased glomerular filtration and greater

reabsorption by the proximal tubule. The augmented intra-epithelial concentrations, in turn, induce the reabsorption of urate by promoting the URAT1-dependent anion exchange of filtered urate (trans-stimulation).

Urate reabsorption by the proximal tubule thus exhibits a form of *secondary* Na^+ dependency, in that Na^+-dependent loading of proximal tubular cells stimulates brush border urate exchange. Urate itself is not a substrate for the Na^+–anion transporter. The molecular identity of the relevant Na^+-dependent anion cotransporter(s) remains unclear. However, a leading candidate gene is *SLC5A8*, which encodes a Na^+-dependent lactate and butyrate cotransporter (1). The SLC5A8 protein may also transport both pyrazinoate and nicotinate, potentiating urate transport in *Xenopus* oocytes that co-express URAT1 (1).

The anti-uricosuric mechanism explains the long-standing clinical observations that hyperuricemia is induced by increases in beta-hydroxybutyrate and acetoacetate in diabetic ketoacidosis, lactic acid in alcohol intoxication, or nicotinate and pyrazinoate in niacin and pyrazinamide therapy, respectively (Table 12B-1). Urate retention is provoked also by a reduction in extracellular fluid volume and by excesses of angiotensin II, insulin, and parathyroid hormone. URAT1 and the Na^+-dependent anion cotransporter(s) may be targets for these stimuli (Table 12B-1).

Certain anions that interact with URAT1 have the dual potential to either increase or decrease renal urate excretion, through either trans-stimulation or cis-inhibition of apical urate exchange in the proximal tubule (1). For example, a low concentration of pyrazinoate stimulates urate reabsorption through trans-stimulation. A higher concentration, in contrast, reduces urate reabsorption via extracellular cis-inhibition of URAT1. Biphasic effects on urate excretion, that is, anti-uricosuria at low dose and uricosuria at high dose, are also well described for salicylate (1). Salicylate cis-inhibits URAT1, explaining the high dose uricosuric effect; low anti-uricosuria reflects a trans-stimulation of URAT1 by intracellular salicylate, which is evidently a substrate for the Na^+–pyrazinoate transporter.

PATHOLOGY OF GOUT

Neutrophilic synovitis is the hallmark of acute gouty attack. Acute gouty synovitis shows diffuse superficial and perivascular infiltration with polymorphonuclear leukocytes in the synovium, as well as exudate containing polymorphonuclear neutrophilic leukocytes and fibrin adhering to the synovial surface (13). Some proliferation of synovial cells and infiltration of lymphocytes, macrophages, and occasional plasma cells have also been observed during the acute gouty synovitis.

The tophus represents the most characteristic lesion of gout and can be found in the synovium as well as elsewhere (13). Crystals in the tophi in synovium and elsewhere are needle shaped and often are arranged radially in small clusters. The histopathology of tophi shows foreign body granulomas surrounding a core of amorphous mass or monosodium urate (MSU) crystals by mono- and multinucleated macrophages, fibroblasts, and lymphocytes. Other components of tophi include lipids, mucopolysaccharides, and plasma proteins. At least in some cases, tophi in the synovium have been observed at the time of first gouty attack (13). These synovial tophi often lie near the joint surface and are weakly encapsulated so that minor trauma or changes in the crystal equilibrium within the tophus would likely allow release of crystals into the joint to precipitate attacks (13).

URATE CRYSTAL–INDUCED INFLAMMATION

Urate crystals in joint fluid at the time of the acute attack may derive from rupture of preformed synovial deposits or precipitate de novo (2). However, the finding of crystals in synovial fluids of asymptomatic joints illustrates that factors other than the presence of crystals are important in modulating the inflammatory reaction (14).

Urate crystals initiate, amplify, and sustain intense inflammatory attacks by stimulating the synthesis and release of humoral and cellular mediators (1,2). Urate crystals interact with the phagocyte through two broad mechanisms. First, they activate the cells through opsonized and phagocytosed particles, eliciting a stereotypical phagocyte response of lysosomal fusion, respiratory burst, and release of inflammatory mediators. The other mechanism involves the particular properties of the urate crystal to interact directly with lipid membrane and proteins via cell membrane perturbation and cross-linking of membrane glycoproteins in the phagocyte. This interaction leads to the activation of several signal transduction pathways including G proteins, phospholipase C and D, Src tyrosine kinases, the mitogen-activated protein kinases ERK1/ERK2, 9c-Jun N-terminal kinase, and p38 mitogen-activated protein kinase (1,2). These steps are critical for crystal-induced interleukin (IL) 8 expression in monocytic cells, which plays a key role in the neutrophil accumulation (1,2). Recently, innate immune responses involving Toll-like receptors (TLR) 2 and 4 have been implicated in the chondrocyte and macrophage signaling (14). Furthermore, induction of triggering receptor expressed on myeloid cells 1 (TREM-1) has been implicated as another potential mechanism for the early, induced innate immune response to amplification of acute gouty inflammation (15).

Animal models of gout indicate that whereas monocytes and mast cells participate during the early phase of inflammation, neutrophilic infiltrates occur later (1). Macrophages from noninflamed joints may contain urate crystals (1). The state of differentiation of mononuclear phagocytes determines whether or not the crystals will trigger an inflammatory response. In undifferentiated monocytes, induction of proinflammatory cytokines [tumor necrosis factor alpha (TNF-alpha), IL-1 beta, IL-6, IL-8, and cyclooxygenase-2 (COX-2)] and endothelial cell activation occur after urate crystal phagocytosis. In contrast, well-differentiated macrophages failed to induce these cytokines or activate endothelial cells. These findings suggest that monocytes play a central role in stimulating an acute attack of gout. Conversely, differentiated macrophages play an anti-inflammatory role, helping to terminate acute attacks and restore the asymptomatic state (1). Furthermore, animal models of gout suggest that mast cells are involved in the early phase of crystal-induced inflammation. In response to C3a, C5a, and IL-1, mast cells release histamine and other inflammatory mediators (1). The vasodilatation, increased vascular permeability, and pain so characteristic of gout are also mediated by kinins, complement cleavage peptides, and other vasoactive prostaglandins.

Neutrophilic–endothelial cell interaction leading to neutrophilic influx, a central event in gouty inflammation, provides the basis for the pharmacologic effect of colchicine. Neutrophil influx is believed to be promoted by endothelial–neutrophil adhesion, triggered by IL-1, TNF-alpha, IL-8, the neutrophil chemoattractant protein-1 (MCP-1), and other cytokines and chemokines (1). Neutrophil migration involves neutrophilic–endothelial interaction mediated by cytokine-induced E-selectin clustering on endothelial cells. Colchicine interferes with the interactions by altering the number and distribution of selectins on endothelial cells and neutrophils (15).

Once in the synovial tissue, the neutrophils follow concentration gradients of chemoattractants such as C5a, leukotriene B4, platelet activating factor, IL-1, and IL-8 (1). Among these factors, IL-8 and growth-related gene chemokines play a central role in neutrophil invasion (16). For example, IL-8 alone accounts for approximately 90% of the neutrophil chemotactic activity of human monocytes in response to urate crystals. Neutralization of IL-8 or its receptor therefore offers a potential therapeutic target in gout. Several other neutrophil chemotactic factors, including the calgranulin family members S100A8 and S100A9, are also involved in neutrophil migration induced by urate crystals.

Several processes contribute to the self-limited nature of acute gout. Clearance of urate crystals by differentiated macrophages in vitro has been linked to inhibition of leukocyte and endothelial activation. Neutrophil apoptosis and other apoptotic cell clearance represent a fundamental mechanism in the resolution of acute inflammation. Transforming growth factor beta, abundant in acute gouty synovial fluid, inhibits IL-1 receptor expression and IL-1–driven cellular inflammatory responses (1). Furthermore, urate crystals can induce peroxisome proliferator-activated receptor-gamma receptor (PPAR-gamma) expression in human monocytes, promoting neutrophil and macrophage apoptosis. Similarly, upregulation of IL-10 expression has been shown to limit experimental urate-induced inflammation and may function as a native inhibitor of gouty inflammation. Inactivation of inflammatory mediators by proteolytic cleavage, cross-desensitization of receptors for chemokines, release of lipoxins, IL-1 receptor antagonist, and other anti-inflammatory mediators may all facilitate the resolution of the acute gout. The entry of large molecules such as apolipoprotein B and E, and other plasma proteins into the synovial cavity due to increased vascular permeability also would contribute to the spontaneous resolution (1).

Chronic gouty arthritis typically occurs after years of gout. Cytokines, chemokines, proteases, and oxidants involved in urate crystal–induced inflammation also contribute to the chronic inflammation, leading to chronic synovitis, cartilage loss, and bone erosion (1). Low rade synovitis may persist in involved joints with ongoing intra-articular phagocytosis of crystals by leukocytes even during the remissions of acute flares (13). Tophi on the cartilage surface observed through arthroscopy may contribute to chondrolysis despite adequate treatment of both hyperuricemia and acute gouty attacks (1). Adherent chondrocytes phagocytize microcrystals and produce active metalloproteinases. Furthermore, crystal–chondrocyte cell membrane interactions can trigger chondrocyte activation, gene expression of IL-1 beta and inducible nitric oxide synthase, nitric oxide release, and matrix metalloproteinases, leading to cartilage destruction (17). The crystals can also suppress the 1,25-dihydroxycholecalciferol–induced activity of alkaline phosphatase and osteocalcin. Thus, crystals can alter the osteoblast phenotype by reducing their anabolic effects that may contribute to damage to the juxta-articular bone (1).

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CHAPTER 12

Gout
C. Treatment

ROBERT A. TERKELTAUB, MD

- The three major considerations on comprehensive gout therapy include: (1) the treatment of acute flares; (2) management of the complications of chronic tophaceous gout; and (3) prophylaxis through urate-lowering agents designed to prevent disease flares and long-term sequelae.
- In the absence of contraindications, nonsteroidal anti-inflammatory drugs (NSAIDs) are considered first-line therapy for acute gout.
- Systemic glucocorticoids, also effective therapy for acute gout, are very useful for patients in whom NSAIDs are contraindicated.
- Intra-articular glucocorticoid injections may be effective if only one or two joints are affected by acute gout.
- Colchicine (generally 0.6 mg once or twice daily) is an appropriate therapy for prophylaxis against recurrent gout flares.
- The two standard urate-lowering therapies are allopurinol (most popular) and the uricosuric agents, for example, probenecid.
- Asymptomatic hyperuricemia does not require treatment.
- The dose of allopurinol must be decreased in the setting of renal insufficiency.
- Febuxostat, a relative newcomer to gout therapy, also achieves its effects through the inhibition of xanthine oxidase, albeit through a different mechanism than allopurinol.

Gout management involves two primary components: (1) treatment and prophylaxis of acute joint and bursal inflammation and (2) lowering of serum urate levels with the objectives of avoiding recurrent, painful inflammatory flares, suppressing progression of joint damage, and preventing the occurrence of urolithiasis. All too often, current strategies for treating gouty arthritis and lowering urate levels are based more on practitioner preferences than on evidence-based medicine (1).

MANAGEMENT OF ACUTE GOUTY ARTHRITIS

Choices for both anti-inflammatory and antihyperuricemic therapy in gout are reviewed below.

Nonsteroidal Anti-Inflammatory Drugs and Other Analgesic Agents

The primary goal in treatment of acute gout is rapid, safe resolution of pain and functional incapacity. Because acute gout attacks are self-limited, results of clinical trials for this condition warrant careful consideration. Nonsteroidal anti-inflammatory drugs (NSAIDs) typically produce major symptom reduction within 24 hours. In the absence of contraindications, NSAIDs are considered first-line therapy for acute gout. No specific NSAID has clear superiority over others in the treatment of gout. Ibuprofen in full doses (e.g., 800 mg q.i.d.), for example, is as likely to be effective as indomethacin (50 mg t.i.d.). Unfortunately, NSAID gastrointestinal and renal toxicity are major concerns in many patients. The comparable efficacy of etoricoxib

and indomethacin in a head-to-head comparison in acute gout (2) suggests that selective cyclooxygenase-2 (COX-2) inhibition provides an alternative approach when nonselective COX inhibitors are contraindicated in the acute setting. However, cardiac safety of selective COX-2 inhibitors remains controversial. Opiates are useful adjuncts for analgesia early in acute gout treatment, though this has not been evaluated in controlled clinical trials (1).

Glucocorticosteroids and Adrenocorticotrophic Hormone

Glucocorticosteroids (systemic or local) and adrenocorticotrophic hormone (ACTH) are reliably effective second-line treatments for acute gout. These drugs also are limited by the potential for toxicity, particularly the exacerbation of hyperglycemia. Relatively large doses of systemic glucocorticosteroids often are required to treat acute gout effectively, particularly when the arthritis is polyarticular or when it affects a large joint such as the knee. A typical regimen in such a scenario would be prednisone, initiated at 30 to 60 mg/day (perhaps in divided doses), with a steady taper to discontinuation over 10 to 14 days. The use of a tapering oral methylpredisolone dose package regimen has not yet been systematically evaluated for acute gout. The effectiveness of intra-articular injection of a depot glucocorticosteroid ester for gout affecting one or two large joints has been supported by small, open-label studies (1).

Synthetic ACTH appears to be effective within hours for acute oligoarticular and polyarticular gout and was superior to indomethacin in acute gout treatment in one controlled clinical trial (1). A controlled study of patients with acute gout suggested that systemic anti-inflammatory doses of glucocorticosteroids and ACTH have comparable effectiveness (1). Peripheral anti-inflammatory effects of ACTH mediated by melanocortin receptor 3 activation, preceding induction of adrenal glucocorticosteroid release, could be responsible for the rapidity of ACTH efficacy in acute gout. ACTH is relatively expensive, however, and is not universally available. Primary treatment of acute gout with systemic glucocorticosteroids or ACTH also can be associated with rebound arthritis flares. Therefore, initiation of low dose prophylactic colchicine simultaneously with systemic glucocorticosteroids or ACTH is often useful as an adjunctive treatment.

Colchicine

Colchicine, administered either orally or intravenously, was once a standard approach to the treatment of acute gout attacks. Colchicine is no longer recommended for the treatment of acute gout flares, however, because of the length of time required for oral colchicine to suppress an attack and the narrow therapeutic window and high potential for serious toxicities associated with intravenous colchicine. In nearly all patients, NSAIDs, glucocorticoids, or ACTH provide better options for the treatment of acute gout. As discussed below, colchicine continues to play a major role in the prophylaxis against gout attacks.

Prophylactic Therapy for Acute Gouty Arthritis

Low dose colchicine (i.e., 5 or 6 mg p.o. once or twice daily) is a highly appropriate choice for prophylaxis of recurrent acute gout (1). Although colchicine is not a potent anti-inflammatory agent, the medication is particularly effective for prophylaxis against gout and calcium pyrophosphate dehydrate deposition disease (CPPD) crystal-induced inflammation. Even low concentrations of colchicine modulate neutrophil adhesion to the endothelium (3). High concentrations of colchicine suppress urate crystal-induced activation of the NALP3 inflammasome (4). It is less clear that low dose NSAIDs work reliably for gout prophylaxis.

Gouty arthritis is a particularly common event in the first few months after initiation of uric acid–lowering treatment. Standard clinical practice is to prescribe daily oral colchicine (0.6 mg p.o. bid in patients with intact renal function) for the first 6 months of antihyperuricemic therapy. The dosage of low dose prophylactic colchicine should be lowered in the presence of renal dysfunction and with age over 70 (1). Even so, caution is needed, as low dose daily colchicine may be associated with severe toxicities, including neuromyopathy and bone marrow suppression. Concurrent treatment with erythromycin, statin drugs, gemfibrozil, and cyclosporine predispose to colchicine toxicity by altering colchicine elimination (1). Because colchicine is not dialyzable, it should not be employed in dialysis-dependent renal failure (1).

Uric Acid Lowering Approaches

The decision to initiate antihyperuricemic therapy in gout requires thoughtful consideration, as antihyperurcemic agents have multiple potential drug interactions and toxicities. Gout does not always progress in the absence of urate-lowering therapy, and in some patients serum urate levels can be normalized through lifestyle changes, without antihyperuricemic drugs. Lifestyle alterations that may affect urate levels include cessation of alcohol abuse, weight reduction, and the replacement of thiazide diuretics with another class of antihypertensive agent. Conventional purine-restricted diets are unpalatable and only modestly effective in lowering serum urate. A palatable, calorie-restricted, low carbohydrate diet tailored to improve insulin sensitivity appears

to diminish hyperuricemia by 15% to 20% (5). Other dietary measures, such as specifically limiting beer consumption and increasing low fat dairy product consumption, merit further direct investigation.

Pharmacologic Antihyperuricemic Treatments

The two major indications for chronic uric acid–lowering therapy in gout are macroscopic subcutaneous tophi and unacceptably frequent attacks of gouty arthritis (e.g., three or more per year). Standard practice is to delay initiating uric acid–lowering treatment until resolution of the inflammatory phase of acute gout. This practice is due to concern that antihyperuricemic therapy could worsen acute gout by mobilizing urate crystals from remodeling microscopic and macroscopic tophi. Precipitation of acute gout through this mechanism is a common side effect in the first few months after initiation of antihyperuricemic therapy (1,6).

The currently available pharmacotherapies for serum urate lowering are: (1) allopurinol, a xanthine oxidase inhibitor, which reduces uric acid production; or (2) uricosuric agents (exemplified by probenecid), which increase renal uric acid excretion. Probenecid and other uricosurics act through inhibition of the organic anion exchanger URAT1 in the proximal renal tubule, thereby inhibiting urate reabsorption.

In traditional evaluations of gout, patients were divided into two groups on the basis of 24-hour urine uric acid exretion results: uric acid overproducers and underexcreters. Overproducers—the great majority of gout patients—have been defined as those gout patients whose daily urinary uric acid excretion exceeds 800 mg. Unfortunately, such urine collections are inconvenient to patients, prone to inaccuracy, and may fail to identify combined uric acid overproduction and underexcretion. Moreover, 24-hour urine collections fail to identify uric acid overproduction reliably in subjects with creatinine clearances <60 mL/min. Measurement of uric acid in spot urine samples does not distinguish reliably between uric acid overproduction from underexcretion (1). Thus, in practice, the usual approach to therapy once the need for urate-lowering therapy is determined is allopurinol, regardless of the 24-hour uric acid excretion measurement. Twenty-four–hour urine uric acid collections may be used to screen for uric acid overproduction in the absence of an obvious cause of hyperuricemia such as renal failure, diuretic use, or myeloproliferative disease. This test is particularly useful in subjects presenting with gout before the age of 30 or with gout and a history of urolithiasis. The optimal target level for serum urate reduction is held to be below 6.0 mg/dL, given that this is approximately 1 mg/dL lower than the level of urate solubility in physiologic solutions in vitro. Standard clinical practice is to achieve this level of serum urate lowering via gradual escalation of antihyperuricemic drug dosages over the first few months of therapy (1). However, lowering serum urate to levels above 6.0 mg/dL is associated with at least partial clinical efficacy in many patients. Allopurinol and uricosuric therapy promote shrinkage of tophi at similar rates when serum urate is also diminished to a similar level.

Allopurinol is the most frequently used antihyperuricemic agent among practitioners, due to the convenient single daily dosing and the generally predictable efficacy of allourinol irrespective of etiology of the hyperuricemia in gout (1). The usual starting dose of allopurinol for most patients should be on the order of 100 mg/day (lower for patients with renal insufficiency, possibly higher for young patients with normal renal function). This dose is titrated upward over a period of several weeks according to the serum uric acid level. Doses of up to 300 mg/day and even higher may be used. A broad issue limiting effective allopurinol use appears to be poor patient compliance, which challenges practitioners to educate patients better regarding the long-term objectives of antihyperuricemic therapy.

Side effects of allopurinol include minor hypersensitivity reactions such as pruritus and dermatitis, which occur in approximately 2% of patients (1). Approximately half of the patients with such minor reactions have been reported to be desensitized successfully in small, open-label studies (1). However, allopurinol toxicity, including hepatic damage and major hypersensensitivity reactions, can become severe. A mortality rate of ~20% is seen with the allopurinol major hypersensitivity syndrome, which is dose dependant and typically manifests as severe dermatitis, accompanied by features including vasculitis, fever, eosinophilia, hepatic and renal dysfunction (1). Renal insufficiency and possibly concomitant thiazide therapy are predisposing factors for the severe allopurinol hypersensitivity syndrome. In Han Chinese, human leukocyte antigen (HLA)-B5801 is strongly linked to severe allopurinol cutaneous hypersensitivity (7). Fortunately, major allopurinol hypersensitivity syndrome is uncommon and it is believed that adjusting the initial daily dose of allopurinol in direct proportion to creatinine clearance may reduce the risk of developing this drug toxicity (1). Overly aggressive attempts to bring serum urate below 6.0 mg/dL with allopurinol may be hazardous in subjects with advanced renal insufficiency because of dose-dependent toxicities of allopurinol.

When a uricosuric agent is required (e.g., in the setting of allopurinol hypersensitivity), probenecid is usually the agent of choice. Probenecid increases renal uric acid clearance and can be employed effectively for patients with substantially decreased renal uric acid

excretion but creatinine clearance ≥60 mL/min (1). Uricosuric agents require good renal function in order to be effective. Probenecid is started at a dosage of 500 mg twice daily and titrated upward to a maximum dosage of 1 g twice daily (or until the target serum uric acid level is achieved). Subjects taking probenecid are at increased risk for uric acid urolithiasis and should be compliant and able to consume at least 2 L of fluid orally on a daily basis to reduce urolithiasis risk. Low dose acetylsalicylic acid, which reduces renal uric acid excretion, does not appear to significantly block the antihyperuricemic activity of probenecid. Other potent uricosuric agents include sulfinpyrazone and benzbromarone, but these drugs are limited by toxicity and are not universally available (1). Less potent uricosuric agents include the angiotensin 1 (AT1) receptor antagonist losartan, and the lipid-lowering agents atorvastatin and fenofibrate. Among these three agents, fenofibrate has the greatest capacity to decrease serum urate levels. The uricosuric effect of losartan appears to have limited sustainability. Use of losartan, atorvastatin, and fenofibrate as a serum urate-lowering primary or adjunctive approach may have potential for selected patients with moderate hyperuricemia associated with gout and comorbid conditions such as hypertension, metabolic syndrome, and hyperlipidemia. However, the place in management of these agents is not yet established and uric acid urolithiasis is a risk as with other uricosuric modalities.

Considerations Regarding Comorbidities in Patients with Gout and Asymptomatic Hyperuricemia

Implicit in the medical management of gout patients is recognition and appropriate therapy of medical conditions commonly associated with gout that may affect both urate levels and longevity. These conditions include the metabolic syndrome, hyperlipidemia, hypertension, alcohol abuse, renal disorders, and myeloproliferative diseases. Asymptomatic hyperuricemia alone does not appear to cause clinically significant renal disease. However, hyperuricemia is both an independent risk factor for atherosclerosis and a powerful predictor of adverse outcomes of ischemic cardiovascular diseases (8). Serum urate positively correlates with blood pressure in children, and extensive studies in rodents have suggested that hyperuricemia exerts direct, deleterious and pro-atherogenic effects on arterial endothelial and smooth muscle cells, as well as toxic effects on the glomerular microvasculature, renal function, and systemic blood pressure (8). There is no evidence basis to support treatment of asymptomatic hyperuricemia at this time.

Gout in the Patient with Organ Transplantation

A striking example of refractory gout is provided by patients with major organ transplantation. In such patients, cyclopsporine or tacrolimus are critical to the success of the allograft (1). In this condition, nephropathic and renal urate transport–altering effects of cyclosporine or tacrolimus drive the potential for marked hyperuricemia and remarkably accelerated tophi development. Consequently, the diagnosis of transplantation-associated gout nearly always calls for the institution of antihyperuricemic therapy. Low dose cyclosporine microemulsion regimens and ongoing development of cyclosporine-free immunosuppression regimens for major organ transplant recipients should diminish the scope and extent of this iatrogenic condition.

Treatment of Refractory Gout Patients: Current Options and Drugs in Advanced Development

Limitations in antihyperuricemic therapy often become a major clinical problem in subjects. The most common issues are intolerance to allopurinol, renal insufficiency or urolithiasis (rendering uricosuric agents ineffective or contraindicated), and extensive tophi. Several potential new agents for the treatment of gout—oxypurinol, febuxostat, and uricase—are discussed below.

Limitations of allopurinol are not confined to hypersensitivity and other forms of drug intolerance. The major active metabolite of allopurinol, oxypurinol, binds to the reduced form of xanthine oxidase with very high affinity but does not efficiently bind and inhibit the oxidized form of xanthine oxidase. This may contribute to lack of efficacy of allopurinol seen in some patients at doses as high as 300 mg daily (6). Oxypurinol is tolerated in some allopurinol-hypersensitive patients, but the oral absorption of oxypurinol is poor relative to that of allopurinol, and oxypurinol doses may need extended titration to achieve satisfactory reduction of serum urate. Cross-reactivity with allopurinol and dependence on intact renal function for efficient elimination of oxypurinol may further limit the utility of oxypurinol in the treatment of refractory gout in allopurinol-intolerant patients.

Febuxostat, which inhibits xanthine oxidase through a different mechanism than allopurinol and oxypurinol, blocks substrate access to xanthine oxidase by occupying a channel in the enzyme leading to the active site (9). This leads to the potent inhibition of both the oxidized and reduced forms of xanthine oxidase, but has minimal effects on other enzymes involved in purine and pyrimidine metabolism. Furthermore, unlike the

currently available xanthine oxidase inhibitors, febuxostat is metabolized primarily by hepatic glucuronide formation and oxidation and is excreted in approximately equal amounts in stool and urine. The efficacy of febuxostat (80 and 120 mg daily) in serum urate–lowering in gout patients with starting serum urate levels of ≥8.0 mg/dL was superior to that of allopurinol 300 mg daily in a phase III study in which the primary endpoint was the percentage of patients with serum urate level <6.0 mg/dL (6). Nevertheless, after 1 year of treatment, reductions in the incidence of gout flares and in the size of tophi were seen in similar fractions of subjects in all treatment groups (6).

The hepatic enzyme uricase, the expression of which is lacking in human beings, oxidizes relatively insoluble uric acid in a reaction that generates highly soluble allantoin, and also generates the oxidant hydrogen peroxide as well as reactive intermediates of uric acid oxidation. Uricase has the capacity to lower serum urate levels profoundly and to promote accelerated tophus dissolution (debulking). Recombinant unmodified *Aspergillus flavus* uricase (Rasburicase) is US Food and Drug Administration–approved for prevention of the hyperuricemia-mediated tumor lysis syndrome. However, this form of uricase is highly immunogenic and can trigger severe and potentially lethal side effects including anaphylaxis. Administration of unmodified uricase beyond a single, short-term course is limited by hypersensitivity reactions and development of uricase-neutralizing antibodies. Reduced antigenicity and prolonged half-life of uricase activity are being optimized via mutation of specific amino acids in uricase and by polyethyleneglycol (PEG) modification of the recombinant enzyme (10). PEGylated uricase has appeared promising in studies of gout patients, though intravenous infusion may be superior to subcutaneous injection with respect to immunogenicty (10). However, uricase-induced injection or infusion reactions are a concern, as is redox stress. In this context, uricase can induce hemolysis and methemoglobinemia, most predictably so in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Therefore, the therapeutic niche for modified uricases in the treatment of gout will most likely be for the short-term induction of tophus de-bulking in carefully selected patients intolerant or unresponsive to other forms of antihyperuricemic therapy.

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