Hyperuricemia and Gout

Presenter – Dr Umar Jin

introduction

- An extremely painful condition, xtised by inflammatory arthritis, predominantly affecting males.
- Ass with hyperuricemia with serum URIC ACID levels of greater than 404.
- Humans lack uricase, hence cannot convert URATE to soluble ALLANTOIN, which is renally excreted.

- Rome Criteria for defn of gout
  - >7mg/dl uric acid in males
  - Painful joints, acute onset.
  - Urate crystals in synovium
  - Presence of tophi

  - *Any two sufficient to make the diagnosis*.

Epidemiology

- 6.1m adults in the USA have had gout, prevalence increase with age. M:F ratio is 3-4:1. sex disparity declines with age as Estrogen has Uricosuric effects.
- The incidence has doubled over the last 2 decades,
- Factors implicated,
  - 1) graying population and polypharmacy
  - 2) widespread use of diuretics , both loop and thiazides.
  - 3) altered dietary trends present
  - 4) low dose ASA due to increased incidence of NCDs.

diagnoses

- Gold standard is the aspiration with identification of NEGATIVELY birefringent MONOSODIUM URATE CRYSTALS. Done under polarized microscopy.
- Hyperuricemia may not be present during Acute Flares.
- Typical presentation
  1. Rapid devt of severe pain (within 24hrs)
  2. Erythema
  3. Swelling.

  1st metatarsophalangeal joint involvement, ie PODAGRA, upto 82% classic presentation.

Differential diagnoses

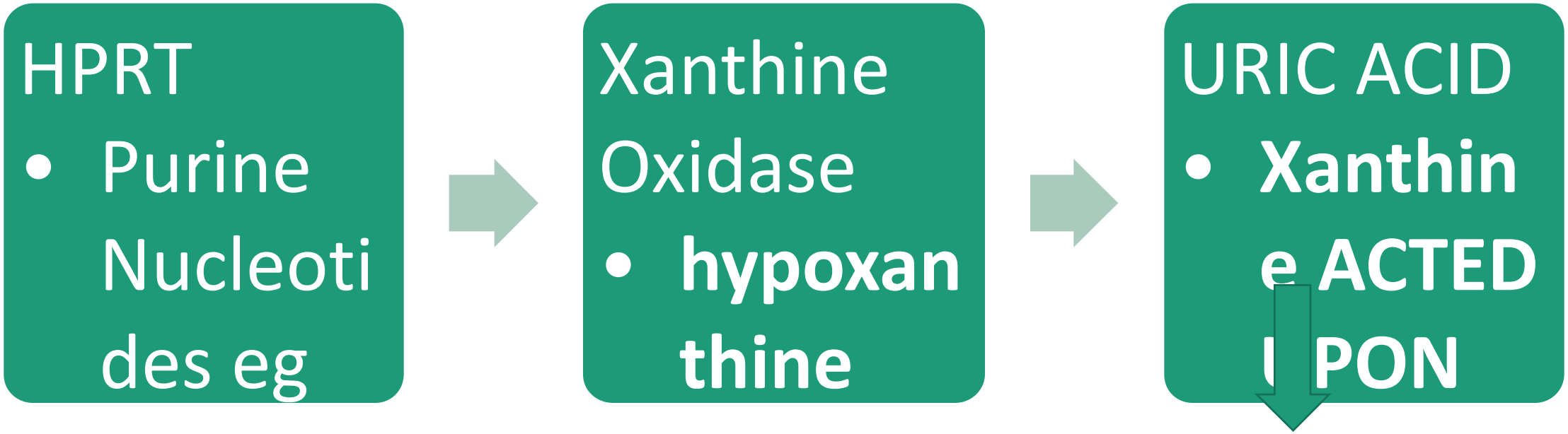
1. Other crystallopathies incl CPPD (calcium pyroPO4 dehydrate)
2. Septic arthritis (mandatory to do MCS and gram stain)

- Older females may present with polyarticular dse and may be mistaken for Rheumatoid arthritis.
- A diagnoses of gout promptly warrants evaluation of other risk factors, incl obesity, HTN, DM, Dyslipidemia.

Uric acid

- Small molecular weight, not bound to proteins, and easily filtered thro the glomerulus.
- The PCT responsible for renal handling of URIC ACID.
- The OATs, are gated channels responsible for the balance. The OATs also responsible for excretion of other organic acids eg lactic acid, ketones, alcohol.
- Most important OAT is the URAT-1.
- Excess of organic ions, eg lactic acidosis, ketoacidosis, these lead to URAT-1 transporter reabsorbing more of the uric acid in exchange for other organic ions, hence hyperuricemia.
- Uricosuiric agents eg losart, probenecid, sulphinpyrazone, benzbromarone and high dose ASA. These meds can displace uric acid from URAT-1 and lead to its excretion into the lumen with eventual loss into the urine. These drugs are CI in the event of nephrolithiasis.

So how is URIC ACID produced…



Pathogenesis of GOUT

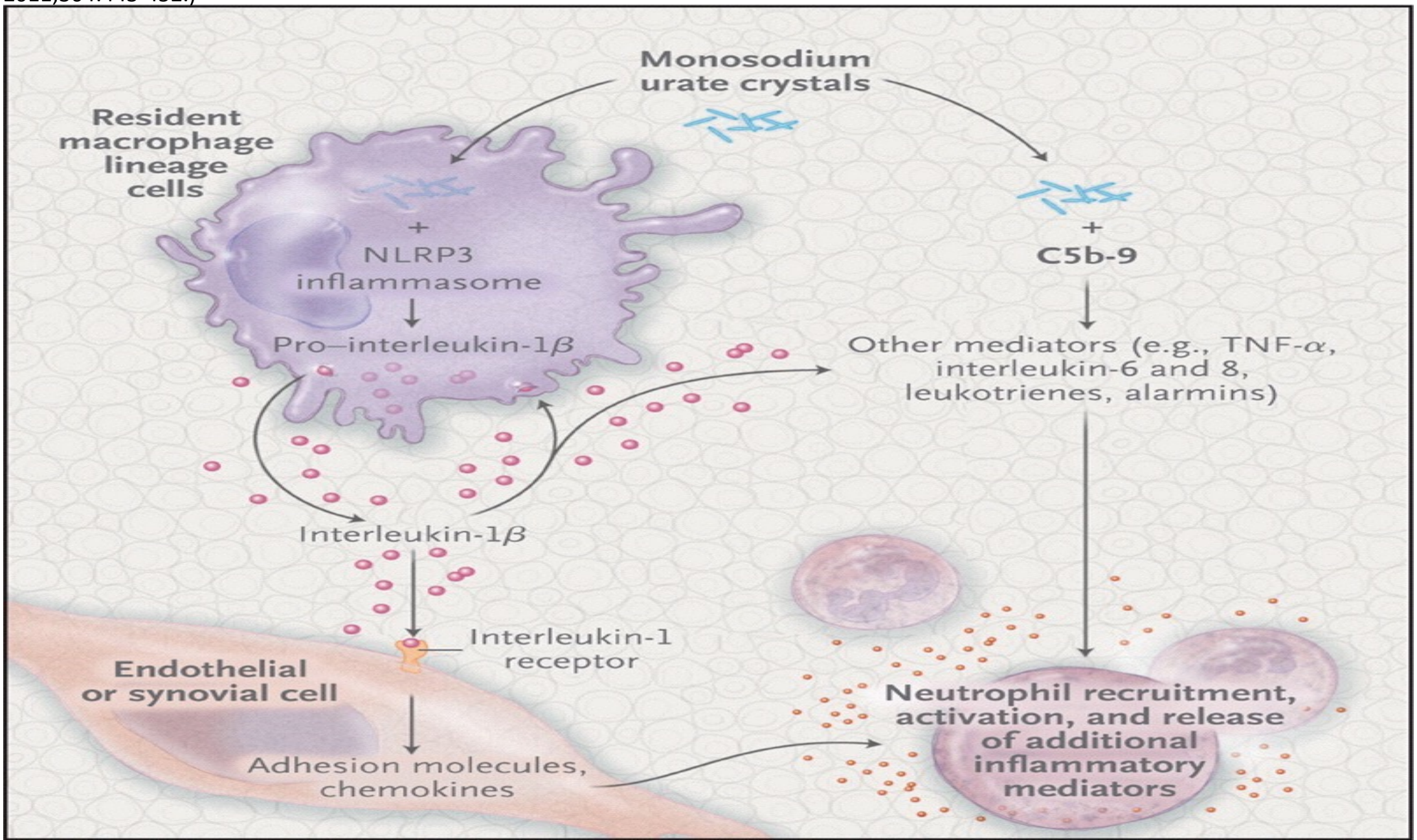
- Triggers present
  - Hypothermia
  - Low pH/acidosis
  - Dehydration esp joint, leading to supersaturation
  - Injury to the joint
- The MSU, made up of uric acid, present in the joint space crystallise with the above triggers. With crystallization, theres a nucleation factor, IgG, that promotes growth of MSU crystals. These crystals deposit into the joint spacelong before dx progresses. These are referred to as microtophi. These microtophi grow slowly onto the cartilage and synovial lining cells. When bone is injured, these microphi disintegrate and release the uric acid crystals into the joint space. These uric acid are considere foreign by the PRRs, and hence an interaction btwn them and Macrophages and dendritic cells ensues.
- The innate Immune response is activated.

Pathogenesis contd…

- These crystals also activate the complement pathways, (ALTERNATE pathway, (with activation of C3b, Bb, C3b, C5-9 Terminal-MAC)
- There's activation of NLPR3 inflammasome, once these MSU crystals undergo phagocytosis, with exponential release of IL1β.
- **IL1β** release leads to
  - IL1,6,8, TNF-α, NP chemotactic factor.
- The NPs have an oxidative burst with release of Arachidonic acid metabolites, TXA2, and more recruitment of inflammatory cells.
- Histamine , bradykinin, leads to vascular permeability, edema, and release of substance P and Neurokinin ⟶ pain mediators.
- Endothelial cell activation also occurs, ICAM/VCAM upregulation with activation of P, E and L selectins.
- There's also increased release of Nitric oxide with increased blood flow to the region.
- MSU are also known to activate the HAGEMAN factor, with formn of microthrombi and subsequent fibrinolysis.

PATHOGENESIS OF GOUT

(Neogi T. N Engl J Med 2011;364:443-452.)



Management principles in hyperuricemia

- Should be noted that not all patients with elevated uric acid develop gout. In one prospective cohort, over 5 yr period, gout developed in only 22% of those pts with uric acid levels greater than 535µM. (ie 9mg/dL)
- 2 phases present
- 1) acute intermittent self resolving attacks
- 2) chronic tophaceous gout
- Thus, Mx involves.. Pharmacologic vs non pharmacologic
- Pharmacologic – acute gout vs chronic tophaceous gout

Pharmacologic approach

- Purpose is to reduce flares, and decrease devt of tophi. Recommendation for therapy is for those pts with hyperuricemia, and 2 or more more gout attacks/year. And / or evidence of tophi (clinical / radiological)
- Urate lowering therapy should not be started during acute attacks but after 2-4 weeks post resolution.therapy is contd indefinitely.

Treatment plan…

- 1) **acute gout- rapid relief of pain caused by intense inflammation**
  a) **NSAIDS-** avoid use in renal/hepatic dysfxn, CCF or allergy. Useful one is CELECOXIB. Others incl, naproxen, indomethacin.
  b) **Colchicine** – 1.2mg orally stat, then 0.6mg BD. Can use with NSAIDs. Avoid/ decrease dose in pts with eGFR <30ml/min. can be used as weekly dose of 0.6mg. AE- diarrhea.
  c) Oral glucocorticoids eg prednisone. Start at 30-60 mg/day. For 2 days, taper dose. May be used in pts with moderate to severe renal insufficiency.
- These meds can be contd upto 7-10 days for effective terapy and prevent acute recurrences.

Treatment of Acute gout.

(adapted from NEJM)

Table 1. Pharmacologic Management Options for Acute Gout Attacks.

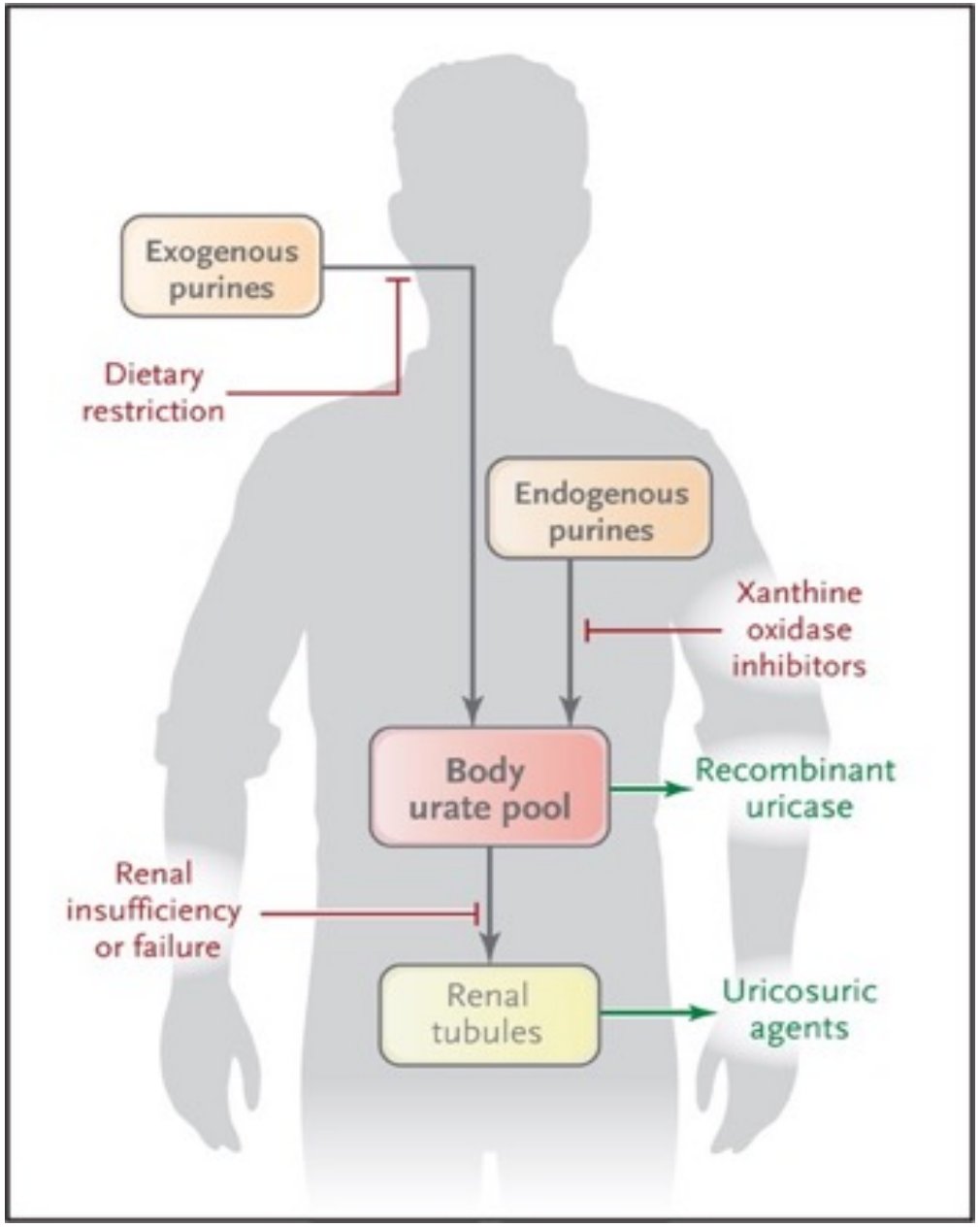
Drug	Examples of Regimens from Randomized Clinical Trials	Alternative Regimens for Complete Attack Resolution*	Precautions
Nonsteroidal antiinflammatory drug†			Avoid in patients with renal or hepatic insufficiency, bleeding disorder, congestive heart failure, or allergy; associated with an increased risk of adverse thrombotic and gastrointestinal events; may be administered with a proton-pump inhibitor in patients at risk for gastrointestinal events.
Naproxen	500 mg orally twice daily for 5 days	375–500 mg orally twice daily for 3 days, then 250–375 mg orally twice daily for 4–7 days or until attack resolves	
Indomethacin	50 mg orally three times daily for 2 days, then 25 mg orally three times daily for 3 days	50 mg orally three times daily for 3 days, then 25 mg orally three times daily for 4–7 days or until attack resolves	
Colchicine	1.2 mg orally at first sign of gout flare, followed by 0.6 mg orally 1 hr later	Consider additional acute gout regimen to continue managing attack 12–24 hr after colchicine regimen (e.g., 0.6 mg of colchicine twice daily, a nonsteroidal antiinflammatory drug regimen, or an oral glucocorticoid regimen until attack resolves)	Avoid (or use lower dose) in older adults and those with renal insufficiency, hepatic dysfunction, or known gastrointestinal symptoms; adjust dose (and avoid in patients with renal or hepatic impairment) if used in conjunction with P-glycoprotein or CYP3A4 inhibitors (e.g., cyclosporine, clarithromycin, certain antiretroviral agents, certain antifungal agents, certain calcium-channel blockers, and grapefruit juice); avoid for gout-flare therapy in patients with renal or hepatic impairment who are already receiving colchicine prophylaxis; monitor for gastrointestinal symptoms, myotoxicity, and blood dyscrasias (details are available at www.fda.gov).
Oral glucocorticoids (prednisone or prednisolone)‡	Prednisolone, 30–35 mg daily for 5 days	Prednisone, 30–60 mg daily for 2 days (depending on severity of attack), then reduce by 5–10 mg every 2 days (depending on starting dose) in 10-day taper	Use caution in patients with hyperglycemia or congestive heart failure; may be used in patients with moderate-to-severe renal impairment.

* Longer durations of therapy may be necessary for patients with long-standing disease and severe flares.
† There are no published trials establishing the efficacy of celecoxib, the only selective cyclooxygenase-2 inhibitor available in the United States, for use in acute gout.
‡ Although there are insufficient data to recommend the use of intraarticular glucocorticoid injection, it may be a useful alternative for attacks that are limited to one or two joints and amenable to aspiration and in the absence of joint sepsis.

Managing hyperuricemia

- First modality – dietary restriction

- Classes of drugs present
- 1) Xanthine Oxidase inhibitors –
- 2) uricosuric agents
- 3) uricase Analogs
- 4) IL1 Receptor Antagonists



Xanthine oxidase inhibitors

- Hypoxanthine 

Xanthine 

Uric acid  GIT 33% RENAL 66%

- Block synthesis of uric acid.
- 1) **allopurinol** – effective in reducing flares and tophi. Good maintenance therapy. 2% develop rash after therapy and severe HSR should never be rechallenged. Majority receive upto 300mg/d. daily doses of upto 800 have been used. Can cause hepatitis and nephrotoxic at higher doses, hence limited use.
- 2) **FEBUXOSTAT** – launched in 2009, daily doses of 40 – 80mg/day.
  - A)daily doses of 80mg/d – 2.5fold greater efficacy in reducing Serum uric acid levels compared to 300mg/d of allopurinol, over the same amount of time.
  - B) at 120 mg/d – 3 fold efficacy over Allopurinol.
  - Drug is safe in pts with RENAL IMPAIRMENT AND LESSER INCIDENCE OF HEPATOXIC EFFECTS AS COMPARED TO ALLOPPURINOL.

URICOSURIC AGENTS

- URIC ACID excess is 20 to
  - 1) renal uric acid underexcretion
  - 2) overproduction
- Renal urate underexcretion – accounts for upto 90% of pts with gout. These incl
  1. hypertensives,
  2. pts with acidosis (lactic, ketoacids, pyruvate excess, alcohol).
  3. Patients with nephron loss and CKD.
  4. Drugs eg HCTZ, low dose ASA, ethambutol, PZA, cyclosporine.
  5. Patients with Pb poisoning, Downs Syndrome and Berylliosis

Uricosuric agents

- Drugs e.g. Probenecid, Benzbromarone, Losartan, Sulphinpyrazone and High Dose ASA.
- These drugs displace the uric acid from the URAT – 1 transporter at the PCT and lead to its excretion in the urine.
- These agents are C/I in Nephrolithiasis.

Uricase analogs

- Uric acid 

allantoin

- The above happens in non primates, allantoin is a soluble molecule, easily excreted via urine.
- Pegloticase (2010 FDA approved) – must be given IV
- Rasburicase – approved for Tumor Lysis only, use in Gout limited literature.

IL 1 Receptor Antagonists

- Anakinra.. – shown to improve acute gout. Targets the IL 1 receptor, which is central to the pathogenesis.

- Rilonacept – not effective for acute pain relief, useful in chronic tophaceous gout.

Other modalities of drug therapy..

- 500mg/day Vit C – shown to decrease urate levels.
- Milk (and dairy produce) – upto 10% decrease in urate levels noted.. (? Uricosuric effects)
- Losartan + fenofibrate – useful combn in pts with HTN, Dyslipidemia and hyperuricemia.

Difficult GOUT…

- Gout intolerant to standard therapy…
  1. destructive tophi
  2. polyarticular gout
  3. allopurinol HSR
  4. renal insufficiency (eGFR <60ml/min)
  5. CVS, GIT, RENAL, DM, Hepatic dysfunction
  6. intolerant to NSAIDs.

Take home message

- Predominantly male disease. Extremely painful. Ass with hyperuricemia but not always.
- Triad of joint pain, swelling and erythema.
- Podagra – 1st metatarsophalangeal joint involvement.
- Renal urate underexcretion – predominantly the cause of Hyperuricemia. (90%)
- The Neutrophil response and IL 1 β are central in the pathogenesis.
- Treatment modalities incl Mx of acute pain (NSAIDs, Colchicine and Oral glucocorticoids) and
- Maintenance Mx for hyperuricemia (Xanthine oxidase inh ((febuxostat>>allopurinol)), Uricosuric agents, Uricase Analogs (pegloticase), IL 1 RA (anakinra)

thanks…