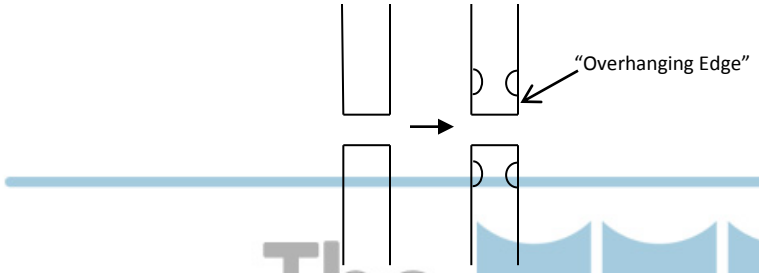
Crystal Induced Arthritis

Gout

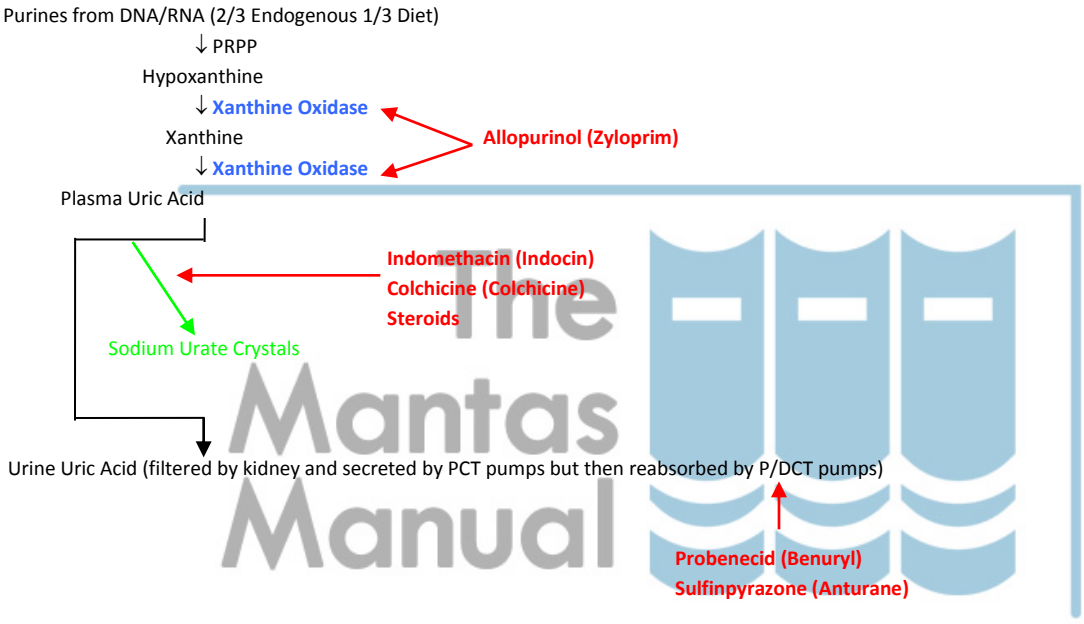
- Epidemiology
  - adult male (rare in women especially premenopausal b/c estrogen promotes uric acid excretion)
  - Occurs more commonly in pts with SLE and sickle cell disease vs occurs less commonly in pts with RA
  - Even though humans have the uricase gene which would breakdown uric acid, it is non functional, teleologically speaking b/c uric acid is an antioxidant and its benefit in this capacity likely outweighs its risk of gout, thus the only way for uric acid to be eliminated is by renal excretion and secretion>reabsorption
- Pathophysiology
  - Crystallization of monosodium urate in joint (synovial fluid, bursa, tendon sheaths) 2/2 increased urate levels, after crystallization IgG coat the crystals which stimulate phagocytosis by PMNs leading to inflammation with specific cytokines (IL-8, Leukotriene B4, Complement, TNF)
    - Increased Production (10%) consider if young pt and high 24hr uric acid secretion (>800mg/d)
      - underactivity of hypoxanthine guanine phosphoribosyltransferase (HGPRT) (eg. X-Linked Lesch-Nyhan Syndrome)
      - overactivity of phosphoribosyl pryophosphatase (PRPP) (eg. X-Linked ?)
      - cell death and thus release of contents (eg. chemotherapy, chronic hemolysis, hematologic malignancies, Paget's, psoriasis)
      - increased conversion of ATP to AMP which is in turn converted to uric acid (eg. alcohol)
    - Decreased Excretion (90%) consider in old pt and low 24hr uric acid secretion (<800mg/d)
      - CKD 2/2 HTN, DM, et al
      - Secretion transporter genetic heterogeneity
      - Substances that compete with secretion transporter (eg. thiazide diuretics, cyclosporine, any acids: organic acids, lactic acid, alcoholism resulting in starvation resulting in ketoacidosis, et al)
  - Crystallization Precipitants
    - Decreased temperature
    - Dehydration
    - Stress (both physical and emotional)
    - High Purine Diet (eg. esp meats/fish)
    - Obesity
    - Trauma/Surgery
    - IV Contrast
    - Acute Alcohol (above)
    - Acute Drugs (above)
- Clinical Features
  - Stage 1 Asymptomatic Hyperuricemia
    - Pt can have hyperuricemia for decades before the onset of symptoms HOWEVER this does not mean that pts should be treated b/c 95% of hyperuricemic never produce symptoms
  - Stage 2 Acute Gouty Monoarthritis
    - Sudden onset of exquisite (eg. bed sheet is too painful!!!) pain involving one joint in the lower extremity often waking the pt up b/c usually occurs at night, accompanied by visible inflammatory signs including desquamation/pruritus after resolution, if untreated the attack last 7-14d but usually pts present acutely b/c maximizes w/in 12hrs
      - 1° First Metatarsophalangeal (MTP) Joint aka "Podagra" Why? Lowest temperature
      - 2° Feet/Ankles and Knees
      - 3° other more proximal and more upper extremity joints
      - 10% polyarticular ESP in women who use thiazides
  - Stage 3 Intercritical Gout
    - After the first attack there is an asymptomatic period which varies in duration until the next attack which usually involves more joints with increased severity and increased frequency
      - Have next attack in <1yr (60%)
      - Have next attack in >1yr (30%)
      - Never have an attack again (10%)
  - Stage 4 Chronic Tophaceous Gout and other complications
    - Only occurs in pts who have poorly controlled gout for decades resulting in aggregation of urate crystals surrounded by giant cells forming non inflammatory "tophi" which cause deformity and destruction of joints extending to surrounding cartilage, bone, and soft tissue (just like rheumatoid nodules)
      - Extensor Joint Surfaces of Elbows, Knees, Ankles
      - Earlobe and Eyelid
      - Under skin at points of trauma
      - Aortic Wall and Cardiac Valves
    - Chronic Degenerative Poly-Arthritis: seen in 15% of pts, more chronic joint pain without true acute attacks, looks like seronegative RA
    - Nephrolithiasis: seen in 1% of pts

- Screening & Diagnosis
  - Clinical: monoarticular to polyarticular, men, uric acid stones
  - Joint Aspiration of Synovial Fluid (Arthrocentesis): **Needle**-Shaped, **Negatively** Birefringent (**yellow** under parallel light vs **blue** under perpendicular light) Crystals, need this for diagnosis, cannot be based on clinical picture, labs, x-ray, NB the presence of crystals does not mean that the arthritis is crystal induced, there have been many cases where a pt has infectious arthritis on a background of chronic currently asymptomatic gout, therefore always check culture, Gram stain, and cell count with differential, 2,000-20,000 (but sometimes up to 100k) WBC/mm^3 w/ 50-70% PMNs
  - Labs: Serum Uric Acid is NOT helpful because it does always correlate with attacks but the higher the level the higher the risk for developing gout, urate crystallizes and deposits at physiologic pH when concentration is >6.7mg/dL (but note that this level is in the "normal" range), in the setting of chronic hyperuricemia acute increases and even decreases in uric acid can precipitate an attack, during attacks urate can be low b/c it is depositing in tissue and not floating around in blood, recently a correlation between urate levels and CAD, metabolic syndrome, and HTN has been noted
  - X-ray: punched out erosions with overhanging rim of cortical bone lateral to where synovium attaches to bone (not at the exact point where synovium attaches to bone or in the joint itself) such that it looks like a "rat bite", lobulated soft tissue masses on extensor surfaces with some underlying bone erosions representing tophi, nl mineralization, nl joint space, asymmetric but bilateral



    - NB unlike RA which has symmetric non-overhanging (meaning at synovial attachment) erosions
- Prevention & Treatment
  - Acute Treatment
    - Fluids, Bed Rest, Avoid Above Precipitants
    - Inhibit Inflammation
      - 1° NSAIDs
        - indomethacin (Indocin)
          - Other NSAIDs are also effective BUT REMEMBER THAT SALICYLATES ARE CONTRAINDICATED (although anti-inflammatory concentrations (high) of salicylates are uricosuric, analgesic concentrations (low) of salicylates antagonize the uricosuric effect of probenecid and sulfinpyrazone and thus salicylates should not be used in conjunction with other uricosuric drugs)
      - 2° Microtubule Polymerization Inhibitors (preventing chemotaxis/phagocytosis)
        - colchicine (Colchicine)
          - Secondary treatment b/c 80% of pts develop diarrhea and ab pain if given enterally and multiorgan failure and death if given parenterally
          - Only effective for a few days
          - Chronic usage can result in reversible axonal neuropathy, vacuolar myopathy, and BM suppression in the setting of renal/hepatic insufficiency or concomitant usage of macrolides, statins, cyclosporine which can inhibit its metabolism
      - 3° Enteral/Intra-Articular Corticosteroids
        - prednisone
          - Tertiary treatment b/c steroids!!!
  - Prevention
    - NB when you start preventative treatment YOU MUST concurrently start acute treatment w/ ESP colchicine but can use NSAIDs/steroids (difficult b/c long term SEs) for a few weeks before and 6-12mo after!!! b/c changes in uric acid levels stimulate attacks
    - Avoid Above Precipitants
    - Adjuvants: losartan, vitC, fenofibrate
    - Before you treat pharmacologically be sure that pt has chronic gout (aka $\geq$2 attacks/yr) b/c the second attack may take years to occur if at all and thus the risk-to-benefit ratio for prophylaxis is not favorable after 1 attack
    - Target Urate Level: <6mg/dL
    - Tx is lifelong never stop
    - If Urine Uric Acid is >800mg/d then you want to decrease production
      - Xanthine Oxidase Inhibitor
        - allopurinol (Zyloprim)

        - the precursor (hypoxanthine) accumulates but it is more soluble and thus is able to excreted more easily
        - SEs: hypersensitivity reaction including SJS, N, V, D, drug interactions esp in pts w/ renal insufficiency
    - febuxostate (Uloric) good in pts w/ allopurinol hypersensitivity
- If Urine Uric Acid is <800mg/d then you want to increase secretion by decreasing reabsorption
  - PCT Reabsorption Inhibitors aka Uricosuric Agents
    - sulfinpyrazone (Anturane)
    - probenecid (Benuryl)
    - NB contraindicated in pts w/ uric acid stones b/c these agents precipitate them
    - NB give w/water and bicarb to ensure that it stays in its ionized form so that it forms sodium urate rather than staying as uric acid b/c sodium urate is more soluble than uric acid therefore prevents precipitation
    - NB excretion of other drugs can be altered in the presence of uricosuric agents
    - SEs: rash and GI upset



Psuedogout (Calcium Pyrophosphate Deposition Disease - CPDD)

- Epidemiology
  - Less common than gout and pts are usually older (but in this population quite common --- 4% of pts >72yo) however this condition may occur in young pts with calcium homeostasis abnormalities
- Pathophysiology

  ATP
  ↓ NTPPPH (found in synovial fluid)
  PPi ⟶ binds with calcium to form calcium pyrophosphate crystals in joints leading to an inflammatory process
  ~ to gout
  ↓ Alkaline Phosphatase
  Orthophosphate

  - Old Pt: primary cause is idiopathic but usually associated with
    - Hypothyriodism
    - Hemochromatosis
    - OA
    - Trauma/Post-Op (a very common and yet unrecognized cause of post-op fever)
  - Young Pt: consider conditions below
    - Increased NTPPPH
    - Increased Calcium (esp HyperPTH, HypoPO4, HypoMg)
    - Decreased Alkaline Phosphatase
    - Mutations of ANKH transporter which is involved in PPi transport out of joint
- Clinical Features
  - It is called psuedogout b/c it mimics the acute arthritis seen in gout
  - Wrists esp the trapezioscaphoid joint and 1st carpometacarpal joint

- Screening & Diagnosis
    - Clinical: monoarticular to polyarticular
    - Joint Aspiration of Synovial Fluid: **Rod**-Shaped, weakly **Positively** Birefringent (**blue** under parallel light vs **yellow** under perpendicular light) Crystals, 2,000-20,000 (but sometimes up to 80k) WBC/mm^3 w/ 50-70% PMNs
    - Labs: similar to urate, calcium levels do not correlate, check Mg, TSH, Fe, UA, et al
    - X-ray: **chondrocalcinosis** (cartilage/meniscus calcification) esp in the wrist, knee, vertebra, symphysis pubis
- Prevention & Treatment
    - Prevention: treat the underlying disorder
    - Treatment: ~gout with NSAIDs being the main treatment modality

Hydroxyapatite aka Basic Calcium Phosphate (BCP) Disease

- Seen w/ aging
- Nonbirefringent crystalline calcium phosphate apatite deposition
- Large minimally inflammatory shoulder / knee effusions with destruction of rotator cuff / knee ligaments aka “Milwaukee Shoulder”, “frozen shoulder”, and calcinosis cutis