Gout and Hyperuricemia

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Objectives

• To understand the pathophysiology of gout, including pathology, predisposing factors, presenting signs and symptoms, and pharmacotherapy.

• To be able to outline a therapeutic plan for therapy of acute gout, including drugs, dosage, route of administration, monitoring parameters and adverse effects.

• To be able to outline a therapeutic plan for therapy of chronic gout and hyperuricemia, including drugs, dosage, route of administration, monitoring parameters and adverse effects.

• To identify patient parameters that would influence the selection of drug therapy, including age, renal function and chronicity of disease.
Gout and Hyperuricemia

- Hyperuricemia: serum urate concentration > 7 mg/dl

- Gout: recurrent attacks of acute arthritis caused by monosodium urate crystal accumulation in the synovial fluid

- Renal complications:
  - Inflammation/crystal deposition in glomerular, tubular, and interstitial tissues and blood vessels
  - Uric acid nephrolithiasis

- Tophi: Aggregates of sodium urate monohydrate crystals deposited chiefly in and around joints,
  - may lead to deformity
Epidemiology

• Hyperuricemia
  – Prevalence varies by population: 2.3 - 41.4 %
  – Higher in males, post-menopausal females
  – Body weight/SA/BMI most important predictor across populations

• Gout
  – overall prevalence < 1 - 15.3%
Uric acid metabolism and excretion

- Gout and hyperuricemia are disorders of purine metabolism
  - primary vs. secondary hyperuricemia
  - overproducers (>600 mg/d) vs. undersecretors (<600 mg/d)
Purine Metabolism
Uric acid metabolism and excretion

Excretion of uric acid:

- freely filtered by glomerulus; 98-100% reabsorbed in early proximal tubule, secreted back into lumen, and reabsorbed again. Result: 6-12% of filtered excreted into urine.
- GI also excretion route; in renal failure can inc. several times
Factors affecting uric acid solubility

- Concentration
- pH
- Temperature
Annual incidence of gout by serum uric acid

![Bar graph showing annual incidence of gout by serum uric acid levels.](image-url)
Natural history of gout

Asymptomatic hyperuricemia

Acute gouty arthritis

Intercritical (interval) gout

Chronic tophaceous gout
Predisposing Factors for Gout and Hyperuricemia

• Gender
• Ethanol
• Obesity
• Heredity
• Diabetes
Predisposing Factors for Gout and Hyperuricemia

• Drugs:
  – thiazide diuretics
  – ethambutol
  – salicylates (low dose)
  – pyrazinamide
  – nicotinic acid
  – cytotoxic drugs
Presenting signs and symptoms

- 85-90% present as monoarticular
- Classic presentation
  - Hot, throbbing, red, swollen, extremely painful joint
  - Great toe most often
  - Sudden onset, often at night
- Duration several hours to weeks if severe
- Definitive dx: joint aspiration revealing needle-shaped crystals
- Serum uric acid may be normal during attacks
American College of Rheumatology
Criteria for diagnosis of gout

The presence of characteristic urate crystals in the joint fluid, or a tophus proved to contain urate crystals by chemical means or polarized light microscopy, or the presence of 6 of the following 12 clinical, laboratory, and radiographic phenomena:

- More than one attack of acute arthritis
- Maximal inflammation developed within 1 day
- Attack of monarticular arthritis
- Joint redness observed
- First metatarsophalangeal joint painful or swollen
- Unilateral attack involving first metatarsophalangeal joint
- Unilateral attack involving tarsal joint
- Suspected tophus
- Hyperuricemia
- Asymmetric swelling within a joint (radiograph)
- Subcortical cysts without erosions (radiograph)
- Negative culture of joint fluid for microorganisms during attack of joint inflammation
Tophi

Harris: Kelley's Textbook of Rheumatology, 7th ed
Pharmacotherapy of gout
Acute gouty arthritis

• Goals
  – Reduce inflammation
  – Reduce pain
  – Shorten duration of attack
Colchicine

- Formerly gold standard for treatment; little actual evidence
- Effective in 75-95% if taken within 24 hours of attack onset, but only 20-50% of patients can tolerate the drug
- Mechanism of action in gout unclear: impairs PMN chemotaxis by inhibiting mitosis and binding to microtubular proteins
- Dose:
  - **Traditional:** p.o 0.5-0.6 mg. Q1h until relief/nausea/vomiting/diarrhea, or 12 tablets taken
  - Alternate: p.o. 1 mg followed by 0.5 mg q2h until pain relief
  - iv: 2 mg, may repeat w/ 1 mg at 6 and 12 hrs if needed. Use ½ doses if creatinine clearance 10-50 ml/min. Avoid in neutropenia, creatinine clearance <10 ml/min, combined renal/hepatic insufficiency.
- Onset of effect 12-24 hours p.o., 4-12 hours i.v.
Colchicine

• Adverse effects: bone marrow suppression, neurotoxicity, myopathy - more likely w/ renal impairment, high dose
• Drug interactions:
  – erythromycin, clarithromycin – colchicine toxicity
  – interferon alfa-2A- reduced antiviral effectiveness in chronic hepatitis C
  – cyclosporine – increased GI, hepatic, renal and neuromuscular toxicity with combination
• Role: third line agent for acute attacks
NSAIDS

- equally effective as colchicine
- contraindicated in acute renal failure, GI bleed, caution in CHF or uncontrolled HTN
- duration of therapy 4-5 days or until relief
- Dose:
  - naproxen 750 mg x 1 then 250 mg tid
  - ibuprofen 800 mg tid or 600 mg qid
  - indomethacin 50 mg tid-qid x 2-3 days then 25 mg tid-qid until resolution
Corticosteroids

- As effective as NSAIDs
- Taper to avoid rebound gout attack
- Use where NSAIDs contraindicated
- Prednisone 40 mg x 3-5 days, taper over 10-14 days
- I.v. methylprednisolone
- Intraarticular injections
Narcotic analgesics

- No antiinflammatory effects
- Use as adjunct to other txs for acute pain relief
Natural history of gout

Asymptomatic hyperuricemia → Acute gouty arthritis → Intercritical (interval) gout → Chronic tophaceous gout
Intercritical or chronic tophaceous gout

- About 60% will have recurrence within one year
- If > 2-3 attacks/yr, or very severe attacks, or joint destruction due to tophi, or uric acid >9 mg/dl, may opt to treat chronically
- Colchicine 0.5-0.6 mg qd - bid; use concurrently with initial urate lowering therapy to reduce gout flare
- Urate lowering therapy:
  - Allopurinol
  - Uricosurics
  - Goal serum uric acid < 6 mg/dl
Allopurinol

- Mechanism of action: inhibits xanthine oxidase and the metabolism of hypoxanthine to xanthine to uric acid
- Useful for overproducers, undersecretors
- Dose: 200-300 mg/d, titrate to desired uric acid (<7 mg/dl)
- Onset: 1-2 days, maximum 7-10 days
Allopurinol

• Elimination:
  – Primarily renal parent/metabolites (oxypurinol)

• Adverse effects:
  – Hypersensitivity: erythema multiforme or toxic epidermal necrolysis, fever, hepatic cellular injury, worsened renal function, eosinophilia, leukocytosis, death
  – Cataractogenesis

• drug interactions:
  – azathioprine, mercaptopurine
  – ampicillin
Uricosuric agents

In low doses, block secretion of urate
In therapeutic doses, block tubular reabsorption of urate
Uricosuric agents: probenecid, sulfinpyrazone

• Mechanism of action: block tubular reabsorption of uric acid

• Dose:
  – Probenecid 250 mg bid x 1 -2 weeks, 500 mg bid x 2 weeks, up to 3 gm/day. 1-1.5 gm/day effective in most patients
  – Sulfinpyrazone 50 mg do bid x 3-4 days, then 100 mg bid x 1 week, then ↑ by 100 mg /week to a maximum of 400 mg/day

• Ineffective when creatinine clearance <25 ml/min

• Contraindicated in overproducers

• Adverse effects: renal stones, allergy, GI distress

• drug interactions:
  • salicylates: decreased uricosuric effect, dose dependent
  • warfarin (sulfinpyrazone): increased hypoprothrombinemic effect
Uricosurics

- Hydration
  - 2-3 L/day

- Urinary alkalinization
  - acetazolamide
  - sodium bicarbonate 2-6 gm/day
  - Shohl’s solution 20-60 ml/day
Treatment Summary

• Tx of acute gout focuses on relief of inflammation/pain
• Tx of chronic/recurrent gout focuses on urate lowering therapy
  – Initial concurrent colchicine or NSAID may be used to suppress rebound acute gout