

GOUT



1. Definition and Description

Gout is an acute arthritic condition of peripheral joints which results from deposition, in and about the joints and tendons, of crystals of monosodium urate from supersaturated hyperuricemic body fluids. A gout condition may remain simply as asymptomatic hyperuricemia, or it may develop into a painful acute arthritic attack. Untreated gout can potentially lead to chronic tophaceous gout requiring more aggressive treatment.

2. Pathophysiology

Increased serum uric acid (hyperuricemia) may be caused by various abnormalities of purine metabolism. The two main abnormalities are: (1) excessive purine synthesis and (2) decreased renal clearance of uric acid. Excessive uric acid in serum can cause the formation of monosodium urate crystals because of the limited solubility in tissue. These crystals can form in and about joints and tendons as well as in interstitial tissue of the kidney.

3. Signs and Symptoms

Hyperuricemia can lead to an acute gout attack without warning. It may be precipitated by minor trauma, indulgence in particular foods or alcohol, surgery, fatigue, infection, or emotional stress. Medications such as thiazide or loop diuretics also precipitate attacks. Joint or tendon pain in one or more tissue areas is usually the first symptom. Examination of the painful area resembles an acute infection due to swelling, warmth, and tenderness. Frequently, the overlying skin is shiny and red or dark purple in color. Common joint areas affected are metatarsophalangeal joint of the great toe, ankle, knee, wrist, and elbow. Fever, tachycardia, chills, and malaise may occur as systemic reactions to hyperuricemia. Rheumatoid arthritis (RA) can be confused with hyperuricemic gout attacks, however, RA tends to be symmetrical in joints whereas gout is asymmetric. RA also has a gradual onset with a long duration as compared to the sudden onset and short duration of a gout attack.

4. Lab Investigations

The uric acid (urate) level is normally below 430 $\mu\text{mol/L}$ in adult males and below 350 $\mu\text{mol/L}$ in adult females. In patients with chronic renal failure (CRF), uric acid levels may be significantly higher and patients may still be completely asymptomatic. However, hyperuricemia may be associated with the progression of renal failure.

5. Goals of Therapy

Treatment objectives are: (1) termination of an acute gout attack, (2) prevention of recurrent acute attacks and, (3) prevention of further deposition of monosodium urate crystals and resolution of existing tophi, and (4) prevention of renal failure progression.

6. Treatment

(I) Pharmacological

Medicinal agents include colchicine, NSAIDS, oral or intra-articular corticosteroids, and allopurinol. Allopurinol is not used for acute attacks, but rather for prevention of future attacks, for treatment of chronic tophaceous gout, and for prevention of further deterioration of renal function. For acute attacks, adjunctive therapy with the analgesics acetaminophen and/or codeine may also be used. Uricosuric agents rely on functioning kidney tissue, so agents such as probenecid and sulfinpyrazone are to be completely avoided in treatment of gout in CRF.

(a) Colchicine

Colchicine may be used both in treatment of acute attacks and in prevention of gout attacks. Colchicine has no analgesic activity nor uricosuric activity. The precise mechanism of its anti-gout effect is unknown, however it is postulated that it reduces the inflammatory response to deposition of monosodium urate crystals in joint tissues possibly by inhibiting polymorphonuclear leukocyte (PMNL) metabolism, mobility, chemotaxis, and/or other leukocyte functions. For attacks, colchicine may be used with a dose of 0.6mg po to start and then 0.3mg po QID until relief or abdominal side effects occur. Nausea, vomiting, abdominal cramping, and especially diarrhea are common side effects. Peripheral neuropathies may occur if dosing is too high in CRF patients, so this must be monitored. Dosing of 0.6mg po daily or every other day may be used to prevent further attacks.

(b) NSAIDS

NSAIDS such as indomethacin, ibuprofen, and naproxen may be used for treatment of acute gout attacks as well as for treating the pain and inflammation of chronic tophaceous gout. They are not used for prevention of gout attacks. Dosing of NSAIDS is reduced in CRF, for example, indomethacin 25mg po tid for short term (several days) is commonly used.

(c) Corticosteroids

Corticosteroids such as prednisone may be given orally with a dose such as 30mg daily x 5 days to treat an acute gout attack. Corticosteroids are used simply for their anti-inflammatory effects. Doses below 20mg/day tend to be ineffective. Simultaneous low-dose colchicine (0.6mg/day) or NSAID may help prevent gout rebound when the steroid is stopped. When a steroid cannot be given orally, a dose of methylprednisolone sodium succinate such as 50-100mg IV x 1 dose during an attack may be given. Intra-articular (IA) injection into affected joints is another option. IA injection gives rapid control of inflammation at the site. The disadvantage of IA injection is its high cost and risk of infection. Triamcinolone hexacetamide 10-20mg IA may be used into large joints and 2-6mg IA into small joints. Methylprednisolone acetate 20-80mg IA may be used into large joints, 10-40mg into medium joints, and 4-10mg into small joints. Dose reduction of corticosteroids is not necessary in CRF.

(d) Allopurinol

Allopurinol is used for the prevention of gout attacks, for the treating of chronic tophaceous gout, and to reduce the rate of progression of renal failure. It is not used for the treatment of acute gout attacks. It inhibits xanthine oxidase, the enzyme that catalyzes the conversion of hypoxanthine to xanthine and xanthine to uric acid. Allopurinol's metabolite, oxypurinol, also inhibits this enzyme. By inhibiting this conversion, the serum uric acid concentration decreases. Allopurinol may work as an oxygen free radical scavenger to reduce tubulo-interstitial damage. Allopurinol has no analgesic, anti-inflammatory, or uricosuric activity. Dosing regimens vary in CRF, however, dosing must be reduced in these patients as compared to patients with normal kidney function. Regimens of 100mg po daily or 300mg po every other day may be effective in preventing gout attacks in CRF patients. When starting allopurinol therapy, CRF patients must be carefully observed for side effects. The most common side effects are nausea, vomiting, and abdominal cramping. However, there is a wide array of other adverse effects including adverse haematological effects which should be monitored for when starting allopurinol and increasing the dosage.

(e) Acetaminophen and/or Codeine

Acetaminophen and/or codeine can also be of some benefit in treating the pain associated with attacks. These analgesics should only be used as adjunctive therapy with other medications as they will not help with the inflammatory process caused by urate deposits in tissue.

(II) Non-pharmacological

Dietary factors can precipitate gout attacks. It is important for the patients to recognize these factors and to avoid them to prevent future attacks. Purine-rich foods such as liver, anchovies, sardines, organ meats (kidney, liver, heart, etc), meat gravies, boullion cubes, and brewer's yeast should be avoided. However, it should be noted that monitoring of dietary purine intake may have only minimal to only moderate benefit. Current drug therapy generally makes strict dietary monitoring of purine intake unnecessary. In patients with normal renal function, advice to increase fluid intake can be of value in treating and preventing gout attacks. However, in CRF there may be strict fluid restrictions imposed on CRF patients and this advice may be detrimental. It is wise to have the patient ask their physician if an increase in fluid intake is warranted.

Gout: Useful References

1. Johnson R.J. Reappraisal of the Pathogenesis and Consequences of Hyperuricemia in Hypertension, Cardiovascular Disease, and Renal Disease - *AJKD* 1999; 3 : 225 - 34.
2. The Merck Manual of Diagnosis and Therapy, Fifteenth Edition, 1987, Third Printing 1989, Robert Berkow (Editor-in-Chief).
3. Therapeutic Choices, Canadian Pharmaceutical Association, Jean Gray (Editor-in-Chief), 1995.