Drug Therapy of Gout

Modified By Dina Rafaiah

Drug therapy of gout

What Is Gout?

Inflammatory disorder caused by deposition of MSU crystals in joints

(So we wanna treat this inflammatory reaction or the cause of it "hyperuricemia")

For cases questions you need to know:

Gouty arthritis - characteristics

- sudden onset
- middle aged males
- severe pain
- distal joints
- intense inflammation
- recurrent episodes
- influenced by diet
- bony erosions on Xray
- hyperuricemia

→ High protein diet increases uric acid

Treating acute gouty arthritis

- colchicine
- NSAID's
- steroids
- rest, analgesia, ice, time

Drugs used to treat gout

(for the inflammation itself)

Acute Arthritis Drugs

- colchicine
- steroids
- NSAID's

Reducing inflammatory reactions (swelling, pain, redness ...) by inhibiting the production of inflammatory mediators (AA, PG, LTs)

(for the main cause)

Urate Lowering Drugs

- allopurinol
- probenecid
- febuxostat

Inhibits polymerization of microtubules → disrupting inflammatory responses (chemotaxis, inflammasome activation, generation of leukotrienes .....)

↳ All of these are mediated by rearrangement of cytoskeleton of the cell

rest + analgesia + time

Drugs used to treat gout

NSAID's (Analgesic + anti inflammatory)

- Indomethacin (~~Indocin~~) 25 to 50 mg four times daily
- Naproxen (~~Naprosyn~~) 500 mg two times daily
- Ibuprofen (~~Motrin~~) 800 mg four times daily
- Sulindac (~~Clinoril~~) 200 mg two times daily
- Ketoprofen (~~Orudis~~) 75 mg four times daily

* Doses of NSAIDs are usually higher for an anti-inflammatory effect compared with the analgesic dose

DONT MEMORIZE DOSES

Colchicine - plant alkaloid (Natural Source)

colchicum autumnale
(الزعفران البري)
(autumn crocus or meadow saffron)

Colchicine

- “only effective in gouty arthritis”
- not an analgesic
- does not affect renal excretion of uric acid
- does not alter plasma solubility of uric acid
- neither raises nor lowers serum uric acid

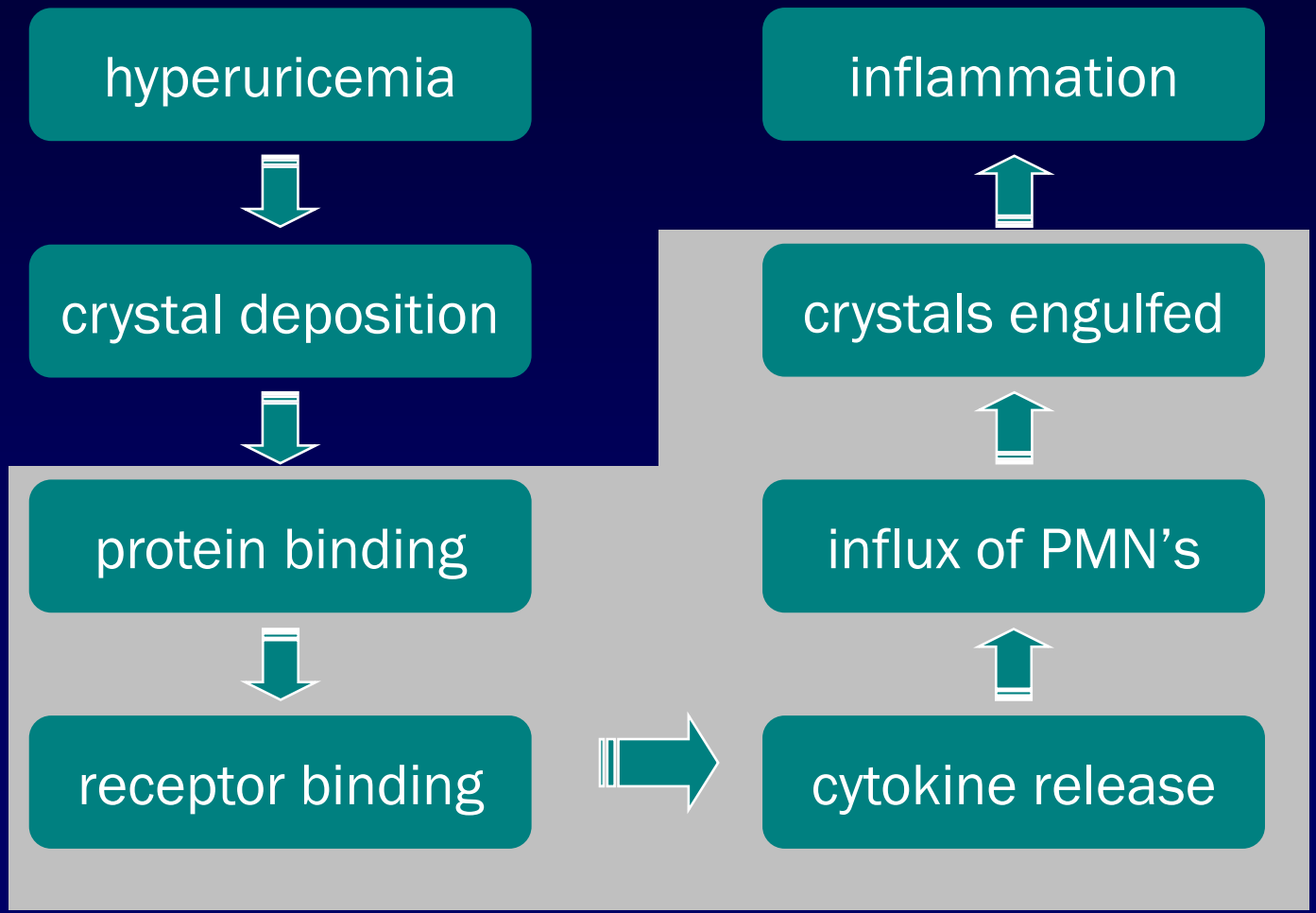
Colchicine Mechanism of action

- Colchicine inhibits (microtubule) polymerization by binding to tubulin, one of the main constituents of microtubules
- reduces inflammatory response to deposited crystals
- diminishes PMN phagocytosis of crystals
- blocks cellular response to deposited crystals

component of cytoskeleton, involved in cell division, inflammatory responses .....

very important for the inflammatory cascade

Crystal-induced inflammation



PMN is critical component of crystal-induced inflammation

Colchicine - indications

Dose	*Indication*
high	(treatment) of acute gouty arthritis
low	(prevention) of recurrent gouty arthritis

→ Because of its side effects ↓

Colchicine - toxicity

- gastrointestinal (nausea, vomiting, cramping, diarrhea, abdominal pain)

→ it affects cell division (remember the MOA) so it has side effects on blood cell production

- hematologic (agranulocytosis, aplastic anemia, thrombocytopenia)
- muscular weakness

adverse effects (dose-related) & more common when patient (has renal or hepatic disease)

Gout - colchicine therapy

- more useful for daily prophylaxis (low dose)
  - ✓ prevents recurrent attacks
  - ✓ colchicine ~~0.6~~ mg qd - bid

- declining use in acute gout (high dose)

Nowadays Colchicine isn't used as first choice drug for the treatment of gout, it's safer for low doses use (prophylaxis)

Hyperuricemia - mechanisms

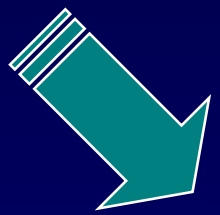
- excessive production
- inadequate excretion

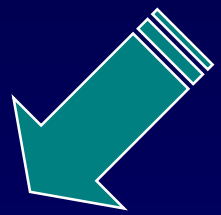
hyperuricemia

Urate-lowering drugs

✓block production

✓enhance excretion





net reduction in total body pool of uric acid

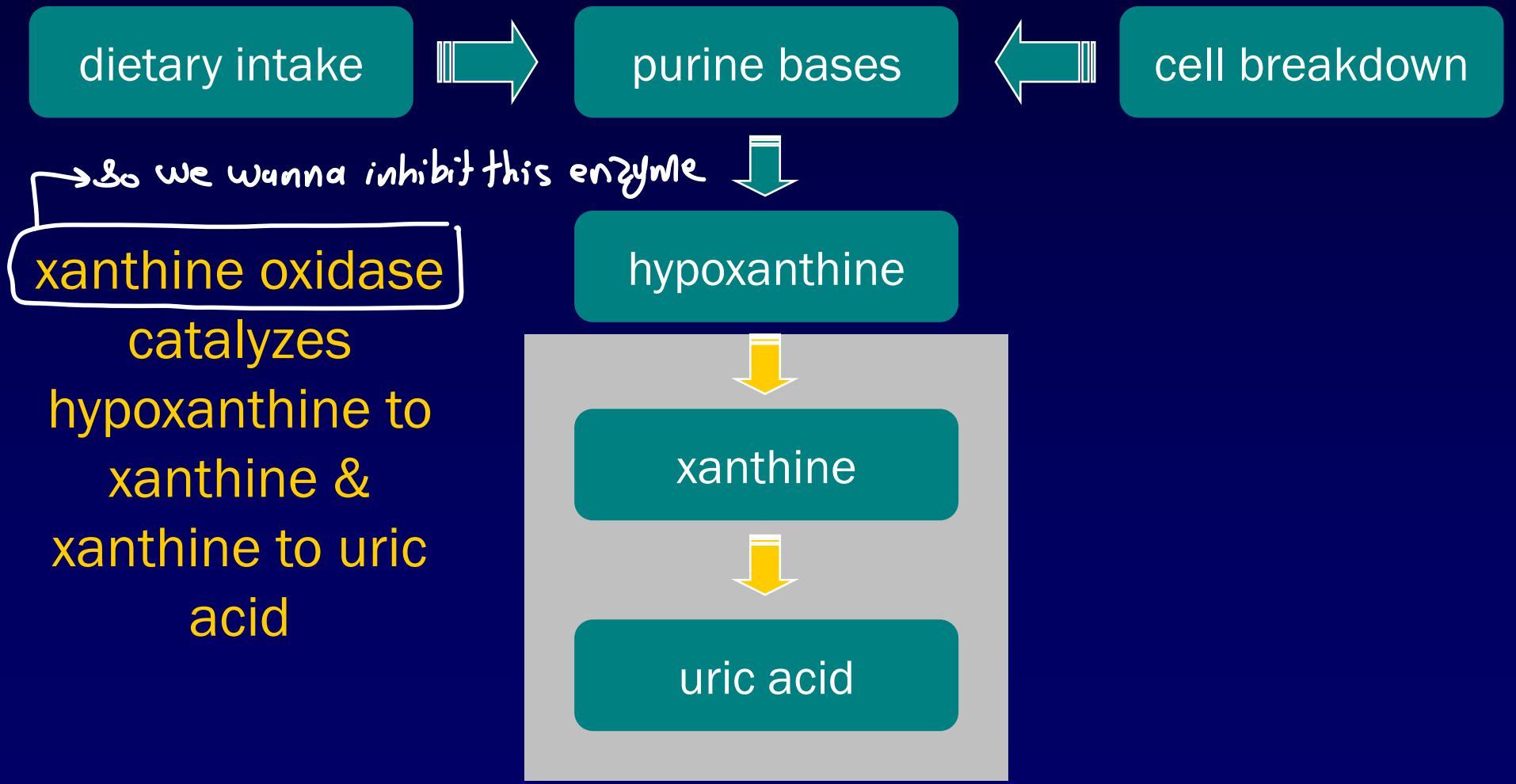
Gout - urate-lowering therapy

- prevents arthritis, tophi & stones by lowering total body pool of uric acid
- not indicated after first attack
- initiation of therapy can worsen or bring on acute gouty arthritis (it causes gout flares because it may cause mobilization of urate to kidneys and other joints)
- no role to play in managing acute gout

Drug therapy of gout

Drugs That Block (Production) of Uric Acid

Uric acid metabolism



Allopurinol (Zyloprim™)

- inhibitor of xanthine oxidase
- effectively blocks formation of uric acid
- how supplied - 100 mg & 300 mg tablets
- pregnancy category C
  - ↳ Can be used with cautions (No enough studies on human that have proven it can cause fetus malformations)

Allopurinol - usage indications

it's not used in acute attacks, it's used in between attacks so it's a maintenance therapy to prevent recurrent attacks

- management of hyperuricemia of gout and hyperuricemia of other conditions
- management of hyperuricemia associated with chemotherapy → Kills cells → degradation of its contents including purines
- prevention of recurrent calcium oxalate kidney stones

Allopurinol - common reactions

- diarrhea, nausea, abnormal liver tests
- acute attacks of gout
- rash

Allopurinol - serious reactions (Rare)

- fever, rash, toxic epidermal necrolysis → Similar to Stevens-Johnson syndrome (an autoimmune disease targetting mucous membranes)
- hepatotoxicity, marrow suppression
- vasculitis
- drug interactions (ampicillin, thiazides, mercaptopurine, azathioprine)
- death

Stevens-Johnson syndrome

- target skin lesions
- mucous membrane erosions
- epidermal necrosis with skin detachment

Febuxostat(Uloric /Adenuric)

- approved by FDA (2008)
- oral(xanthine oxidase inhibitor)
- chemically distinct from allopurinol
- minimal adverse events(compared with Allopurinol)
- can be used in patients with renal disease

PEG-uricase

An enzyme from natural Sources (animals)

- approved in the United States in 2010 Administered IV
- PEG-conjugate of recombinant porcine uricase (**urate oxidase**)
- !! it metabolises uric acid to allantoin !!

Indications

- severe, treatment-refractory, chronic gout.
- uricase speeds resolution of tophi
- it lowers uric acid levels
- glucose-6-phosphate dehydrogenase deficiency, pegloticase may precipitate a severe, life-threatening hemolysis

- Uricase → an enzyme that catalyzes the oxidation of uric acid to allatonin, Reducing its levels. So we wanna utilize this enzyme (found in animals) in the management of -Hyperuricemia-

For that to happen, PEGylation process should take place

⟹ PEGylation is intended to reduce immunogencity of uricase and greatly prolong its half life, and it's a process where multiple strands of polyethylene glycol (PEG) is attached to uricase.

Drug therapy of gout

Drugs That Enhance Excretion of Uric Acid

Uricosuric therapy

- probenecid
- blocks tubular reabsorption of uric acid
- enhances urine uric acid excretion
- increases urine uric acid level
- decreases serum uric acid level

Uricosuric therapy

- moderately effective
- increases risk of nephrolithiasis (it may cause mobilization of uric acid from joints to the kidneys)
- not used in patients with renal disease
- frequent, but mild, side effects

Uricosuric therapy

- contra-indications
  - ✓history of nephrolithiasis
  - ✓elevated urine uric acid level
  - ✓existing renal disease
- less effective in elderly patients (since Kidney functions deteriorate with age)

Choosing a urate-lowering drug