Drug Therapy of Gout

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Gouty arthritis - characteristics

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

Chronic tophaceous gout

tophus = localized deposit of monosodium urate crystals

Gout - X-ray changes

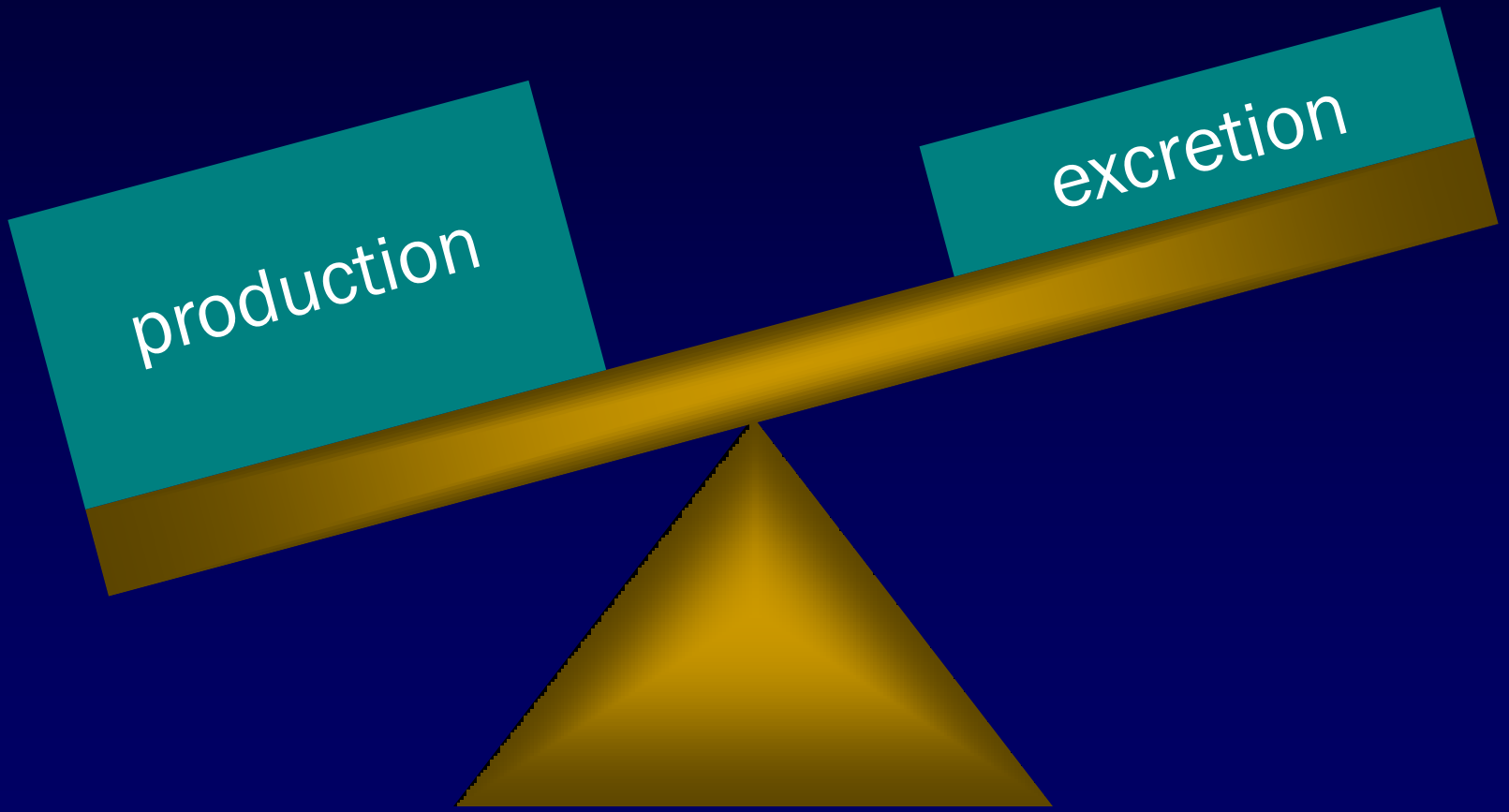
DIP joint destruction

phalangeal bone cysts

Gout - X-ray changes

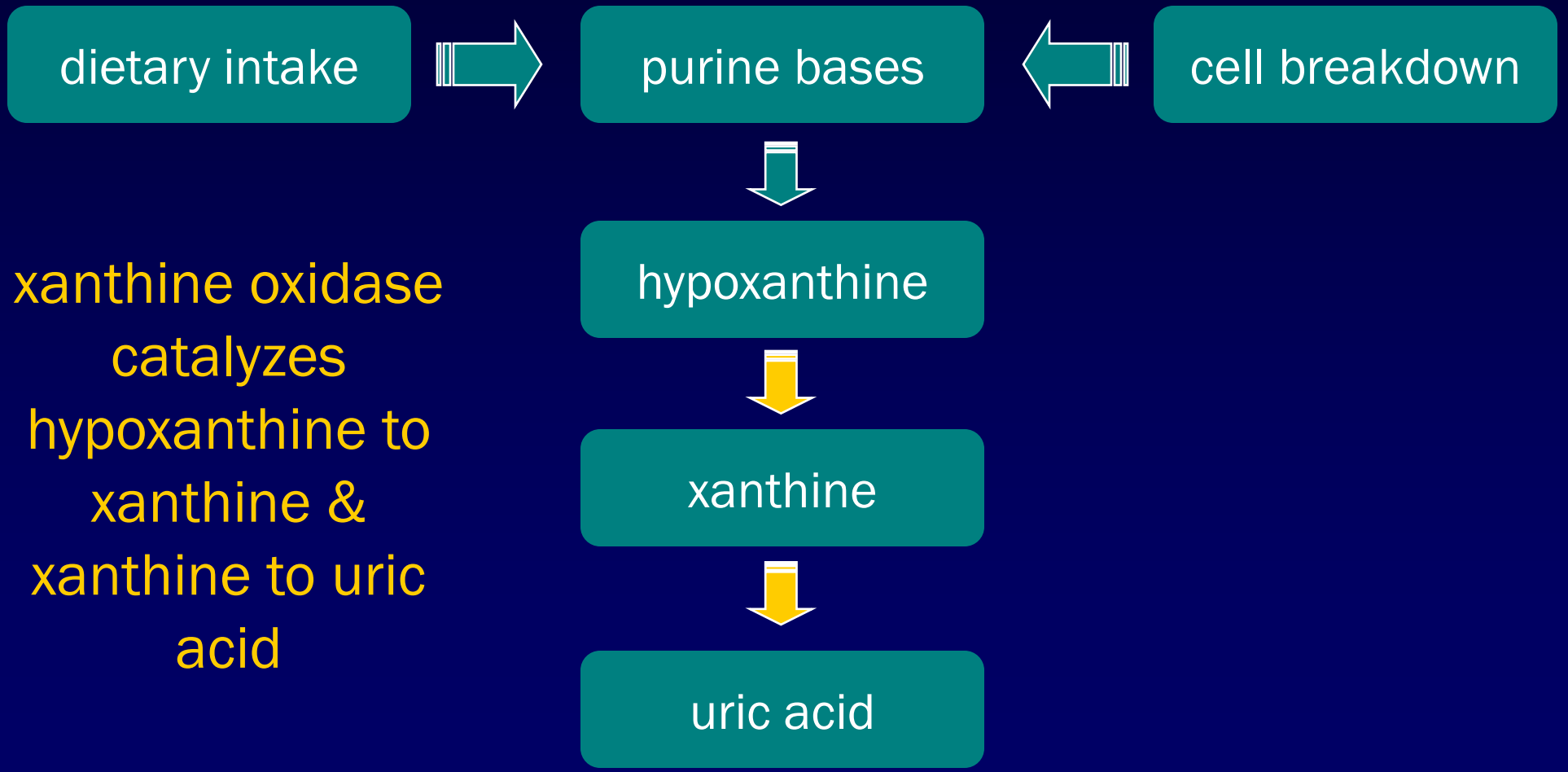
bony erosions

Hyperuricemia



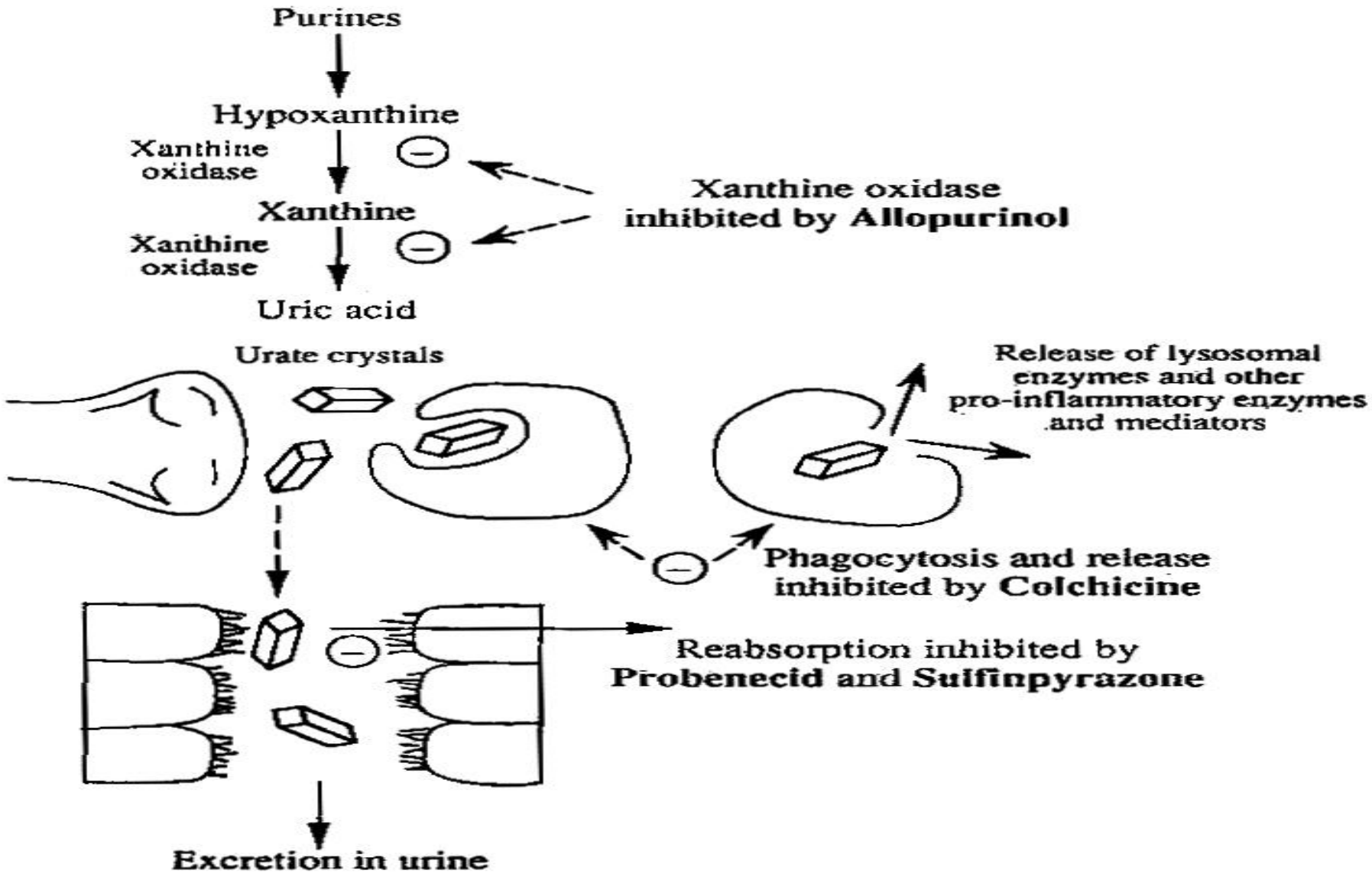
hyperuricemia results when production exceeds excretion

Uric acid metabolism



xanthine oxidase catalyzes hypoxanthine to xanthine & xanthine to uric acid

Treatment of Gout



Drugs used to treat gout

Acute Arthritis Drugs

- colchicine
- steroids
- NSAID's

Urate Lowering Drugs

- allopurinol
- probenecid
- febuxostat?

rest + analgesia + time

Non-steroidal anti-inflammatory drugs (NSAIDs)

- FDA approval for this indication
  - Indomethacin: 25–50 mg four times a day for 3 days, then taper to twice daily for 4–7 days
  - Naproxen: 500 mg twice daily for 3 days, then 250–500 mg daily for 4–7 days
  - Sulindac: 200 mg twice daily for 7–10 days
- Aspirin is **contraindicated**, because it competes with uric acid for the organic acid secretion mechanism in the proximal tubule of the kidney??

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 poorly understood
- reduces inflammatory response to deposited crystals
- diminishes PMN phagocytosis of crystals
- blocks cellular response to deposited crystals

Colchicine - indications

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

Colchicine - toxicity

- **Gastrointestinal** (nausea, vomiting, cramping, diarrhea, abdominal pain)
- **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)

Corticosteroids

- Corticosteroids may be used to treat acute attacks of gouty arthritis, but they are reserved primarily for patients:

  - with a contraindication or who are unresponsive to NSAID or colchicine therapy.
  - Patients with multiple-joint involvement may also benefit.

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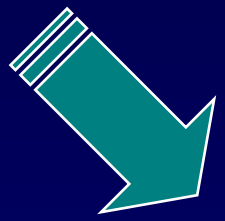
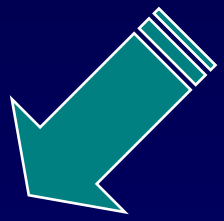
Urate-lowering drugs

block production

enhance excretion





net reduction in total body pool of uric acid

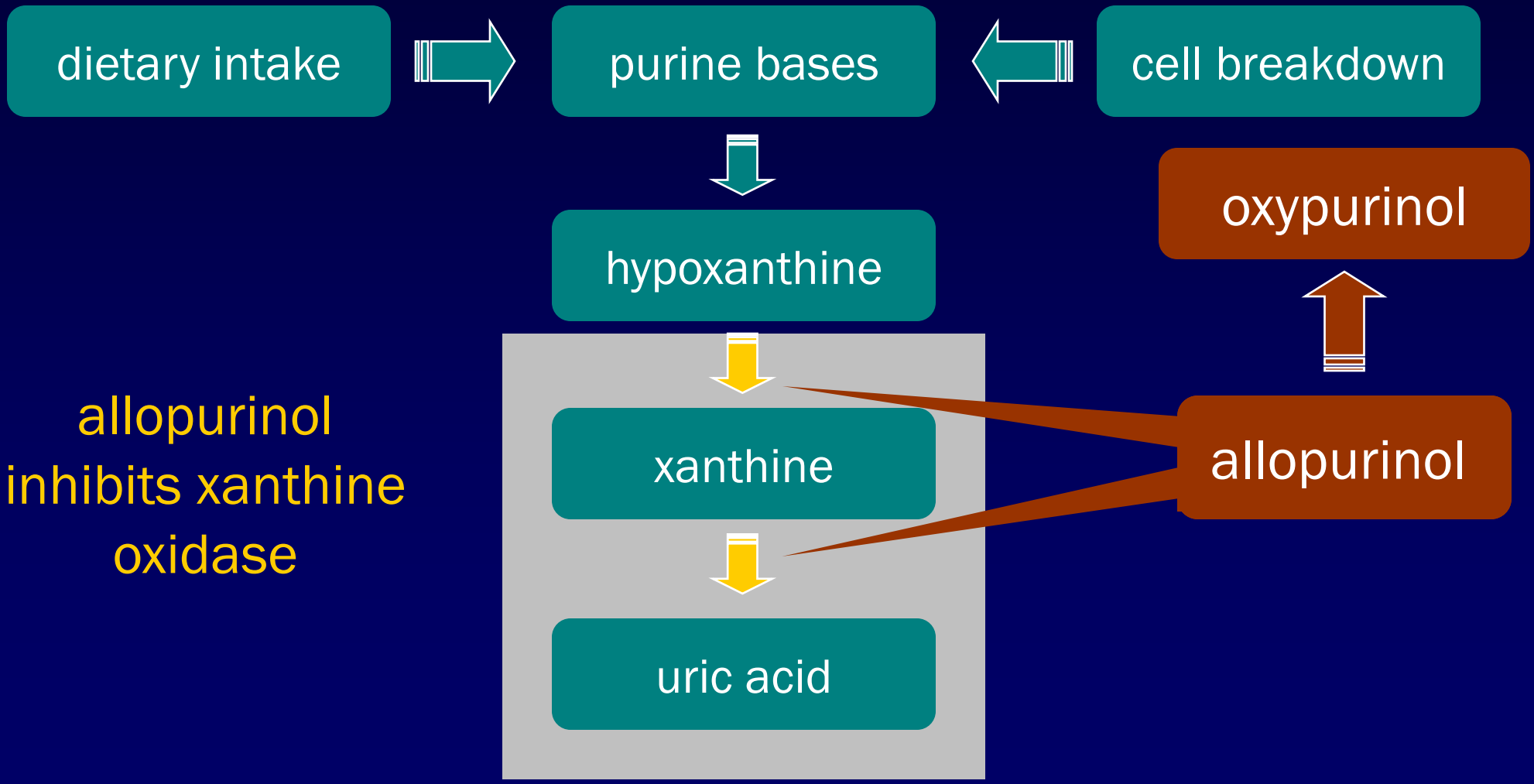
Gout - urate-lowering therapy

- 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
- no role to play in managing acute gout

Allopurinol

- inhibitor of xanthine oxidase
- effectively blocks formation of uric acid
- how supplied - 100 mg & 300 mg tablets
- pregnancy category C

Uric acid metabolism



Allopurinol

- 90% absorption from the gut
- metabolized to oxypurinol
- **once daily dosing**
- lowers serum uric acid levels
- lowers urine uric acid levels
- side effects rare, but potentially lethal

Allopurinol - usage indications

- management of hyperuricemia of gout
- management of hyperuricemia associated with chemotherapy
- prevention of recurrent calcium oxalate kidney stones

Allopurinol - common reactions

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

Allopurinol - serious reactions

- fever, rash, toxic epidermal necrolysis
- 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

Allopurinol hypersensitivity

- extremely serious problem
- prompt recognition required
- first sign usually skin rash
- more common with impaired renal function
- progression to toxic epidermal necrolysis & death

Febuxostat

- recently approved by FDA
- oral xanthine oxidase inhibitor
- chemically distinct from allopurinol
- 94% of patients reached urate < 6.0 mg/dl
- minimal adverse events
- **can be used in patients with renal disease**

Uricosuric therapy

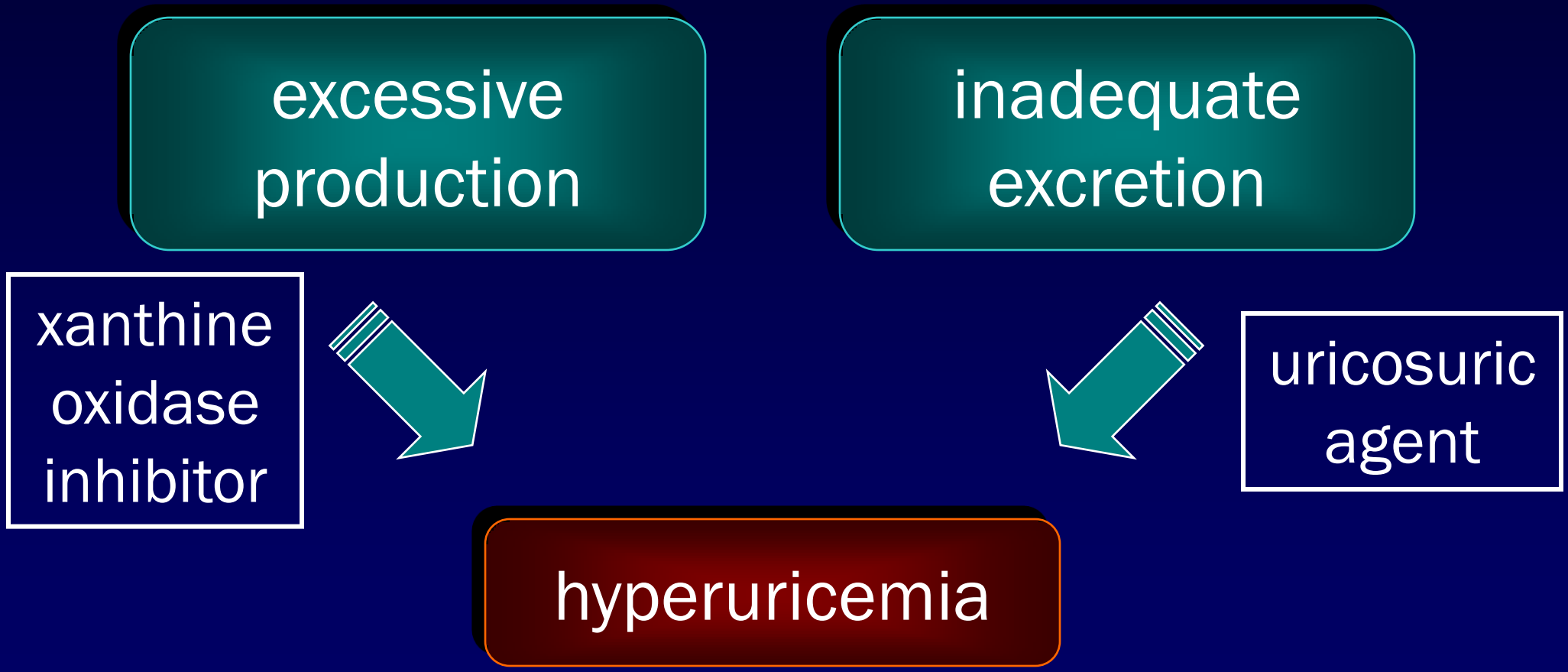
probenecid

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

Uricosuric therapy

- contra-indications
  - ✓history of nephrolithiasis
  - ✓elevated urine uric acid level
  - ✓existing renal disease
- less effective in elderly patients

Choosing a urate-lowering drug



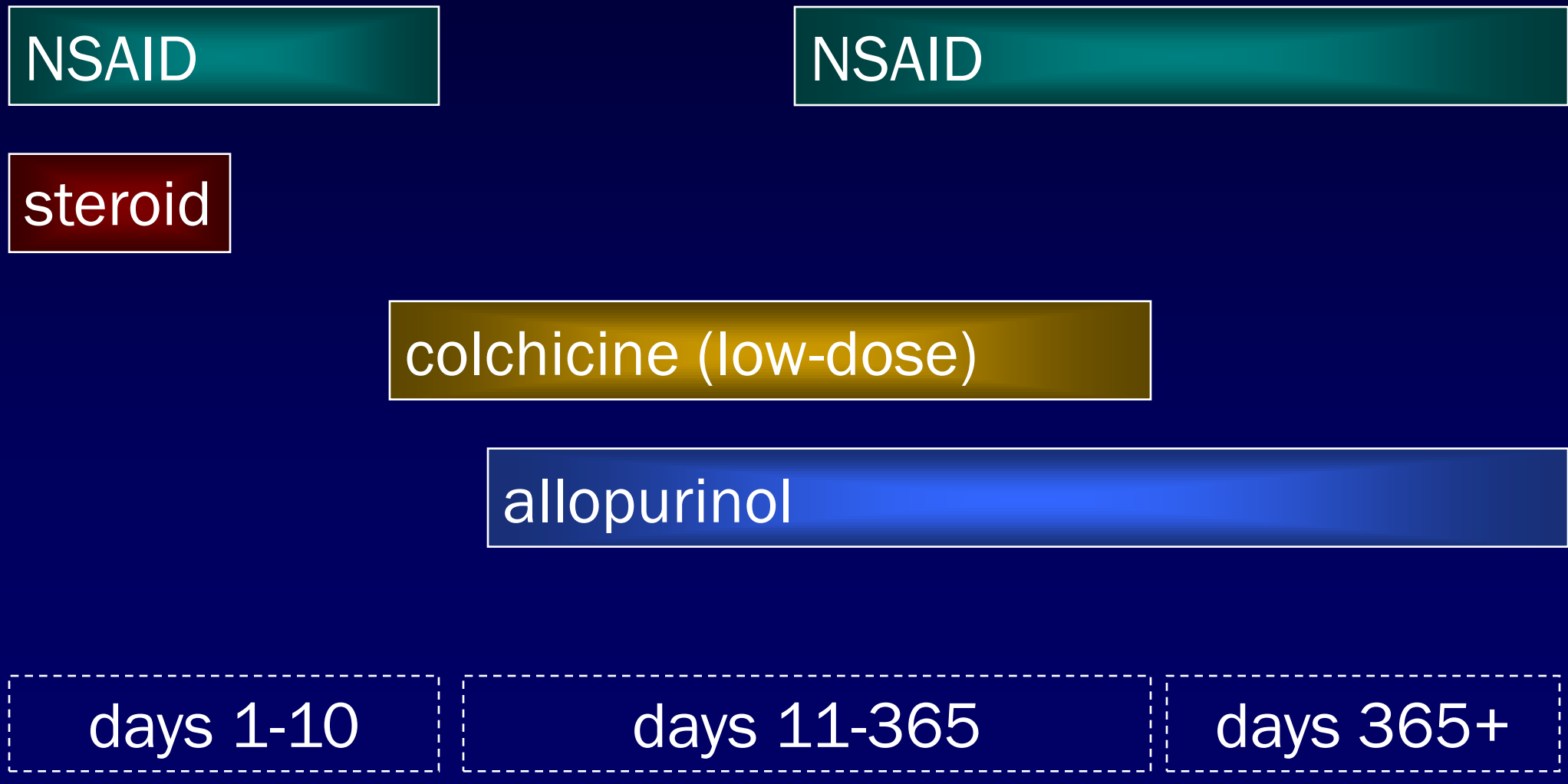
Urate-lowering therapy

- no anti-inflammatory activity
- can precipitate acute gout
- can prolong attack of gout

Prophylactic Therapy Of Gout

- Patients are candidates for **prophylactic therapy :**
  - if they have had more than two of gouty arthritis per year,
  - the first attack is severe or complicated with kidney stones,
  - serum urate is greater than 10 mg/ dL
- **Colchicine given in low oral doses (0.5 to 0.6 mg twice daily) may be** effective in patients with no evidence of visible tophi and a normal or slightly elevated serum urate concentration

Case presentation - therapy



Pegloticase

- Pegloticase is approved for the treatment of hyperuricemia in patients with treatment-refractory gout.
- Pegloticase achieves its therapeutic effect by enzymatically converting uric acid to the more soluble metabolite allantoin.

Clinical case

A patient presented with an attack of acute gout.
He was treated with a 10 day course of NSAID.
His blood uric acid level is high.

What future line of treatment ???????????

Select the first choice drug for acute gout:

a. Cochicine
b. Indomethacin
c. Allopurinol
d. Dexamethasone

Select the drug which is used in chronic gout but is not uricosuric:

a. Probenecid
b. Phenylbutazone
c. Sulfinpyrazone
d. Allopurinol


Best
Wishes