# MSS

## Pharmacology

LEC no. 8


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# Drug Therapy of Gout

# Drug therapy of gout

## *What Is Gout?*

Gout is a form of complex arthritis. It is characterized by sudden, severe attacks of pain, swelling in the joints, redness, and tenderness. It could happen to one or more joints. Usually, one of the joints that is inflamed or having this reaction with gout is the big toe.

Now, an attack of gout can happen suddenly. Maybe when somebody is sleeping in the middle of the night, he would feel that the big toe is on fire. The affected joint would be hot, swollen, and painful. And these are usually happening because of an inflammatory reaction that's occurring at that site. So we can summarize that gout is an inflammatory disease. But what is the cause of gout? Actually, gout can be also considered as a metabolic disease. It happens because we have inflammation or what we call arthritis. It happens because of deposition of monosodium urate crystals. It can deposit in the joints, as we said, but also in other places such as the cartilage. Additionally, we can see some of these deposits of uric acid in the kidneys. So we can have renal calculi(kidney stones). Also, we can have intestinal nephritis (the spaces between the kidney tubules become swollen (inflamed)).

# Gouty arthritis-characteristics:

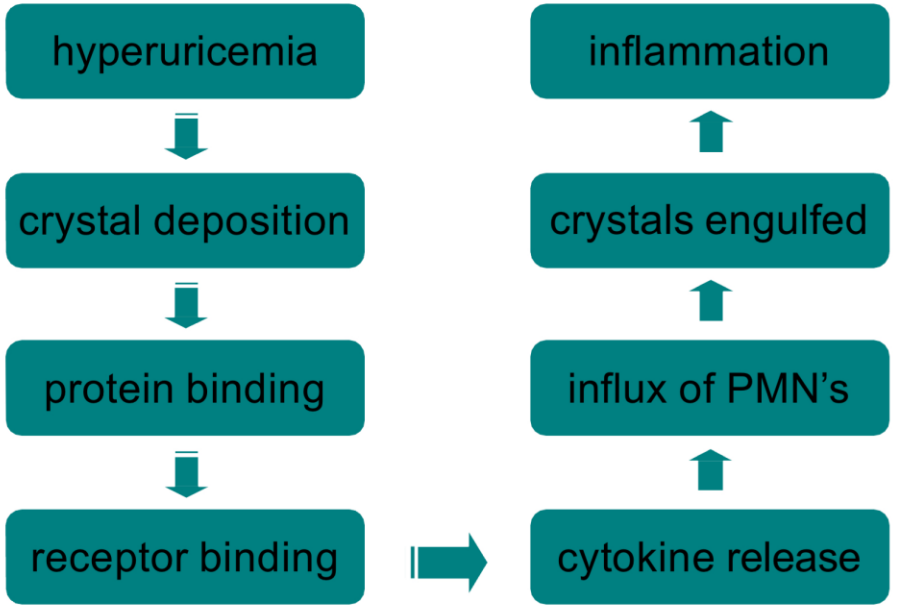
- sudden onset

it can start in the middle of the night

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

Bone erosion is the loss of bone from disease processes.

# Crystal-induced inflammation




-Uric acid is a poorly soluble substance that is the major end product of purine metabolism. Now many of the mammals, they have an enzyme called uricase, and uricase usually converts uric acid to more soluble allantoin.

-PMN is critical component of crystal-induced inflammation

Unfortunately, humans do not possess this enzyme. So we have to control the levels of uric acid through its excretion from the kidneys. So in any instance where we have an imbalance between the uptake and the elimination or secretion of uric acid, we might have elevated levels of uric acid in the serum, leading to the position of the substance, as we said, in joints, in the kidneys, in the intestine, sometimes in cartilages as well. So these urate crystals bind to certain protein and receptors in the surface of cells that are lining the joints, which we call synovial sites (fluid-filled sacs between tendons and bone) .Synovial sites will then engulf these urate crystals. This will lead to release of many cytokines, PGs, lysosomal enzymes, and IL-1. So this cytokines releasing will cause attraction of a number of cells. From these cells are PMNs. These cells will migrate into the joint space and amplify the ongoing inflammatory process. The PMN is a critical component of crystal-induced inflammation.

# Gouty arthritis- characteristics

- sudden onset
- middle aged males
- severe pain

This is because of the cytokine release, especially IL-1 and PGs

- distal joints

Although it can happen in other places.

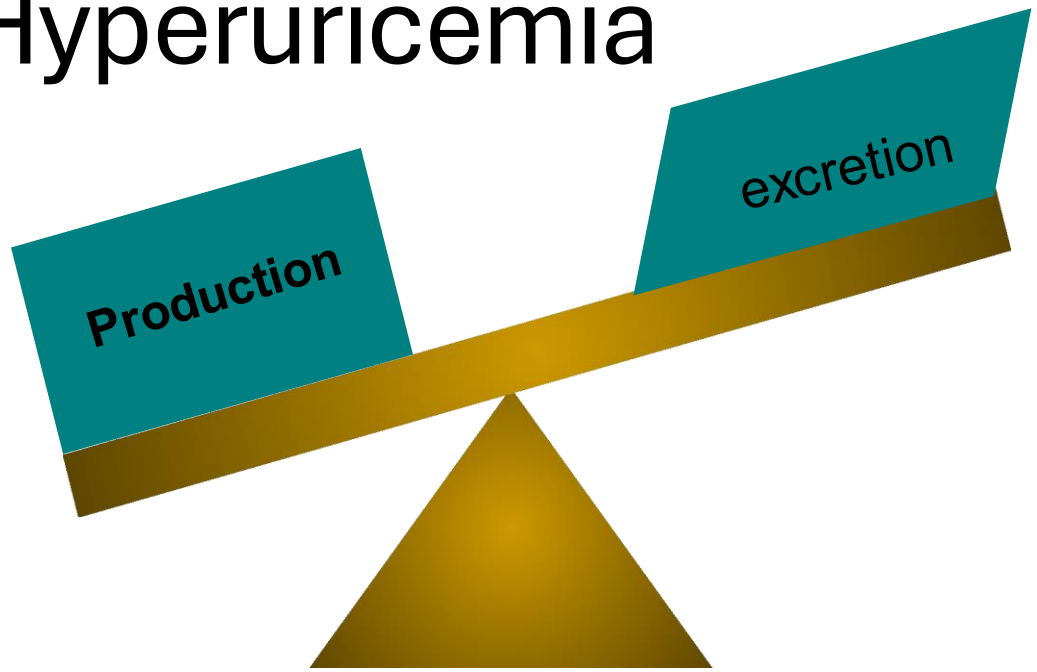
- intense inflammation

That keeps propagating with the presence or the chemotactic of the different cells, mainly PMNs.

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

Now, at later stages of the attack, there is an increased number of these mononuclear phagocytes or macrophages. They will start ingesting the urate crystal, and they will release more inflammatory mediator. So, how can we diagnose acute gouty arthritis? We can see the bony erosions on the x-ray, but also it is characterized by hyperuricemia.

# Hyperuricemia

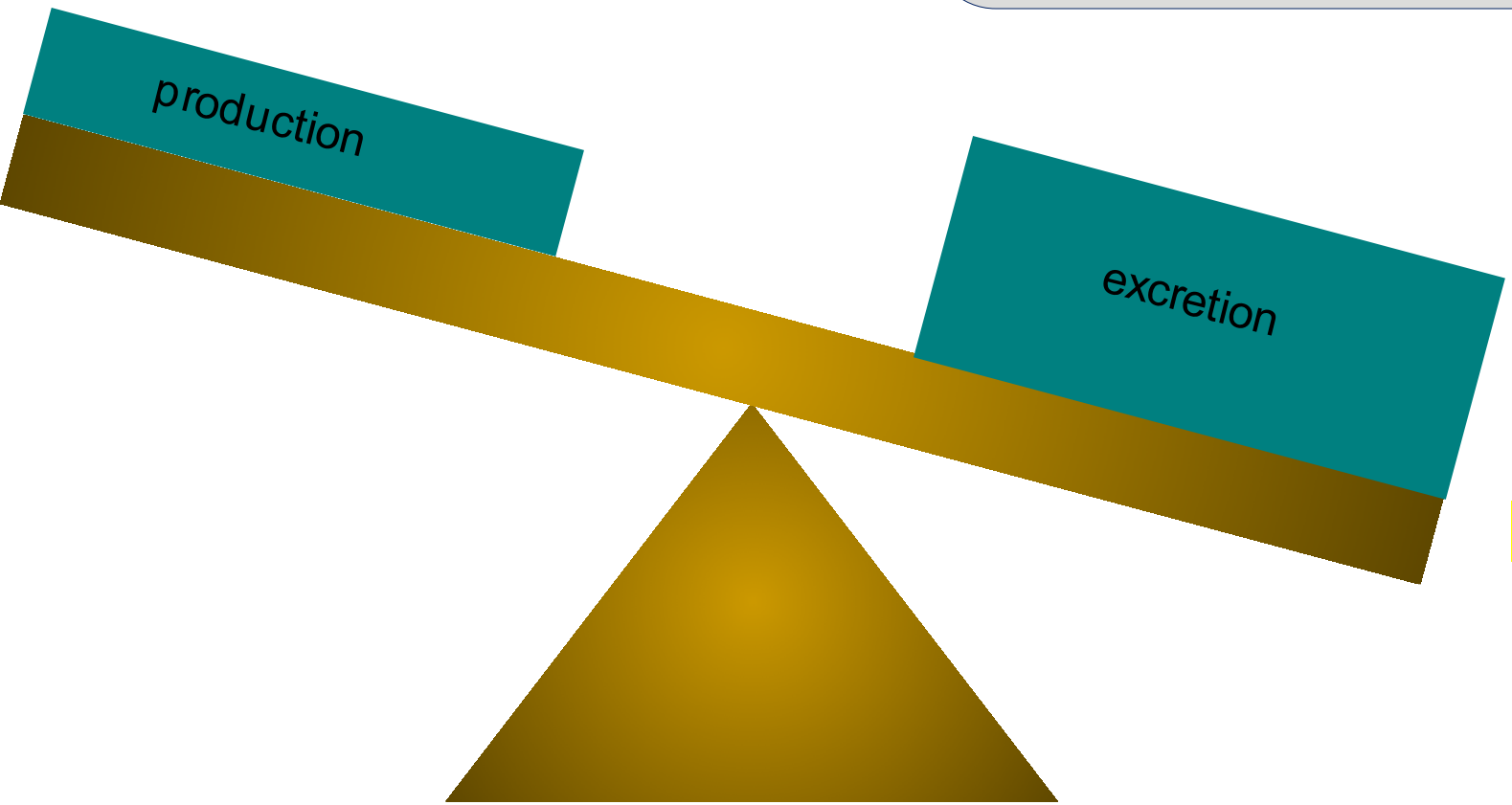



hyperuricemia results when production exceeds excretion

It is influenced by diet, and this is very important. Note, there are two reasons for hyperuricemia happening. The first one is when the production of uric acid exceeds the secretion of uric acid. The other is when the net uric acid loss results in excretion exceed production. So, we usually have to have a balance. So, either if we intake too much substances that gets converted in our body to uric acid. So, what kind of substances are we talking about? Usually meat, red meats. Red meats will get digested in our body. They will produce purine. Purine will get metabolized to uric acid. So, if people who have the problem of gout and there is too much meat or proteins, usually they will end up with hyperuricemia.

# How is Hyperuricemia corrected ?

The other thing which we are talking about here is where we have imbalance between the excretion part. So, if the kidney does not excrete enough uric acid, this will lead to build up of uric acid in the bloodstream. Again, we will have hyperuricemia.




Here, Dr said there is abnormal excretion so there is uric acid retention which leads to hyperuricemia

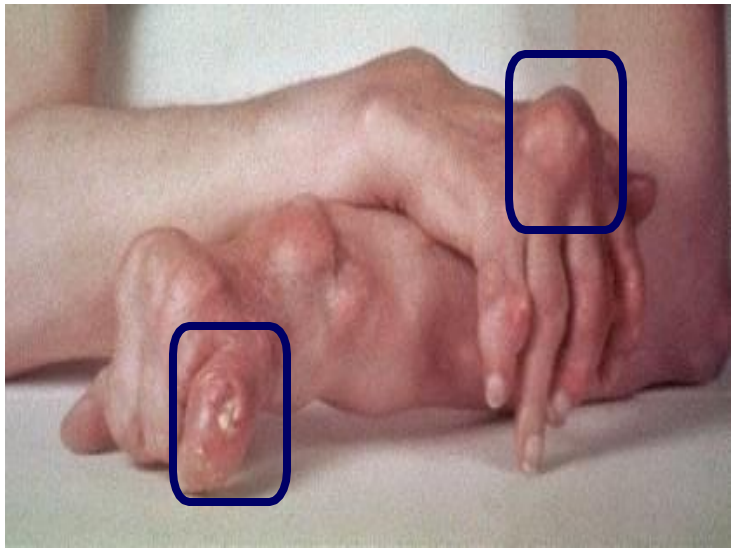
الرسمة يفترض تكون العكس، صح؟😅
يعني التخلص من اليوريك أسيد بكون أقل

V2:
بعد ما رجعنا للڤار (الدكتورة 🙂)، طلع قصد الدكتورة هون كيف بنعالج الHyperuricemia

net uric acid loss results when excretion exceeds production

# Chronic tophaceous gout

Remember that not only gout presents as arthritis, but it also can present in other forms, such as chronic tophaceous gout.
So, tophus means localized deposits of monosodium urate crystals.
So, tophaceous gout is a chronic form of gout, where we see nodular masses, so in the nodes of uric acid crystals, that are deposited in different tissues areas of the body. Usually, these tophi are present as hard nodules, most commonly around the fingers, as we can see in this picture. And this not only is a painful inflammatory process, but also a disfiguring pain for the patient. So, we said these tophi can be present in the toes, in the fingers, in the elbows.

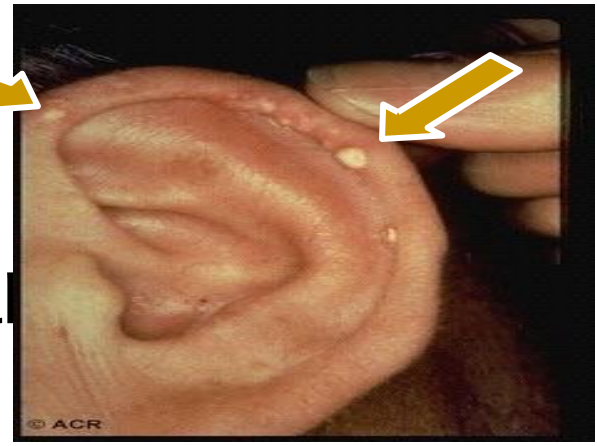


tophus=localized deposit of

monosodium urate crystals

**Gout - tophus**

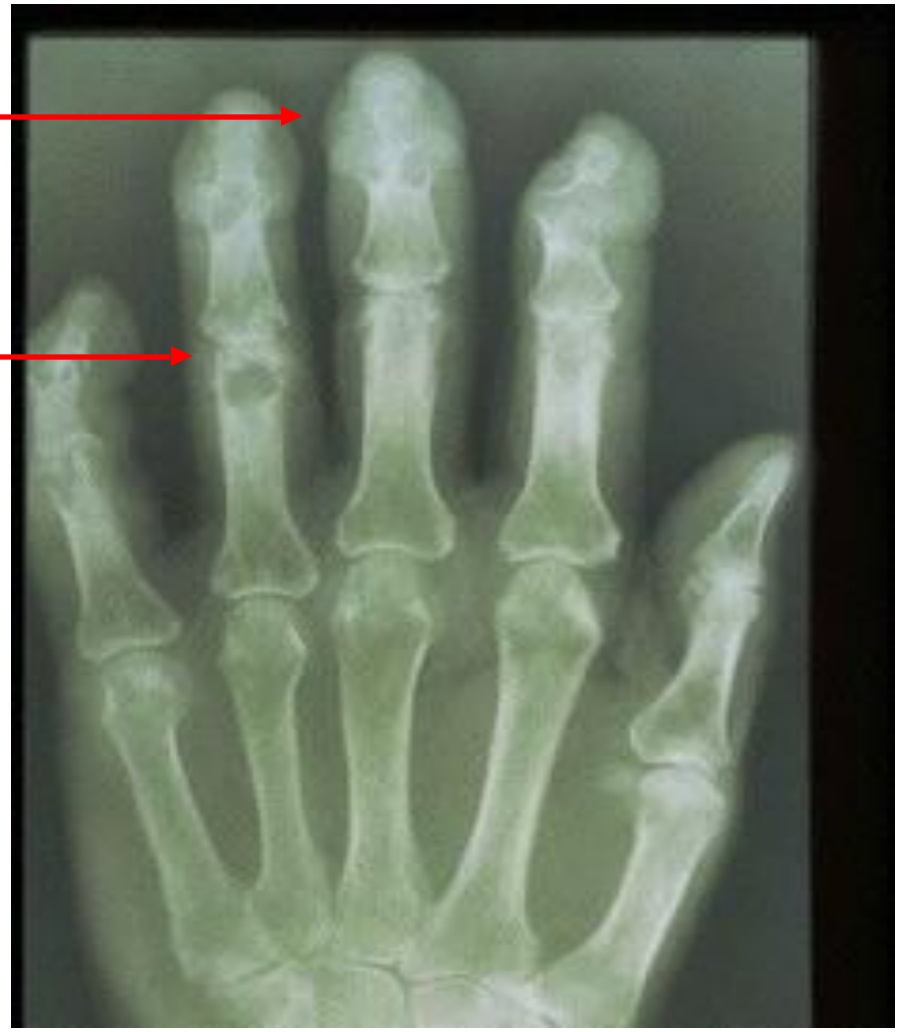
classic location of tophi on helix of ear



# Gout - X-ray changes

DIP (*Distal interphalangeal joint)* joint destruction

phalangeal bone cysts

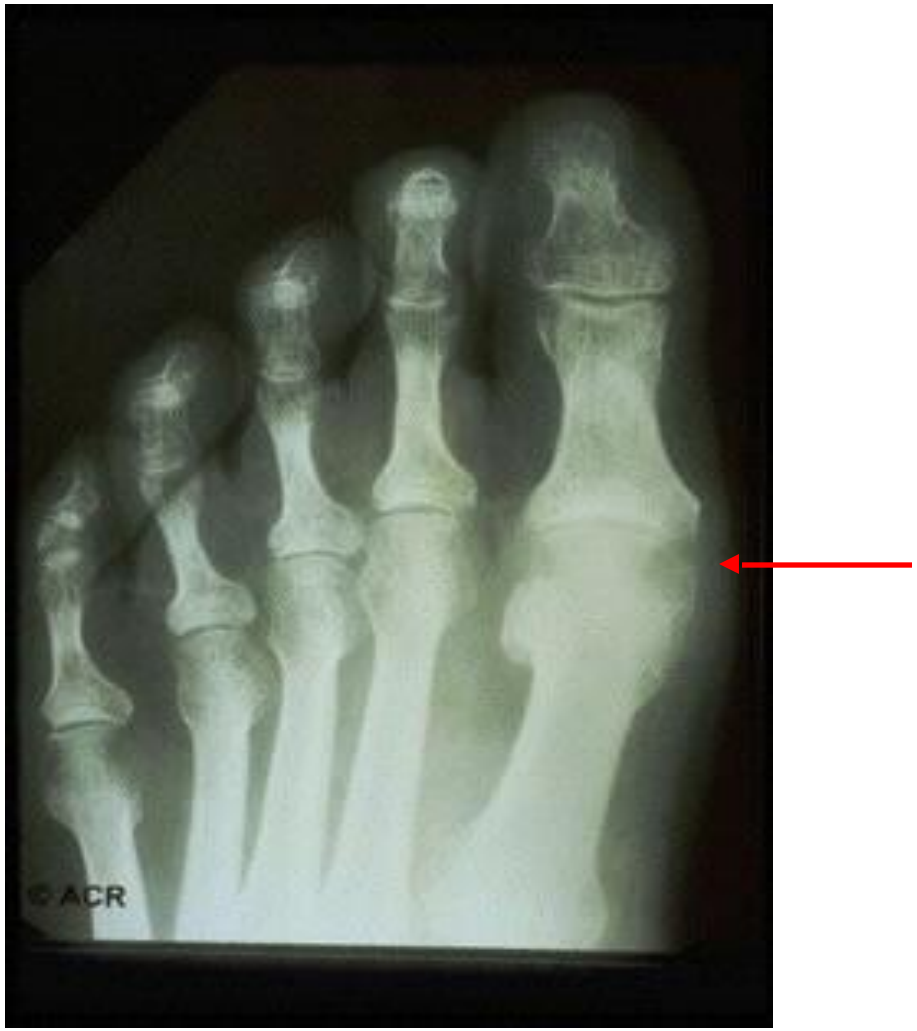


You can note in the distal interphalangeal joint, we can see that there is joint destruction, and we can see that there are the formation of cysts in the bone.

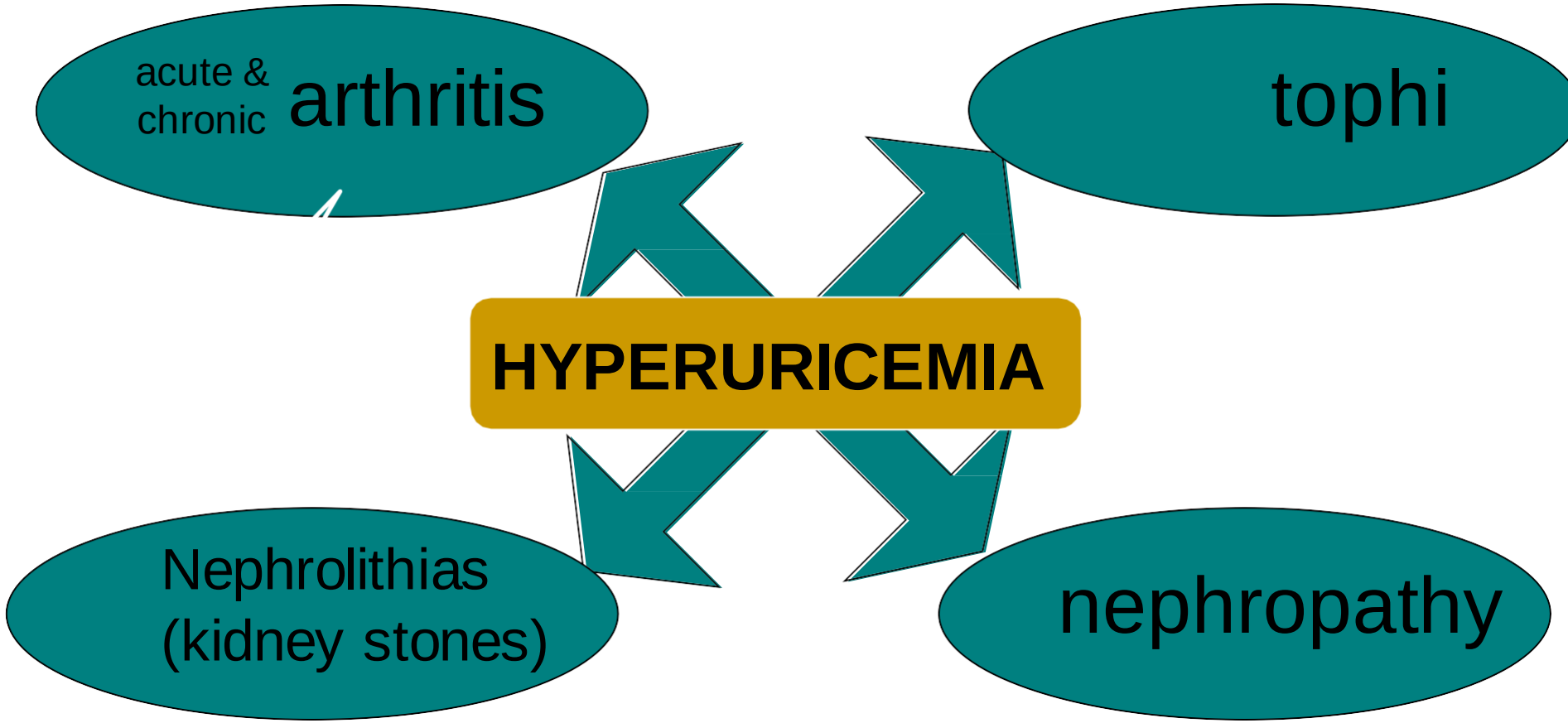
# Gout - X-ray changes

## bony erosions

Additionally, here we can see bony erosions in the joints. So, these are some of the clinical manifestations of gout in the body. Again, it can also happen in other areas of the body. We said, we have uric acid renal calculi, which means stones in the kidneys.



# Gout - cardinal manifestations

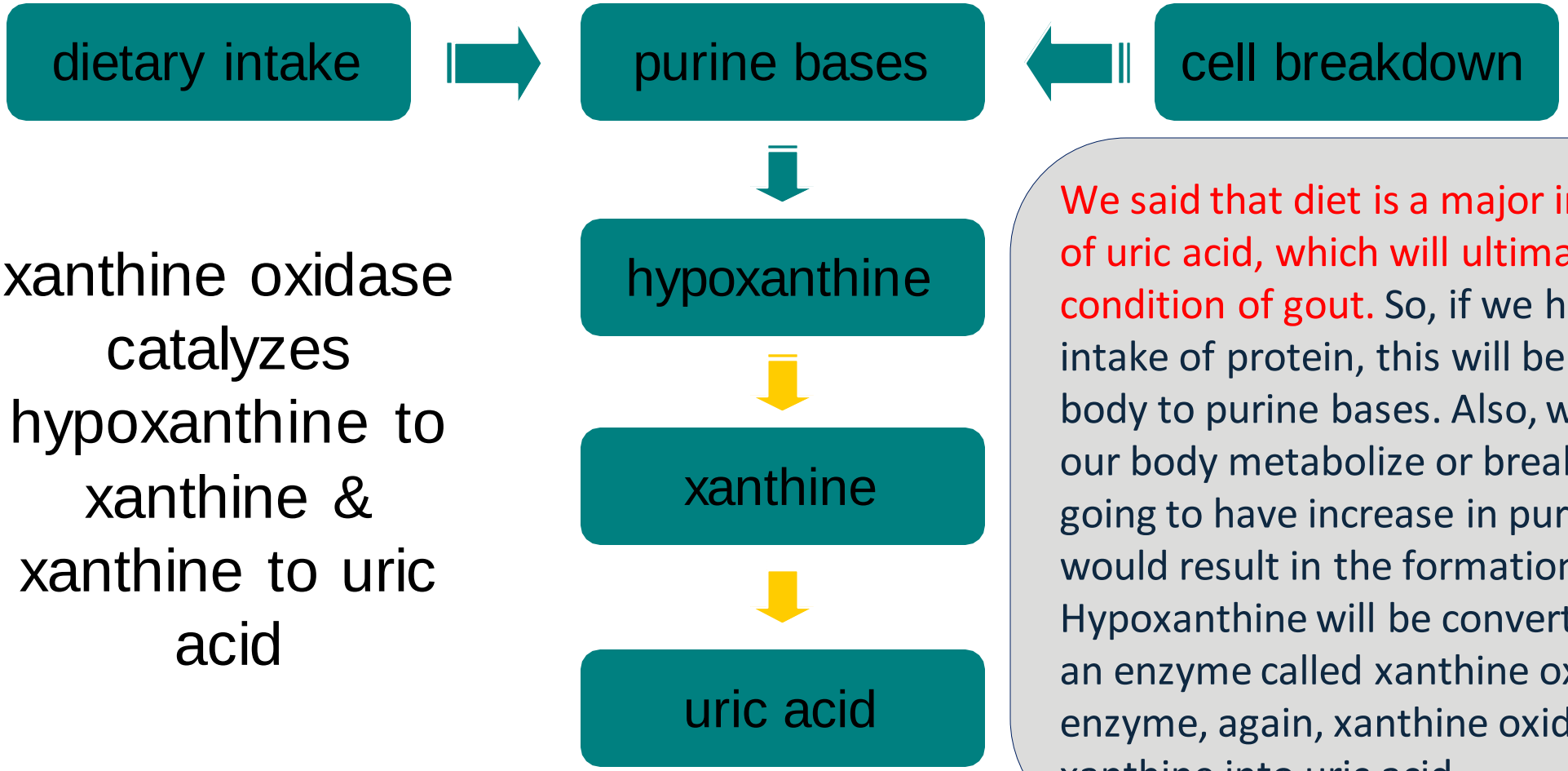


While clinical gouty episodes are usually associated with hyperuricemia, most individuals with hyperuricemia may never develop a clinical event from these urate crystal deposition. So before starting the chronic urate- lowering therapy for gout patient, where hyperuricemia is associated with gout and also with deposition of urate stones, we need to distinguish which individuals have only hyperuricemia, and which individuals have gouty episodes resulting from that hyperuricemia. Because usually the efficacy of long-term drug treatment of asymptomatic, that means hyperuricemia without symptoms, is not proven to be effective. So even in some individuals where we can see high levels of uric acid, maybe they would go throughout their whole life without having adverse consequences. So what are the cardinal manifestations that make a person characterized of gout and needing of pharmacological treatment? The first one is the presence of arthritis. So we have inflammation in this case. Also, we have tophi. We can also have nephrolithiasis. Or it can end up resulting in nephropathy. Now arthritis can be either acute or chronic, and the treatment we're going to mention for both chronic and acute gouty arthritis. All of these are associated with increased levels of uric acid in the bloodstream, which we call hyperuricemia.

# Drug therapy of gout

*The Role of Uric Acid in Gout*

# Uric acid metabolism

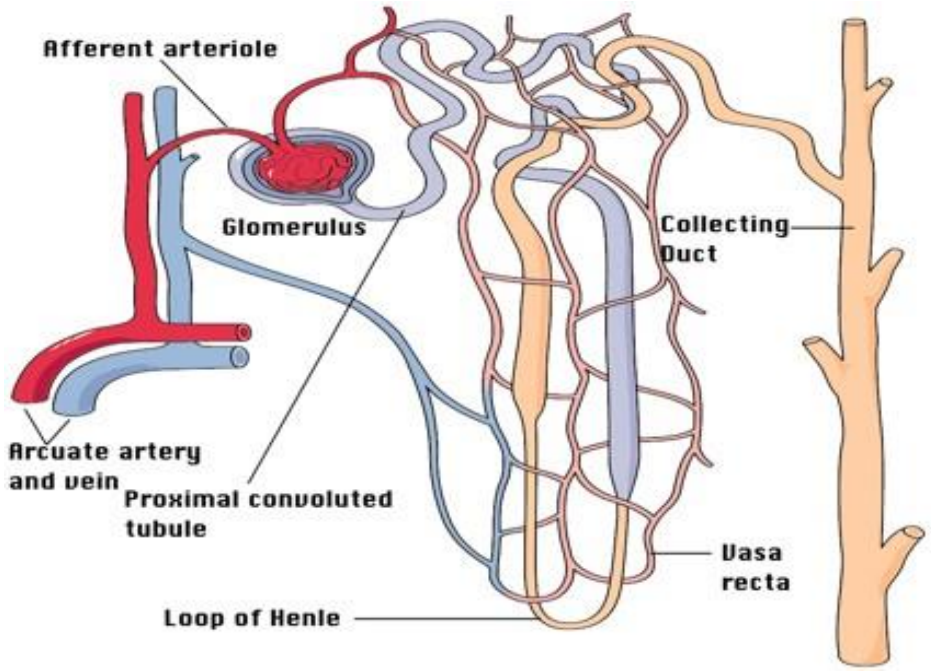



xanthine oxidase catalyzes hypoxanthine to xanthine & xanthine to uric acid

We said that diet is a major influence on levels of uric acid, which will ultimately affect the condition of gout. So, if we have a high dietary intake of protein, this will be metabolized in our body to purine bases. Also, when the cells in our body metabolize or break down, we're also going to have increase in purine bases. This would result in the formation of hypoxanthine. Hypoxanthine will be converted to xanthine by an enzyme called xanthine oxidase. Also, this enzyme, again, xanthine oxidase, will convert xanthine into uric acid.

# Renal handling of uric acid

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




Now, in the kidneys, how is uric acid handled? What's very important to remember is that the net effect of all the different events that happen throughout the kidney glomeruli is net excretion of uric acid. So we start off with glomerular filtration. This will lead to a decrease of concentration of uric acid in the plasma. Later on, at the proximal convoluted tubule, we have reabsorption. Later on, a stage of tubular excretion. And then finally, we have some post secretory reabsorption. But ultimately, the total, or the net effect, is excretion of uric acid. So if you want to control this process, you can prevent the process of tubular reabsorption or the post secretory reabsorption by the use of certain pharmacological agents that we're going to mention it.

# 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 gout arthritis, but it was the primary treatment for many years.

In addition to all of the drug treatments and the condition of acute gouty arthritis, we need to have bed rest, analgesia, pain relief, and time will help in resolving this problem.

# 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**

Remember that all of these share a common mechanism of action, which is inhibition of the synthesis of prostaglandin by inhibition of the enzyme COX. In addition to that, indomethacin can inhibit urate crystal phagocytosis. In addition, most of the other NSAIDs that we mentioned also have this property, except for one drug, which is aspirin. Aspirin actually is not used in the treatment of acute gouty arthritis because it can cause renal retention of uric acid when used at low doses, and this is lower than 2.6 grams per day. Actually, 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 use? Usually, indomethacin is commonly used in the initial treatment of gout as a rplacement for colchicine. How do we administer it? We can use 25-50 mg up to 4 times a day, and this is usually for 5-7 days.

# 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

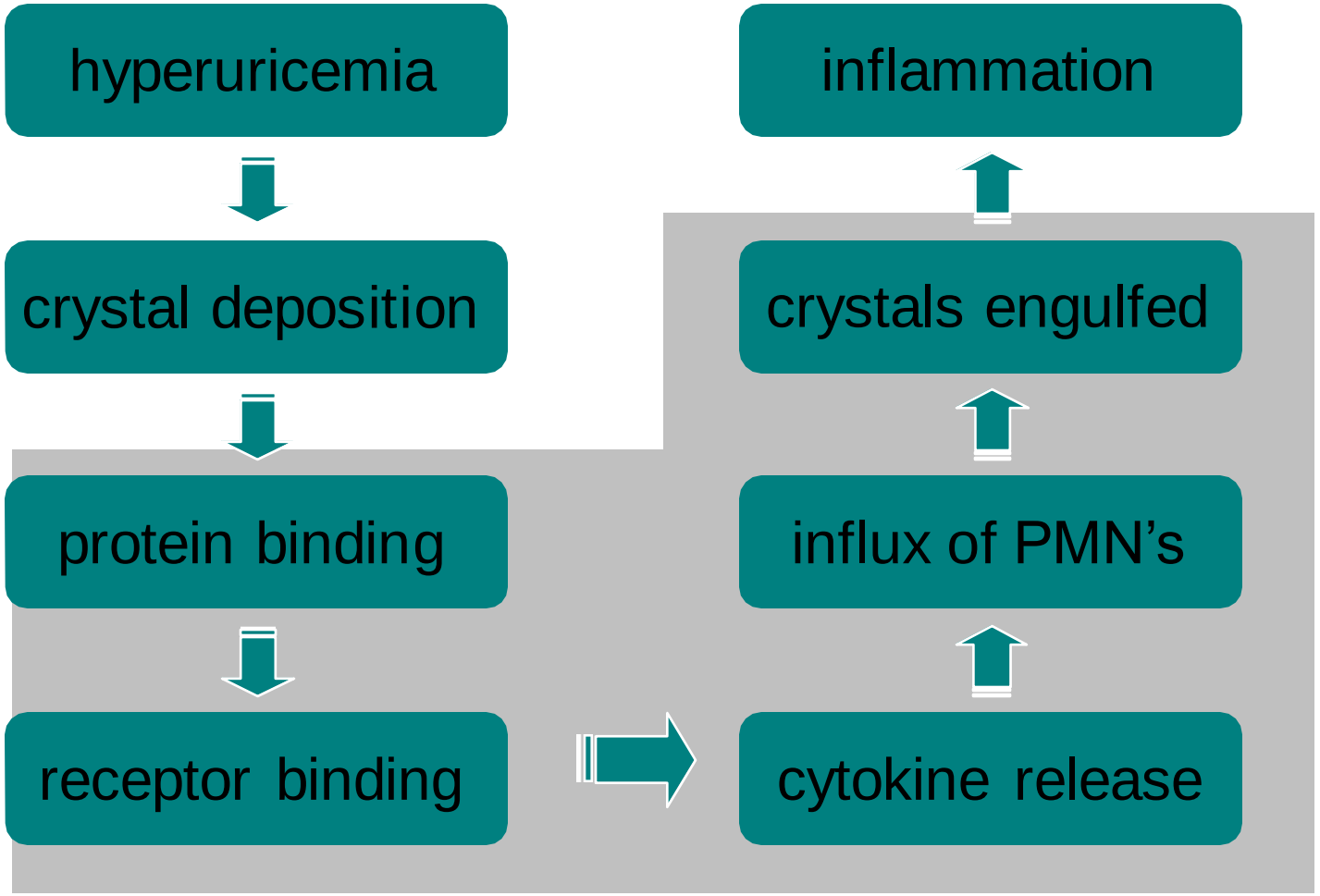
When do we use colchicine? Mainly, it is effective in gouty arthritis. It does not have the property of being an analgesic. So remember, NSAIDS in addition to their anti-inflammatory effect, they're also painkillers, so they have the property of analgesia. On the other hand, colchicine is not an analgesic.

# 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

So how does colchicine help in the treatment of gouty arthritis? It does so by inhibition of microtubule polymerization. So it binds to tubulin, which is one of the main constituents of microtubule, and prevents the polymerization of these subunits of tubulin to form the microtubule. Remember, we said the phagoycytosis is a major part of the inflammatory process associated with gout or gouty arthritis. So for the cells to engulf these urate crystals, for them to move around and to be able to perform the process of phagoycytosis, they need to have continuous formation and polymerization of microtubule. Thus, if we inhibit the microtubule polymerization, we would inhibit this process for the activation of phagoycytosis, thus we would reduce inflammatory response to these deposited crystals. Additionally, we can diminish the polymorph nuclear leukocyte phagoycytosis of crystals, and this will block the cellular response to deposited crystals, blocking the inflammation, blocking the cytokine release, thus help in reduction of the signs and symptoms of inflammatory arthritis associated with gout.

# Crystal-induced inflammation




PMN is critical component of crystal-induced inflammation

**Colchicine prevents the synoviocytes from engulfing the crystal urate crystals, preventing cytokines release, preventing the influx of PMNs, and again, preventing the cascade of events that lead to the propagation of 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

***These adverse effects are dose-related, and they are more common with a patient who has adrenal or hepatic disease.***

**Remember, we said colchicine prevents the polymerization of microtubules. And remember, microtubules are very important for the formation of the mitotic spindle. So in highly replicating cells, colchicine can affect the replication process of these cells. That's why it would affect the blood-forming cells, such as platelets, red blood cells, and also white blood cells**

# Gout - colchicine therapy

- more useful for daily prophylaxis (low dose)
  - ✓ prevents recurrent attacks
  - ✓ colchicine 0.6 mg Qd - Bid

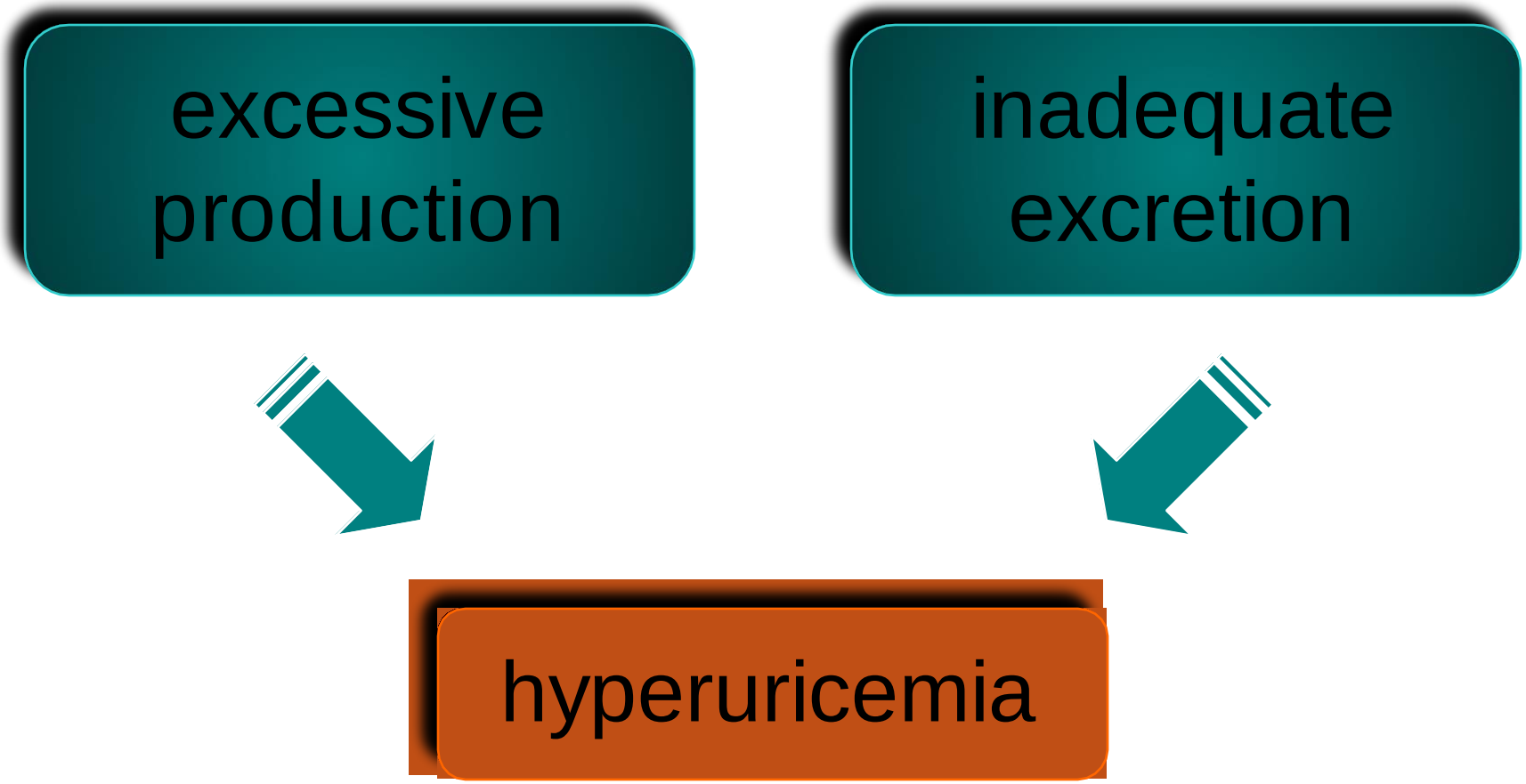
**Qd= once daily**
**Bid= twice a day**

- declining use in acute gout (high dose)

**decline in colchicine use in acute gouty arthritis, which is the high dose, and it's more replaced now by non-steroidal anti-inflammatory drugs as first-line drugs for those acute conditions.**

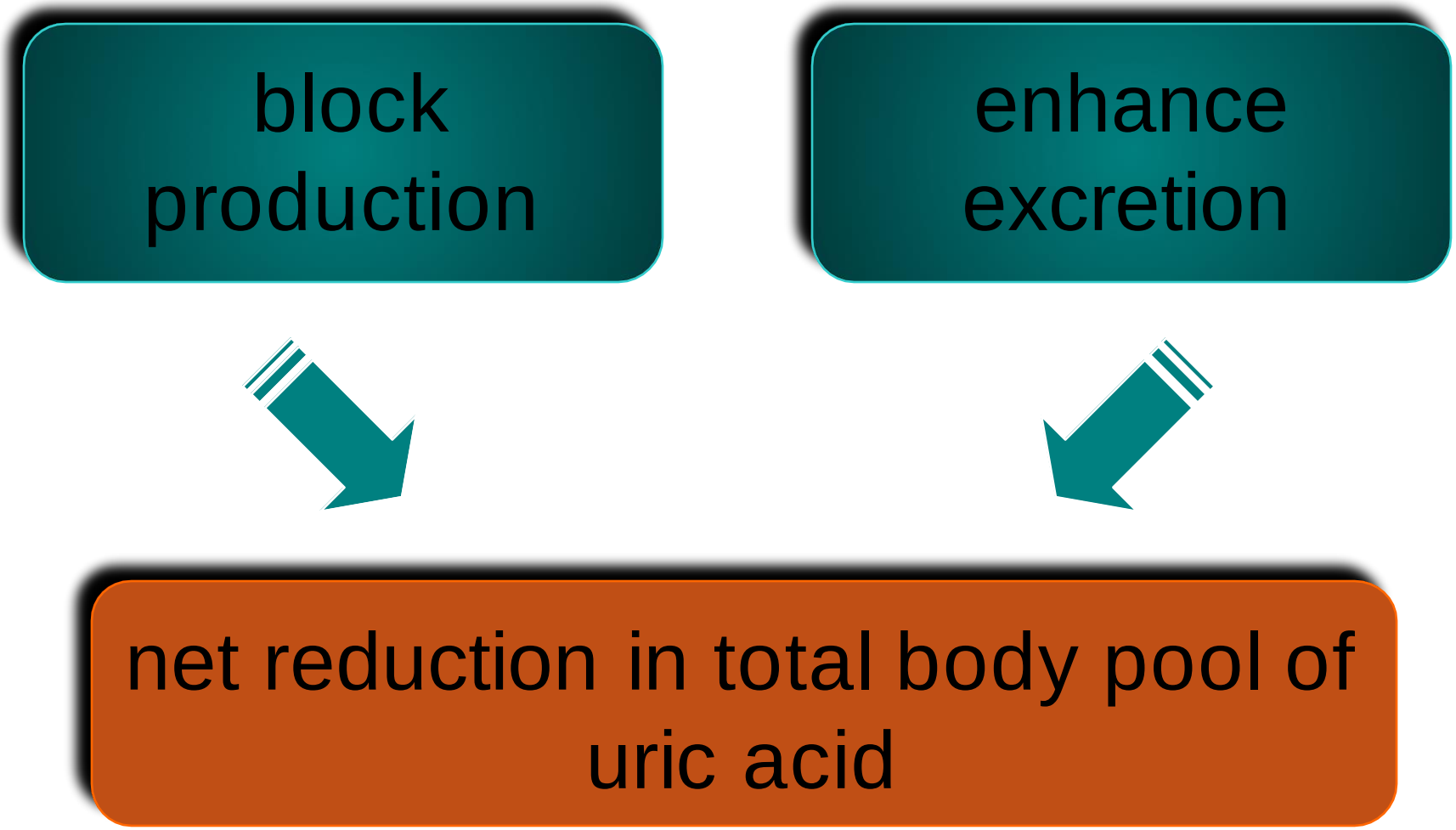
# Hyperuricemia - mechanisms

The causes.



# Urate-lowering drugs

The solutions.



# 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

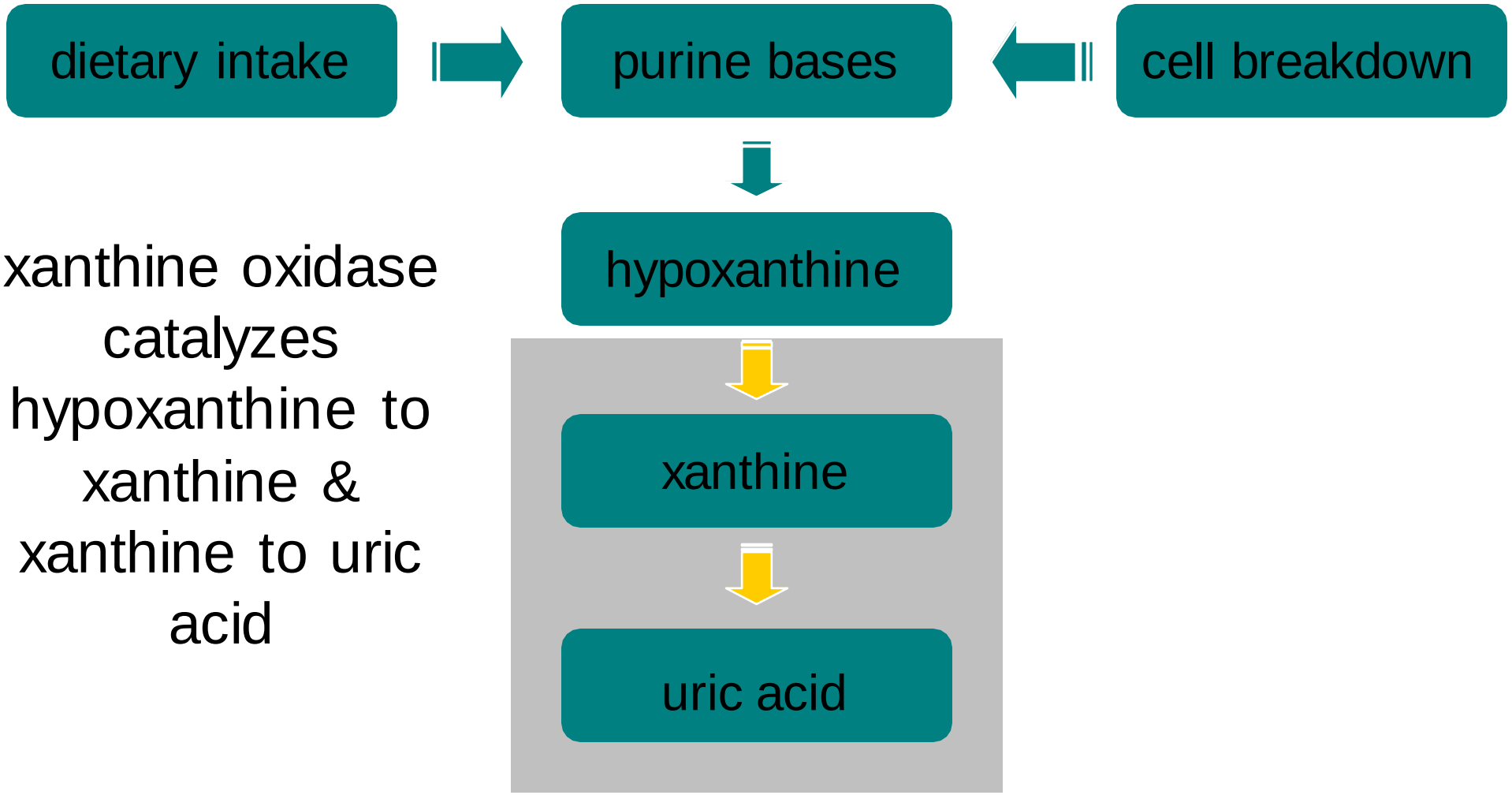
**This is because when we use these urate-lowering drugs, this would result in urate crystal being shed from the cartilages from the joints into the joint space, and this can result in flare-up of acute inflammation.**

- no role to play in managing acute gout

# Drug therapy of gout

*Drugs That Block Production of Uric Acid*

# Uric acid metabolism




xanthine oxidase catalyzes hypoxanthine to xanthine & xanthine to uric acid

# Allopurinol (Zyloprim™)

- inhibitor of xanthine oxidase
- effectively blocks formation of uric acid
- how supplied - 100 mg & 300 mg tablets **(2 concentrations 100 & 300,administered orally)**
- pregnancy category C

**This means we can use this drug if the benefits of this drug outweigh the risk of use. Of course, it would interfere with the synthesis of uric acid in the infants, affecting their purine metabolism. So it can pose some risk 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

# Allopurinol - common reactions

**Adverse effects:**

- diarrhea, nausea, abnormal liver tests
- acute attacks of gout **(as we said before)**
- rash

**Also, they can cause:**
**Very rarely aplastic anemia can occur.**
**Interstitial nephritis have also been reported.**
**Sometimes, allergic skin reaction, starting from pruritus or rash into maculopapular lesions can happen in almost 3% of the patients.**
**Some patients also develop exfoliation of the skin, namely or called exfoliated dermatitis, and in very rare cases, allopurinol can become bound to the lens resulting in cataracts.**

# Allopurinol – serious reactions

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

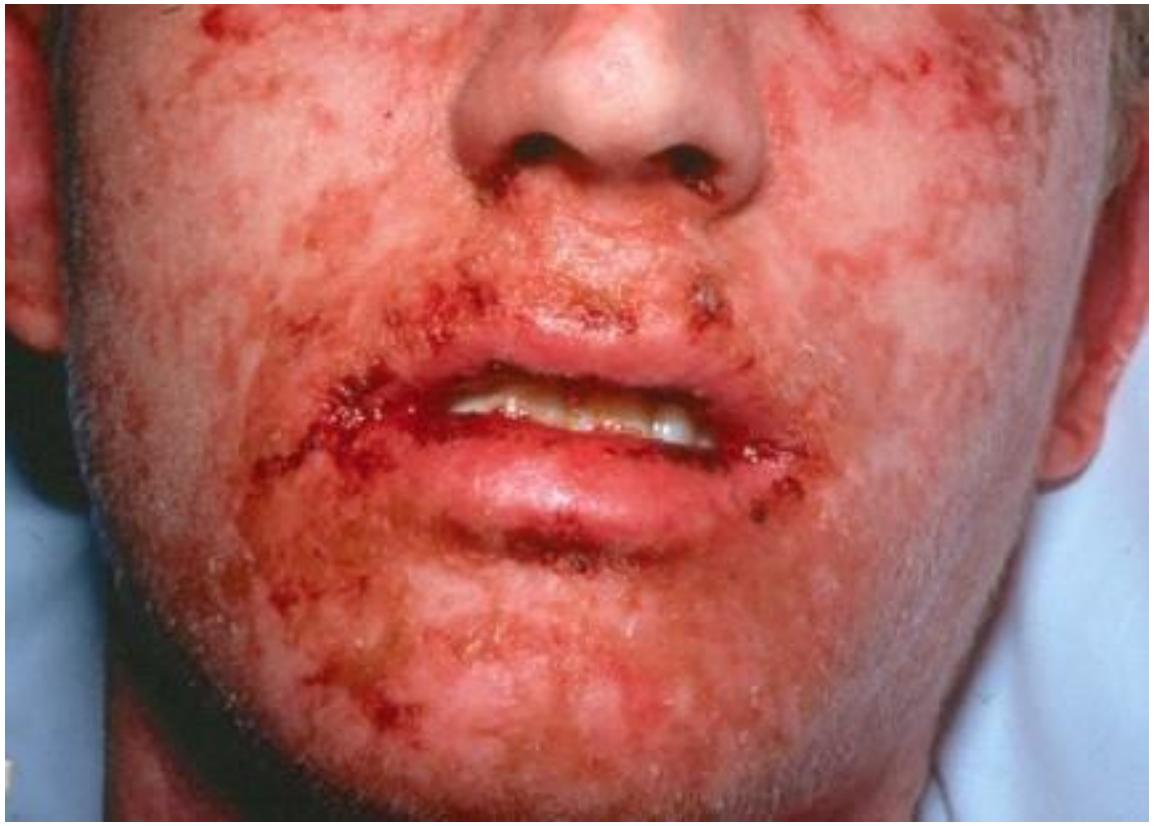
# Stevens-Johnson syndrome

target skin lesions

mucous membrane erosions

epidermal necrosis with skin detachment

**Very rare and it can happen in less than 2% of the patients.**



# Allopurinol hypersensitivity

- extremely serious problem **(we have to recognize early on.)**
- prompt recognition required
- first sign usually skin rash, **it can develop to:**
- more common with impaired renal function
- progression to toxic epidermal necrolysis & death

# Febuxostat

- recently approved by FDA **(2009)**
- oral xanthine oxidase inhibitor
- It is structurally different from allopurinol, although it does show the same mechanism of action
- chemically distinct from allopurinol
- 94% of patients reached urate < 6.0 mg/dl
- minimal adverse events

**It can cause reduction of urate levels below 6 mg/dl, which is the amount we want or the level we aim for in about 94% of the patient**

**As compared to allopurinol, it can cause diarrhea, headache, and nausea, but it seems to be more well tolerated in patients who have sensitivity or intolerance to allopurinol. So it is a good alternative to allopurinol in patients who cannot use that drug.**

# PEGLOTICASE

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

**Pegloticase is the newest urate-lowering therapy drug. It was approved by the FDA in 2010 for the treatment of refractory chronic gout. What do we mean by refractory? Refractory means it is not responding to other medication.**

So what is this pegloticase ? It is a recombinant mammalian uricase that is conveniently attached to monomethoxy-Polyethylene glycol (MPEG).

What is this enzyme? Remember, we said humans do not possess the enzyme that's necessary for the breakdown of uric acid, which is called uricase, while other mammals have it. So this drug is actually the recombinant form of the enzyme that's present in pigs, or porcine.

By pig, we mean animal here, but the PEG in the name comes from the chemical compound, again,Polyethylene glycol. And the addition of PEG or polyethylene glycol conjugation is to increase the half-life of this drug. Also, it helps in diminishing or lowering the immune response for this enzyme that's not coming from a human source, but rather so from an animal source.

So we need to decrease the antigenicity of this enzyme or protein in our body, so we do that by the addition of Polyethylene glycol.

Pegloticase is an intravenously administered drug. It works fast, within 24 to 72 hours, to reach its peak concentration. Usually, it stays in the body for days, between 6 to 13 days. Usually, the clearance of this drug is by an antibody response.
The importance of adding the PEGylation or polyethylene glycol is to kind of minimizes antibody response in the body.

Adverse effects associated with it include infusion reactions. It can also cause a flare-up of the gout, especially during the first three months of treatment. Other side effects include nephrolithiasis (kidney stones), arthralgia, muscle pain, muscle spasms, headache, anemia, and nausea.
Lots of the frequent side effects include respiratory tract infection, peripheral edema, urinary tract infection, and diarrhea.

**The most important thing:**
Now, one concern is the use of this drug in patients with glucose-6-phosphate dehydrogenase deficiency because of the formation of hydrogen peroxidase by the enzyme uricase. Therefore, this drug should be avoided in these patients.

# Drug therapy of gout

**Now, another way to control the level of uric acid in the blood is the drugs that enhance the excretion of it.**

*Drugs That Enhance Excretion of Uric Acid*

# Uricosuric therapy

- Example of uricosuric therapy: probenecid
- Probenecid will block tubular reabsorption of uric acid
- And enhances urine uric acid excretion which will lead to:
- increases urine uric acid level
- decreases serum uric acid level

# Uricosuric therapy

- moderately effective
- increases risk of nephrolithiasis

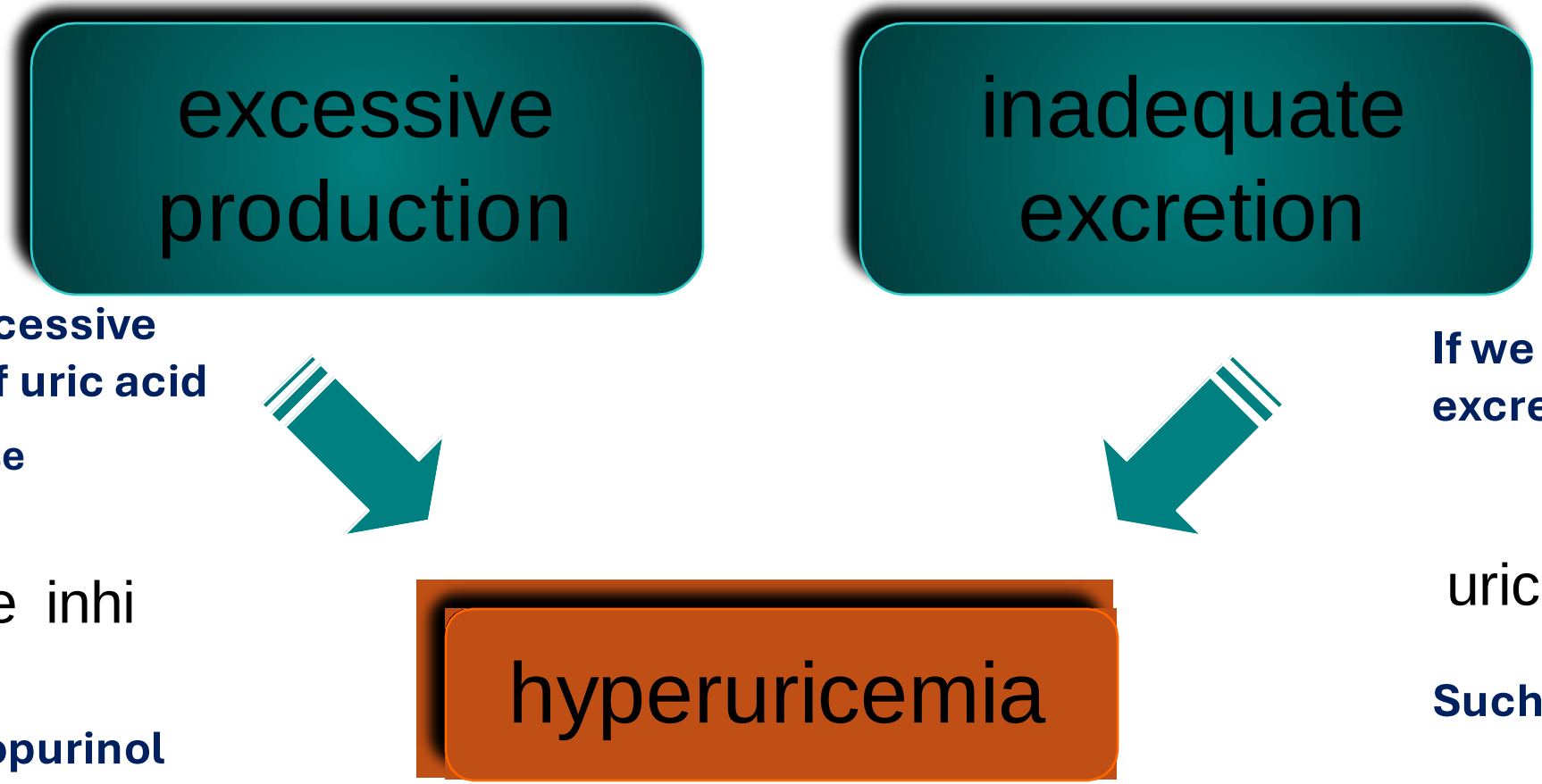
**They are mainly used in patients who have tophaceous gout, or patients who have frequent gouty attack. While in patients who usually squeeze large amounts of uric acid, these agents will not be used**

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

# Uricosuric therapy

- Contra-indications, **Patient Has:**
  - ✓ History of nephrolithiasis
  - ✓ Elevated urine uric acid level
  - ✓ Existing renal disease
- Less effective in elderly patients **because elderly patients usually have deteriorated kidney function**

# Choosing a urate-lowering drug



# Drug therapy of gout

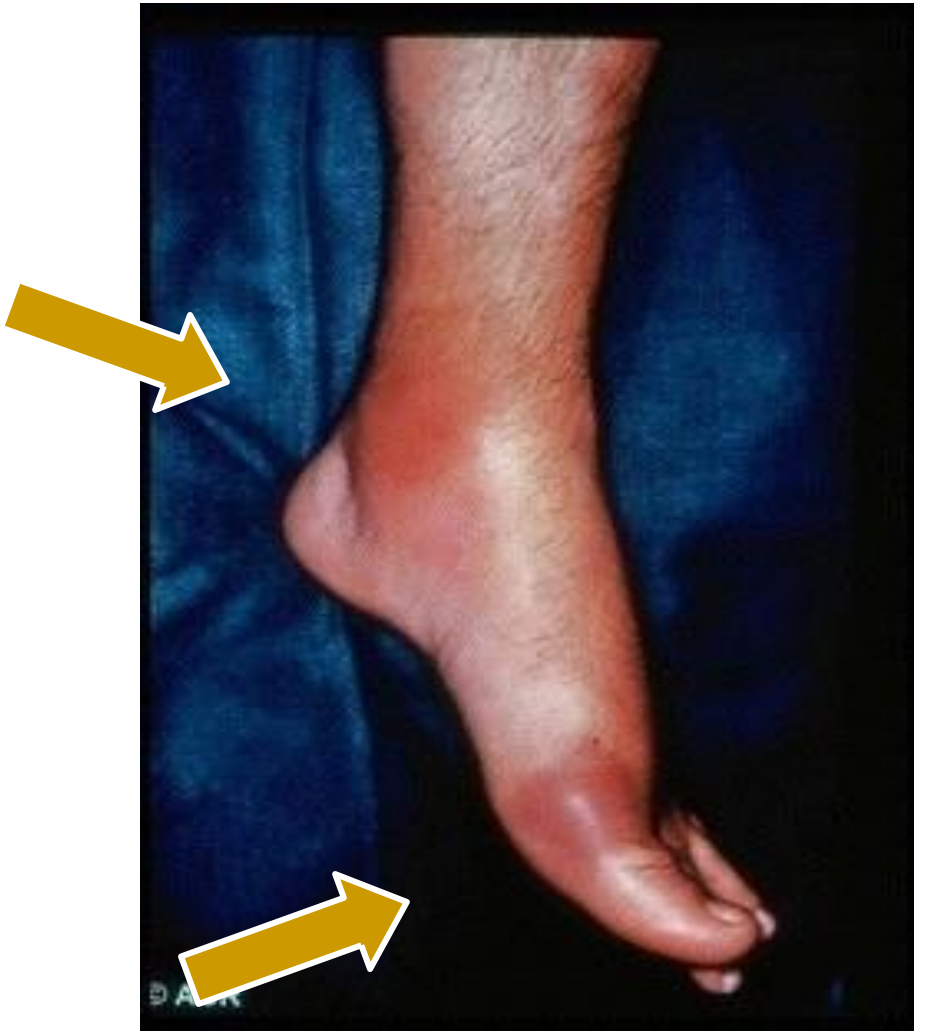
*Case Presentation*

# Case presentation

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

# Gout - acute arthritis

**Upon clinical examination, the patient appears to have acute synovitis in the ankle. Also, the metatarsophalangeal joints, or articulations, they are also inflamed.**

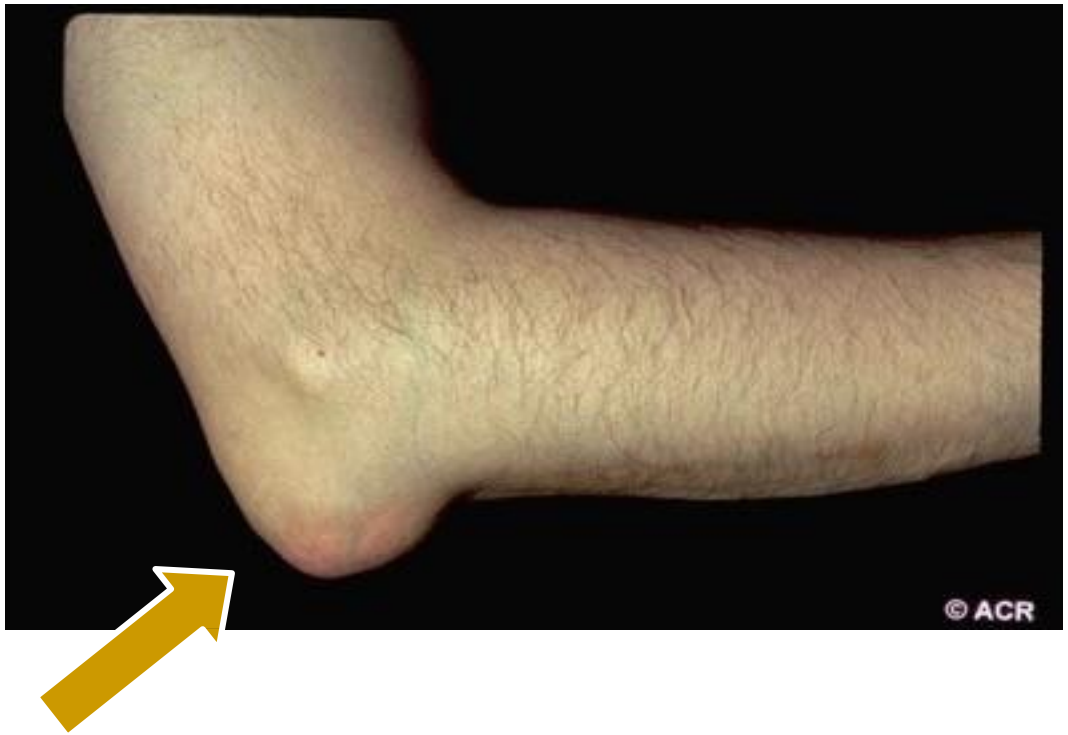


acute synovitis, ankle & first MTP joints

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

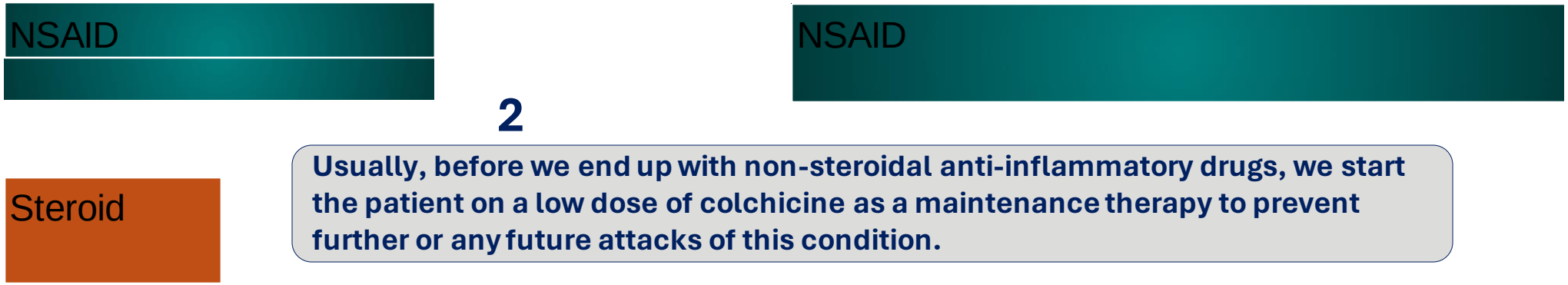
# Gout - acute bursitis

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

# Case presentation - therapy



# Interleukin 1 receptor antagonist

Example:

- Anakinra
- Canakinumab
- Rilonacept

**These are drugs that are used for the treatment of rheumatoid arthritis, and they're also now currently being investigated for the treatment of gout.**
**So what do they do? They are targeting the interleukin-1 pathway. Thus, they would suppress the inflammation.**
**So in conditions where we have a patient not responding to NSAIDs or Colchicine, we would try using these drugs as a treatment.**

# Glucocorticoids

Prednisone

- Oral
- Intra-articular
- Sub cutaneous

**We said we can use glucocorticoids during an acute gouty arthritis attack. One example of these drugs is prednisone, which can be given orally, inside the joint (intra-articularly) or subcutaneously, and this depends on the degree of the acute attack, the degree of pain, and the inflammation in the patient.**

عندما أنظر إلى أولئك الذين يفرحون بالتآمر على أهلنا والمساعدة على قتلهم وتشريدهم وإمداد الصهاينة بأسباب الحياة والعتاد والتكسب من ذلك، ثم بعد ذلك يريدون أن يُحمدوا بأنهم يقدمون لأهل غزة المساعدات!! فإني أتذكر قول الله تعالى:
(لَا تَحْسَبَنَّ الَّذِينَ يَفْرَحُونَ بِمَا أَتَوا وَّيُحِبُّونَ أَن يُحْمَدُوا بِمَا لَمْ يَفْعَلُوا فَلَا تَحْسَبَنَّهُم بِمَفَازَةٍ مِّنَ الْعَذَابِ ۖ وَلَهُمْ عَذَابٌ أَلِيمٌ (188) ).
روى البخاري في سبب نزولها أن رجالا من المنافقين على عهد رسول الله ﷺ كان إذا خرج رسول الله ﷺ إلى الغزو تخلفوا عنه، وفرحوا بمقعدهم خلاف رسول الله صلى الله عليه وسلم، فإذا قدم رسول الله صلى الله عليه وسلم اعتذروا إليه، وحلفوا وأحبوا أن يحمدوا بما لم يفعلوا، فنزلت هذه الآية.

أما أشباههم اليوم فلم يتخلفوا فحسب، بل شاركوا أعداء المسلمين ضدهم، ثم يريدون أن يُحمدوا بالفُتات.
فإن هلكوا على ما هم عليه، (فَلَا تَحْسَبَنَّهُم بِمَفَازَةٍ مِّنَ الْعَذَابِ ۖ وَلَهُمْ عَذَابٌ أَلِيمٌ).

اللهُمَّ إنا نستودعُك غزّة وأهلَها، كبارَها
وصغارَها، رجالَها ونساءَها، شبابَها وبناتِها،
أرضَها وسماءَها، فاحفظها يا ربنا من كل
سوء.

**V2:**

**Page 3 (not imp)**

**Page 8**

دُمتم موفّقين مسدّدين