**Gout**

Disease characterized by deposition of monosodium crystals in soft tissues (cartilage, tendons, bursa) → recurrent episodes of acute joint pain & inflammation

**Epidemiology**

Most prevalent inflammatory arthritis in developed countries (4% of adults)
- Males > females (estrogen has uricosuric effect)
- Incidence increases with age
- Often undertreated

**Pathophysiology**

- Hyperuricemia occurs secondary to:
  - **Overproduction** (<10% of cases)
    - ↑ purine intake (meat, seafood, alcohol)
    - ↑ endogenous purine (genetics, malignancy)
  - **Hypoexcretion** through kidneys (>90% of cases)
    - ↓ glomerular filtration
    - ↓ tubular secretion

**Uric acid crystal deposition:** occurs at saturation point > 360 umol/L into soft tissues and form hard nodules = **tophi** (mostly in toes, fingers, elbows)

**Conditions influencing deposition**

- Decreased solubility at lower temperature & lower pH (acidic urine)
- Trauma or tissue injury
- Reabsorption of water from joint resulting in super saturation (increased at night)

**Individual responses to hyperuricemia**

- Gout pts may have urate crystals in asymptomatic joints (not feel pain)
- Asymptomatic patients w/ hyperuricemia may not have urate crystals

**Pathogenesis of acute attacks**

- **Symptoms**
  - Abrupt onset of extreme pain, tenderness, redness, swelling (max severity within 12-24 h of onset; often can’t tolerate light pressure on affected joint)
  - Lower extremity involvement (1st metatarsophalangeal joint = big toe most common)
  - 80% of first attacks in single joint
    - Polyarticular involvement → disease progression

  - **Sx with disease progression**
    - More frequent and longer attacks
    - Polyarticular joint involvement (> 4 joints)
    - Chronic, persistent arthritis results with superimposed acute attacks
    - Progressive joint damage develops (bony erosions, deformity, disability)

**Stages of disease**

1. Asymptomatic hyperuricemia (elevated UA > 360 umol/L without clinical manifestations)
2. First gout flare (only 20-25% of pts progress to acute flare)
3. Intercritical phase (latent painless phase between attacks) – increasing frequency & duration of flares until reach advanced gout
4. Chronic tophaceous gout (collections of solid urate in CT → joint damage & painful intercritical phases)
### Diagnosis of gout
- Presence of needle-shaped urate crystals from joint aspiration
- Serum uric acid (UA) $> 360$
  - May be elevated, normal, or low during acute flare
- Presence of tophi (hard nodules)
  - Not usually palpable in initial flares
- Imaging: X-ray showing subcortical bone cysts; CT imaging showing urate deposits
- Differential: rheumatoid arthritis, septic arthritis, trauma, pseudogout (calcium phosphate crystal deposition)

### Risk factors
- Male, postmenopausal women
- Age $> 65$
- Chronic kidney disease (decreased GF)
- Hypertension
- Hyperglycemia/T2DM/metabolic syndrome
- Hyperlipidemia
- Genetics
- Drugs: diuretics, tacrolimus, cyclosporine, ASA $< 2g/day$, XOIs (at initiation), uricosurics
- Lifestyle: high diet purines (meat, seafood, alcohol)
- Malignancy: leukemia, lymphoma, multiple myeloma
  - Chemotherapy: lysis spills out uric acid
- Other: trauma, surgery, acute illness

### Diuretics and gout: eliminate less than the usual 8%
- Reduced excretion of uric acid by:
  - Decreasing circulating volume and GF
  - Increasing reabsorption in proximal tubule

### Treatment of asymptomatic hyperuricemia
- May be an independent risk factor for CVD (hypertension, metabolic syndrome, CAD, cerebrovascular disease) & progression of renal insufficiency
- Clinical controversy: current consensus
  - Re-assess reversible causes of elevated UA
  - Address cardiac risk factors
  - Not an indication for urate lowering therapy due to limited data = DON’T TREAT

### Treatment of acute attacks
- Non-pharmacologic treatment: rest, ice, time
  - Can resolve in 7-10 days without intervention
- Pharmacologic options: start therapy in first 24 hours
  - NSAIDs, colchicine, oral/intra-articular corticosteroids, IL-1 antagonists
### Treatment of acute attacks (cont.)

**NSAIDs:** reduction of inflammatory response through inhibition of COX-2 & prostaglandin synthesis
- Higher doses required to reduce inflammation; continued until attack resolves
  - Naproxen 500 mg BID
  - Ibuprofen 600 mg QID
  - Diclofenac 50 mg TID
  - Indomethacin 50 mg TID
  - Celecoxib 200 mg BID
- No benefit of one drug over another

**ADRs:** GI upset, GI bleed, fluid retention, elevated BP, increased risk of MI

**Colchicine:** reduces activation, mobilization & degranulation of neutrophils

#### Pharmacokinetics
- **A:** 45% bioavailability; **Tmax = 0.5 – 3h; onset = 18-24 h**
- **D:** leukocytes, kidney, spleen, liver
- **M:** CYP3A4
- **E:** $T_{1/2} = 27-31$ h; 40-65% excreted in urine

#### Dosing
- Low dose (AGREE study): 1.2 mg stat, then 0.6 mg within 1 h
  - Initiated w/in 24 h of sx onset
- Alternative (sx > 24 h or if sx persist):
  - 0.6 mg BID x 5-7 days

#### Safety
- Renal impairment (GFR < 30): lower doses recommended (0.6 mg stat + 0.3 mg within 1 h; alternative 0.3 mg daily)
  - Txt courses shouldn’t be repeated more than q14d
- Drug interactions
  - Strong CYP3A4 inhibitors (macrolides, antiretrovirals, azole antifungals, disulfiram)
  - Strong p-glycoprotein inhibitors (cyclosporine)
- ADRs: GI toxicity (NVD), abdominal pain, fatigue, headache, hepatotoxicity, bone marrow suppression

### Oral corticosteroids
- Similar efficacy compared to NSAIDs
- Prednisone 30 mg daily x 5-7 days (~ 0.5 mg/kg/d)
- ADRs: elevated BP, edema, increased blood glucose, GI upset, sleep disturbances, psychosis/mania
- Generally don’t use oral corticosteroids for acute gout, but often used if patient has renal kidney disease

### Intra-articular corticosteroids
- Limited to 1-2 large joints
- Patients report relief; has not been studied in clinical trials
- Option of patients can’t tolerate oral treatment
- Low risk of ADRs
- Options
  - Methylprednisone 40-80 mg x 1 dose
  - Triamcinolone 10-40 mg x 1 dose

### Interleukin-1 (IL-1) antagonists: inhibits cytokine
- IL-1 → reduction of neutrophils to site → reduction of pain/inflammation
- Off-label indication for acute gout treatment
- Only for severe cases resistant to conventional therapy due to expense
  - Canakinumab 150 mg x 1 dose
  - Anakinra 100 mg SC daily x 3-5 days
  - Riloncept

**ADRs:** increased risk of infection, abdominal pain, injection site reactions

### Combination therapy: for severe attack (pain > 7/10) or polyarticular joint involvement
- Colchicine + NSAID
- Colchicine + oral corticosteroid
- Intra-articular steroid + colchicine, or NSAID
Initiation of chronic suppressive therapy
- ≥ 2 gout attacks/year
- Presence of tophi
- Past urolithiasis (urinary stones)
- CKD ≥ stage 2

Gout flare prophylaxis
- Initiation of uric acid lowering therapy may precipitate attacks (mobilization of tophi → acute inflammatory response)
- Methods to minimize:
  - Start low and go slow
  - Adequate hydration (>2 L fluids per day)
  - Add anti-inflammatory medication
    - Colchicine 0.6 mg BID x 3-6 months
      - Dose adjust for CrCl <30 or strong CYP3A4/p-gp inhibitor
    - Low-dose NSAIDs: Naproxen 250 mg BID x 3-6 mos
    - Longer prophylaxis may be required if ongoing sx, or ≥ 1 tophi present
  → ULT can be started during acute gout attack if effective anti-inflammatory management has been initiated

Uric acid lowering therapies (ULT)
- Xanthine Oxidase Inhibitors: allopurinol, febuxostat
  - First line
- Uricosurics: probenecid, sulfinpyrazone, losartan, fenofibrate
- Uricolytics: pegloticase, rasburicase

Target to treat
- In most pts < 360 umol/L
- If presence of tophi < 300 umol/L

Allopurinol (Xanthine Oxidase Inhibitor)
→ XOIs inhibit xanthine oxidase to prevent conversion of hypoxanthine and xanthine to uric acid

Pharmacokinetics
- A: 50% bioavailability; Tmax = 30-12 min; peak effect 1-2 weeks
- D: Vd = 1.6 L/kg
- M: 75% metabolism → oxypurinol (active metabolite)
- E: T1/2 = 1-3 hrs (prolonged in renal failure); oxypurinol 18-30 h
  - Urine excretion: 12% unchanged; 76% oxypurinol

Dosing: 100 mg/day and titrate by 100 mg increments q2-5 wks to max dose 800 mg/day
- ~ 60 umol/L decrease in serum UA per 100 mg
- Target 60-120 umol/L reduction in UA per month to prevent gout flares
- Adjust initial dose in CKD stage 4-5: 50 mg daily; titrate by 50 mg increments
  - Can exceed 300 mg/day with caution (old maximum but only 40% have < 360 UA at this dose)

ADRs: rash, nausea, diarrhea, hepatotoxicity, gout flares, bone marrow suppression, AHS

AHS = allopurinol hypersensitivity syndrome: occurs within 3-6 mo or with dose increase
- ↑ risk: thiazide, renal impairment, CVD, older age, high starting dose of allopurinol, genetic risk
- Presentation: flu-like sx (arthritis, malaise, fever); burning rash on face or upper torso (skin & mucous membranes); papule lesions form & burst → desquamation (sloughing of skin) → ulceration, necrosis, and secondary infections
- May progress to Stevens-Johnson Syndrome (>30% of skin) or Toxic Epidermal Necrolysis (TEN) or mortality 20-25%

Drug interactions
- Azathioprine, Mercaptopurine: WBC suppression, NV
  - Reduce dose of these drugs to 25-30% of usual dose
- Cyclophosphamide: bone marrow suppression
- Warfarin: increased anticoagulant effect
- Didanosine: increased concentrations of this drug
- Pegloticase: enhanced toxicity of this drug (anaphylaxis, infusion related reactions)
**Febuxostat** (Xanthine Oxidase Inhibitor)

**Pharmacokinetics**
- **A:** 50% absorption
- **D:** $V_d = 50 \text{ L}
- **M:** hepatic conjugation + CYP 1A2, 2C8, 2C9
- **E:** $T_{1/2} = 5-8 \text{ h}$; excretion 50% urine metabolites, 50% feces

**Dose:** 40 mg daily, may increase to 8 mg daily at 2 weeks if uric acid > 360 umol/L

**ADRs:** GI upset (ND), headache, arthralgia, rash, ↑ liver enzymes

**Drug interactions**
- Azathioprine, mercaptopurine: increased serum concentrations of these drugs
- Pegloticase: enhanced toxicity of this drug
- Didanosine: increased concentrations of this drug (diarrhea, abd pain, peripheral neuropathy)

**Febuxostat vs. allopurinol 300 mg daily**
- More efficacious for reduction of serum uric acid at higher doses
- No difference in reduction of tophi
- Increased acute flares with higher doses
- Increased ADRs with allopurinol (diarrhea, increased LFTs)
- Major limitation of trials: allopurinol dosing max of 300 mg daily; unclear risk of bias in larger trials

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**Uricosurics:** increase uric acid excretion by inhibiting urate reabsorption in the proximal tubule
→ Increased risk of urolithiasis & not recommended with renal impairment (GFR < 50 mL/min)

**Probenecid:** 250 mg BID to start → increase to 500 mg BID after 1-2 weeks → increase to 500 mg per month to a max of 2000 mg/day in divided doses

**ADRs:** GI upset, rash, headache
* increase fluid intake to prevent renal stones

**Drug interactions**
- B-lactam abx: increased concentrations of abx → can be useful
- Methotrexate: increased MTX concentrations → bone marrow suppression, hepato & GI toxicity
- Pegloticase: enhanced toxicity
- Acetaminophen: decreased APAP metabolism → hepatotoxicity
- NSAIDs: decreased elimination
- ASA: inhibition of salicylate excretion, decreased uricosuric effect of probenecid

**Sulfinpyrazone:** 50 mg BID x 3-4 days → 100 mg BID → increasing at 100 mg increments q7 days until UA < 360
** max 800 mg/day

**ADRs:** dyspepsia, GI upset, reactivation of peptic ulcer disease, rash, dizziness, pancytopenia, decreased platelet aggregation

**Drug interactions**
- Acetaminophen: increased hepatotoxicity
- Warfarin: increased anticoagulant effect
- ASA: decreased uricosuric effect

**Other uricosurics:** may be option in patients with hypertension or hyperlipidemia/hypertriglyceridemia (not actually studied in gout patients)
- Losartan (hypertension): effect plateaus at 50 mg daily
- Fenofibrate (hyperlipidemia): 200 mg daily
**Pegloticase**: pegolated pig uricase (which humans don’t have) – resolution of tophi in weeks to months

→ NOT available in Canada

- Treatment of resistant gout with UA > 475 umol/L + significant burden of disease
- 8 mg IV q2 weeks
  - Onset 24h; duration 12.5 days
  - Cost: $10,000 / 8 mg dose
- ADRs: infusion reactions, anaphylaxis, antibody development

**Recommendations for all patients with gout**

- Educate regarding diet & modifiable risk factors
- Reassess secondary causes of hyperuricemia
- Eliminate, where able, medications that induce hyperuricemia
- Evaluate disease burden (frequency & severity of sx, presence of tophi)
- Reassess indications for initiation of ULT with disease progression
  - Treat to target serum uric acid < 360 umol/L or < 300 umol/L if tophi present