Gout and Hyperuricemia

Gout is a disease characterized by recurrent episodes of acute joint pain and inflammation resulting from the deposition of uric acid crystals in joint spaces, leading to an inflammatory reaction that causes intense pain, erythema, and joint swelling. Historically, gout has been referred to as the "disease of kings" since it was often associated with rich foods and excessive alcohol consumption. Most gout patients are men (7 to 9 times more often than women); most women with the disease are postmenopausal. Gout has a familial tendency; 10% to 60% of cases occur in family members of patients with the disease.

Pathophysiology

The concentration of uric acid in body depends on the balance between dietary intake, synthesis, and excretion. A defect in the renal clearance of uric acid is the main cause of hyperuricemia and gout (about 90% of patients) and in many cases, this is genetically determined.

Some patients develop gout because they overproduce uric acid. Extreme hyperuricemia can occur because of rapid tumor cell destruction in patients undergoing chemotherapy for certain types of cancer (e.g., leukemias). This phenomenon is known as tumor lysis syndrome (TLS).

When serum uric acid concentrations are above 7 mg/dL, urate crystals are likely to form. Deposition of urate crystals in synovial fluid results in an inflammatory reaction that is associated with intense joint pain, erythema, warmth, and swelling.

Uric acid nephrolithiasis (stone) occurs in 10% to 25% of patients with gout. Tophi (urate deposits) are uncommon and are a late complication of hyperuricemia. The most common sites of tophi deposits are the base of the great toe, the helix of the ear, knees, wrists, and hands.

Another important point to remember in regard to the pathophysiology of Gout is that the solubility of uric acid decreases in cold weather and under low pH conditions. This most likely accounts for why gout primarily affects the joints of the extremities (big toe), particularly when the weather is cold.

Risk Factors

Obesity, hypertension, hyperlipidemia, diabetes, and alcohol abuse are often associated with hyperuricemia and gout.

Clinical manifestations

Asymptomatic hyperuricemia:

Characterized by an elevated serum uric acid level, but without evidence of urate deposition (arthritis). Most patients as many as two-thirds of patients remain asymptomatic. Asymptomatic Hyperuricemia usually does not require treatment.

Acute gouty attack:

The initial attack is abrupt, usually occurring at night or in the early morning as synovial fluid is reabsorbed. Most cases of (first attacks) are monoarticular (one joint only is affected). Acute attacks more commonly involve the joints of the lower extremities. The joint at the base of the big toe is classically affected.

Acute attacks of gouty arthritis are characterized by:

A- Severe pain, often described as the 'worst pain ever'.

B-The affected joints typically become hot, swollen, erythematous and extremely tender such that the patient is unable to wear a sock or to let bedding rest on the joint.

Some people never have a second episode after an acute attack. In others, several years may elapse before the next attack. In many, however, a second attack occurs within 1 year. This period shortens in untreated patients.

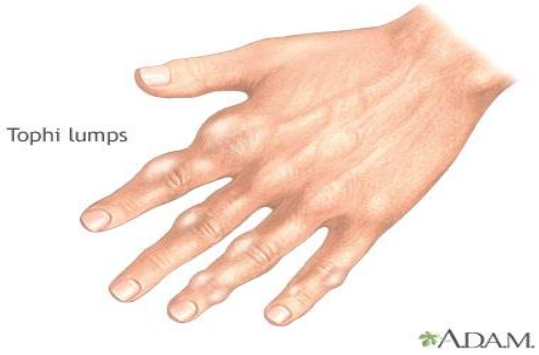
Chronic tophaceous gout

Crystals may be deposited in the joints and soft tissues to produce irregular firm nodules called tophi (aggregations of urate crystals). It appears clinically as firm nodules or swellings with a shiny, yellowish appearance of the overlying skin.

Tophi can occur at any site, with the most common being the fingers or toes, the elbow usually suffered with gout for at least 10 years before tophi develop.

Gouty nephropathy

resulting in acute renal failure or urate stone formation.
Uric acid nephrolithiasis (renal stone) occurs in 10% to 25% of patients with gout.



Diagnosis

A definitive diagnosis requires aspiration of synovial fluid from the affected joint and identification of intracellular crystals of monosodium urate monohydrate in synovial fluid leukocytes. When joint aspiration is not a viable option, the diagnosis of acute gouty arthritis is based on the presence of the characteristic signs and symptoms, as well as the response to treatment.

Although hyperuricemia is usually present, this does not confirm the diagnosis. Conversely, normal uric acid levels during an attack do not exclude gout, as serum urate falls during the acute phase response.

Treatment

Desired outcome

The goals in the treatment of gout are to terminate the acute attack, prevent recurrent attacks of gouty arthritis, and prevent complications associated with chronic deposition of urate crystals in tissues.

Acute gouty arthritis

Nonpharmacologic Therapy

Immobilization of the affected extremity speeds resolution of the attack, and. Local ice application is the most effective adjunctive treatment.

Pharmacologic Therapy

Nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and corticosteroids are used are considered first-line monotherapy for acute attacks. Treatment should commence within 24 hours of the onset of an attack.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs are the mainstay of therapy for acute attacks of gouty arthritis because of their excellent efficacy and minimal toxicity with short-term use. Most studies have shown similar results among agents, and all NSAIDs are considered to be effective and no one NSAID is preferred over another as first-line treatment. Doses at the higher end of the therapeutic range (i.e. large doses) are often needed.

Following resolution of the attack, tapering of NSAID therapy may be considered, especially in patients with comorbidities such as hepatic or renal insufficiency where prolonged therapy would be undesirable.

Colchicine

Colchicine is an antimitotic drug that is highly effective in relieving acute gout attacks, but it is used infrequently today because of its low therapeutic index. Oral colchicine causes dose-dependent GI adverse effects (nausea, vomiting, and diarrhea). Non-GI adverse effects include neutropenia and neuromyopathy, which may be worsened in patients taking other

myopathic drugs (e.g., statins) or in those with renal insufficiency.

Colchicine should not be used concurrently with macrolide antibiotics (especially clarithromycin) because reduced biliary excretion may lead to increased plasma colchicine levels and toxicity.

Colchicine should not be used for an acute attack if the patient is currently prescribed colchicine for prophylaxis and was previously treated with colchicine for an acute attack within the last 14 days.

Corticosteroids

Corticosteroids provide a safe alternative for patients with contraindications to NSAIDs or colchicine (Corticosteroid efficacy is equivalent to NSAIDs).

For isolated monoarticular attacks, especially of medium or large joints, intraarticular injection of Corticosteroids (e.g. triamcinolone) can quickly terminate an attack. For polyarticular attacks or attacks in smaller joints, systemic corticosteroids (oral or intramuscular) may be employed.

Canakinumab

In 2013 canakinumab became the first biologic agent approved for acute gout in Europe (not FDA approved).

Combination Therapy

In severe polyarticular attacks, particularly attacks involving multiple large joints, colchicine may be used in combination with an NSAID or oral corticosteroid. Intraarticular corticosteroid injections may be used in combination with any other first-line agent (NSAID, colchicine, oral corticosteroid).

Long-Term Urate-Lowering (Antihyperuricemic) Therapy

Following treatment and resolution of the intense pain associated with an acute gout attack, the focus shifts to the prevention of future episodes. Recurrent gout attacks can be prevented by maintaining low uric acid levels.

Non-pharmacological therapy

Patients may be advised to avoid alcohol, increase fluid intake, and lose weight if obese. Low-purine diets are not well tolerated (often unpalatable and impractical) ; instead, dietary recommendations should focus on general nutrition principles.

Pharmacologic Therapy

After the first attack of acute gout, prophylactic pharmacotherapy is recommended if patients have two or more attacks per year, even if serum uric acid is normal or only minimally elevated. Other indications include presence of tophi, chronic kidney disease, or history of urolithiasis. Urate-lowering therapy can be started during an acute attack if anti-inflammatory prophylaxis has been initiated.

The goal of urate-lowering therapy is to achieve and maintain serum uric acid less than 6 mg/dL, and preferably less than 5 mg/dLif signs and symptoms of gout persist. Urate lowering should be prescribed for long-term use. Serum urate can be reduced by decreasing synthesis of uric acid (xanthine oxidase inhibitors) or by increasing renal excretion of uric acid (uricosurics).

Xanthine oxidase inhibitors are recommended first-line therapy; the uricosuric agent probenecid is recommended as alternative therapy in patients with a contraindication or intolerance to xanthine oxidase inhibitors.

In refractory cases, combination therapy with a xanthine oxidase inhibitor plus a drug with uricosuric properties (probenecid, losartan, or fenofibrate) is suggested.

Xanthine oxidase inhibitors (Allopurinol, Febuxostat)

Xanthine oxidase inhibitors reduce uric acid by impairing conversion of hypoxanthine to xanthine and xanthine to uric acid. Because they are effective in both overproducers and underexcretors of uric acid, they are the most widely prescribed agents for long-term prevention of recurrent gout attacks.

Allopurinol

Mild adverse effects of allopurinol include skin rash, GI problems, headache, and urticaria. Allopurinol should not be taken with ampicillin owing to increased risk of rash.

More severe adverse reactions include severe rash (toxic epidermal necrolysis, erythema multiforme, or exfoliative dermatitis) and an allopurinol hypersensitivity syndrome characterized by fever, vasculitis, renal and hepatic dysfunction that occurs rarely but is associated with a 20% mortality rate.

Febuxostat

Febuxostat is a nonpurine xanthine oxidase inhibitor. Due to differences in chemical structure, febuxostat would not be expected to cross-react in patients with a history of allopurinol hypersensitivity syndrome.

Uricosuric Drugs

Uricosuric drugs, such as probenecid or sulfinpyrazone increase the renal clearance of uric acid by inhibiting the renal tubular reabsorption of uric acid. Uricosurics are considered second-line treatment.

Patients with a history of urolithiasis should not receive uricosurics. Start therapy with uricosurics at a low dose to avoid marked uricosuria and possible stone formation.

Maintaining adequate urine flow and alkalinization of the urine during the first several days of therapy may also decrease likelihood of uric acid stone formation.

Lesinurad is a selective uric acid reabsorption inhibitor that inhibits urate transporter 1, a transporter in proximal renal tubules, thereby increasing uric acid excretion. It is approved as combination therapy with a xanthine oxidase inhibitor for treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with xanthine oxidase inhibitor monotherapy.

Other drugs found to have uricosuric effects include fenofibrate, a fibric acid derivative used to treat hyperlipidemia, and the antihypertensives losartan and amlodipine. Losartan, an ARB, might be a useful antihypertensive agent in the patient who has both hyperuricemia and hypertension. Fenofibrate would be a useful agent in the patient with both hyperlipidemia and hyperuricemia.

Anti-inflammatory prophylaxis during initiation of urate-lowering therapy

Initiation of urate-lowering therapy can precipitate an acute gout attack due to remodeling of urate crystal deposits in joints after rapid lowering of urate concentrations. Prophylactic anti-inflammatory therapy is often used to prevent such gout attacks.

The guidelines recommend low-dose oral colchicine and low-dose NSAIDs as first-line prophylactic therapies, with stronger evidence supporting use of colchicine.

For patients on long-term NSAID prophylaxis, a proton pump inhibitor or other acid-suppressing therapy is indicated to protect from NSAID-induced gastric problems.

Low-dose corticosteroid therapy is an alternative for patients with intolerance, contraindication, or lack of response to first-line therapy. The potential severe adverse effects of prolonged corticosteroid therapy preclude their use as first-line therapy. Continue prophylaxis for at least 6 months or 3 months after achieving target serum uric acid, whichever is longer. For patients with one or more tophi, continue prophylactic therapy for 6 months after achieving the serum urate target.