

Gout: A Crystal-Clear Update

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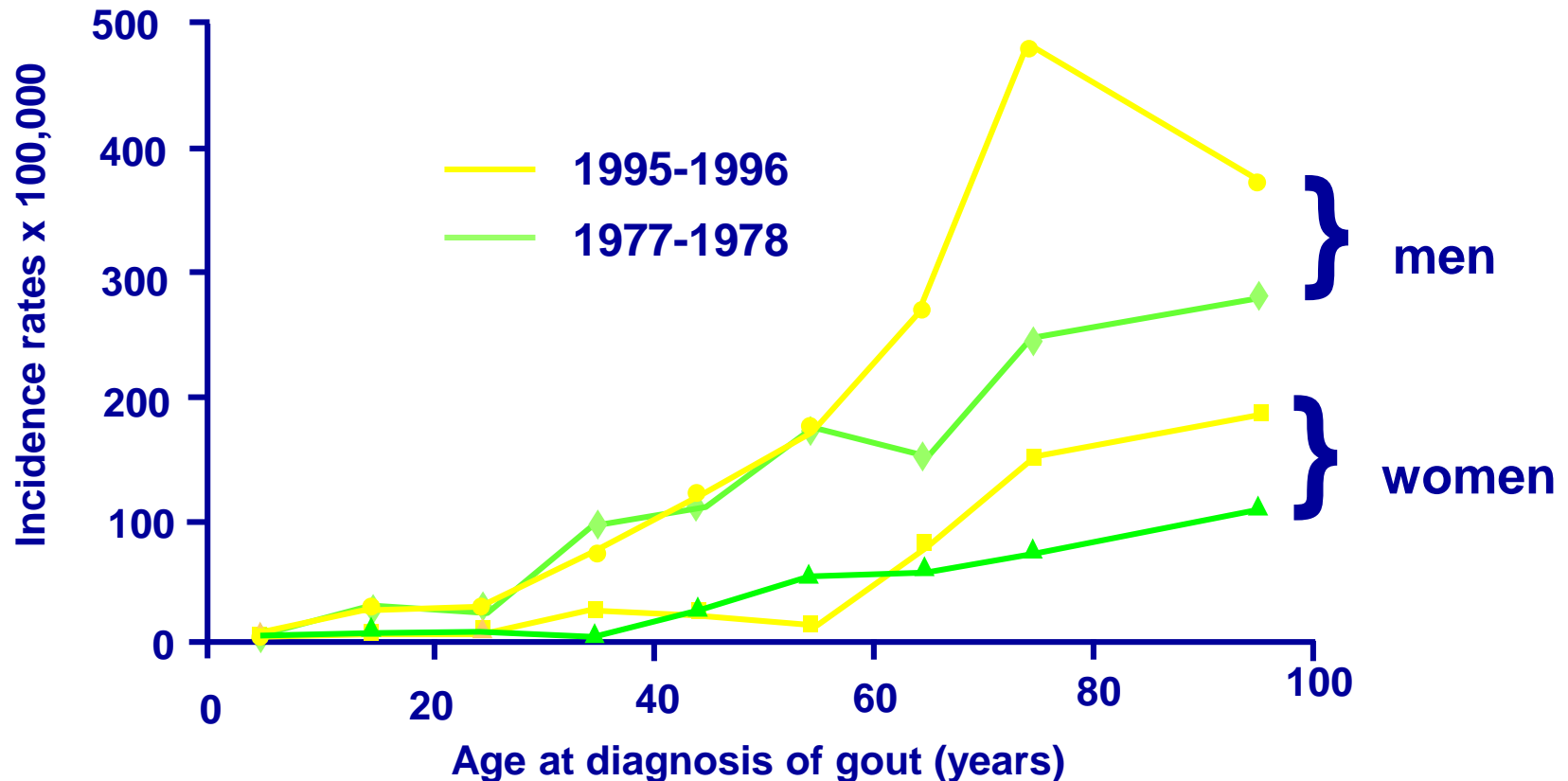


DISCLOSURES

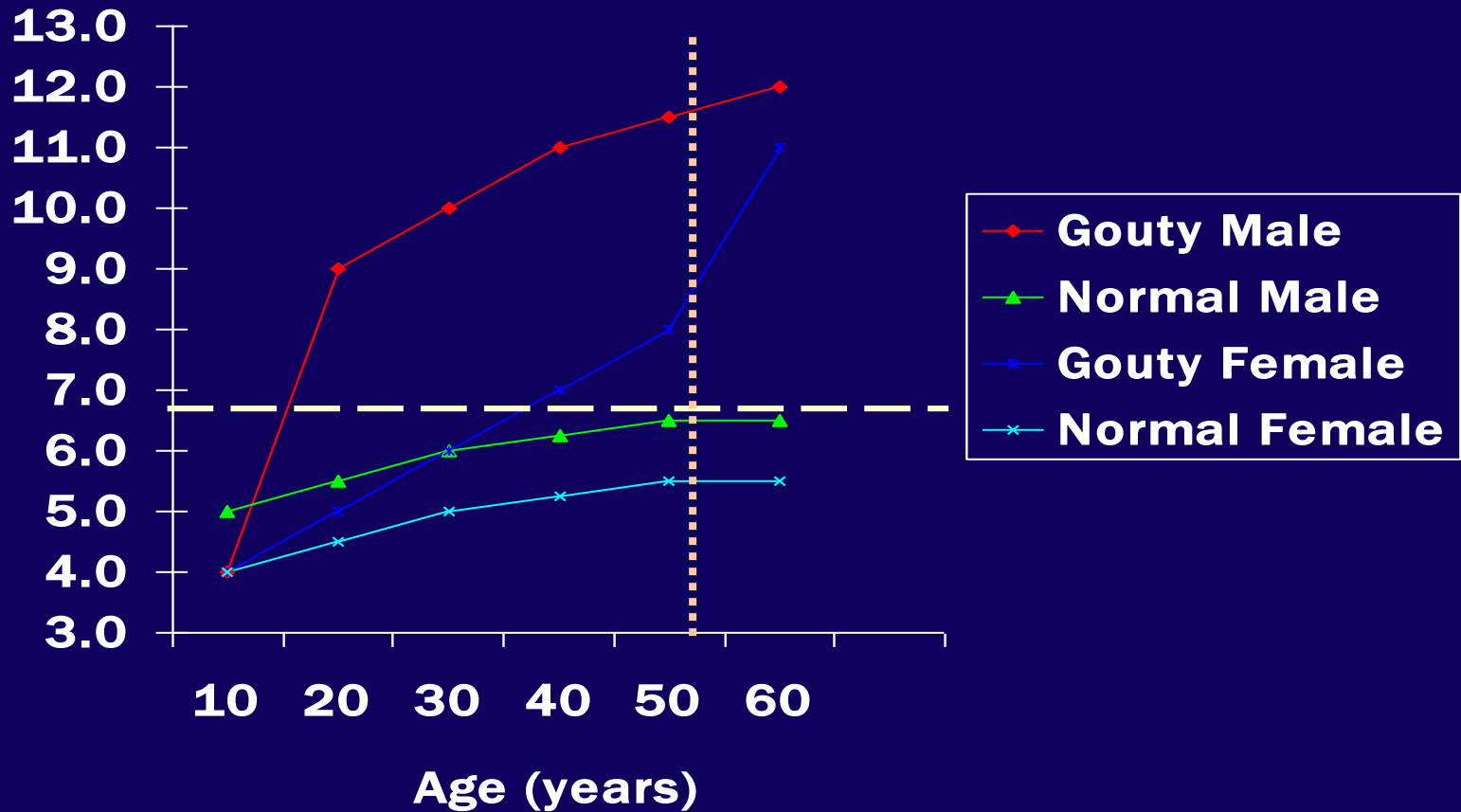
Full Time Employee GlaxoSmithKline

Rising Incidence of Gout

>2-fold increase in the rate of primary gout over 2 time periods assessed



Serum uric acid levels & age



Hyperuricemia & gout

*Serum Uric
Acid Level*

*5-Year
Prevalence*

> 10 mg/dl

30%

< 7 mg/dl

0.6%

Gout

One Chronic Disease, Best Described by 4 Stages

Asymptomatic Hyperuricemia

Elevated serum urate with no clinical manifestations of gout

Acute Flares

Acute inflammation in the joint caused by urate crystallization

Intercritical Segments

The intervals between acute flares

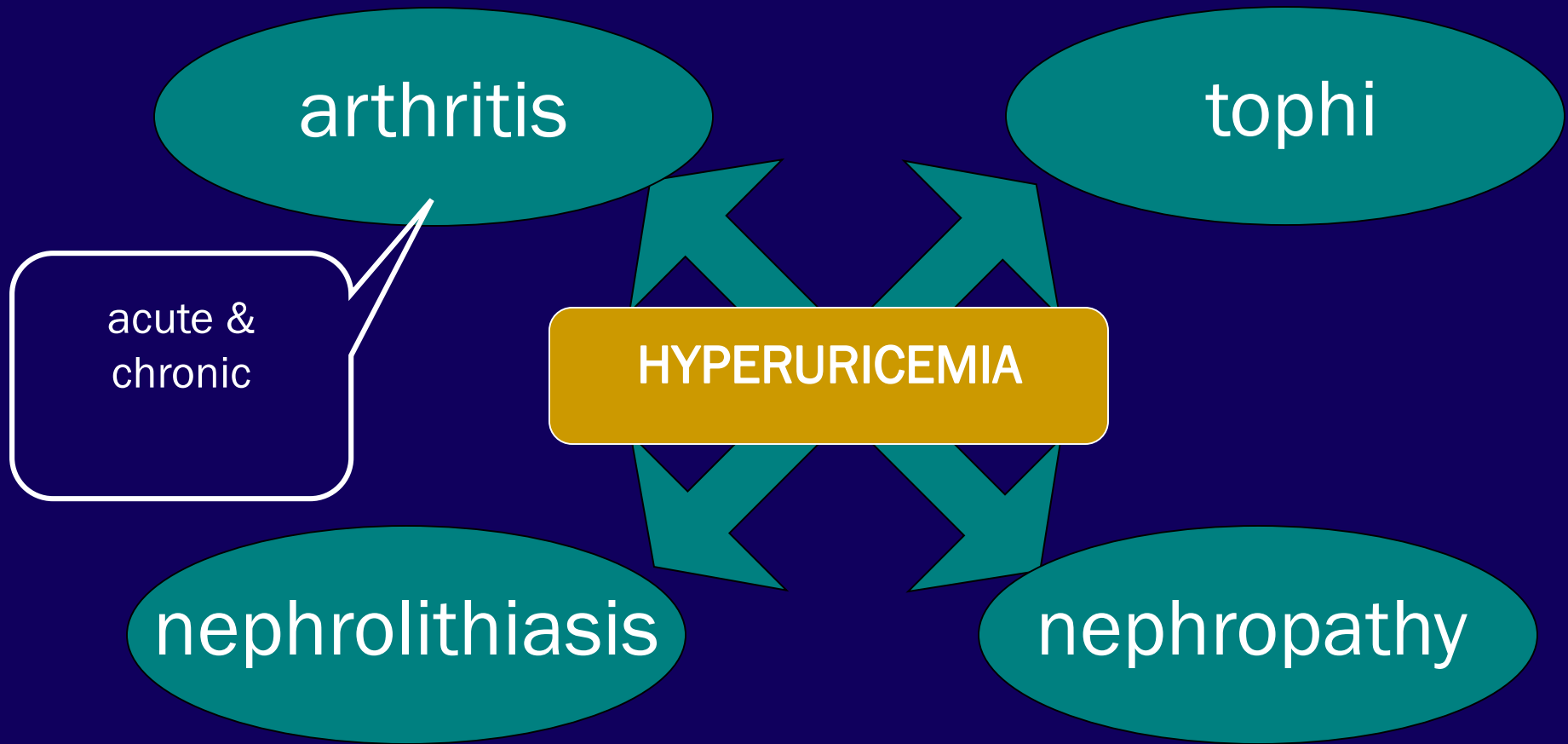
Advanced Gout

Long-term gouty complications of uncontrolled hyperuricemia

Uncontrolled Hyperuricemia



Gout - cardinal manifestations



Drugs used to treat gout

Acute Arthritis Drugs

Urate Lowering Drugs

colchicine

steroids

NSAID's

allopurinol

probenecid

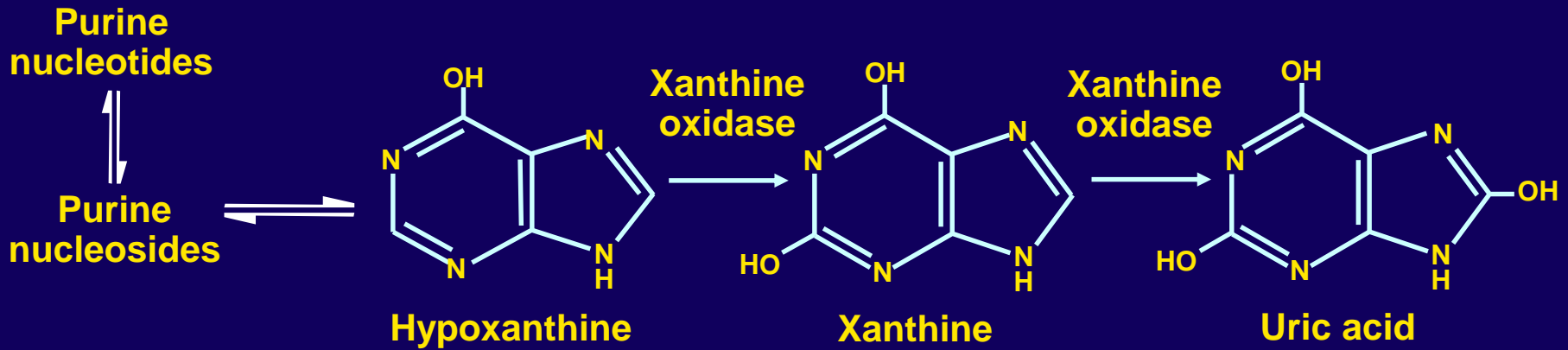
febuxostat

pegloticase

rest + analgesia + time

Asymptomatic Hyperuricemia

- Hyperuricemia alone does NOT make a diagnosis of gout
 - only a subset of people with hyperuricemia will develop gout
 - probability of gout increases with higher uric acid levels
- Asymptomatic hyperuricemia generally requires no treatment



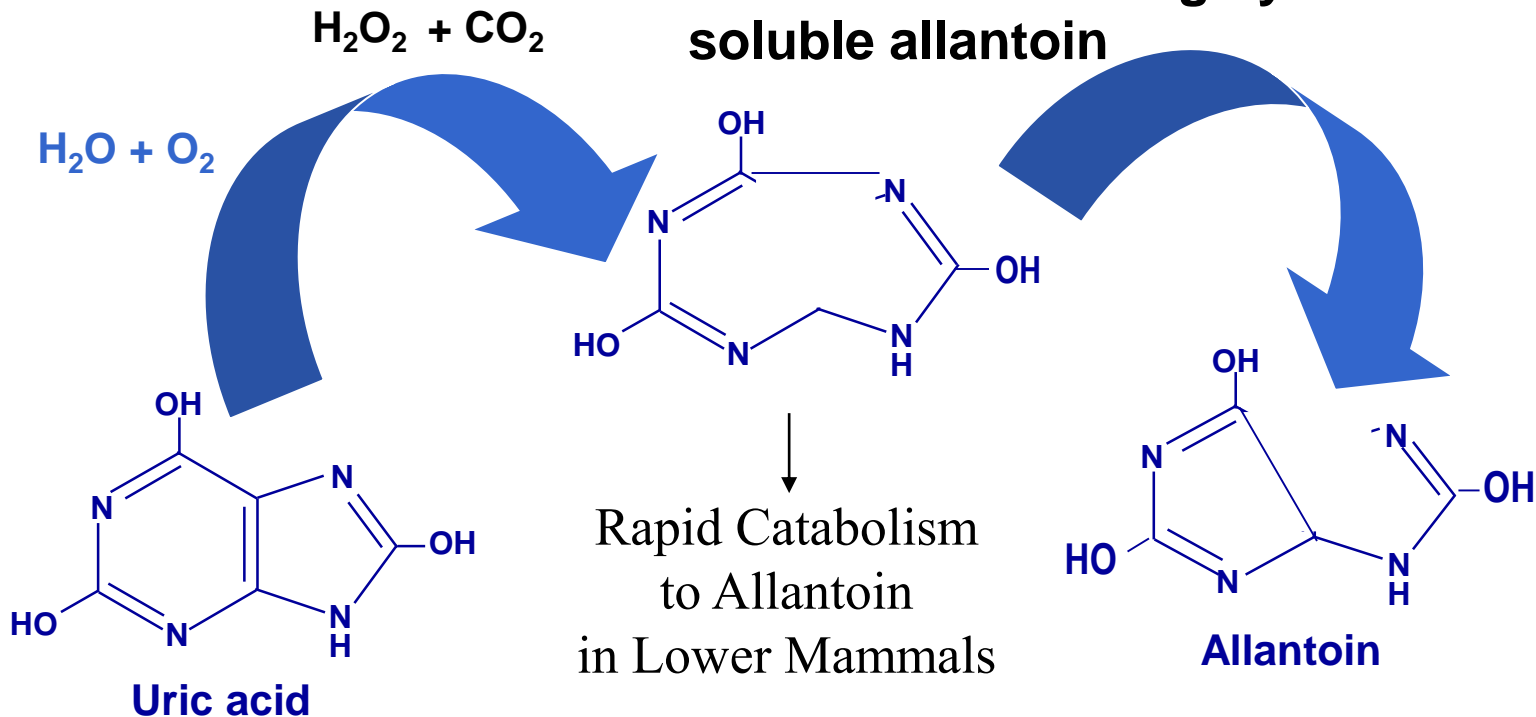
**HYPER-
URICEMIA**



**Tissue Deposition of Monosodium Urate Crystals
Uric Acid Urolithiasis Promoted by Acid Urine pH**

Final Purine Degradation in Non-Primate Mammals and Lower Primates

URICASE (Uric Acid Oxidase) catalyzes conversion of relatively insoluble uric acid to highly soluble allantoin



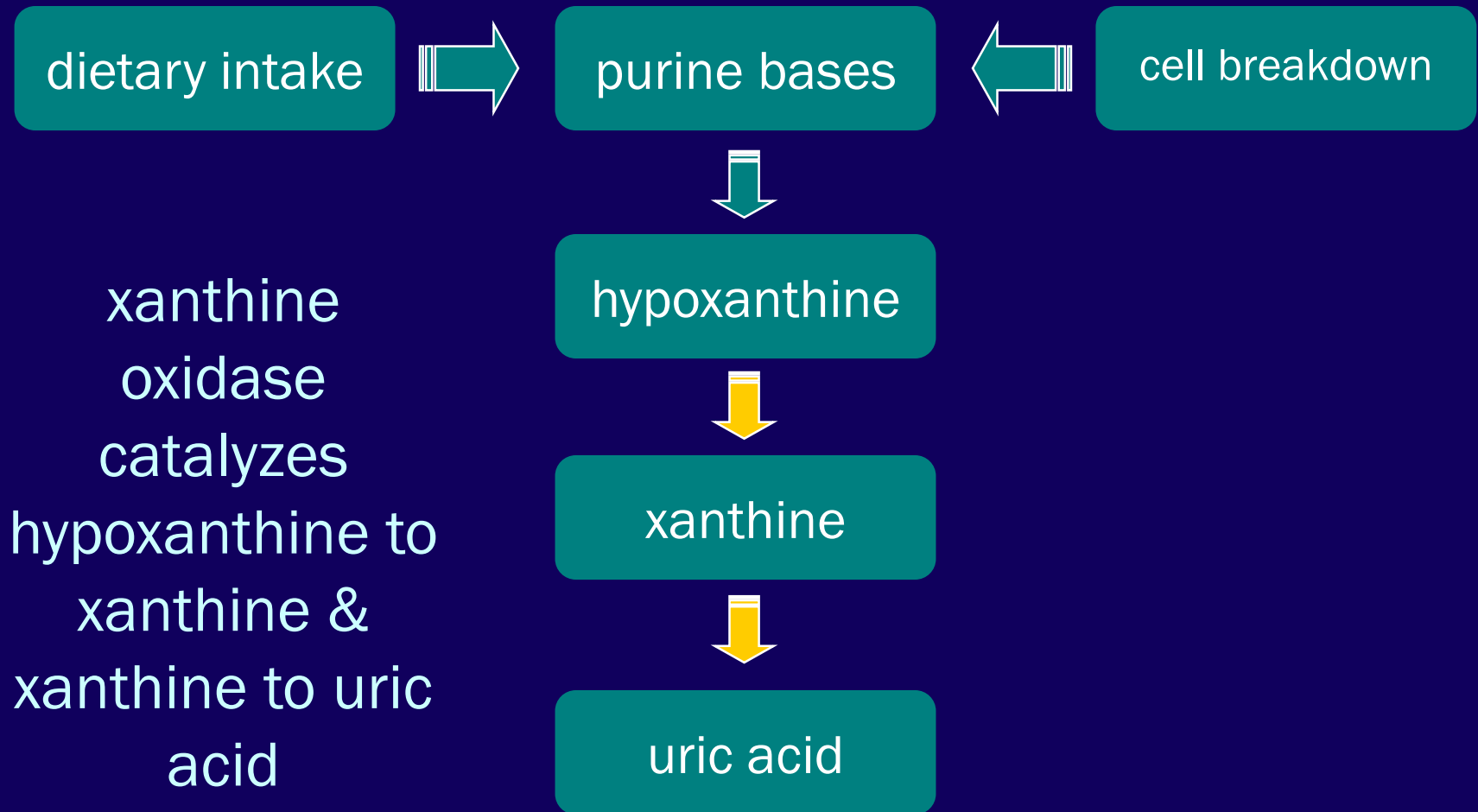
Hydrogen Peroxide is Byproduct

FOUNDATION OF HUMAN HYPERURICEMIA

**LOSS OF EXPRESSION OF URICASE:
AN ANTIHYPERURICEMIC THAT DEGRADES URIC
ACID**

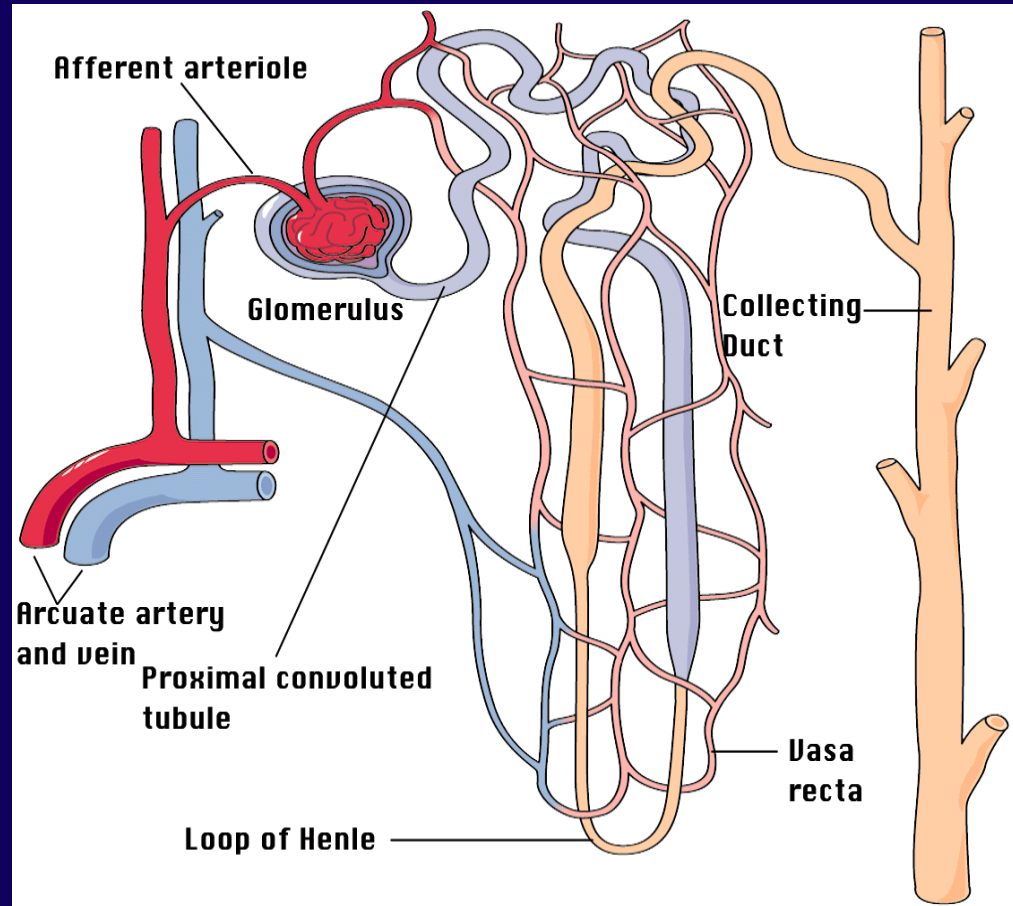
- HUMAN AND HIGH PRIMATE EXPRESSION OF URICASE LOST IN EVOLUTION**
- NORMAL SERUM URATE IN RODENTS ~1 mg/dL**
- NORMAL SERUM URATE IN HUMANS ~6 mg/dL**

Uric acid metabolism



Renal handling of uric acid

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



Drug therapy of gout

We have excellent drugs for managing gout

The drugs used in treating gout make sense!

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

Case presentation

- can barely walk (due to pain)
- right elbow swollen
- exam shows left first MTP joint & left ankle to be red, swollen & tender to touch
- right elbow also swollen

Acute Gouty Arthritis



Gouty arthritis - characteristics

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

Gout - acute bursitis

acute olecranon
bursitis



Gout - acute arthritis

acute synovitis,
ankle & first MTP
joints



Case presentation

- lab studies
 - serum uric acid = 11.5 mg/dl
 - 24-hour uric acid excretion = 300 mg
- left foot X-rays show bony erosion with overhanging edge, medial side of first metatarsal head

Gout - X-ray changes

bony erosions



Gout - acute arthritis

arthrocentesis



acute synovitis,
ankle & first MTP
joints



Monosodium urate crystals

needle shape

negative
birefringence

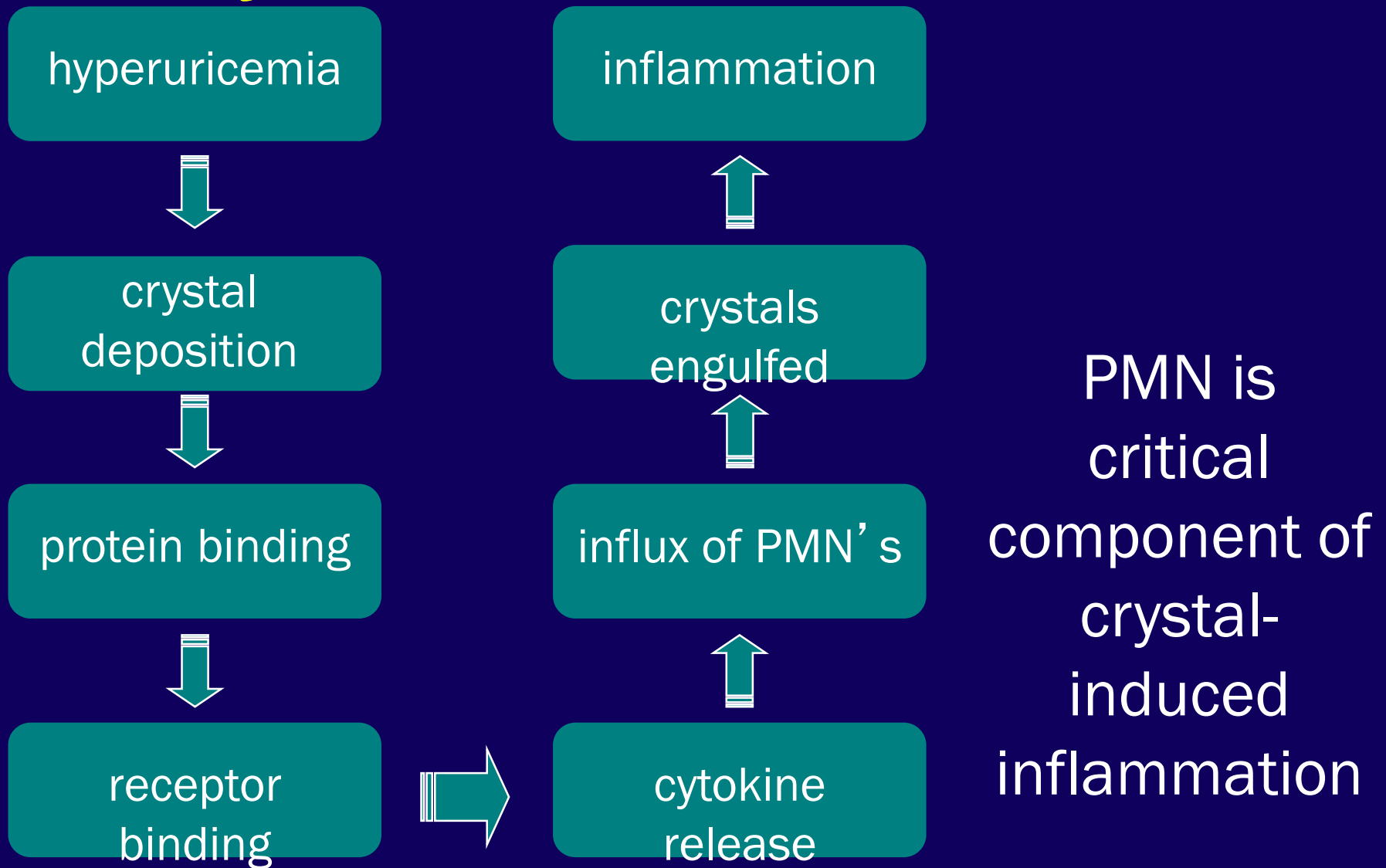


polarized light



red compensator

Crystal-induced inflammation



Inflammasome

A multi-protein signaling complex that leads to inflammation.

It is a “sensor” for inflammatory stimuli.

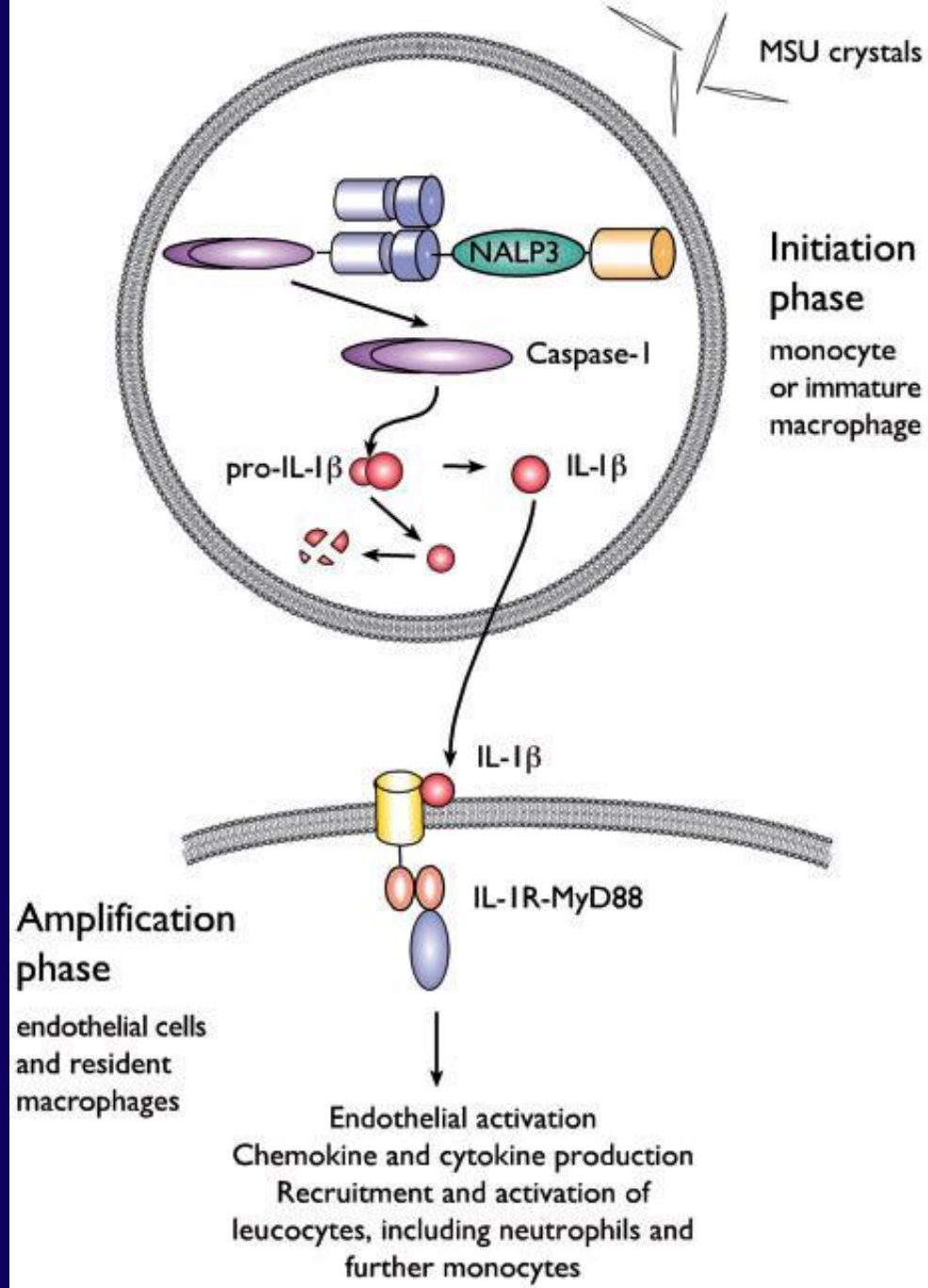
There are multiple inflammasomes, but the NALP3 inflammasome is important in gout.

Mice genetically deficient in components of the NALP3 inflammasome failed to process proIL-1 β

Colchicine can inhibit crystal – induced activation of the inflammasome and the release of IL-1 β

Drenth, NEJM 2006

Pope, Arth Rheum 2007



Acute Gouty Arthritis: Current Treatment Options

- Non-steroidal anti-inflammatory drugs
- Colchicine
- Steroids
 - intra-articular
 - oral
- Joint aspiration
- Analgesics, rest, ice, time

Colchicine - plant alkaloid

*colchicum
autumnale*

(autumn crocus or
meadow saffron)



Colchicine

- mechanism of action poorly understood
- reduces inflammatory response to deposited crystals, in vitro reduces activation of the inflammasome
- 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 Dosing Guidelines for Acute Gout

- EULAR expert consensus-based:

Colchicine 0.5 mg tid daily for multiple days

Zhang W et al, An Rheum Dis, 65:1312-24, 2006

- AGREE trial: Large, randomized, double-blind placebo-controlled trial (n=184 patients treated for early gout flare (<12 hours))

Low Dose Colchicine 1.2 mg, then 0.6 mg 1 hour later (1.8 mg total) equally effective, equal plasma C_{max} , and better tolerated than High Dose Colchicine 1.2 mg, then 0.6 mg hourly x 6 hours (4.8 mg total)

Terkeltaub R et al, Arth Rheum 2009

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)

Colchicine - toxicity

- gastrointestinal (nausea, vomiting, cramping, diarrhea, abdominal pain)
- hematologic (agranulocytosis, aplastic anemia, thrombocytopenia)
- muscular weakness
- dose adjustment with drugs sharing CYP3A4 pathway

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

Colchicine

- 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

Treating acute gout

- What you choose to use is not as important as how **fast** you start it!

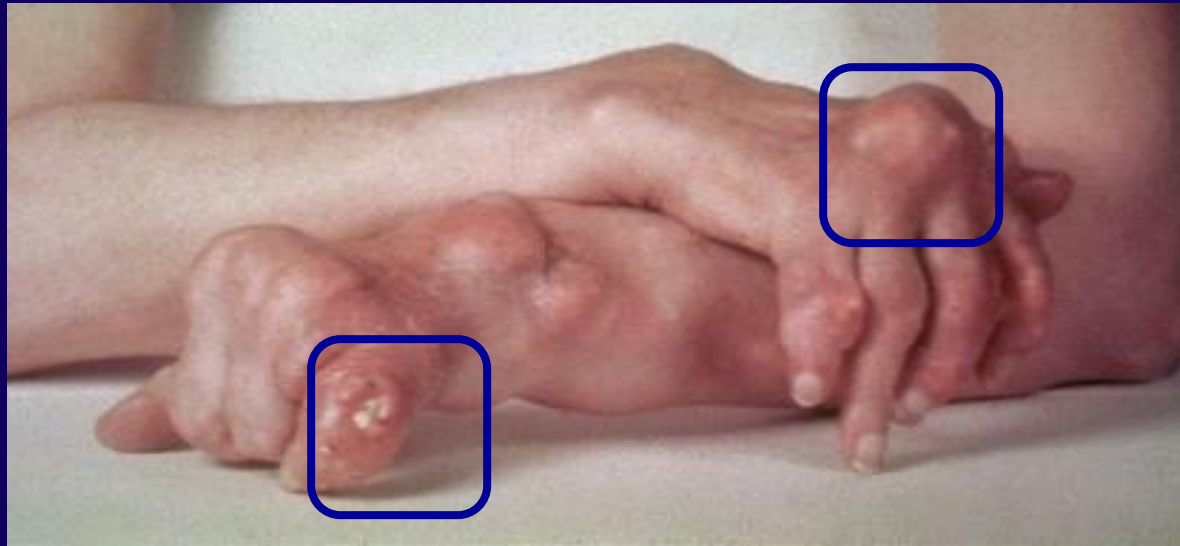
Intercritical Gout

- Symptom-free period between attacks (may be months or years)
- If untreated, episodes of acute gouty arthritis become more frequent, last longer, and often involve more joints (polyarticular)

Diet

- 12 year prospective study of 47,150 men with no history of gout
- 730 new cases of gout
- Conclusions:
 - High levels of meat and seafood increased risk
 - High levels of dairy decreased the risk
 - Moderate intake of purine-rich vegetable or protein not associated with increase risk of gout

Chronic tophaceous gout



tophus = localized deposit
of monosodium urate
crystals

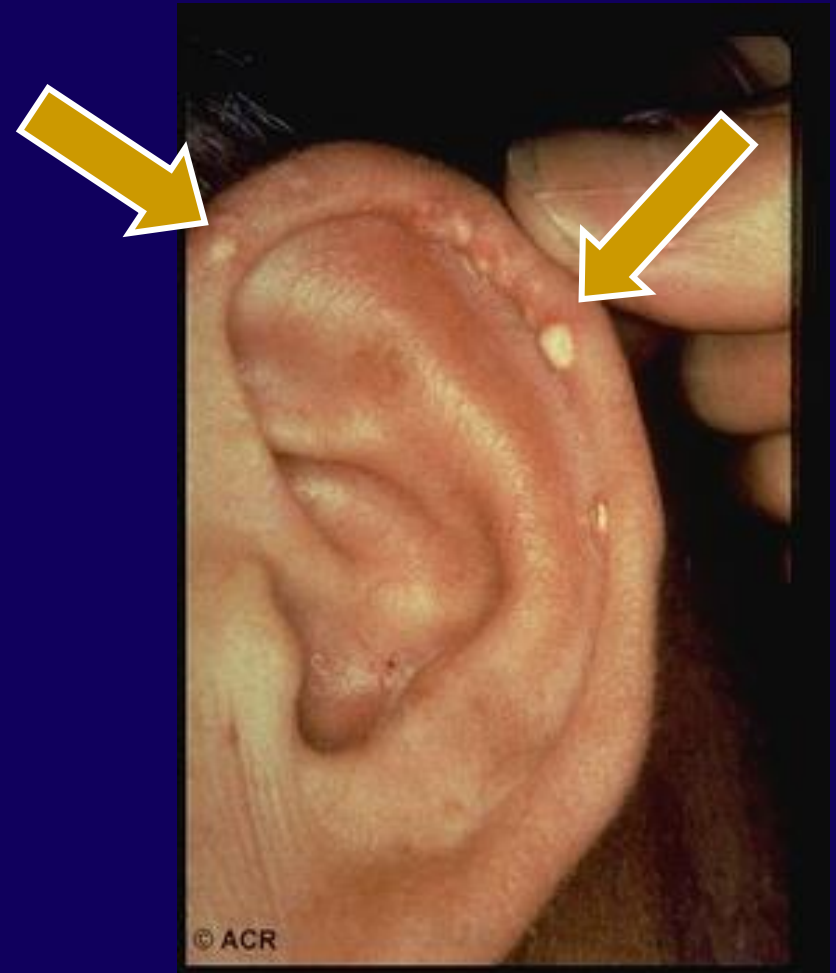
Gout - X-ray changes

DIP joint
destruction
phalangeal bone
cysts



Gout - tophus

classic location
of tophi on
helix of ear





What are the goals of therapy?

- The goal of urate lowering therapy should be a uric acid of <6.0 mg/dl
- A uric acid of <6.0 mg/dl has been shown to reduce the risk of acute attacks, progressive erosive disease, and reduce tophi size

Perez-Ruiz & Liote. Arthritis Rheum 2007

Jordan et al. Rheumatology 2007

Gout - urate-lowering therapy

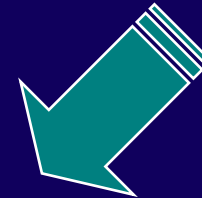
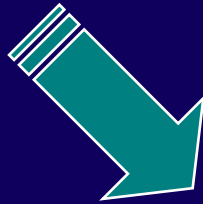
- prevents arthritis, tophi & stones by lowering total body pool of uric acid
- not indicated after first attack
- initiation of therapy can worsen or bring on acute gouty arthritis
- no role to play in managing acute gout

Choosing a urate-lowering drug

excessive
production

inadequate
excretion

xanthine
oxidase
inhibitor



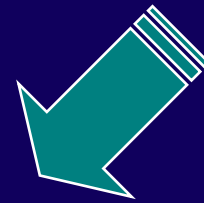
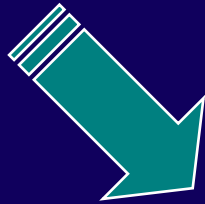
uricosuric
agent

hyperuricemia

Urate-lowering drugs

block
production

enhance
excretion



net reduction in total body pool
of uric acid

Urate-lowering therapy

- mild gout uricosuric
- renal disease allo/feb
- nephrolithiasis allo/feb
- high 24-hr UUA allo/feb
- elderly allo/feb
- tophaceous gout allo/feb/peg

Uricosuric therapy

- moderately effective
- increases risk of nephrolithiasis
- not used in patients with renal disease
- frequent, but mild, side effects
- some drugs reduce efficacy (e.g., aspirin)

Uricosuric therapy

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

Uricosuric therapy

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

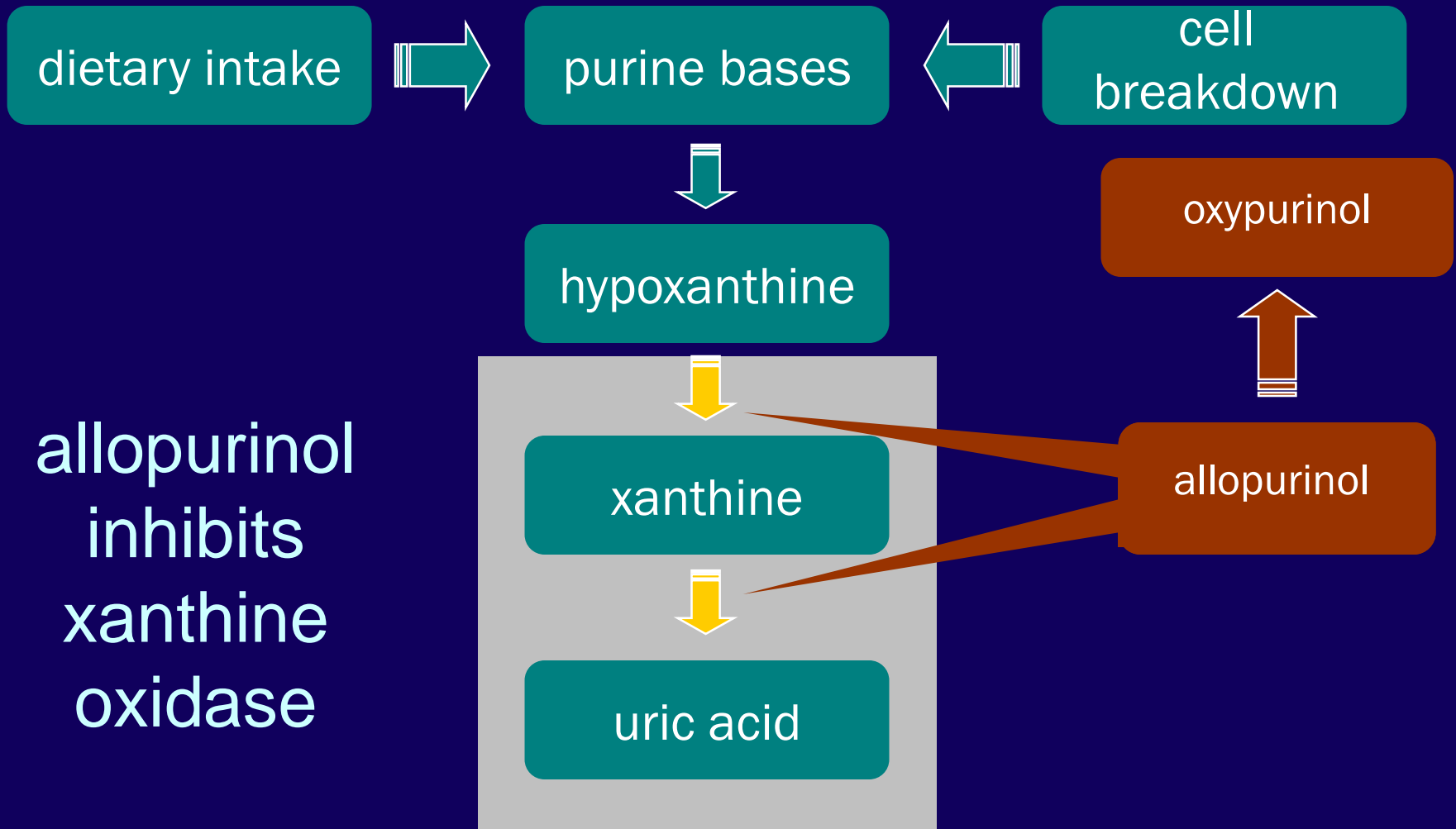
Drug therapy of gout

*Drugs That Block
Production of Uric Acid*

Allopurinol

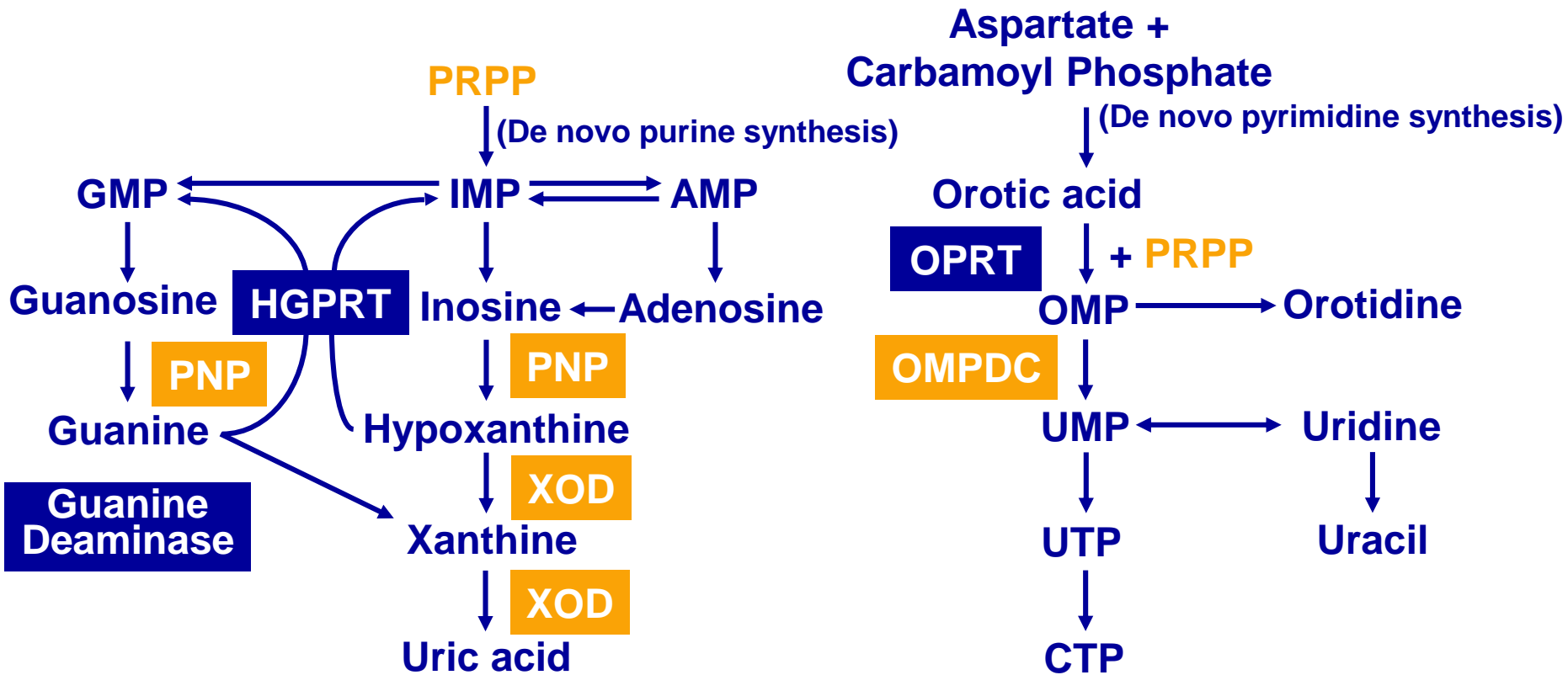
- inhibitor of xanthine oxidase
- effectively blocks formation of uric acid
- how supplied - 100 mg & 300 mg tablets

Uric acid metabolism



Allopurinol is Nonselective Purine and Pyrimidine Metabolism Enzyme Inhibitor: This Could Contribute to Some Allopurinol Side Effects

Purine and Pyrimidine Metabolism Pathways (orange indicates Allopurinol enzyme inhibition)



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

- Allopurinol has been available since the 1960s, but
 - Gout quality of care is poor despite most physicians having a high level of comfort with gout
 - Most allopurinol patients are underdosed
 - Patient compliance and education is marginal
 - Fear of allopurinol hypersensitivity syndrome and renal insufficiency limit its appropriate use
 - We have limited clinical data to support dose escalation (although it is approved up to 800mg/day)

Allopurinol

- Approved from 100mg to 800mg daily
 - The maximum dose is not based on additional toxicity, but rather on limited data
- 65% of prescriptions are for ≤ 300 mg
 - Approximately 40% of patients achieve goal urate levels with ≤ 300 mg/day
 - Recent study of gout patients with CrCL >50 ml/min revealed 78% had uric acid ≤ 5.0 mg/dl when allopurinol increased to 600mg/day

Sarawate et al. Mayo Clin Pro 2006

Becker et al. NEJM 2005

Schumacher et al.. Arthritis Rheum 2008

Reinders et al. Ann Rheum Dis 2009

Allopurinol

- Allopurinol hypersensitivity syndrome (AHS) (0.1-0.4% incidence)
 - Severe cutaneous reactions, eosinophilia, fever, hepatitis, leukocytosis, and renal involvement
 - Mortality up to 25- 30%
 - Isolated rash may occur in up to 2% of Allopurinol patients
 - Risk factors include recent onset of therapy at 300mg/day, thiazide diuretics, chronic kidney disease, and HLA-B*5801 allele

DRESS syndrome

skin lesions

eosinophilia

systemic symptoms

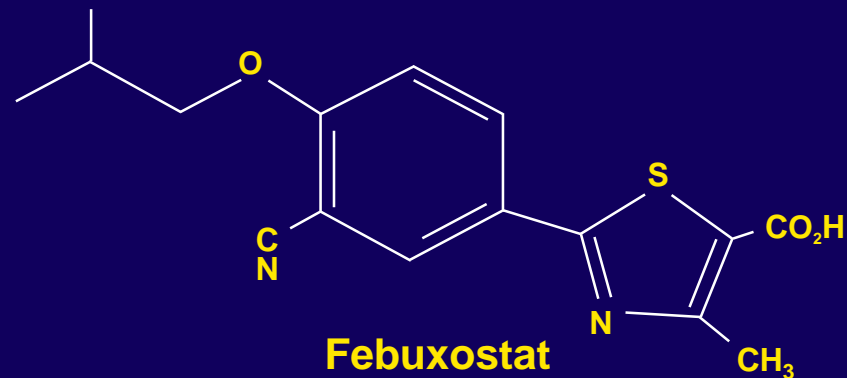


What about patients with renal insufficiency?

- No clear dosing guidelines exist for the treatment of gout patients with a creatinine clearance $<30\text{ml/min}$
- The guidelines set forth by Hande et al. were designed to eliminate AHS, but AHS doesn't appear to be dose-dependent
- Titrate slowly with routine monitoring until the uric acid is $<6.0\text{mg/dl}$

Febuxostat: a non-purine xanthine oxidase inhibitor

- Non-purine backbone, selective inhibitor of xanthine oxidase



- **Pertinent Pharmacology**

- **Primarily metabolized by oxidation and glucuronidation in the liver**

Febuxostat

- Dosing
 - Recommended initial dose of 40mg daily
 - May titrate to 80mg daily after 2 weeks if serum uric acid >6.0 mg/dl
 - No dose adjustment needed if creatinine clearance >30 ml/min
 - Safe in mild to moderate hepatic impairment
 - Avoid in combination with azathioprine and 6-mercaptopurine

FEBUXOSTAT VS. ALLOPURINOL: GOUTY ARTHRITIS FLARES AND SPIKE WHEN PROPHYLACTIC COLCHICINE STOPPED AT 8 WEEKS

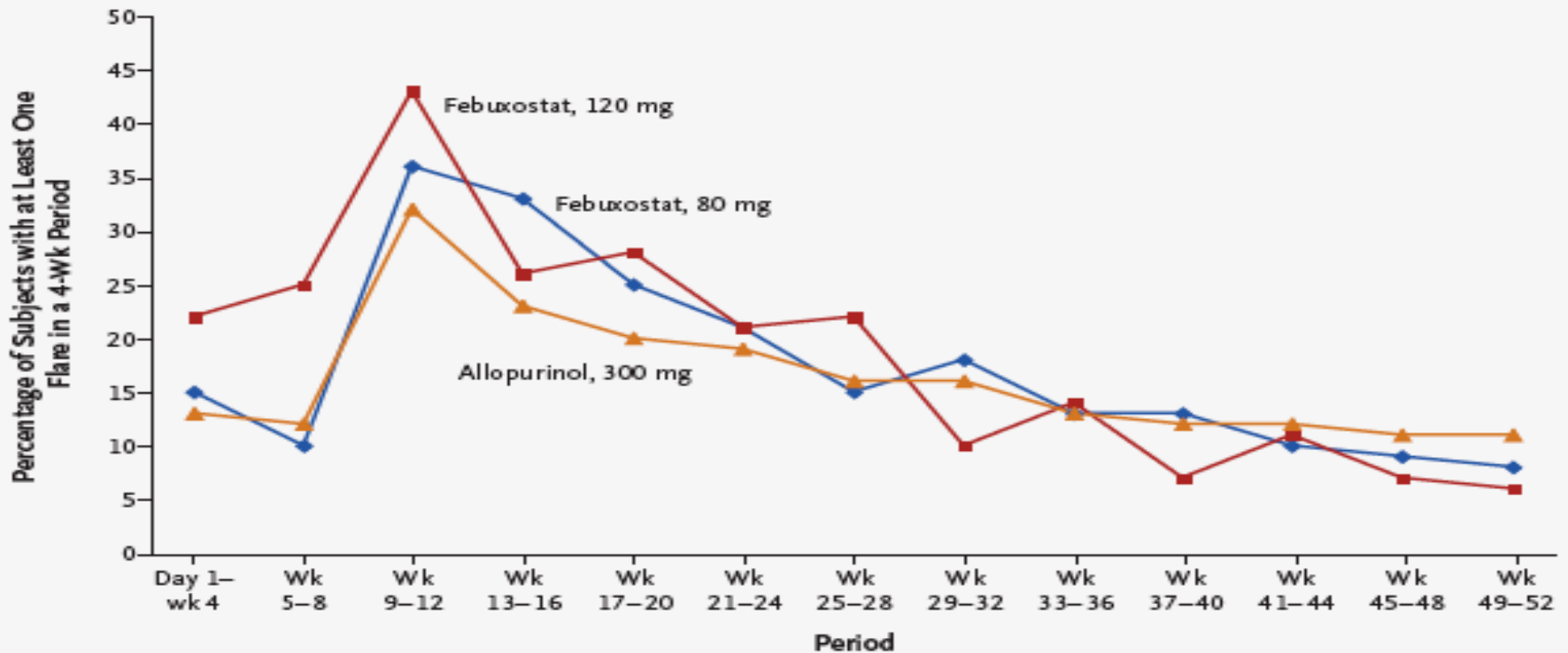


Figure 2. Subjects Requiring Treatment for Gout Flares.

The percentage of subjects in each interval is calculated by dividing the number of subjects with at least one gout flare in that interval by the number of subjects exposed to at least one dose of drug in that interval. Subjects may be counted in more than one interval. The subjects received prophylaxis during the period from day 1 to week 8. The results for the 80-mg febuxostat group are shown in blue, those for the 120-mg febuxostat group in pink, and those for the allopurinol group in yellow.

Febuxostat

- Potential Concerns
 - Cardiovascular risks
 - CARES study indicated gout pts treated with febuxostat had increased risk of cardiac death and all cause mortality. This led to boxed warning.

Pegloticase

- A PEGylated recombinant mammalian uricase
 - Catalyses the oxidation of urate to allantoin
- Indicated for chronic gout in patients refractory to conventional therapy
 - trials reported 42% of patients met the primary endpoint of UA <6.0 at least 80% of the time
 - $>90\%$ of patients had an adverse event (gout flare or infusion reaction) during phase II/III trials

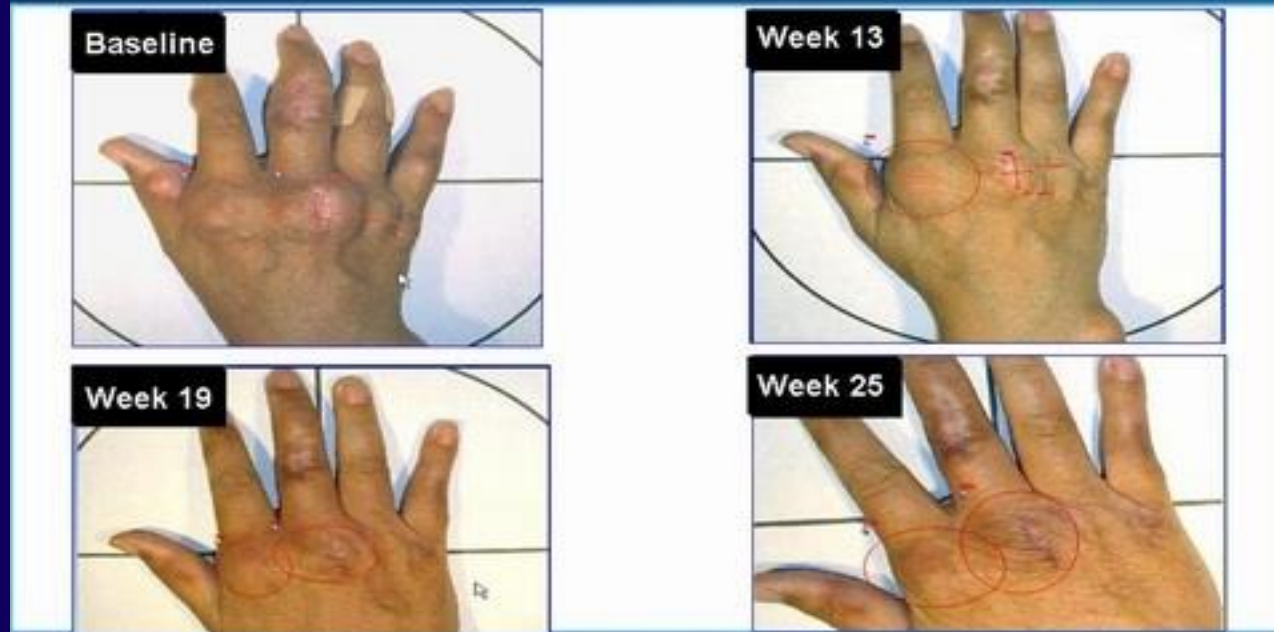
Pegloticase

- A rise in uric acid level above 6.0mg/dl indicates anti-pegloticase/anti-PEG antibodies
 - Therapy should be stopped as this is predictive of infusion reactions and anaphylaxis
 - Approximately 90% of the infusion reactions seen in clinical trials would have been prevented if therapy had been stopped after UA > 6.0mg/dl
 - Uric acid levels are recommended prior to each infusion
 - MIRROR trial

Wright et al. Arthritis Rheum 2009

Botson et al. J Rheum 2021

Phase 3: Assessment of Tophi



Right hand tophi: 8 mg pegloticase q 2 weeks

**DEBULKING OF TOPHI BY PEGYLATED URICASE
IN PHASE III STUDY: 8 mg pegloticase q 2 weeks
better than 8 mg q4 weeks for uric acid
and tophus debulking**

Figure from Sherman M, et al, Adv Drug Deliv Res, 2008

Take Home Messages

- Urate-lowering therapy (ULT) is *strongly* recommended for patients with 2 or more gout flares annually, or tophi, or x-ray changes
- ULT is *conditionally* recommended for patients who have had more than one infrequent flares (<2 annually)
- ULT is *conditionally* recommended for a patient with a first flare if SUA >9 mg/dL; or patient has stage 3 CKD; or urolithiasis
- Allopurinol is *strongly* recommended as first line ULT. Start 100mg/d (50 mg/d for CKD); titrate slowly to goal

Take Home Messages

- A 3-6 month course of concomitant anti-inflammatory therapy is *strongly* recommended when ULT is initiated and titrated
- Colchicine, NSAIDs, and glucocorticoids all are appropriate first-line agents for acute gout flares. Topical ice is *conditionally* also recommended.
- Limiting alcohol, purine, and high-fructose corn syrup is *conditionally* recommended
- For patients with HTN, avoiding HCTZ (increase uric acid) and using losartan (lowers uric acid) are *conditionally* recommended if feasible

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