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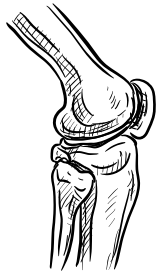

PHARMACOLOGY

FINAL | Lecture 4

Drugs for Gout

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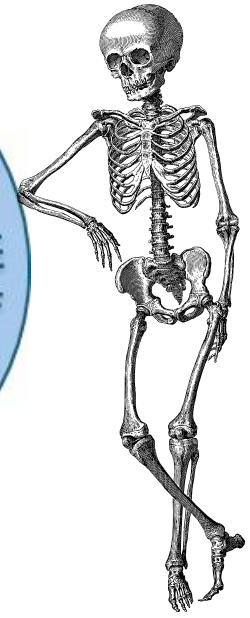
وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم

اللهم استعملنا ولا تستبدلنا



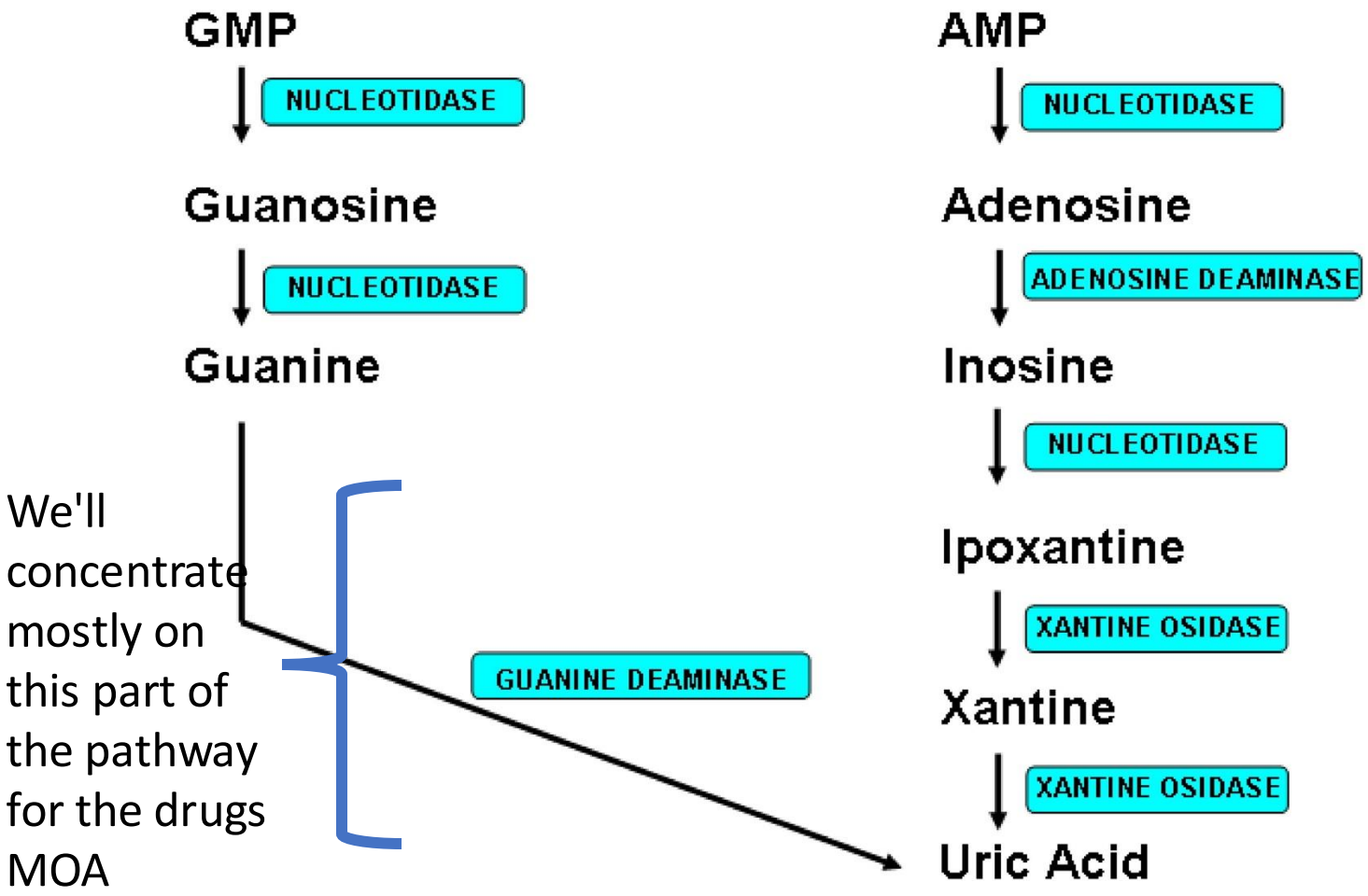
رَمَضَانُ مُبَارَكٌ

Quiz on the previous lecture!

REMEMBER FROM GENERAL PHARMACOLOGY

- Get back and revise purine metabolism .
- You can watch the following video :

https://youtu.be/iA0eROhF3pE?si=UnMDd5e68cX47VzP



Drug Therapy of Gout

Drug therapy of gout

What Is Gout?

Gout is a form of complex arthritis, characterized by sudden, severe attacks of pain, swelling in the joints, redness, and tenderness. It can affect one or more joints, with the big toe being one of the most commonly inflamed joints during a gout attack. These attacks can occur suddenly, often in the middle of the night when someone is sleeping, causing them to feel as if their big toe is on fire. The affected joint will become hot, swollen, and painful. These symptoms are typically the result of an inflammatory reaction at that site.

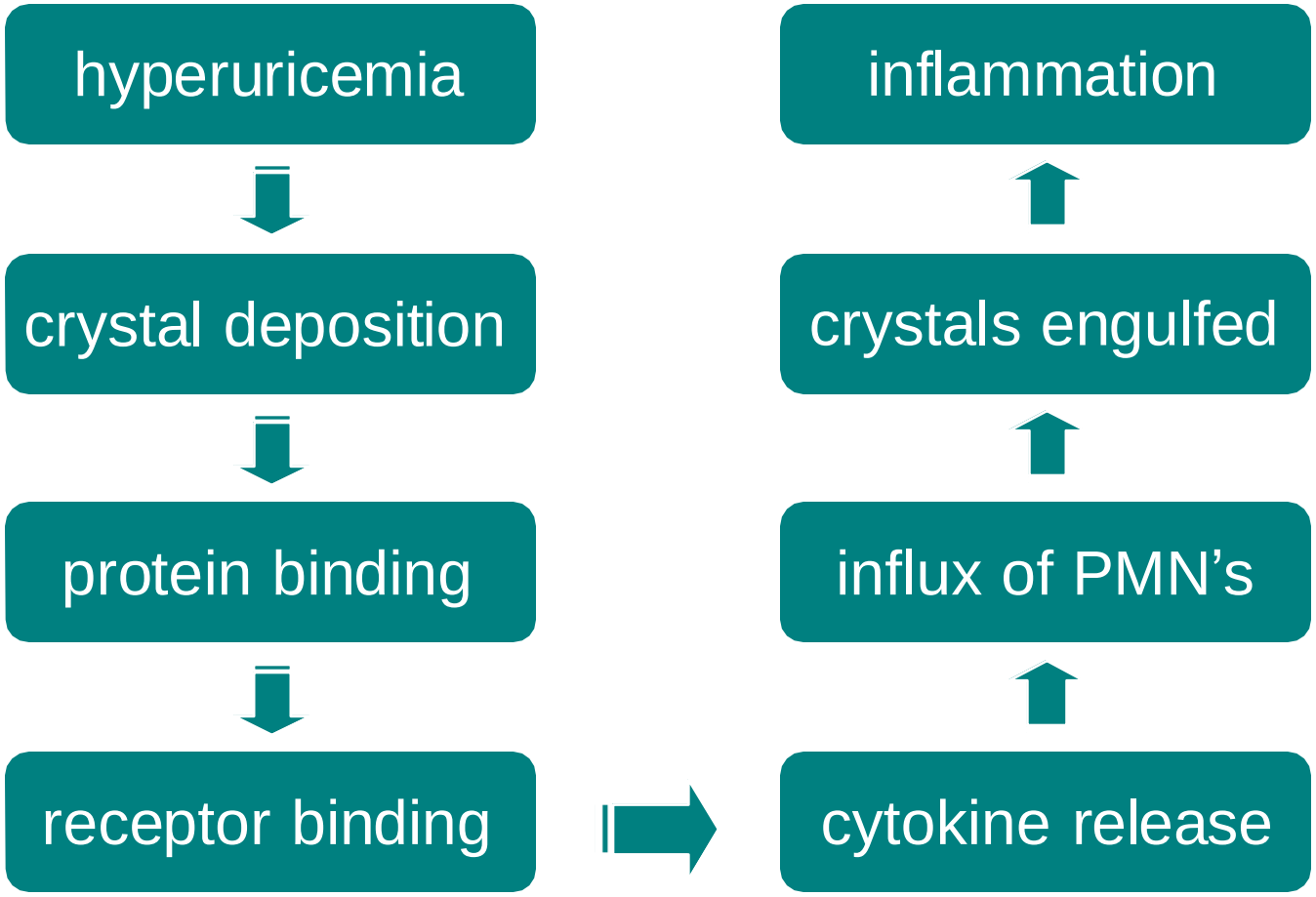
In summary, gout is an inflammatory disease. But what causes it? Gout can also be considered a metabolic disorder. It occurs due to inflammation, or what we refer to as arthritis, which is caused by the deposition of monosodium urate crystals. These crystals can deposit in the joints, as mentioned, but they can also accumulate in other areas, such as the cartilage. Additionally, uric acid deposits can form in the kidneys, leading to renal calculi. This can also result in intestinal nephritis (Although the doctor mentioned "intestinal nephritis" in the lecture, it is probable that **"interstitial nephritis"** was the intended term)

Gouty arthritis-characteristics

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

As mentioned, gout can start in the middle of the night. It usually affects males, particularly middle-aged men. It is characterized by severe pain in the distal joints, such as the toes. The condition involves intense inflammation, and episodes can recur at any time. It is influenced by diet, and changes in the bone can be identified through X-rays.

Crystal-induced inflammation



PMN is critical component of crystal-induced inflammation

Explanation of the previous slide:

So, how does gout start, or what is the cascade of events that lead to this inflammation? As we mentioned, we usually have high levels of serum uric acid, which we characterize as hyperuricemia.

Uric acid is a poorly soluble substance and the major end product of purine metabolism. Many mammals possess an enzyme called uricase, which typically converts uric acid into the more soluble substance allantoin. Unfortunately, humans do not have this enzyme. Therefore, we must control the levels of uric acid through its excretion by the kidneys. In any situation where there is an imbalance between the uptake and elimination (or excretion) of uric acid, we may have elevated levels of uric acid in the serum, leading to deposition of the substance in joints, kidneys, intestines, and sometimes even in cartilage.

These urate crystals will bind to certain proteins and receptors on the surface of the cells lining the joints, which are called synoviocytes. Synoviocytes will engulf these urate crystals, leading to the release of many cytokines, prostaglandins, lysosomal enzymes, and interleukin-1. This cytokine release causes the attraction of various cells, including polymorphonuclear leukocytes. These cells will migrate into the joint space and amplify the ongoing inflammatory process. Polymorphonuclear leukocytes are a critical component of crystal-induced inflammation.

Gouty arthritis-characteristics

- sudden onset

One of the important characteristics of acute gout arthritis is that it can occur at any time.

- middle aged males
- severe pain

This pain is due to the release of cytokines, especially interleukin-1 and prostaglandins.

- distal joints

It typically occurs in the distal joints, although it can affect other areas as well.

- intense inflammation

The condition is associated with intense inflammation, which is further propagated by the presence or chemotaxis of various cells, mainly polymorphonuclear leukocytes. In the later stages of the attack, there is an increased number of mononuclear phagocytes or macrophages, which begin ingesting the urate crystals and releasing more inflammatory mediators.

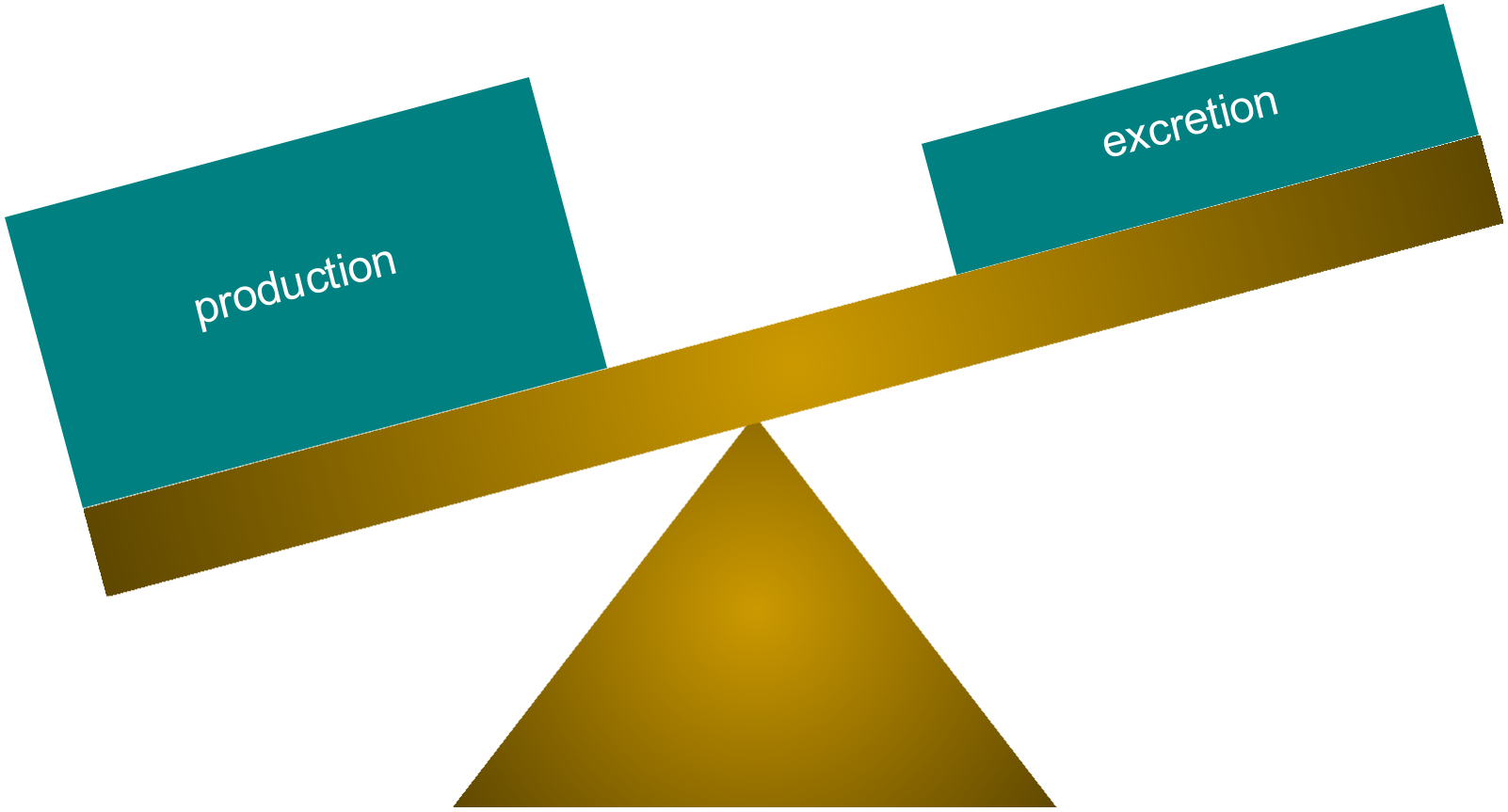
- recurrent episodes
- influenced by diet
- bony erosions on Xray
- hyperuricemia

So, how can we diagnose acute gout arthritis? We can observe bony erosions on an X-ray, but it is also characterized by hyperuricemia

Hyperuricemia

One important note is that it is influenced by diet, and this is very significant. How so?

There are two reasons why hyperuricemia occurs. The first is when the production of uric acid exceeds its excretion.



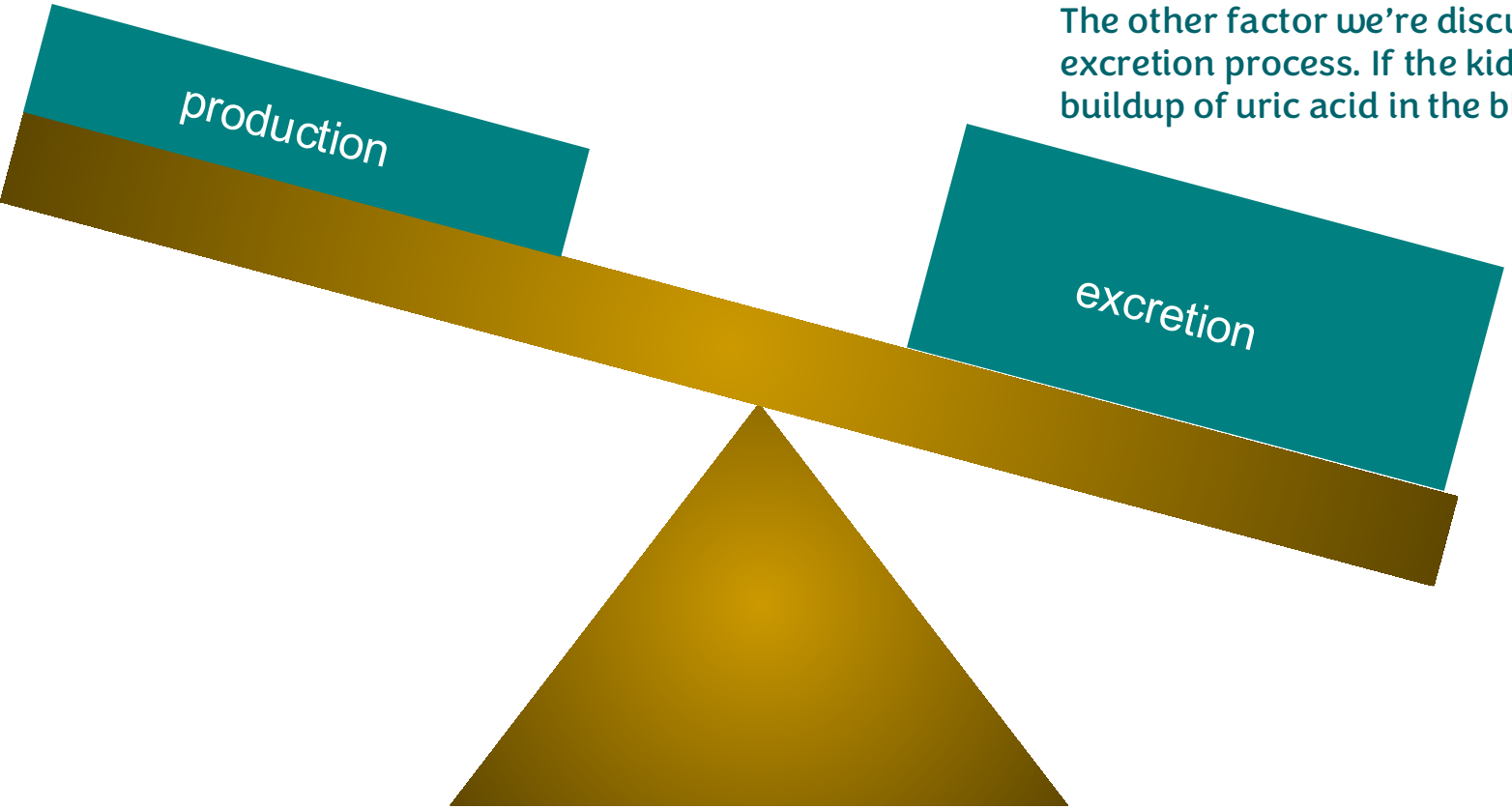
hyperuricemia results when production exceeds excretion

Hyperuricemia

The other reason is when the excretion exceeds production. This what the doctor said in the lecture but I think she means that hyperuricemia can also result when the uric acid loss is impaired (abnormal excretion)

So, we usually have a balance. If we intake too many substances that are converted into uric acid in our body, what kind of substances are we talking about? Typically, red meats are digested in our body and produce purines. These purines are then metabolized into uric acid. Therefore, people with gout who consume too much red meat or protein often end up with hyperuricemia.

The other factor we're discussing here is when there's an imbalance in the excretion process. If the kidneys do not excrete enough uric acid, this leads to a buildup of uric acid in the bloodstream, again resulting in hyperuricemia



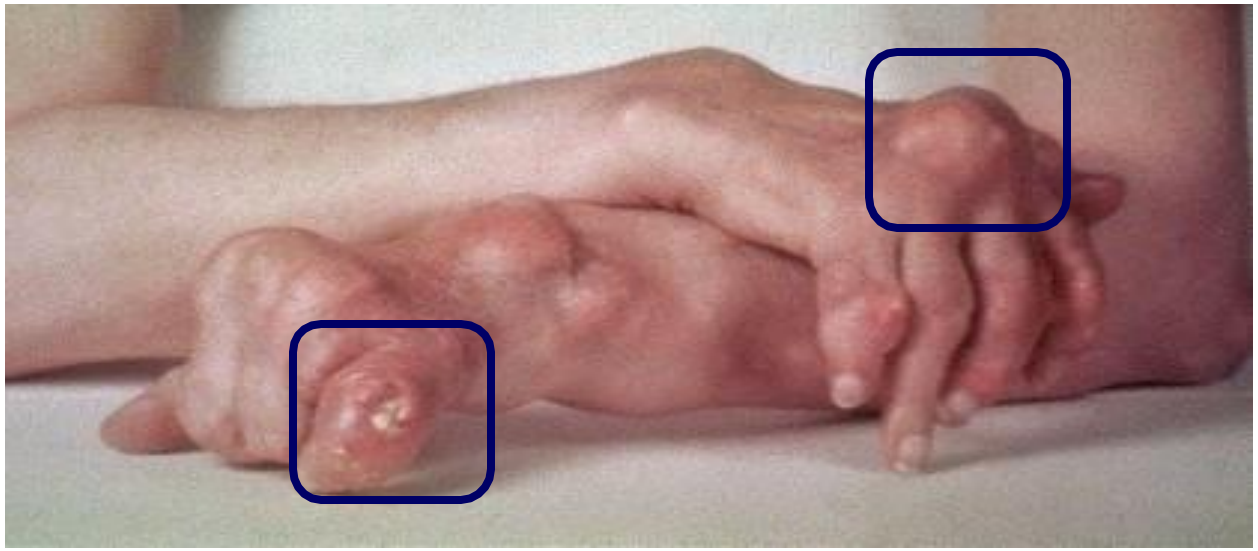
net uric acid loss results when excretion exceeds production

Chronic tophaceous gout

Well, we've discussed some of the characteristics of gout, but let's remember that gout doesn't only present as arthritis.

It can also present in other forms, such as chronic tophaceous gout. Tophaceous refers to localized deposits of monosodium urate crystals. Tophaceous gout is a chronic form of gout where we see nodular masses, or nodes, of uric acid crystals deposited in various tissues and areas of the body. These tophi are present as hard nodules, most commonly found around the fingers, as shown in this picture.

This condition is not only a painful inflammatory process but also disfiguring for the patient. As we mentioned, tophi can be present in the toes, fingers, and elbows.

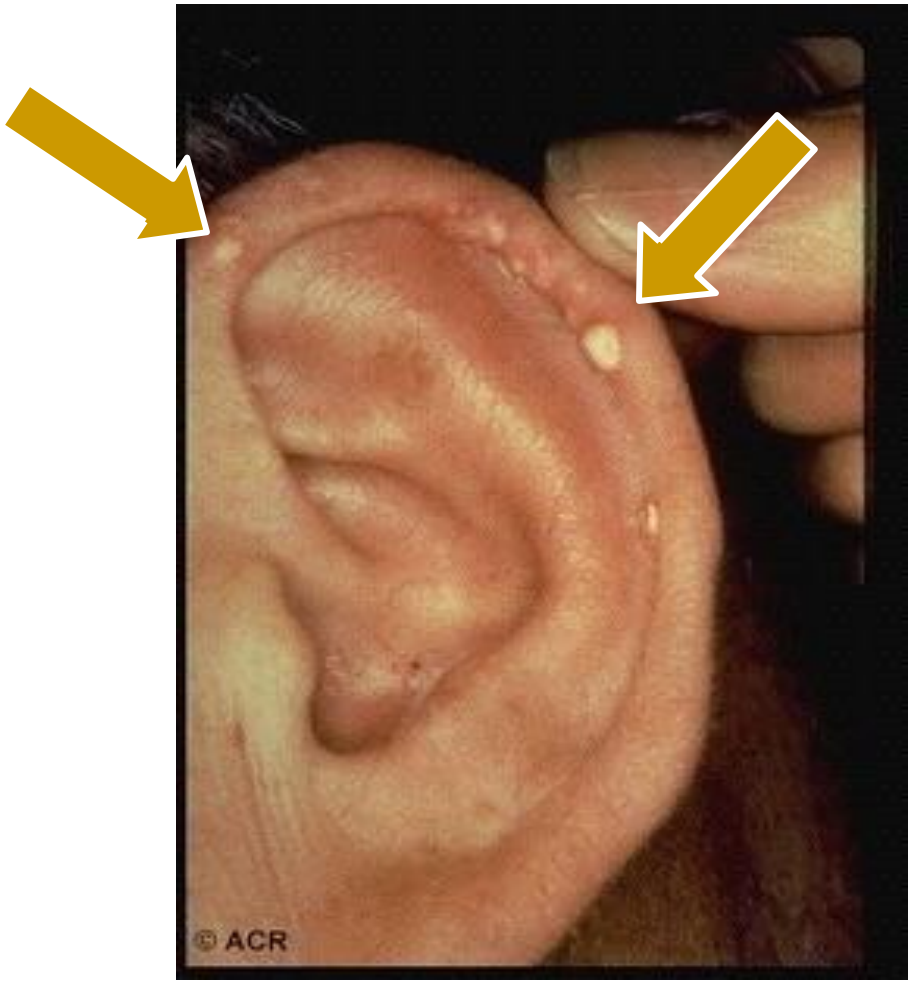


tophus = localized deposit of monosodium urate crystals

Gout - tophus

classic location of tophi on helix of ear

Here, we can also see a classic location of the tophi on the helix of the ear.

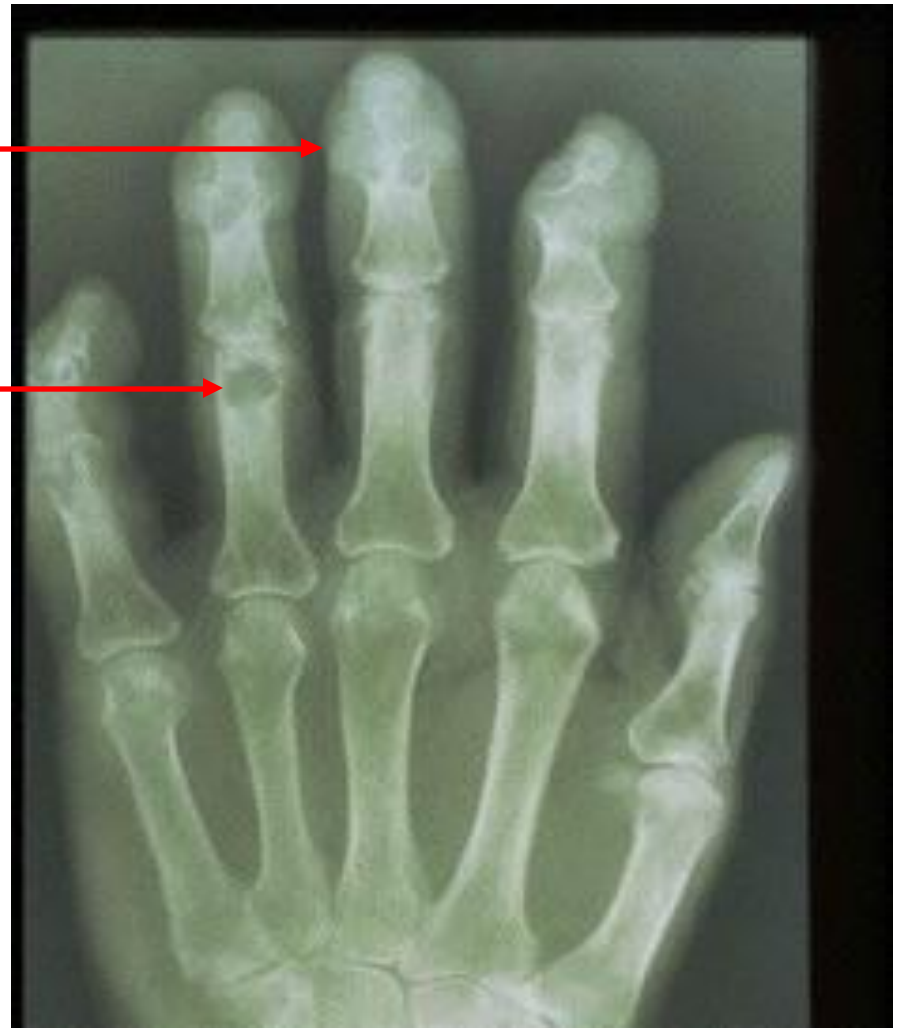


Gout - X-ray changes

DIP (*Distal interphalangeal joint*)

joint destruction

phalangeal bone cysts

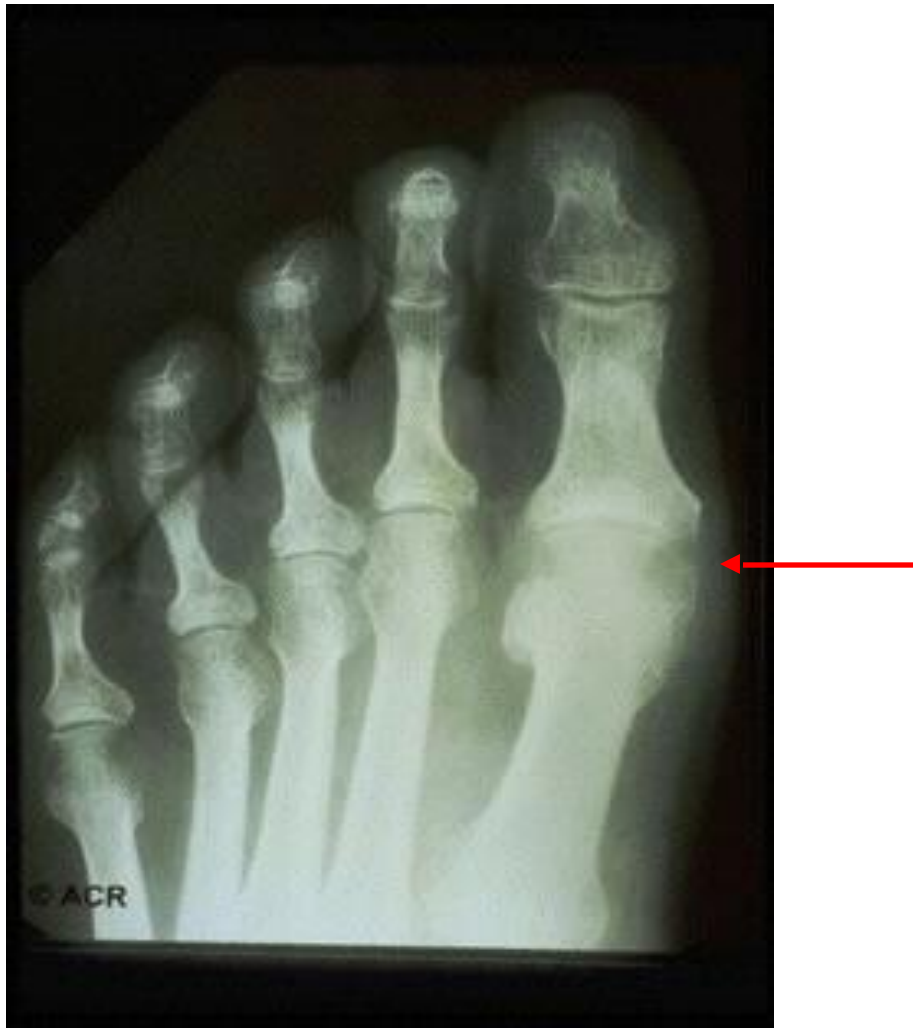


Additionally, we talked about the changes that can be detected on an X-ray. Notably, in the distal interphalangeal joint, we can observe joint destruction, and we can see the formation of cysts in the bone.

Gout - X-ray changes

bony erosions

Here, we can see bony erosions in the joints. These are some of the clinical manifestations of gout in the body. Let's not forget that it can also occur in other areas.As we mentioned, uric acid renal calculi can form, meaning stones in the kidneys.



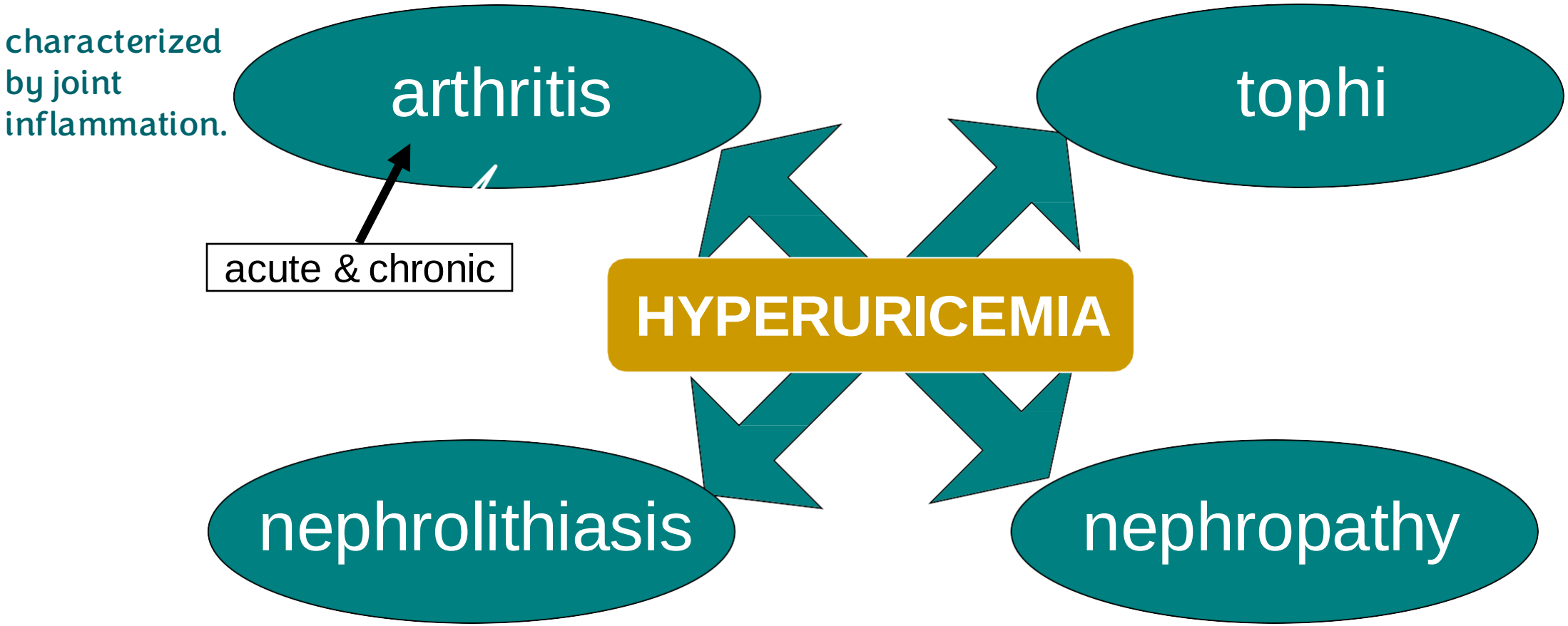
One important note to mention :

clinical gouty episodes are usually associated with hyperuricemia. However, most individuals with hyperuricemia may never develop clinical symptoms from urate crystal deposition.

Before starting chronic urate lowering therapy for gout patients where hyperuricemia is associated with gout and urate stone formation, it is essential to distinguish between individuals who have **asymptomatic hyperuricemia** and those who experience **gouty episodes** due to it.However, Long-term drug treatment for **asymptomatic hyperuricemia** has **not** been proven to be effective, meaning some individuals with high uric acid levels may go through life without developing any adverse consequences.

Gout - cardinal manifestations

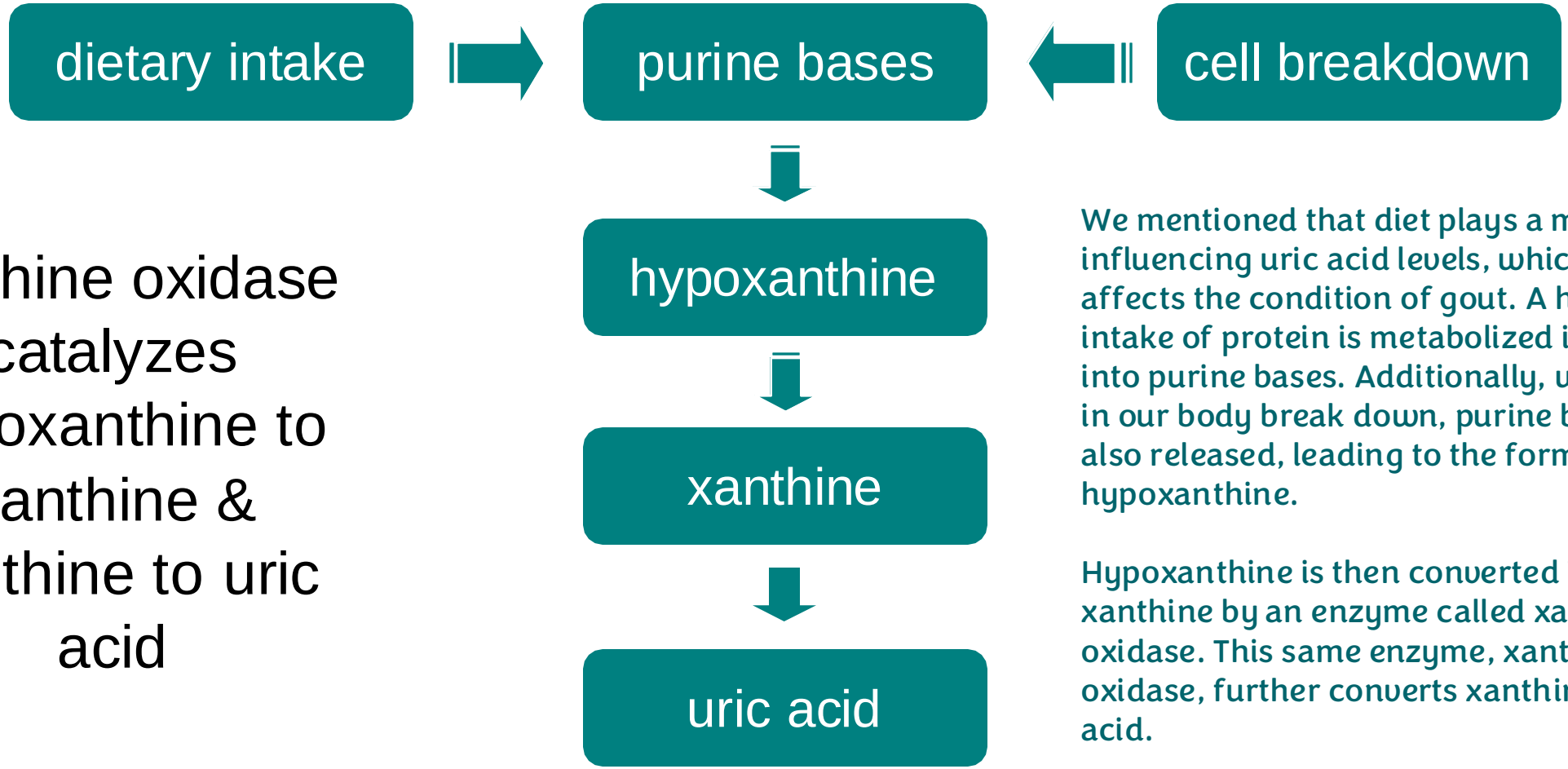
All of these conditions are associated with elevated uric acid levels in the bloodstream, known as hyperuricemia



Drug therapy of gout

The Role of Uric Acid in Gout

Uric acid metabolism



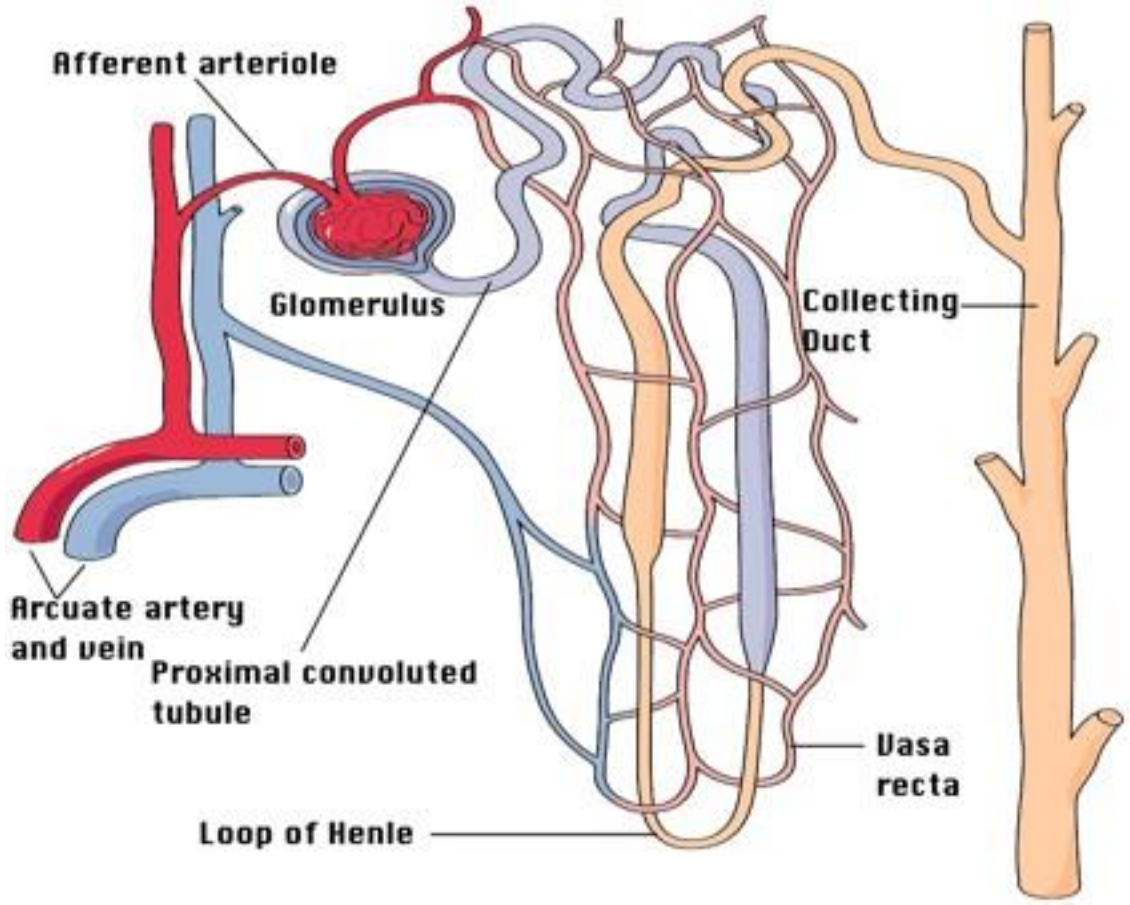
xanthine oxidase catalyzes hypoxanthine to xanthine & xanthine to uric acid

We mentioned that diet plays a major role in influencing uric acid levels, which ultimately affects the condition of gout. A high dietary intake of protein is metabolized in the body into purine bases. Additionally, when cells in our body break down, purine bases are also released, leading to the formation of hypoxanthine.

Hypoxanthine is then converted into xanthine by an enzyme called xanthine oxidase. This same enzyme, xanthine oxidase, further converts xanthine into uric acid.

Renal handling of uric acid

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



Explanation of the previous slide:

In the kidneys, how is uric acid handled?

One key point to remember is that the net effect of all the processes occurring in the renal glomeruli is the excretion of uric acid. The process begins with glomerular filtration, which decreases the concentration of uric acid in the plasma. Later, in the proximal convoluted tubule, uric acid undergoes reabsorption, followed by a stage of tubular excretion. Finally, there is some post-secretory reabsorption. However, the overall net effect remains the excretion of uric acid.

To regulate this process, we can use certain pharmacological agents to inhibit tubular reabsorption or post-secretory reabsorption, thereby promoting uric acid 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

Even though colchicine is not the first-line drug therapy for acute gouty arthritis, it was the primary treatment for many years.

Drugs used to treat gout

Acute Arthritis Drugs

- colchicine
- steroids
- NSAID's

Urate Lowering Drugs

- allopurinol
- probenecid
- febuxostat?

In addition to drug treatments for acute gouty arthritis, bed rest, analgesics for pain relief, and time play a crucial role in resolving the condition.

rest + analgesia + time

Drugs used to treat gout

NSAID's

Indomethacin can inhibit urate crystal phagocytosis. In addition, most of the other NSAIDs we mentioned also have this property, **except** for one drug: **aspirin**. Aspirin is **not** used in the treatment of acute gouty arthritis because it can cause renal retention of uric acid when used at low doses (less than 2.6 grams per day). On the other hand, at high doses, it is uricoseuric, but these are doses higher than 3.6 grams per day.
So, what do we usually use? Indomethacin is commonly used in the initial treatment of gout as a replacement for colchicine.
How do we administer it? We can use 25 to 50 milligrams, up to four times a day, usually for 5 to 7 days.

- 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)

The second drug we are going to talk about is colchicine. Colchicine is a plant alkaloid that comes from a plant called Colchicum autumnale. This plant is also known as 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

So, remember that NSAIDs, in addition to their anti-inflammatory effect, are also painkillers, meaning they have analgesic properties.

Colchicine

How Does Colchicine Help in Gouty Arthritis?

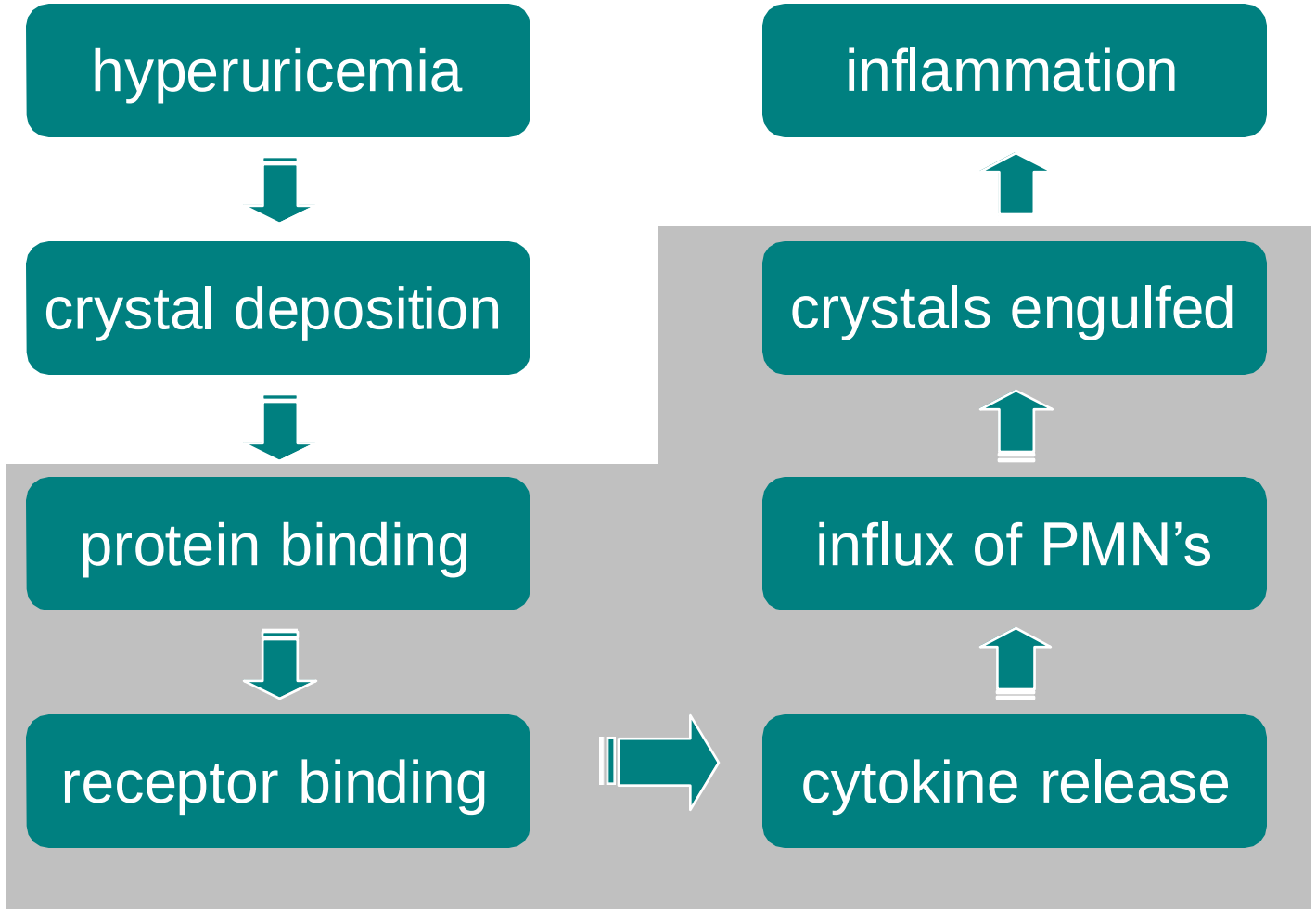
Colchicine works by preventing the polymerization of tubulin subunits, which is necessary for the formation of microtubules.

- 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

We previously mentioned that phagocytosis plays a major role in the inflammatory process associated with gouty arthritis. For cells to engulf urate crystals, they need continuous microtubule formation and polymerization to move and perform phagocytosis.

By inhibiting microtubule polymerization, colchicine prevents phagocytosis, reducing the inflammatory response to the deposited urate crystals. Additionally, it diminishes polymorphonuclear leukocyte phagocytosis of crystals, blocking the cellular response to these deposits. This, in turn, reduces inflammation, cytokine release, and the signs and symptoms of inflammatory arthritis associated with gout.

Crystal-induced inflammation



Colchicine function by preventing the synoviocytes from engulfing the urate crystals preventing cytokines release and the influx of PMNs and preventing the cascade of events that lead to the propagation of inflammation

PMN is critical component of crystal-induced inflammation

Colchicine - indications

Can either be used at a high dose or a low dose

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

Maintenance therapy → to prevent the further flare-ups or attacks of gout

The side effects of Colchicine :

Colchicine - toxicity

- gastrointestinal (nausea, vomiting, cramping, diarrhea, abdominal pain)
- hematologic (agranulocytosis, aplastic anemia, thrombocytopenia)
- muscular weakness

Colchicine prevents the polymerization of microtubules which are very important for the formation of the mitotic spindles meaning that in highly replicating cells Colchicine can affect the replication process of these cells and that is why it affects the blood forming cells (platelet ,RBCs ,WBCs)

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

Gout - colchicine therapy

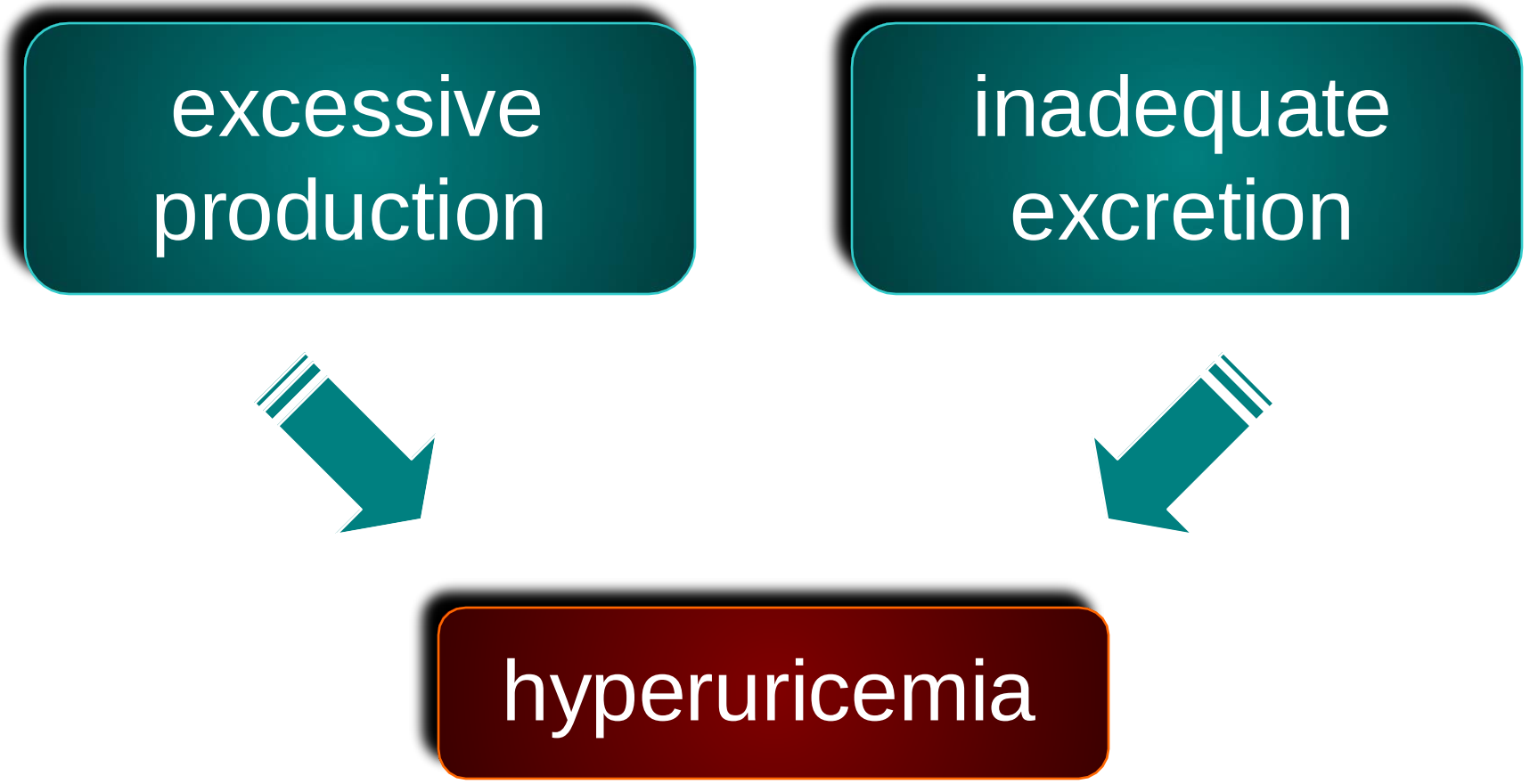
- more useful for daily prophylaxis (low dose)
  - ✓ prevents recurrent attacks
  - ✓ colchicine 0.6 mg qd – bid→ Two times a day
- Recently , there is declining use of it in acute gout (high dose)

Replaced by NSAIDs as the first line drugs for those acute conditions

Predisposing cause of gout :

Hyperuricemia - mechanisms

Which happens either because :



We have certain drugs that we call urate-lowering drugs and they help in the prevention of arthritis tophi and kidney stones by lowering the total body pool of uric acid

Urate-lowering drugs

block production

enhance excretion

One way to address this problem is either by blocking the production or enhancing the excretion and the net result will be net reduction of the total body pool of uric acid

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

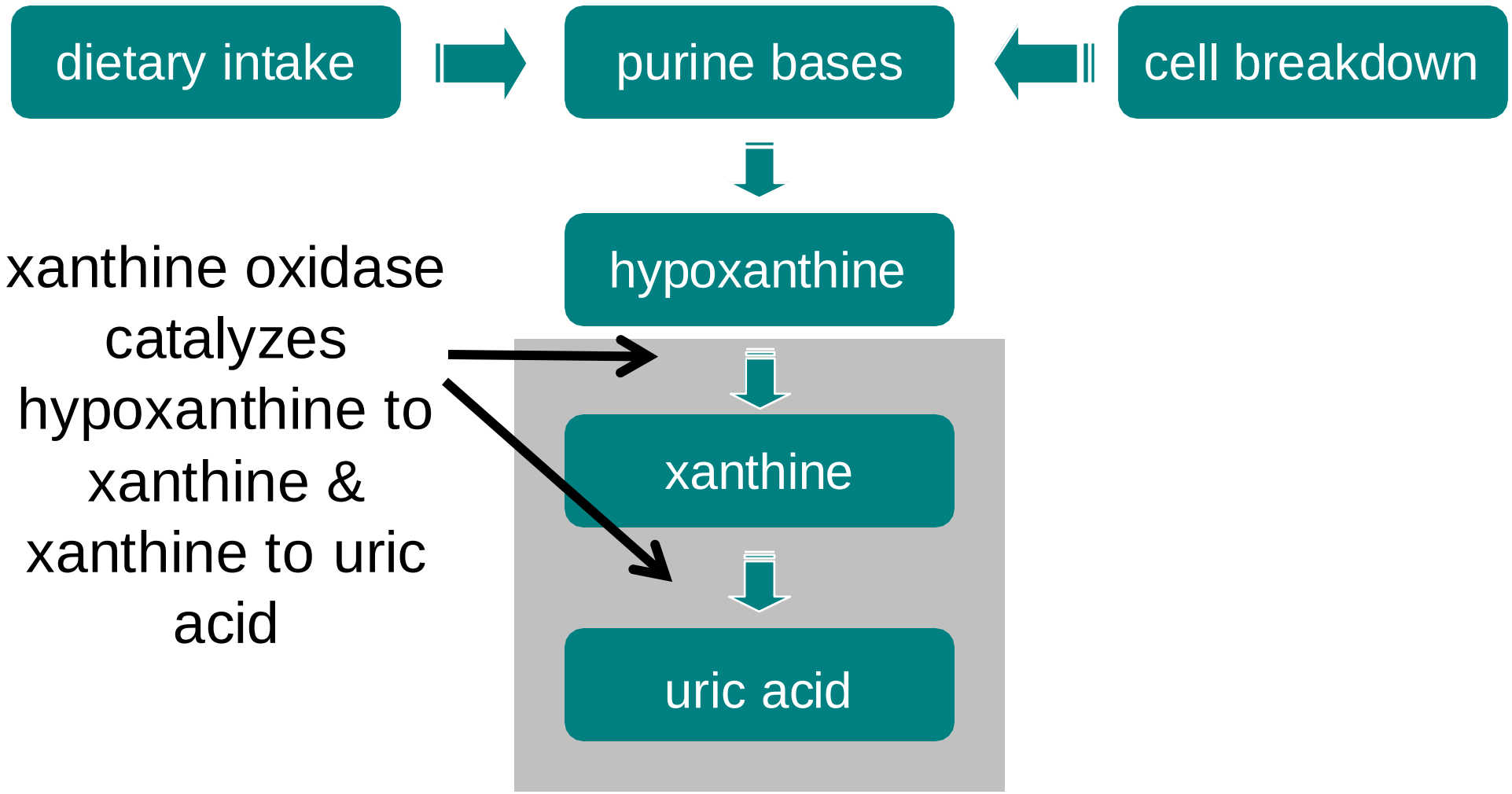
Not indicated immediately but they might worsen the attack if they were used after the first attack

so we must wait for some time before administering these drugs and this is because when we use these urate lowering drugs this would result in urate crystal being shed from the cartilages of the joints into the joint space which results in flare up of the acute inflammation

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 orally
- pregnancy category C

C	Risk cannot be ruled out: Human studies are lacking, and animal studies are either positive for fetal risk or lacking as well. However, potential benefits may justify potential risk.

We can use this drug if the benefits outweigh the risks → it would interfere with the synthesis of uric acid in the infants affecting the purine metabolism meaning it can cause some risks to the fetus

- allopurinol

Allopurinol – usage Indications

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

Adverse effects :

Allopurinol - common reactions

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

After the initiation of allopurinol we'll have mobilization of urate crystals from their attached sides in the joint to the joint spaces and this results in acute changes in the levels of the uric acid serum which can predispose a gout attack.

Additional effects :
-necrotizing vasculitis
-bone marrow suppression
-rarely, aplastic anemia
-hepatic toxicity & interstitial nephritis have been reported
-allergic skin reactions → pruritus or rash → into maculopapular lesions which happens in 3% of the patients
-some patients also develop exfoliation of the skin called exfoliative dermatitis
-in rare cases allopurinol can become bound to the lens resulting in cataract

Allopurinol - serious reactions

Steven Johnson Syndrome

- fever, rash, toxic epidermal necrolysis
- hepatotoxicity, marrow suppression
- vasculitis
- drug interactions (ampicillin, thiazides, mercaptopurine, azathioprine)
- death

Stevens-Johnson syndrome

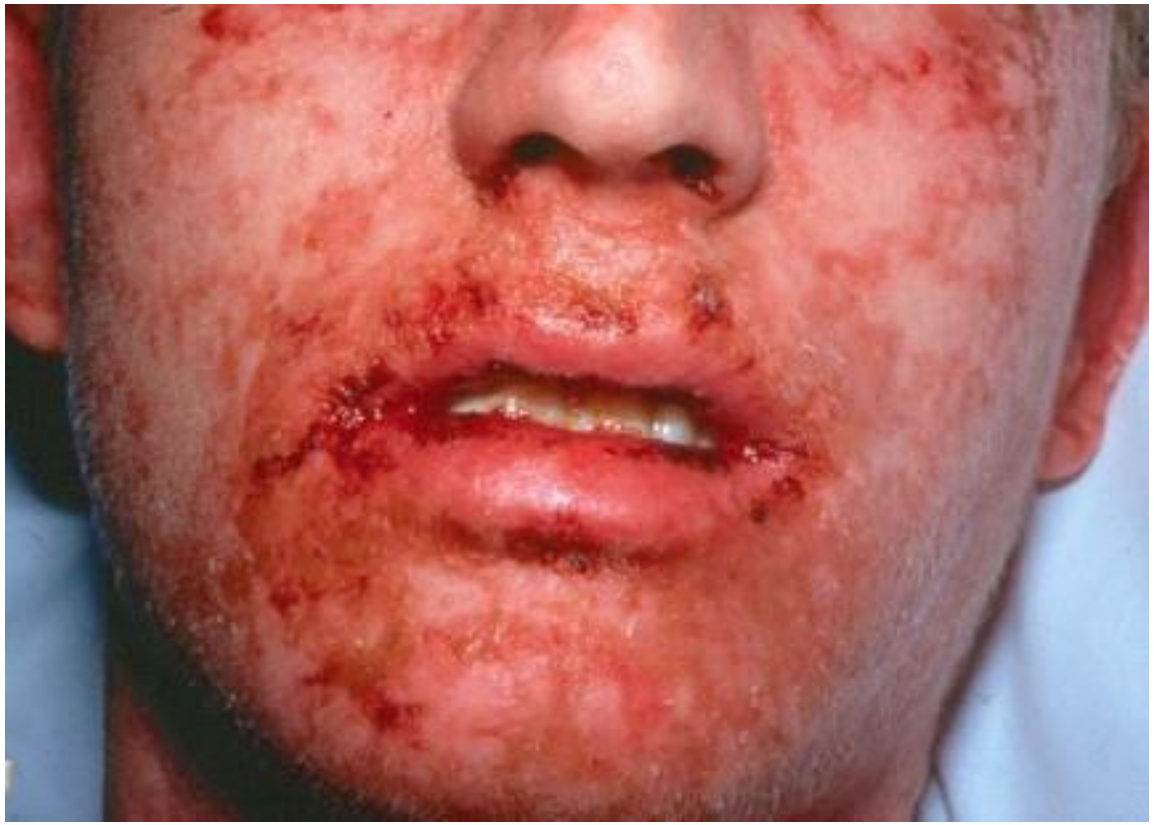
We'll have :

target skin lesions

mucous membrane erosions

epidermal necrosis with skin detachment

Very rare and happens in less than 2% of the patients



Some patients will develop :

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

Must recognize early

Can develop to cause :

Another drug from the same family :

Febuxostat

- recently approved by FDA — In 2009 for treating gout
- oral xanthine oxidase inhibitor
- chemically distinct from allopurinol — structurally — But the same mechanism of action
- 94% of patients reached urate < 6.0 mg/dl
- minimal adverse events

Can cause reduction of urate levels below 6 mg/dl (the level we aim for)

Compared to allopurinol, it can cause diarrhea ,headache and nausea .Also, it seems more well tolerated in patients who have sensitivity or intolerance to allopurinol (great alternative)

The newest urate lowering therapy:

PEGLOTICASE

Pig → the animal
PEG → chemical compound

The addition of PEG conjugation is to increase the half life of the drug and diminish or lower the immune response for this enzyme that is not coming from a human source so it will decrease the antigenicity of the enzyme/protein

- recently approved by FDA 2010
- PEG-conjugate of recombinant porcine uricase
  Covalently bounded to methoxy polyethylene glycol → Humans do not possess the enzyme that is necessary for the breakdown of uric acid (uricase) while other mammals have it, so this drug is the recombinant form of the enzyme that is present in pigs (porcine)
- treatment-resistant gout
- uricase speeds resolution of tophi

It's an IV administered drug that works fast (within 24-72 hour) to reach its peak concentration in the body for days (6-13 days) . Usually clearance is by antibody response _ the importance of adding PEG is to minimize antibody response in the body

The newest urate lowering therapy:

Used for refractory chronic gout (refractory means it doesn't respond to other medications)

PEGLOTICASE

Pig → the animal
PEG → chemical compound

- recently approved by FDA 2010
- PEG-conjugate of recombinant porcine uricase
- treatment-resistant gout
- uricase speeds resolution of tophi

One concern → usage of this drug in patients with Glucose-6-phosphate dehydrogenase deficiency due to the formation of hydrogen peroxidase (Although the term "hydrogen peroxidase" was used in the lecture, it is probable that "**hydrogen peroxide"** was the intended term") by the enzyme(uricase). Therefore this drug must be avoided is these patients.

Adverse effects associated with it :

Infusion reaction + flare-ups of gout → especially during the first 3 months of treatment

Other side effects :

Nephrolithiasis (kidney stones)

Arthralgia

- Muscle pain and spasms
- Headache
- Anemia
- Nausea

less frequent side effects :

- Respiratory tract infection
- Peripheral edema
- UTI
- diarrhea

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
- not used in patients with renal disease
- frequent, but mild, side effects

Mainly used in patients who have tophaceous gout or patients who have frequent gouty attacks

While in patients who secrete large amounts of uric acid or patients with renal disease→ these agents will not be used

Uricosuric therapy

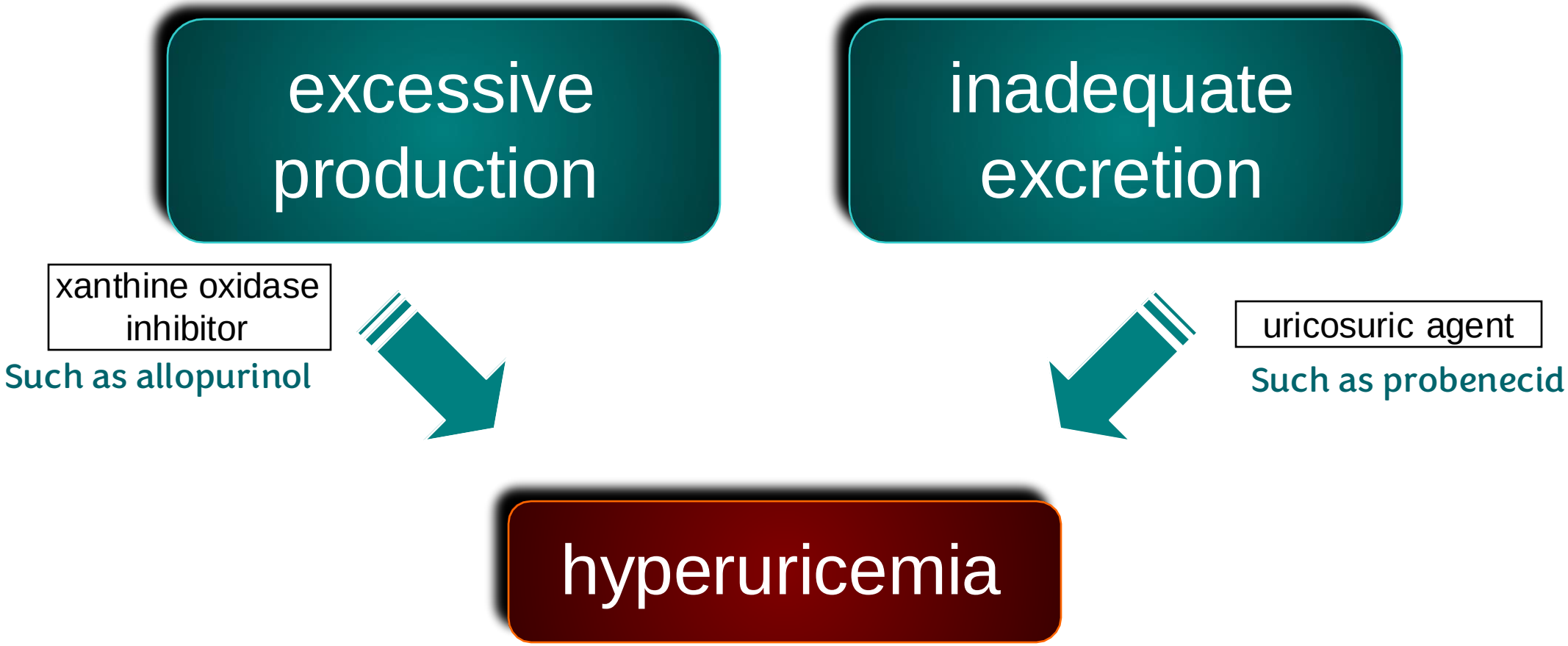
- contra-indications
  - ✓ history of nephrolithiasis
  - ✓ elevated urine uric acid level
  - ✓ existing renal disease
- less effective in elderly patients

Kidney stones

As they have deteriorated kidney function

Mild side effects are associated with such drugs like GI irritation

Choosing a urate-lowering drug



Drug therapy of gout

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

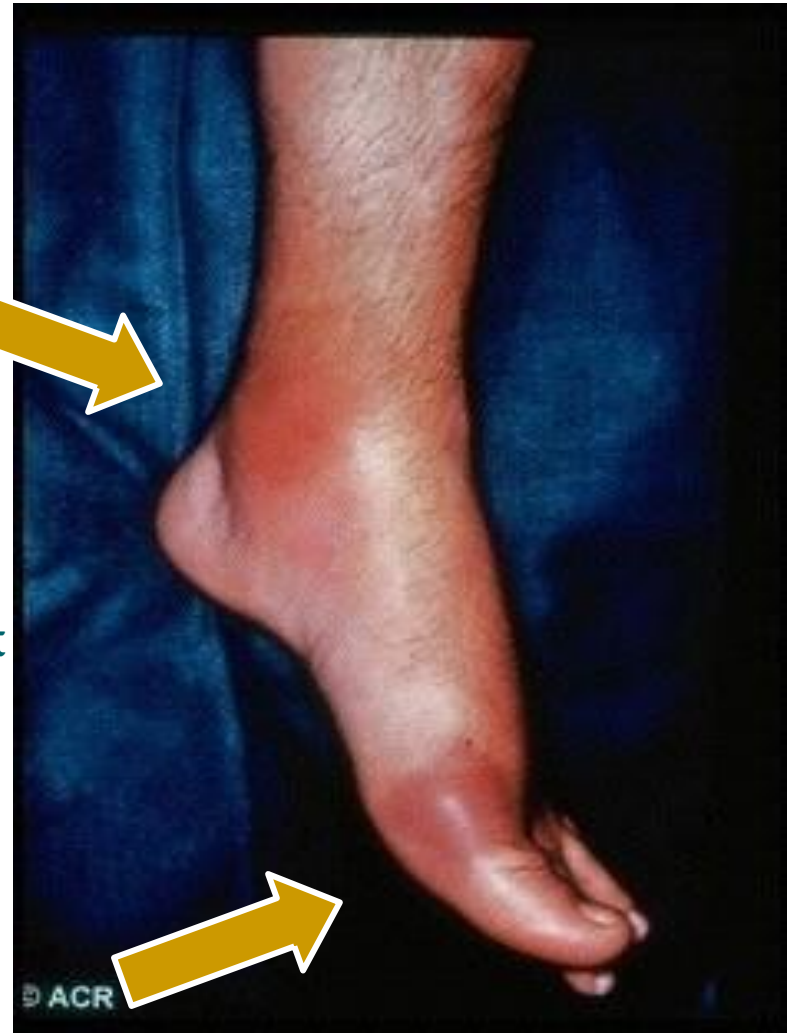
Past medical history

- PMH of similar problems in right ankle & left wrist

Gout - acute arthritis

acute synovitis,
ankle & first MTP
joints

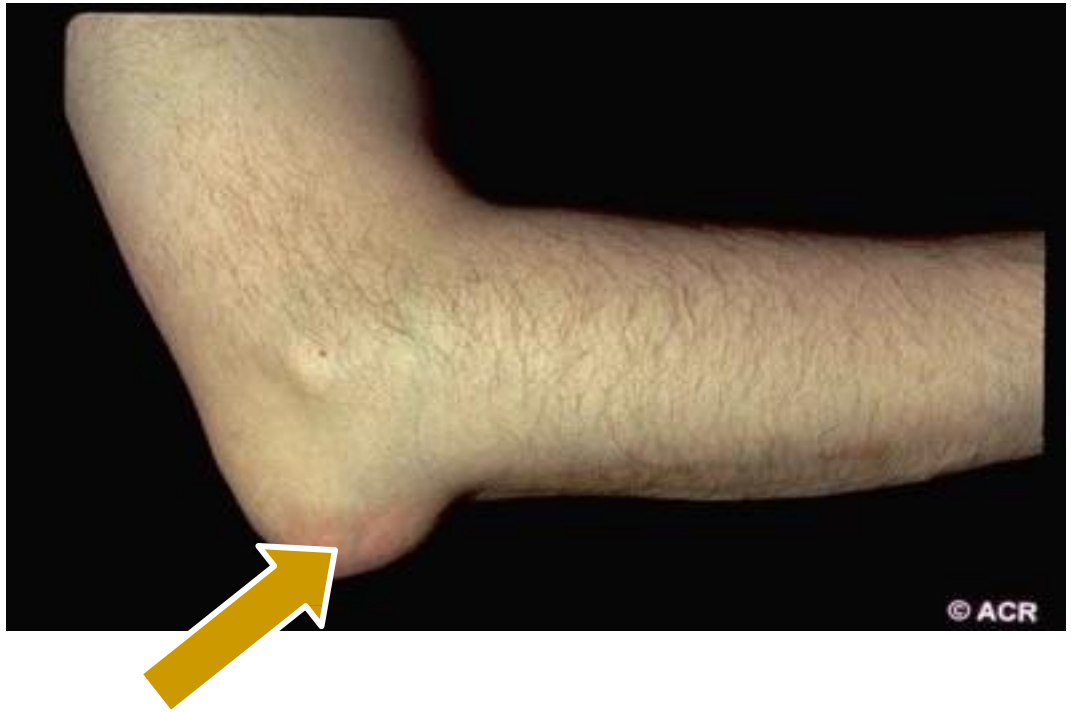
metatarsophalangeal joint



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

Case presentation - therapy

① Start the patient on :

Either are used as first line treatment

- NSAID
- steroid

If there were any flare ups we can give NSAIDs again

NSAID

② Before we end NSAIDs we start :

colchicine (low-dose) — Not recommended due to its side effects

Used as maintenance therapy to prevent further or any future attacks

③ Can't start it immediately after an acute attack so we wait for a period of time while the patient is still on NSAIDs and Colchicine and then we can use it and stop the NSAIDs

allopurinol

Maintenance therapy → maintain low levels of uric acid in the blood and after the attack is subsided we keep the patient on Colchicine and Allopurinol

days 1-10	days 11-365	days 365+

When in the patient is not responding to NSAIDs nor colchicine

Interleukin 1 receptor antagonist

Example:

- Anakinra
- Canakinumab
- Rilonacept

These are drugs used for treatment of rheumatoid arthritis and currently being investigated for gout→ they target IL-1 pathway thus they would suppress the inflammation

Glucocorticotiods

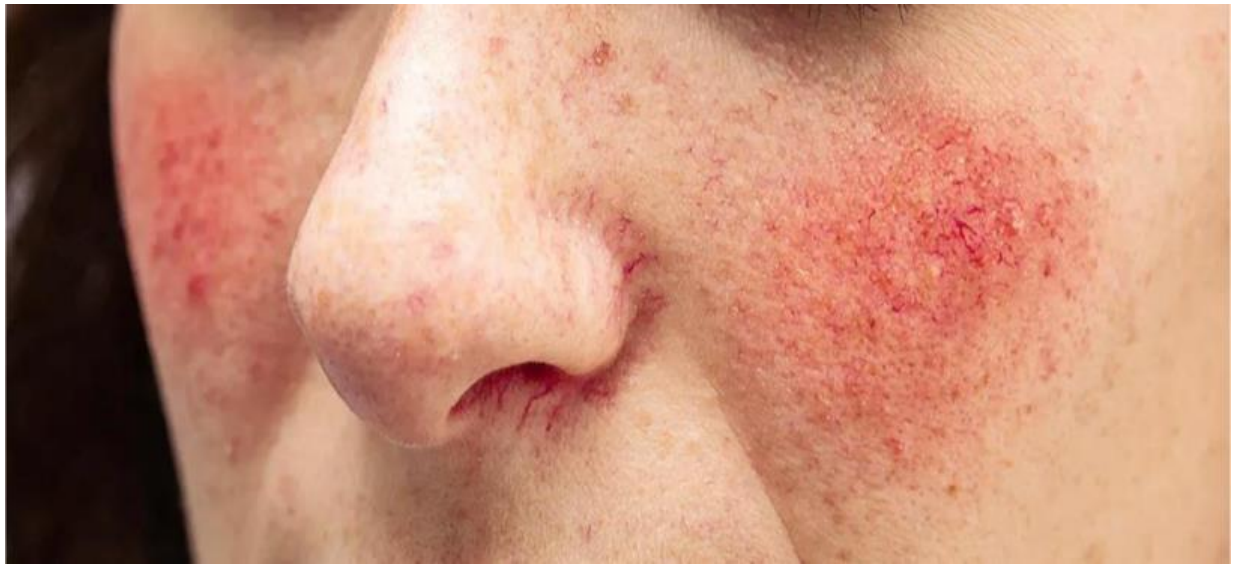
We can use them for acute gouty arthritis

Prednisone

- Oral
- Intra-articular — Inside the joints
- Subcutanous

Depend on the degree of the acute attack and the degree of pain and inflammation in the patient

Choose the correct answer to test yourself in the previous lecture (NSAIDs2)!



How to treat rosacea?

A) Metronidazole

B) Azelaic acid (topical gel treatment)

C) Both Metronidazole and azleaic acid

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	Slide 45 Slide 5 & 46	(6-30 days)	(6-13 days) Clarifications have been added to certain sentences to aid in understanding (grey text)
V1 → V2			

Additional Resources:

رسالة من الفريق العلمي:

Extra References for the Reader to Use:

1. [What happens during a gout attack?]