Gout

**Uric acid:** end waste product of purine catabolism

**Risk factors:**
- Patient characteristics: ↑age, males (6x > females), ↑alcohol intake, family history
- Lab values: ↑Scr, ↑BUN, ↑BP, ↑weight, ↑serum uric acid (normal < 7 mg/dl)

**Etiology & Pathophysiology**
- Main cause: imbalance between uric acid production and excretion
  - **Underexcretion**
    - 2 types of excretion: Gl excretion by colonic bacteria (1/3), urine excretion (2/3)
    - 2 main causes of underexcretion: CKD, diuretics
  - **Overproduction**
    - 3 nucleic acid or uric acid sources: conversion of tissue nucleic acid to purine nucleotides, de novo synthesis, dietary purines
    - 3 main causes of overproduction
      - ↑Cell turnover → ↑tissue breakdown (examples: myeloproliferative or lymphoproliferative disorders, inflammatory disorders, psoriasis)
      - Congenital abnormality in enzyme systems that regulate purine metabolism
      - High dietary purine intake (but alone would not ↑serum uric acid levels)
  - Hyperuricemia results in uric acid deposition in joints
- Synovial effusions throughout day in weight-bearing joints → water reabsorbed at night → uric acid diffuses slower than water across synovial membranes → leaves behind supersaturated solution of MSU crystals → uric acid deposition in joints → inflammatory reaction mediated by leukocytes → gout attack
- Medications that may induce gout: diuretics, ethanol, cytotoxic drugs, cyclosporine, nicotinic acid, salicylates (>2g/day), pyrazinamide, levodopa, ethambutol
- Factors that exacerbate gout: stress, trauma, alcohol, infection, surgery, medications that rapidly lower serum uric acid

**Clinical presentation**
- Podagra: severe pain & swelling in first metatarsophalangeal joint of the big toe
- Joints affected: big toe (most common), feet, knees, hands, elbows
- Usually occurs in one joint but can occur in multiple joints
- Tophi: chalky deposits of MSU in soft tissue, seen as hard nodules on radiography
- Complications: ↑serum uric acid → HTN, metabolic syndrome, CAD, vascular dementia, preeclampsia, cerebrovascular disease, kidney disease

**Diagnosis**
- Upon examination of synovial fluid aspirate: urate crystals inside leukocytes, large quantity of PMN leukocytes
- If cannot do aspiration, diagnosis based on symptoms & criteria (ACR or EULAR)
  - ACR criteria: >1 acute attack, joint pain, joint inflammation maximal w/in 1 day, oligoarthritis, erythema over joints, tophi, unilateral podagra, hyperuricemia, asymmetrical swelling, subcortical cysts on x-rays, MSU crystals, joint fluids negative for organisms
- Differential diagnosis: gout can be confused with other crystal-induced arthritides or other types of arthritis
  - Monosodium urate crystals (MSU) → gout
  - Calcium pyrophosphate dehydrate (CPPD) → pseudogout
  - Calcium hydroxyapatite → calcific periarthritis, tendinitis, arthritis (usually in younger patients)
  - Calcium oxalate → ESRD complication, patients taking high doses of ascorbic acid
  - Septic arthritis

**Treatment**

**Treatment goals:** terminate acute attack, prevent future attacks, prevent complications associated with uric acid crystal deposition, prevent or reverse features associated with the illness (e.g. obesity, hypertension)

**Acute treatment**
General mechanism for all agents: ↓ inflammation associated with uric acid deposition

- **NSAIDs** (most common: indomethacin)
  - Place in therapy: mainstay, highly effective, few SE
  - Regimen: start high doses at symptom onset → continue until symptom resolution → taper over 2-3 days
  - SE: nausea, headaches, GI ulceration, bleeding
  - Caution in patients with: heart failure, CKD, GI bleed history, asthma

- **Corticosteroids (prednisone)**
  - Place in therapy: most potent anti-inflammatory agents, reserved for resistant cases or if other options contraindicated (e.g. in CKD patients)
  - Routes: orally or intraarticularly
    - Oral: varied regimen: start at 30-60 mg/day x 3-5 days → taper gradually by 5mg over 10-14 days to prevent rebound
    - Intraarticular: triamcinolone acetonide 20-40mg
  - SE: fluid retention, hypertension, mood swings, hyperglycemia, infection
  - Caution in patients with: infection, hypertension, cirrhosis, CHF

- **Colchicine**
  - Place in therapy: both for acute & prophylactic therapy
  - Effective if initiated within 24 hours of gout attack onset
  - Caution in patients with renal impairment
    - In general, does not need renal dose adjustment
    - CrCL <30 mL/min → do not give another course for 14 days
    - Dialysis → 0.6 mg x 1 only
  - Many drug interactions: CYP3A4 inhibitors & P-gp inhibitors → dose adjustment needed if these are given within 14 days prior to colchicine
    - Strong CYP3A4 inhibitors: protease inhibitors, macrolides, antifungals, ketolide, antidepressants
    - P-gp inhibitors: cyclosporine, ranolazine
  - SE: GI effects, hepatotoxicity, bone marrow toxicity, neurologic effects, myopathy, renal effects
  - Caution in patients with: infection, hypertension, cirrhosis, CHF
  - Contraindications: concurrent renal + hepatic disease, neutropenia
  - Avoid IV use: narrow therapeutic index

**Maintenance treatment**

- Prophylaxis considerations: attack frequency ≥2x/year, tophi, nephropathy, attack severity, poor response to acute treatment, serum uric acid >10mg/dL, urinary urate excretion >100mg/24hr
- Treatment of hyperuricemia (goal <6mg/dL)
  - **Allopurinol**
    - Xanthine oxidase inhibitor
    - MOA: (−)xanthine oxidase → (−)xanthine to uric acid reaction → ↓ uric acid production
    - Treats both underexcretion & overproduction of uric acid
    - Place in therapy
      - Preferable in patients with CrCl <50 mL/min, history of renal stones, or uric acid overproduction
      - Combination therapy: can be used with colchicine in resistant cases
      - CKD patients: dose adjustments needed
      - Drug interactions: azathioprine
      - SE: rash, hypersensitivity, leukopenia, GI toxicity, acute gout with initiation
  - **Febuxostat** (Uloric)
    - Non-purine xanthine oxidase inhibitor → ↓ uric acid production
    - Compared to allopurinol
      - May not cross-react with allopurinol sensitivity
      - May be more effective than allopurinol
      - May experience more gouty attacks at therapy initiation than allopurinol
    - Renally impaired patients: no dose adjustment, but not recommended in CrCl <30 mL/min
  - **Pegloticase** (Krystexxa)
    - Pegylated recombinant porcine-like uricase
    - Route: IV
    - Place in therapy: reserved for severe cases → profound ↓ serum uric acid within 24hr
    - SE: anaphylaxis (premedicate with antihistamines & corticosteroids), infusion reactions
  - **Probenecid**
• Uricosuric agent: (−) renal tubular reabsorption of uric acid → ↑clearance
• Only treats patients with urate underexcretion
• SE: GI irritation, rash, acute gout or stone precipitation
  - Start at low doses to avoid uricosuria and stone formation; drink more fluids
• Contraindications: CrCl <50 mL/min, history of frequent renal stones
• Place in therapy: rarely used (not as effective as allopurinol)

- Colchicine
  - Place in maintenance therapy: used alone or in combination
  - Should be used for first 3-12 months

**Non-pharmacological treatment**
- Weight loss, ↓salt intake, ↑fluid intake
- Diet restrictions: ↓saturated fats, organ meats, red meat, seafood, alcohol
- Joint rest for 1-2 days, ice application
- Treatment of comorbid conditions

**Complications of gout**
- Nephrolithiasis: renal calculi, renal stone
  - Deposits made out of calcium oxalate, calcium phosphate, or uric acid
  - Treatment: hydration, ↓protein intake, ↓purines, allopurinol, K⁺bicarb or K⁺citrate to maintain pH 6-6.5
- Chronic tophaceous gout: tophi in base of big toe, helix of ear, olecranon bursae, Achilles tendon, knees, wrists, ahnds
  - Treatment: reduce serum uric acid level ≤6mg/dL in order to shrink the tophi
- Gouty nephropathy: acute or chronic
  - Acute uric acid nephropathy: acute renal failure due to uric acid crystals blocking urine flow
  - Chronic urate nephropathy: long-term urate crystal deposition in renal parenchyma → microtophi → inflammation
  - May lead to CKD, HTN, nephrosclerosis

**Pseudogout**
A condition very similar to gout but caused by CPPD deposits (not MSU)

<table>
<thead>
<tr>
<th></th>
<th>Gout</th>
<th>Pseudogout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom duration</td>
<td>3-10 days</td>
<td>Longer</td>
</tr>
<tr>
<td>Comorbid diseases</td>
<td>CKD</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Appearance under microscopy</td>
<td>Needle-shaped</td>
<td>Rhomboid with blunt ends</td>
</tr>
<tr>
<td>Chronic treatment</td>
<td>Urate-lowering therapy, colchicine, NSAIDs</td>
<td>NSAIDs, colchicine</td>
</tr>
<tr>
<td>Acute treatment</td>
<td>Colchicine, corticosteroids, NSAIDs</td>
<td></td>
</tr>
</tbody>
</table>