GOUT

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Objectives

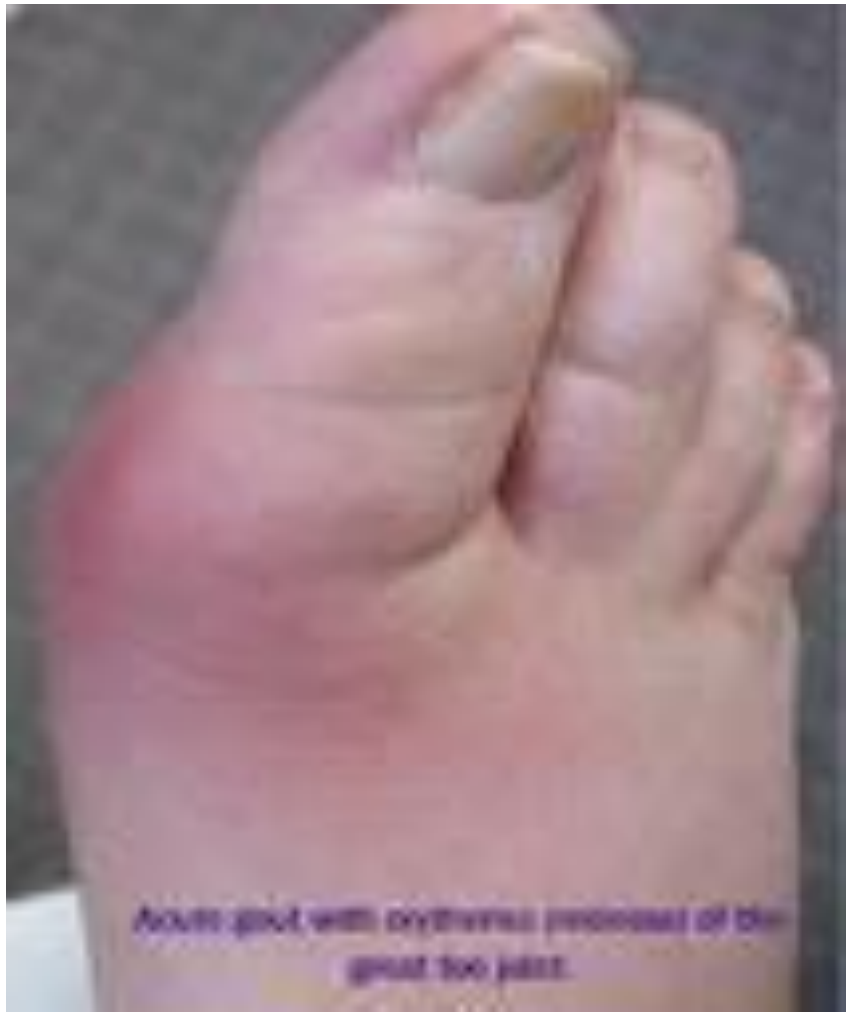
- Describe clinical presentation of gout
- Identify drug & non-drug risk factors for gout
- Compare treatment options for acute gout attacks
- Describe options for control of hyperuricemia / prophylaxis of gout attacks

GOUT - Definition

- Gout is an inflammatory reaction to monosodium urate crystals.

Intro – Gout

- Most common inflammatory arthritis in elderly
  - Increasing prevalence
  - Highest 75-85 y.o.
  - Men > women, (< 65y.o.)
- Deposition of urate crystals in tissue
- Gout in women
  - Usually > 65 y.o.
  - Loss of estrogen induced uricosuric effect



Pathophysiology

- **Precipitation** of monosodium urate crystals in avascular tissues
  - (cartilage, epiphyseal bone, periarticular bone)
  - Hyperuricemia likely asymptomatic for years
- The acute attack - crystals activate plasma proteases
  - Can activate factor XII & C5
  - Can adsorb opsonins in area, attracting phagocytes!

Risk Factors

- Purine rich foods & nutritional supplements
  - ?only animal source?
- Drugs
  - Thiazides
  - Low dose ASA
    - (< 1g/day?)
  - Niacin
  - Cyclosporin
  - Pyrazinamide & ethambutol

Risk Factors

- Obesity & excessive weight gain, (especially in youth)
- Moderate to heavy alcohol intake
- High blood pressure
- Abnormal kidney function
- Leukemias, lymphomas, and hemoglobin disorders
- Trauma & Surgery

Uric Acid Homeostasis

Urate is constantly near its limit of solubility, in a flux balance between production and elimination.

PRODUCTION: Breakdown of purines from nucleic acids

Xanthine oxidase transforms hypoxanthine via xanthine to uric acid.

ELLIMINATION: kidney- 10% of filtered load is excreted

Simultaneous reabsorption and secretion processes.

Proximal tubule, reabsorb filtrated urate anions in exchange for intracellular organic anions such as lactate or ketone bodies

Hyperuricemia

Hyperuricemia in 90% caused by inadequate renal elimination.

Above Serum levels of 6.8 mg/dl (MSU) crystals are forming somewhere in the body. The higher the serum levels over time, the higher the probability of an eventual attack of gout.

CRYSTALIZATION: dependent on pH, nucleating partners and temperature.

Urate is less soluble in synovial fluid and articular cartilage, especially in peripheral joints, is colder than adjacent tissue for lack of blood supply. Therefore, crystallization is likely to initiate in small peripheral joints.

Principles of Management

1. Terminate acute attacks
2. Prevent recurrence & reverse complications
   - Eliminate urate crystals from joints & tissues
3. Address co-morbid conditions
   - Obesity
   - Hypertriglyceridemia
   - Hypertension
   - Diabetes mellitus
   - Excessive alcohol

1) Treatment of Acute Attacks

- Directed at WBC inflammatory response

Options:

NSAIDs

Colchicine

Corticosteroids

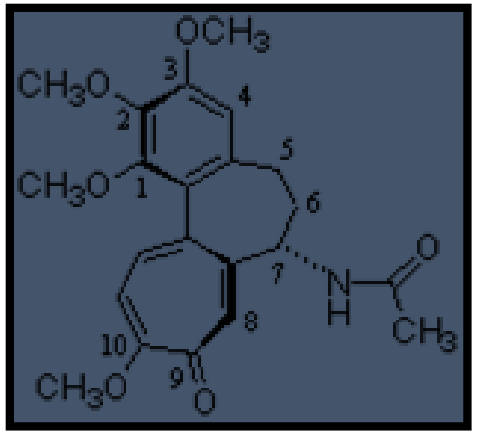
- Choice depends on **co-morbidities & history**
- **More importantly** – *rapidity* of treatment selection!
  - Keep agent close at all times; start ASAP PRN
    - Esp with poor renal function, slower response = *increased* drug exposure over course of a flare

NSAIDS

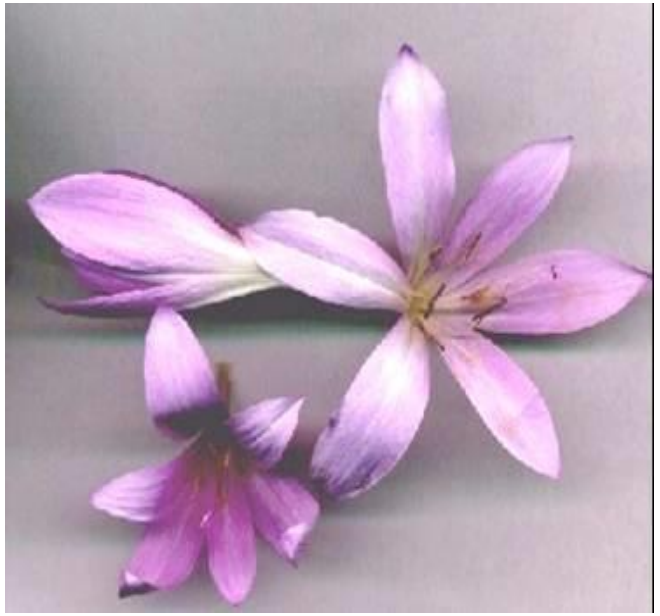
- Choose based on: Toxicity, Cost, Convenience
  - CrCL
    - Avoid in CKD
  - Risk of ADRs
    - (N/V/D, GIB, fluid retention, ARF, etc)
  - Cost & availability
    - Rx vs OTC
  - For elderly: Choose shorter half-life (t½)
    - Ibuprofen (2-4hrs); diclofenac (2hrs); indomethacin (4.5hrs);
    - Avoid in CHF, CKD, peripheral edema, PUD/GERD
    - N.B. increased risk of GIB with concurrent ASA, even 81mg!
      - Consider adding a PPI

Colchicine

- Used for centuries
- Most specific agent in use
  - Decreases leukocyte motility
    - Binds to tubulin and inhibits microtubule formation, arresting neutrophil motility
  - Decreases phagocytosis in joints
    - Decreases lactic acid production
- **<u>OVERALL EFFECT:</u>**
  - *Interruption of inflammatory process*
  - PO or IV
    - Avoid IV - Potentially fatal if mis-dosed!
      - Risk of arrhythmia



Colchicum autumnale
(autumn crocus)
(meadow saffron)



Colchicine

- 1 mg & 0.6 mg tablets - scored
- <u>Alternative regimens</u>
  - 1mg loading dose, then 0.5mg q2-6hrs

  OR
  - 0.5 - 1mg TID

  OR
  - 1.2mg initially, then 0.6mg BID
- Most effective w/i first 12hrs of attack
- Dose low! Try TID dosing first
- D/C if GI distress develops

Corticosteroids

- Reserved for:
  - Intolerant of NSAIDs or colchicine
  - Co-morbidities that prohibit use of other meds
- Good alternative for elderly w/ poor renal function
  - Few trials – choice is empiric
  - Eg. Prednisone 20-60mg /day PO
    - Are lower doses less effective?
      - Noted flares in transplant patients on 7.5-15 mg/day
  - Methylprednisolone 125mg/day IV or IM q1-4 days prn
    - Can give intra-articular – avoid if joint is septic!
    - Use smallest gauge needle (esp if on Warfarin)

Summary
Treatment of Acute Attacks

- Start treatment A.S.A.P.!
- Avoid **NSAIDs** in CKD, CHF
- Consider a PPI for **NSAIDs** + **ASA** or Hx of PUD
- Avoid / Reduce **colchicine** dose in CKD, liver dz, neutropenia, on diuretics, statins, or cyclosporin
- Do not change doses of any med that can alter urate levels when treating acute attacks
- Consider **NSAIDs, colchicine, steroids** at low doses and in combination (different MOA's)

2) Preventing Recurrence

- **Must eliminate excess body urate**
  - Else tophi may continue to enlarge
  - Destructive, chronic mononuclear cell inflammatory response that destroys cartilage and bone, resulting in chronic arthritis
- High likelihood of recurrence
  - 62% w/i 1 yr
  - 78% w/i 2 yrs
  - 90% w/i 5 yrs

Hoskison, KT and Wortmann, RL

Ref: Drugs & Aging 2007;24(1):21-36

- Recommend urate levels < 360 umol/L
  - Normal range 140- 340 (Dynacare)

- At > 360umol/L, fluids are supersaturated and crystal can precipitate
- At < 360umol/L, deposits dissolve, mobilize and are eliminated

Recommendations:
Urate Lowering Therapy

- EULAR:
  - "with recurrent attacks, arthropathy, tophi or radiographic changes"
- US Panel:
  - "if tophaceous deposits, erosive changes on X-ray, or ≥ 2 attacks per year"
- Others:
  - "After first attack"
    - Disease declared, high rate of recurrence
  - "Based on frequency of attacks"
    - Since second attack may not occur for years

Preventing Recurrence

- **Recall:** *Lowering* urate can precipitate a flare!
  - Increased risk w/ more rapid & severe changes
  - ~ 25% of patients
- Start 2-3 weeks *after* flare resolved
  - Uricosuric agents - increase excretion
    - Probenecid
    - Sulfinpyrazone
  - Xanthine Oxidase Inh. – decrease production
    - Allopurinol – *agent of choice*
    - Febuxostat – new agent (ULORIC™)

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Avoiding Flares - Allopurinol

- Start Allopurinol at low dose and *titrate up* to avoid precipitating event
  - Eg. 100mg, increasing by 100mg q2-4 weeks to target dose
  - With renal dysfunction:
    - 50mg initiation, incr by 50mg

Febuxostat (ULORIC™)

- A non-purine, selective xanthine oxidase inh.
  - More potent than Allopurinol
- <u>Efficacy vs Allopurinol</u>:
  - Lower frequency of gout flares
    - **N.B. Higher** frequency of flare with initiation at higher doses!
  - Improved serum urate lowering effect
  - Limited RCTs - need more evidence in:
    - Renal dysfunction, concomitant use of urate raising drugs (eg. ASA, thiazides), comparison against non-fixed doses of Allopurinol

See: Gaffo LA et al. Febuxostat: the evidence for its use in the treatment of hyperuricemia and gout. Core Evid. 2009; 4: 25–36. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2899777/?tool=pubmed Accessed Feb 7th, 2011.

Febuxostat (ULORIC™)

- Start **40mg daily** (+/- food)
  - Up to **80mg** or **120mg qd**
    - after 2 weeks if UA > 360 umol/L
  - CrCL > 30mL/min – no dose adjustment
  - CrCL < 30 mL/min – unstudied – avoid
- Side effects:
  - Rash (1% to 2%)
  - Liver function abnormalities (5% to 7%)
    - F/U LFTs in 2 & 4 months after starting tx
  - Arthralgia (1%)
- Cost: 80mg tabs ~ $65/ month;
  - (no ODB coverage)

- **Treat the same as allopurinol**

Avoiding Flares (2)

- Start prophylaxis before urate lowering therapy
  - Eg. Daily, low dose NSAID or colchicine 2-3 weeks before allopurinol
    - Eg. Colchicine 0.5mg or 0.6mg qd or tid
    - Eg. Indomethacin 25mg bid
  - Continue 3-6 months and/or [urate] < 360 umol/L

Note Bene (N.B.)

- No prophylaxis without urate lowering tx!
  - Acute flare prevented but crystal deposition in tissue continues!
  - Hence no warning signs of continued cartilage and bone damage and deposition in organs, especially kidneys!
  - Remember: Cochicine is NOT uricosuric!

Preventing Recurrence -Allopurinol

- Dosing:
  - 50mg to 800mg qd (usually 300mg)
  - N.B. Only 21-55% attain urate < 360 umol/L on "standard" dose
    - Most insufficient doses – main barrier to control
- **N.B**. Dose adjust for renal function
  - Dosing according to CrCL may not attain control
- **GOAL**: lowest dose to target urate < 360 umol/L

➢ ADRs: (well tolerated)

- Common:
  - GI upset,
  - Rash
    - (esp if on Amox/Amp or Cyclophosphamide)
- Rare:
  - Blood dyscrasias
  - Jaundice
  - TEN
  - Hypersensitivity Syndrome (including rash)
- If mild rash occurs, hold and re-challenge

Preventing Recurrence

Sulfinpyrazone:

- Up to 800mg /day divided bid
- Start: 100mg BID
  - Increase q1wk
- May decrease to 200mg/d once urate controlled
- ADRs: GI upset, rash

Probenecid:

- 500mg to 3g /day divided bid-tid
- Start: 250mg BID
  - Increase by 500mg q4wk
- May decrease by 500mg q6mo if stable > 6 mo till urate starts to rise
- ADRs: GI upset, rash

Summary of Gout Prevention

- High likelihood of recurrence
- Eliminate excess body urate to prevent chronic destructive changes
  - Colchicine is **not** uricosuric!
  - No prophylaxis without urate lowering therapy!
- Manage risk factors
  - Drugs, diet, co-morbidities
- Allopurinol – drug of choice
  - Start low, go slow
  - May have to push dose to attain control

3) Address Co-Morbid Conditions

- Obesity
- Hypertriglyceridemia
- Hypertension and Diabetes Mellitus
- Excessive Alcohol

Obesity & Hypertriglyceridemia

- Weight loss independently lowers urate levels
- Decreased alcohol consumption, regular exercise and weight reduction will lower TGs
  - Fibrates
    - Especially fenofibrate – mild uricosuric effect

Diet Restriction

- Total diet restriction only lowers urate levels by ~ 52.9 umol/L (1mg/dL)
  - Very unpalatable
  - Poor compliance
- Purine sources matter
  - Increase with meat & seafood
  - Decrease with dairy
    - Daily consumption lowers urate levels
  - Oatmeal and purine rich vegetables do not increase risk of gout
    - Peas, mushrooms, lentils, spinach, cauliflower

Dietary sources

High-Purine Content

- Anchovies
- Beer
- Bouillon (meat based)
- Brains
- Broth (meat based)
- Clams
- Consommé
- Goose
- Grain alcohol
- Gravy
- Heart
- Herring
- Kidney
- Lobster
- Mackerel
- Meat extracts
- Mincemeat
- Mussels
- Oysters
- Partridge
- Roe (fish eggs)
- Sardines
- Scallops
- Shrimp
- Sweetbreads
- Yeast (baker's and brewer's) taken as a supplement

Moderate-Purine Content

- Beans, dried
- Fish (except those in the high-purine content list)
- Lentils
- Meat (except those in the high-purine content list)
- Mushrooms