



Drug Therapy of Gout

Drug therapy of gout

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What Is Gout?

Gout - acute arthritis

acute synovitis,
ankle & first MTP
joints



The metatarsophalangeal articulations are the joints between the metatarsal bones of the foot and the proximal bones

Gout - acute bursitis

acute olecranon bursitis



Bursitis is inflammation of the fluid-filled sac (bursa) that lies between a tendon and skin, or between a tendon and bone

Gouty arthritis - characteristics



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

Monosodium urate crystals

needle shape

negative
birefringence

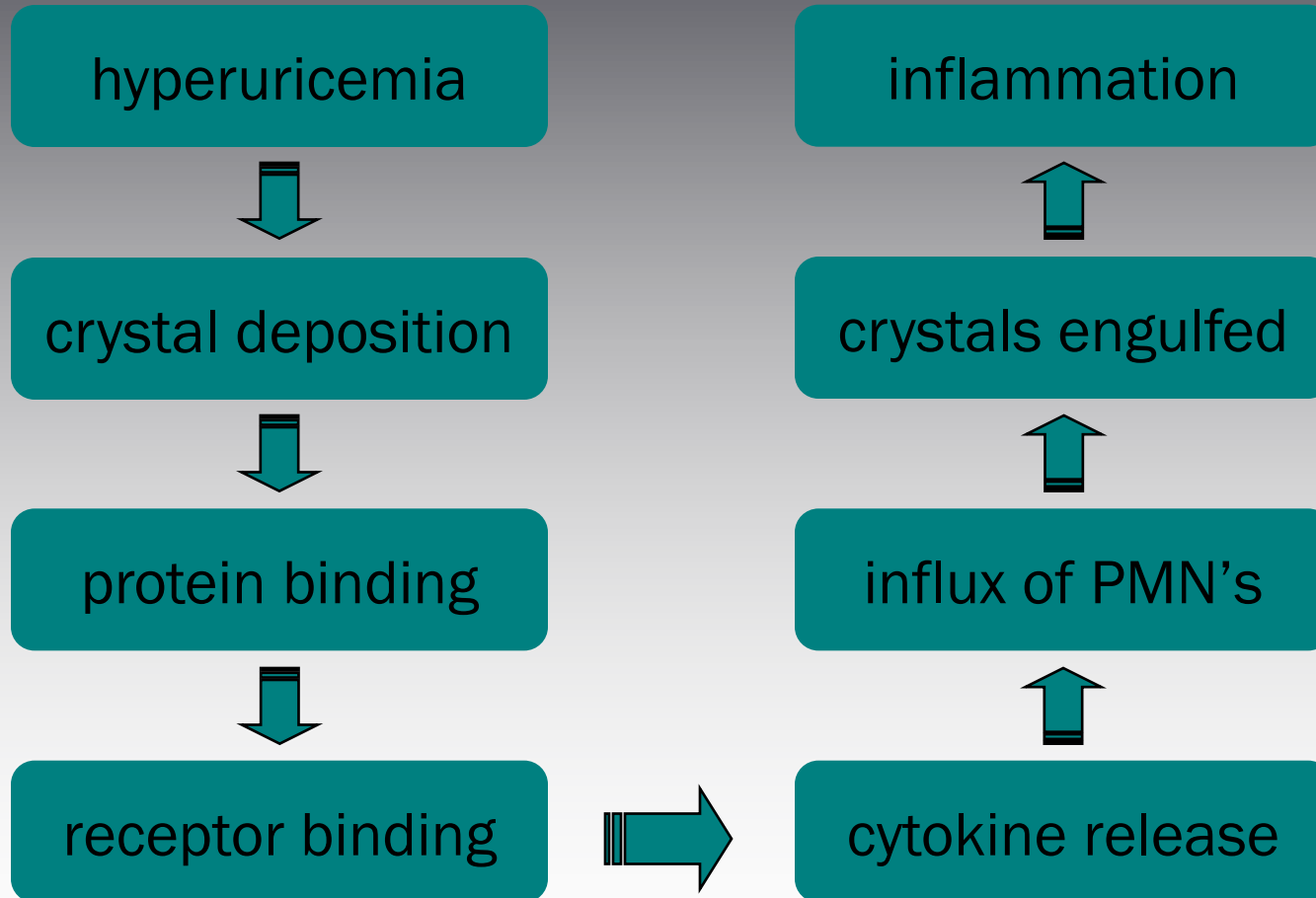


polarized light



red compensator

Crystal-induced inflammation



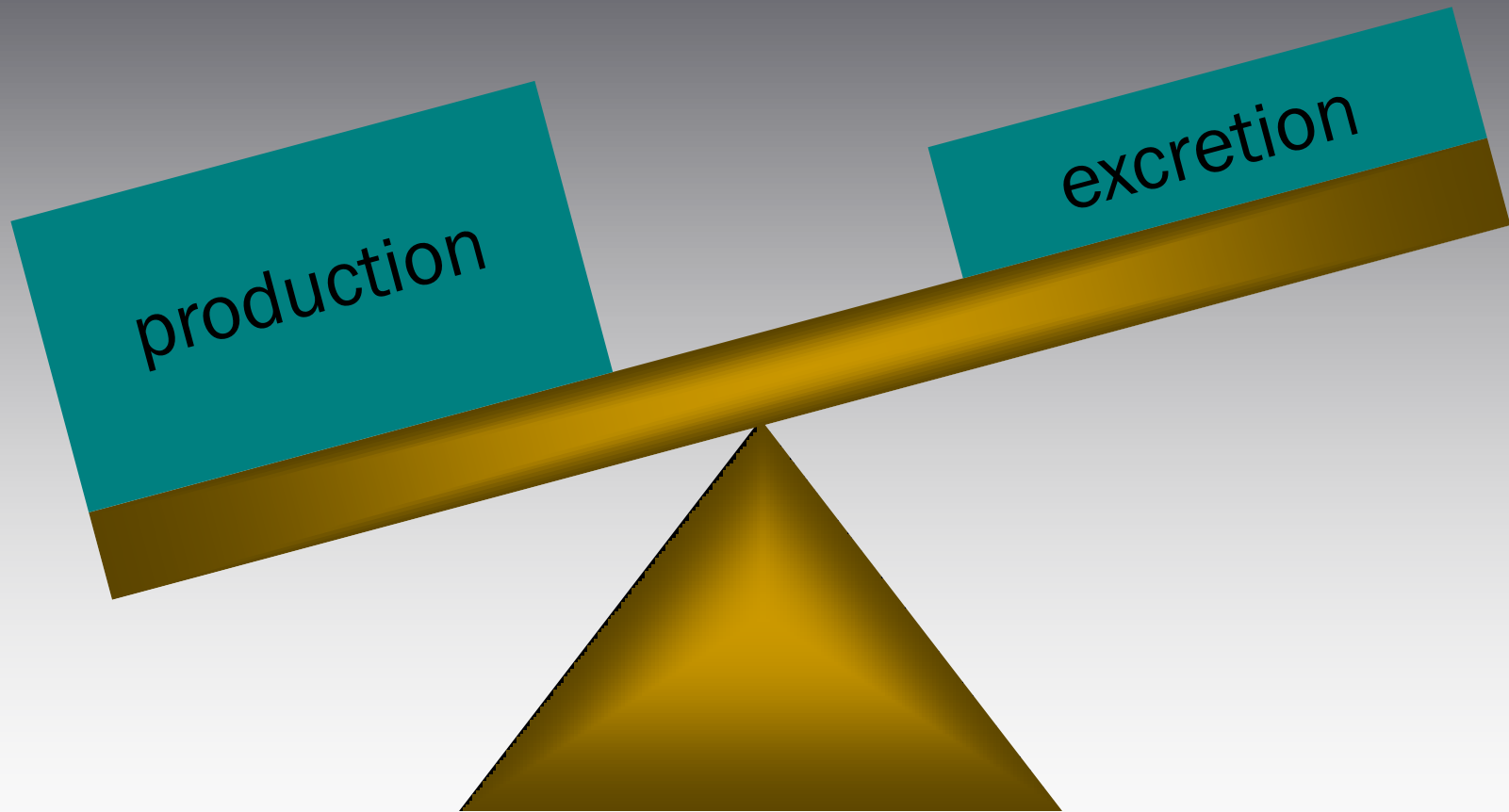
PMN is critical
component of
crystal-induced
inflammation

Gouty arthritis - characteristics



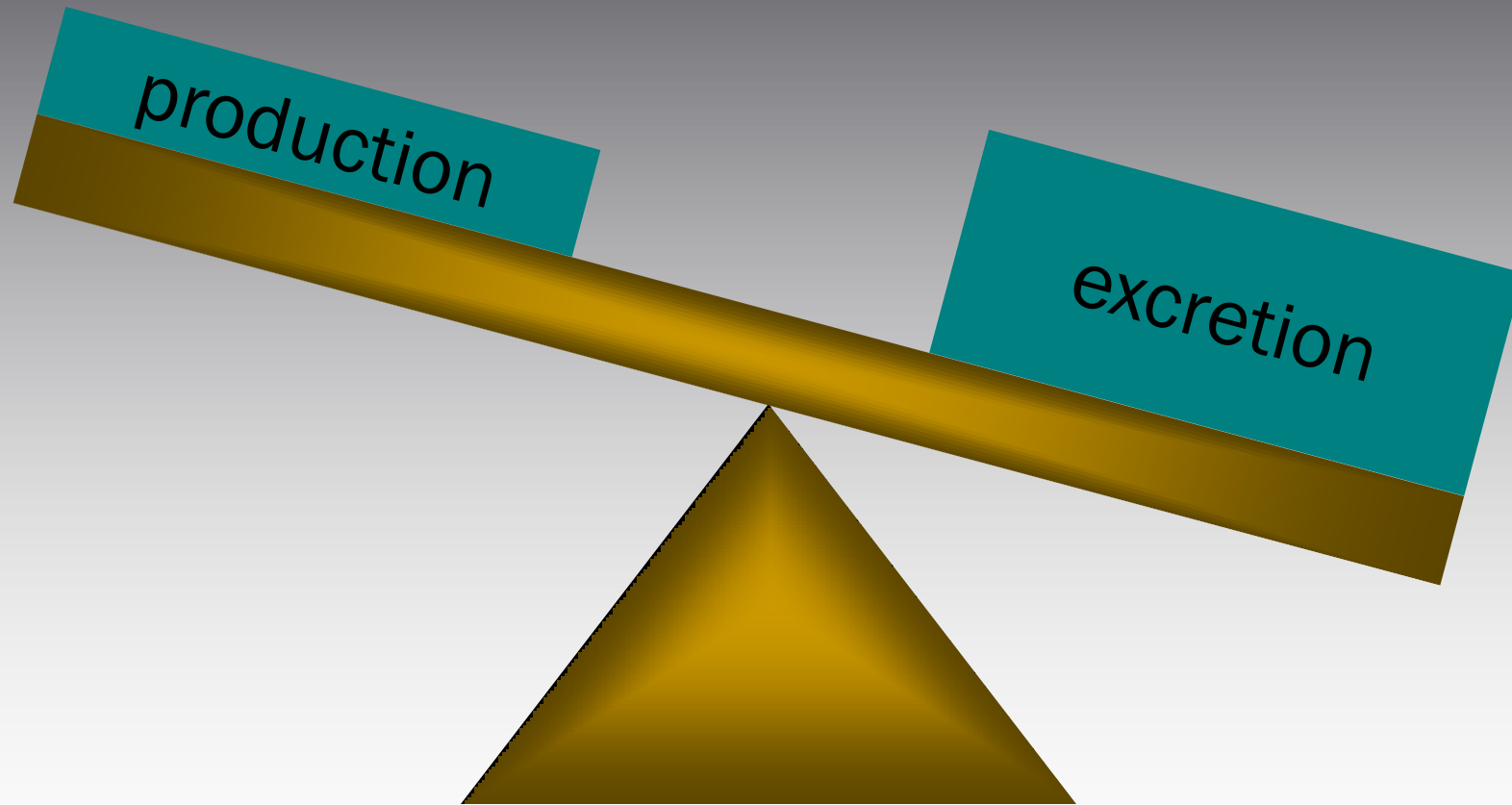
- sudden onset
- middle aged males
- severe pain
- distal joints
- intense inflammation
- recurrent episodes
- influenced by diet
- bony erosions on Xray
- hyperuricemia

Hyperuricemia



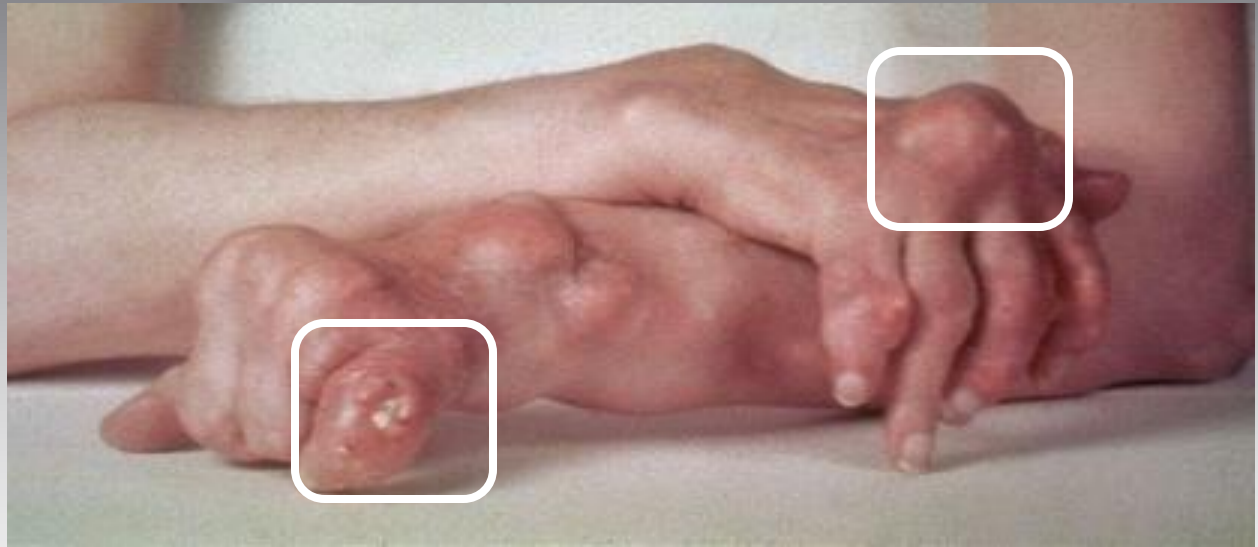
hyperuricemia results when production exceeds excretion

Hyperuricemia



net uric acid loss results when excretion exceeds production

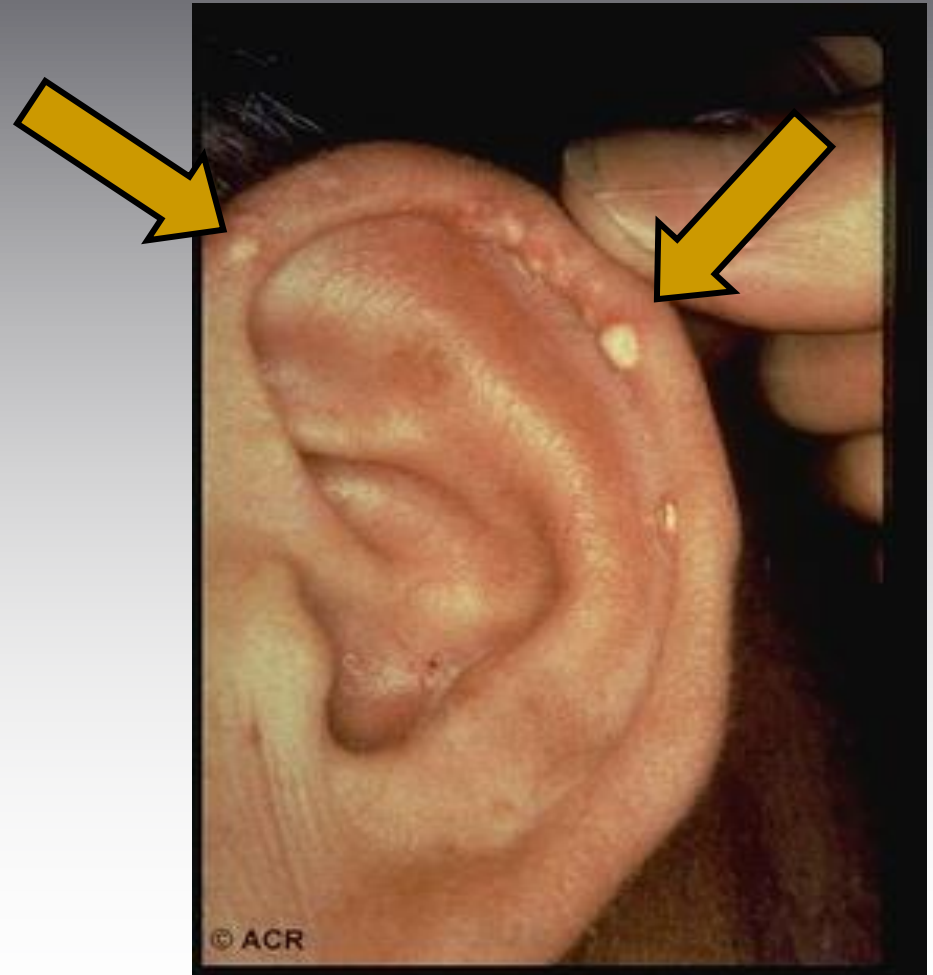
Chronic tophaceous gout



tophus = localized deposit of
monosodium urate crystals

Gout - tophus

classic location of
tophi on helix of ear



Gout - X-ray changes

DIP (*Distal
interphalangeal joint*)

joint destruction

phalangeal bone cysts

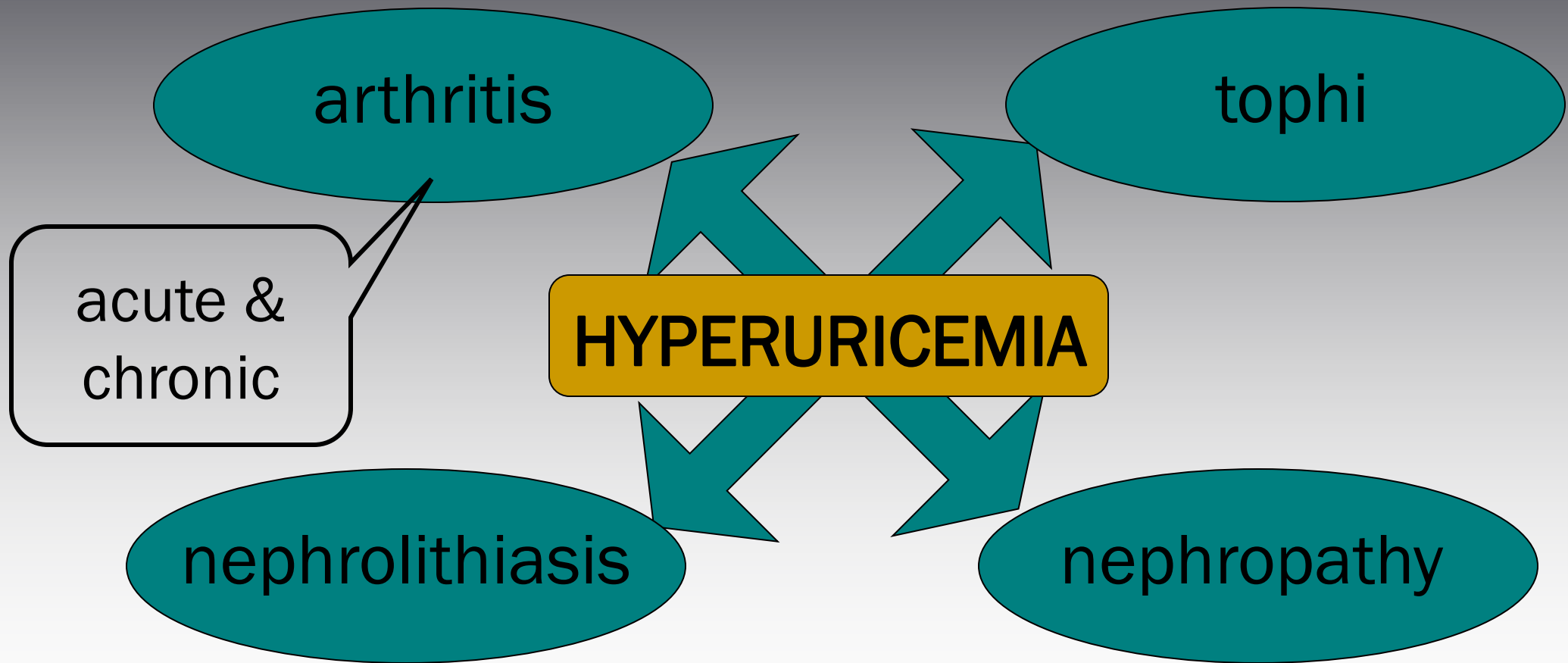


Gout - X-ray changes

bony erosions



Gout - cardinal manifestations

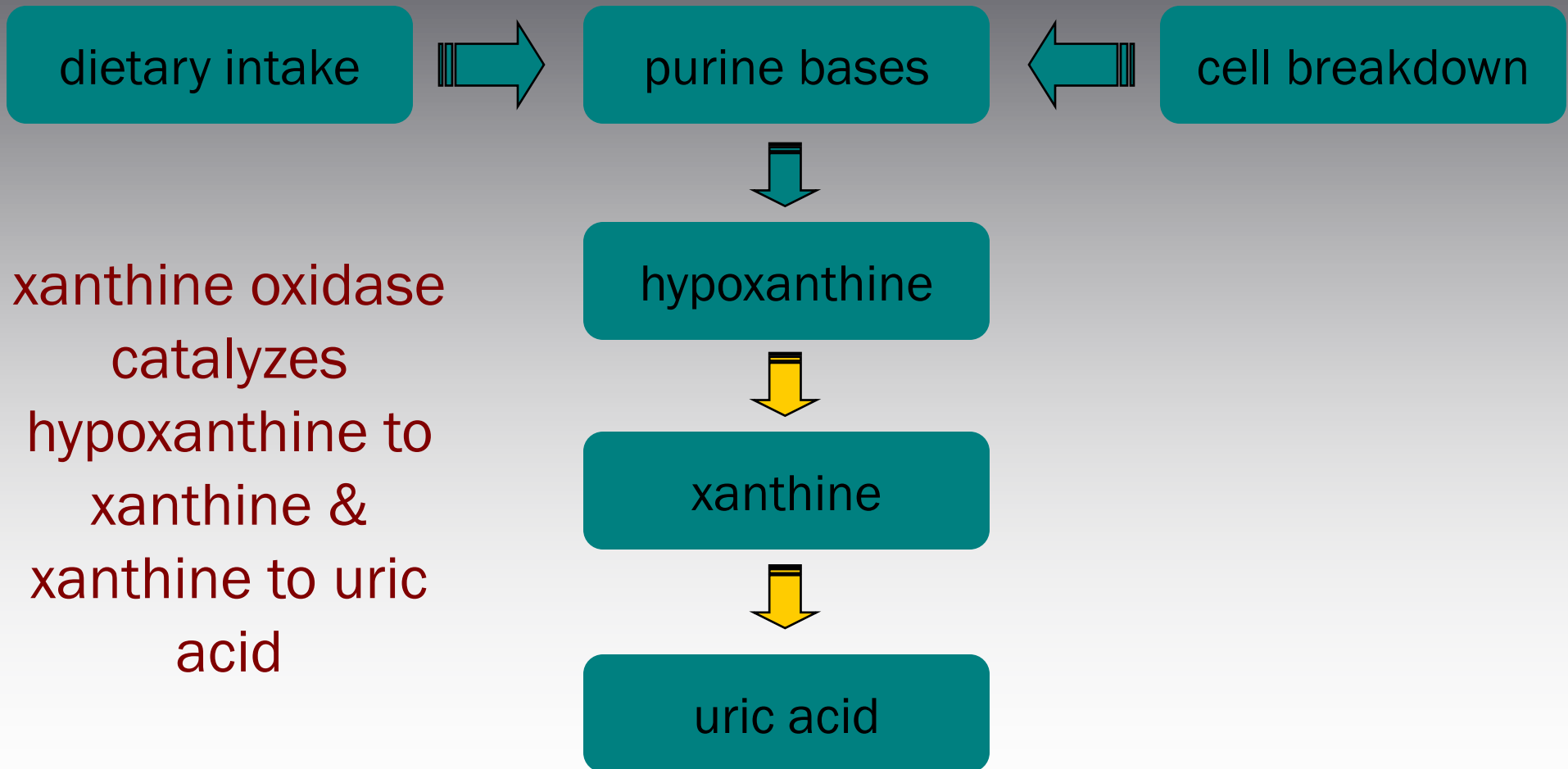


Drug therapy of gout

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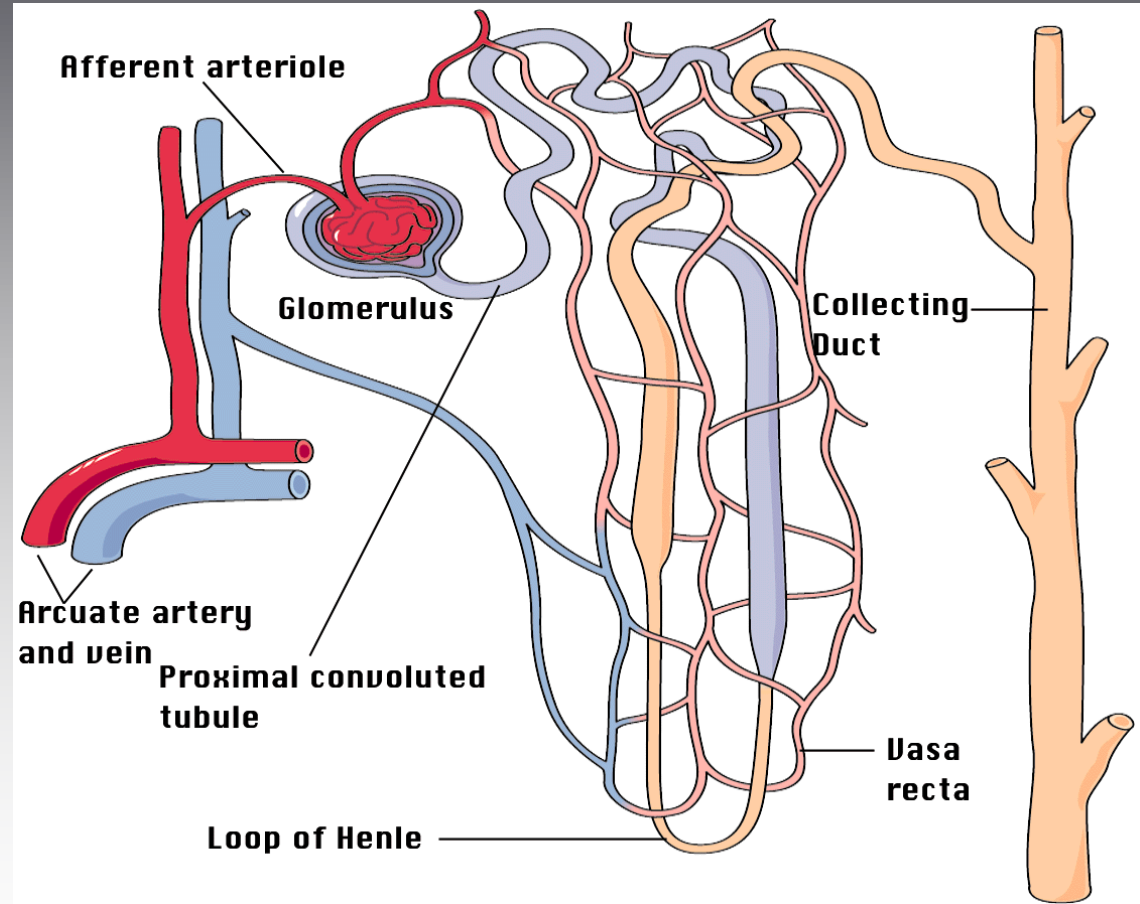
*The Role of Uric
Acid in Gout*

Uric acid metabolism



Renal handling of uric acid

- glomerular filtration
- tubular reabsorption
- tubular excretion
- post-secretory reabsorption
- net excretion



Gout - problems



- excessive total body levels of uric acid
- deposition of monosodium urate crystals in joints & other tissues
- crystal-induced inflammation

Treating acute gouty arthritis



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

Drugs used to treat gout

Acute Arthritis Drugs

colchicine

steroids

NSAID's

Urate Lowering Drugs

allopurinol

probenecid

febuxostat?

rest + analgesia + time

Drugs used to treat gout



NSAID's

- 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

Colchicine - plant alkaloid

colchicum
autumnale

(autumn crocus or
meadow saffron)



Colchicine



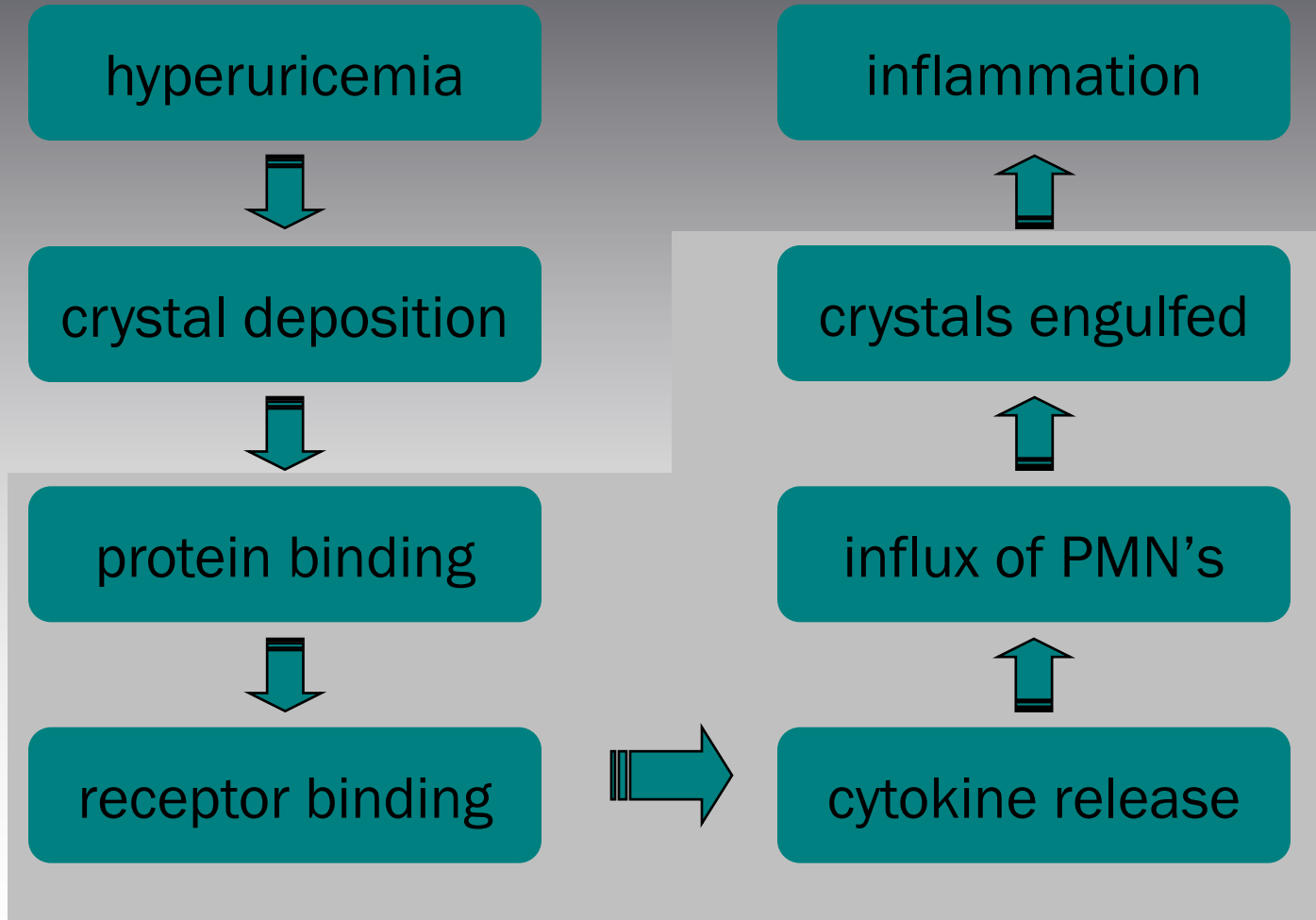
- “only effective in gouty arthritis”
- not an analgesic
- does not affect renal excretion of uric acid
- does not alter plasma solubility of uric acid
- neither raises nor lowers serum uric acid

Colchicine



- 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

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

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

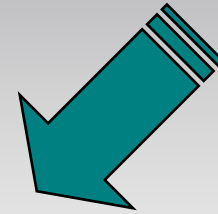
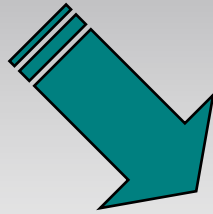
Gout - colchicine therapy

- more useful for daily prophylaxis (low dose)
 - ✓ prevents recurrent attacks
 - ✓ colchicine 0.6 mg qd - bid
- declining use in acute gout (high dose)

Hyperuricemia - mechanisms

excessive
production

inadequate
excretion

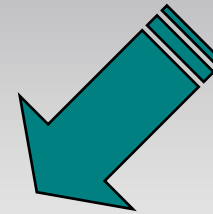
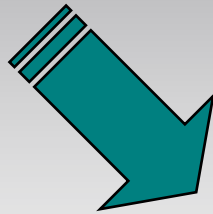


hyperuricemia

Urate-lowering drugs

block
production

enhance
excretion



net reduction in total body pool of
uric acid

Gout - urate-lowering therapy



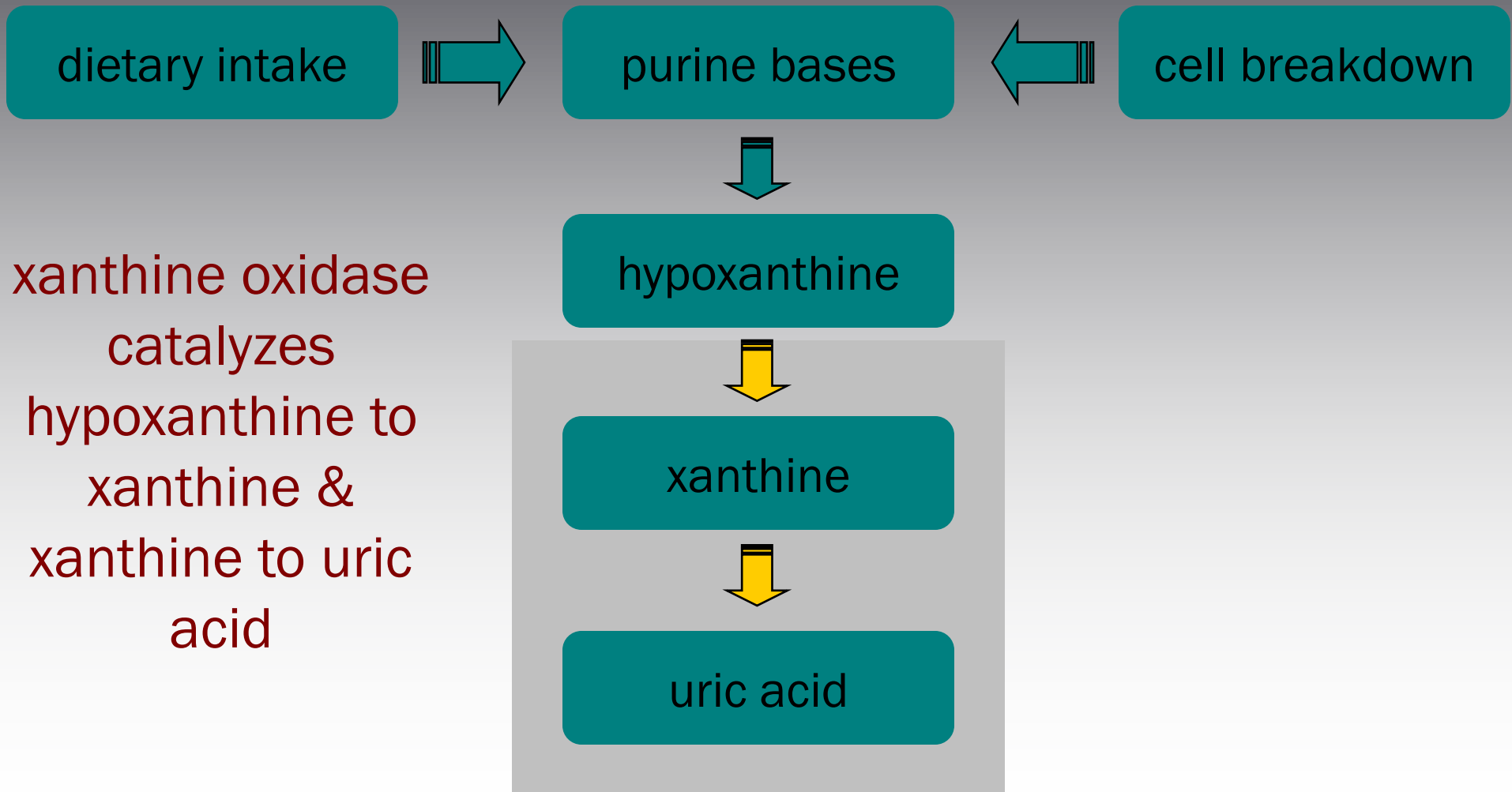
- prevents arthritis, tophi & stones by lowering total body pool of uric acid
- not indicated after first attack
- initiation of therapy can worsen or bring on acute gouty arthritis
- no role to play in managing acute gout

Drug therapy of gout

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*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



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 (not on market)
- 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

PEG-uricase



- investigational drug
- PEG-conjugate of recombinant porcine uricase
- treatment-resistant gout
- uricase speeds resolution of tophi
- further research needed

Drug therapy of gout

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*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



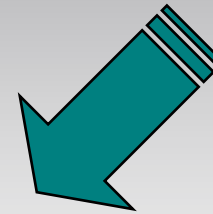
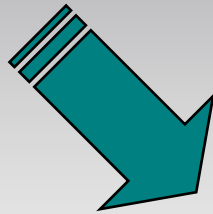
- contra-indications
 - ✓ history of nephrolithiasis
 - ✓ elevated urine uric acid level
 - ✓ existing renal disease
- less effective in elderly patients

Choosing a urate-lowering drug

excessive
production

inadequate
excretion

xanthine
oxidase
inhibitor



uricosuric
agent

hyperuricemia

Drug therapy of gout

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Case Presentation

Case presentation



- 55 y/o male
- 12 hours “pain in my big toe & ankle”
- went to bed last night feeling fine
- felt as if had broken toe this morning
- PMH of similar problems in right ankle & left wrist

Uricosuric therapy



- moderately effective
- increases risk of nephrolithiasis
- not used in patients with renal disease
- frequent, but mild, side effects

Case presentation - therapy

NSAID

NSAID

steroid

colchicine (low-dose)

allopurinol

days 1-10

days 11-365

days 365+