# Pharmacology - MSS


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# Drug Therapy of Gout

# Drug therapy of gout

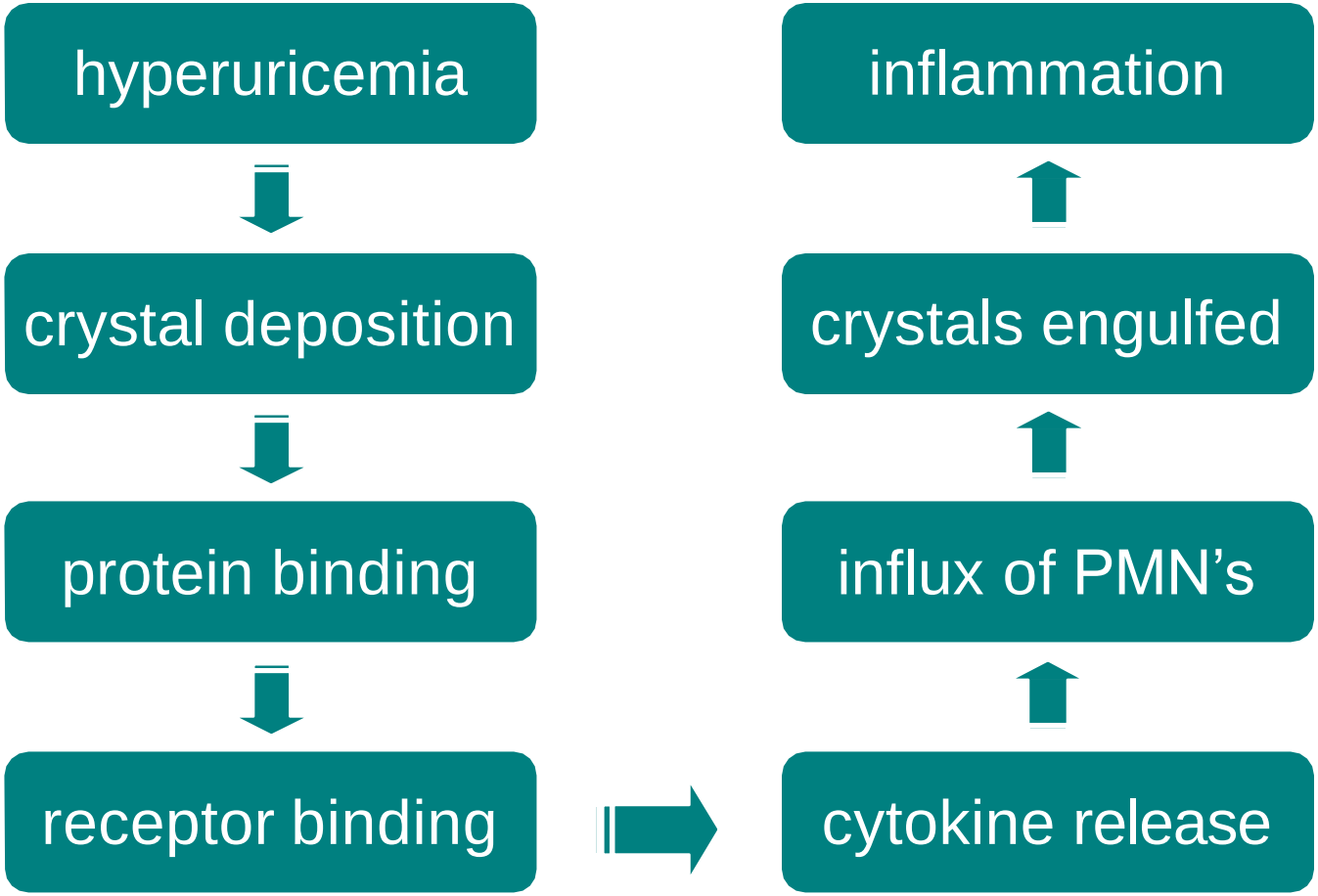
## *What Is Gout?*

- Gout is a form of complex arthritis, it is characterized by sudden severe attacks of pain, swelling in the joints, redness, and tenderness, and it can happen to one or multiple joints. The most common joint, is the joint of the big toe. An attack of gout can happen suddenly, and it feels like the affected joint is on fire, it will be hot, swollen, and painful. These symptoms are usually happening because of an inflammatory reaction that is occurring at that site.
- We can summarize that gout is an inflammatory disease, but what is the cause of gout? Gout can also be considered a metabolic disease characterized by recurrent episodes of acute arthritis due to deposits of monosodium urate in joints and also other locations such as the cartilage and the kidney. In the kidney, it can cause renal caliculi and we can also have intestinal nephritis.

# Gouty arthritis - characteristics

- Sudden onset (It can start in the middle of the night)
- It usually affects middle aged males
- Characterized by severe pain
- Usually effects distal joints
- Intense inflammation (It is an intense inflammation)
- Recurrent episodes
- Influenced by diet
- Bony erosions on Xray (Changes in the bone can be identified by x-ray)

# Crystal-induced inflammation




PMN is critical component of crystal-induced inflammation

# Explanation of the previous slide

- What is the cascade of events that lead to gout? We usually have high levels of serum uric acid, and this case is called hyperuricemia. Urea is a poorly soluble substance that is a major end product of purine metabolism. Many mammals have enzymes called uricase and it usually converts uric acid to more soluble allantoin, but unfortunately humans do not have this enzyme, so we have to control the levels of uric acid through its excretion from the kidneys.
- In any instant where we have an imbalance between the uptake and excretion of uric acid, this will lead to elevated levels of uric acid in the serum leading to deposition of the substance in the joints, in the kidneys and sometimes in the cartilages as well.
- These urate crystals will bind to certain proteins and receptors on the surface of cells that are lining the joints, which are called synoviocytes. These cells will then engulf these urate crystals, this will lead to the release of many cytokines, prostaglandins and lysosomal enzymes and interleukin 1.
- This cytokine release will cause attraction of certain types of cells, such as polymorphic nucleus leukocytes, these will move into the joint space and amplify the ongoing inflammatory process.

# Gouty arthritis - characteristics

- Sudden onset
- Middle aged males
- Severe pain, caused by the cytokine release especially the prostaglandins and interleukin 1.
- Distal joints, although it can happen in other places
- Intense inflammation, this inflammation keeps propagated with the presence or the chemotactic of the of the different cells mainly the PMNs. At later stages of the attack there is an increased number of these mononuclear phagocytes or macrophages, they will start ingesting the urate crystals and release more and more inflammatory mediators.

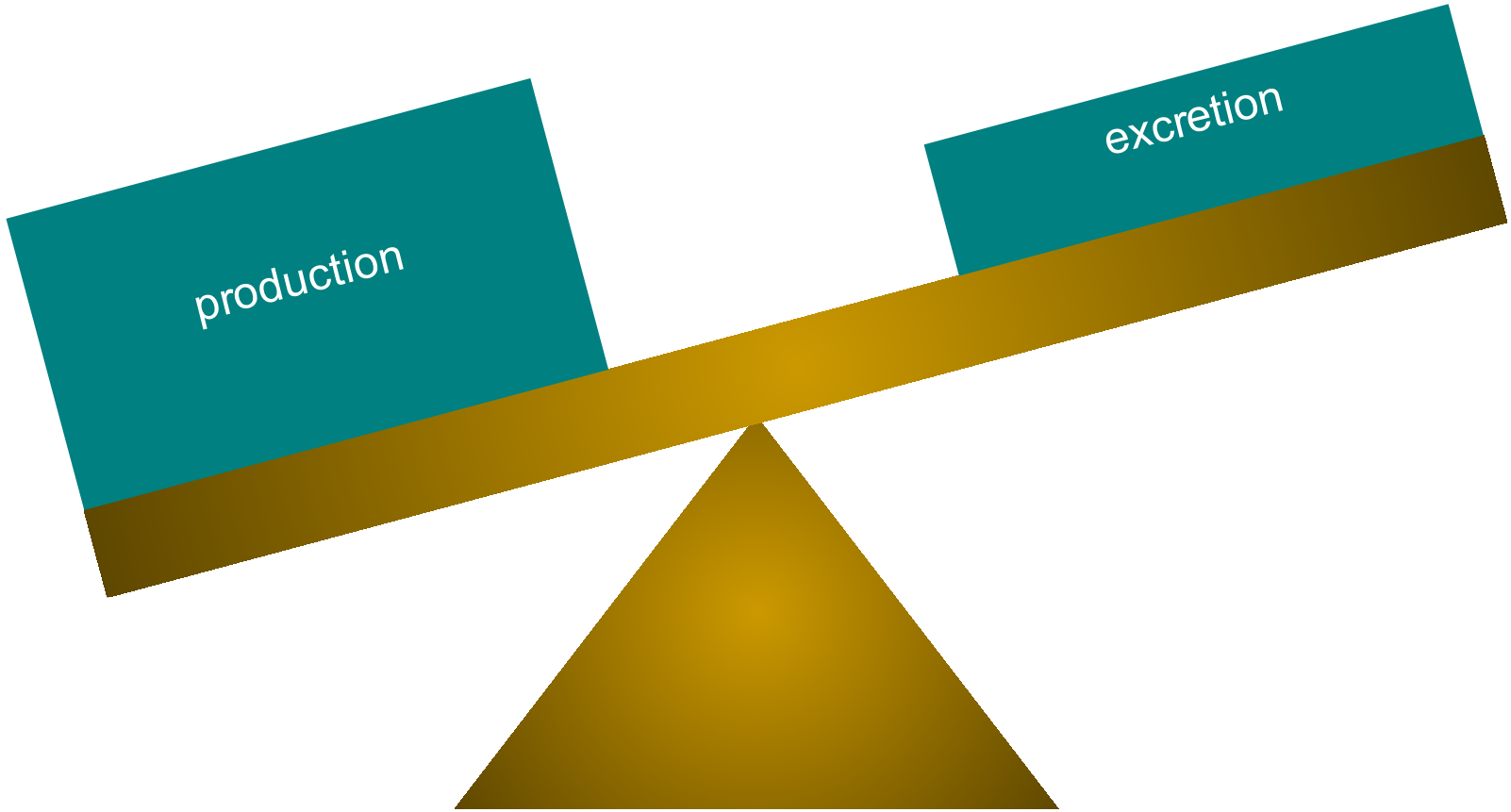
# The rest of the previous slide

- Recurrent episodes
- Influenced by diet, this is very important.
- Bony erosions on Xray.

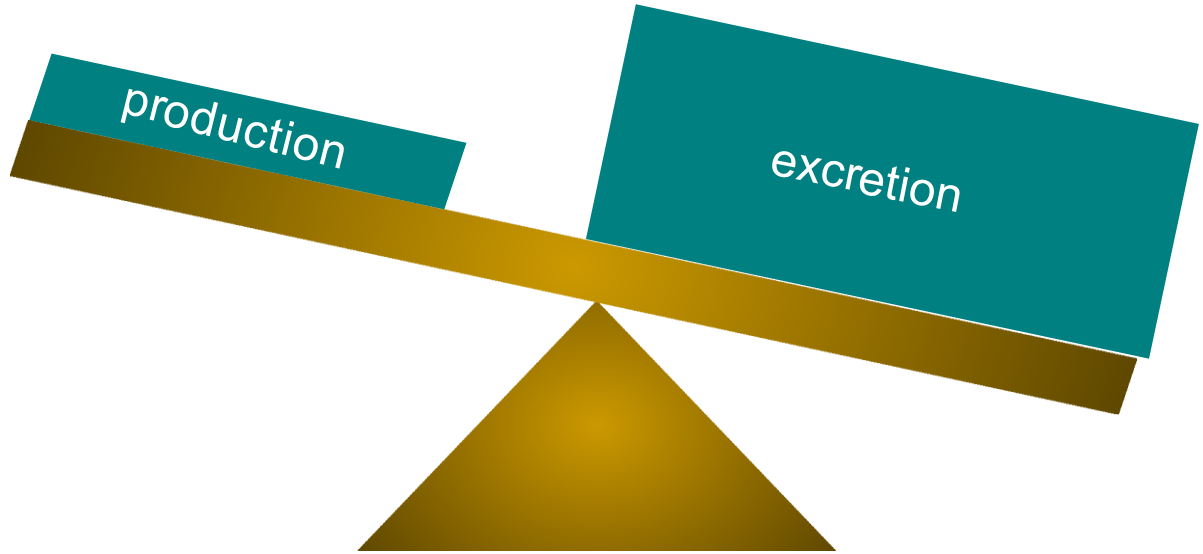
How can we diagnose acute gouty arthritis? We can see the boney erosions on the x-ray, but it is also characterized by hyperuricemia.

- Hyperuricemia

# Hyperuricemia



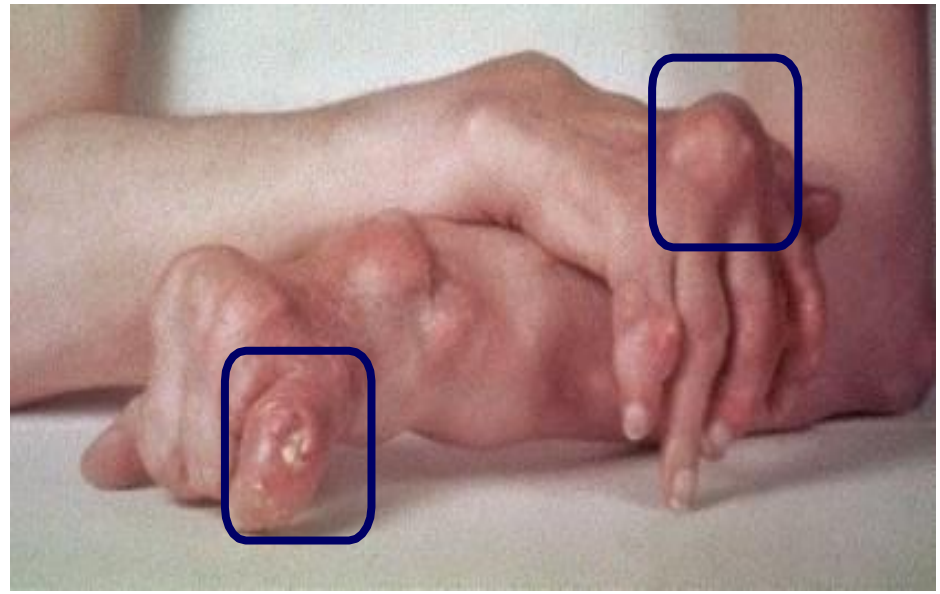
# Hyperuricemia




- If our intake for food or substances that are converted into uric acid increases, such as red meat, they will produce purine and purine will get metabolized to purine acid.
- There could also be imbalance in the secretion of urea, the kidney does not excrete uric acid, this will lead to build up of uric acid in the blood stream and this will lead again to hyperuricemia.

# Chronic tophaceous gout

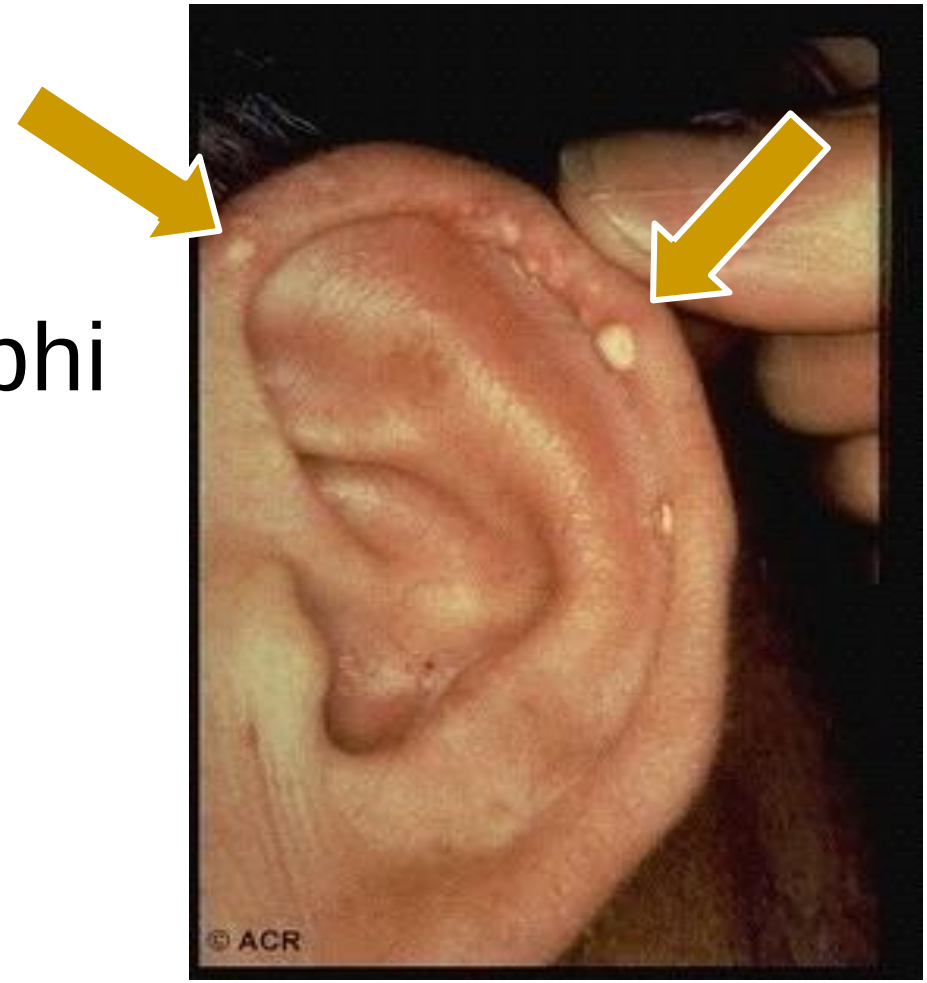
Tophus = localized deposit of monosodium urate crystals



- Gout does not only present as arthritis, but it can also present in other forms such as chronic tophaceous gout. This is a chronic form of gout, where we see nodular masses, of crystals of uric acid, that are deposited in different soft tissues and areas of the body (toes, fingers, elbows, on the helix of the ear). Usually, these tophi are present as hard nodules and most commonly around the fingers, and this not only is painful inflammatory process but it also disfiguring for the patient.

# Gout - tophus

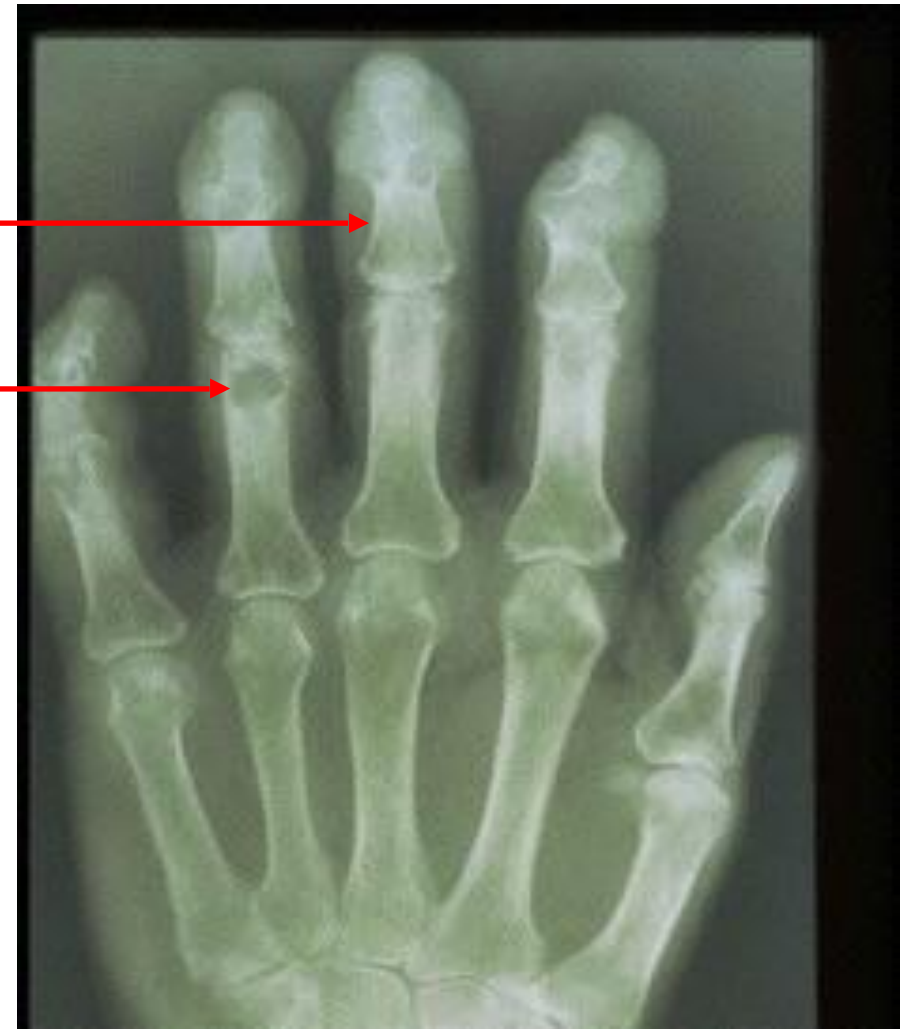
Classic location of  tophi
>> On helix of ear



# Gout - X-ray changes

DIP
(*Distal interphalangeal joint)* joint destruction

phalangeal
bone cysts

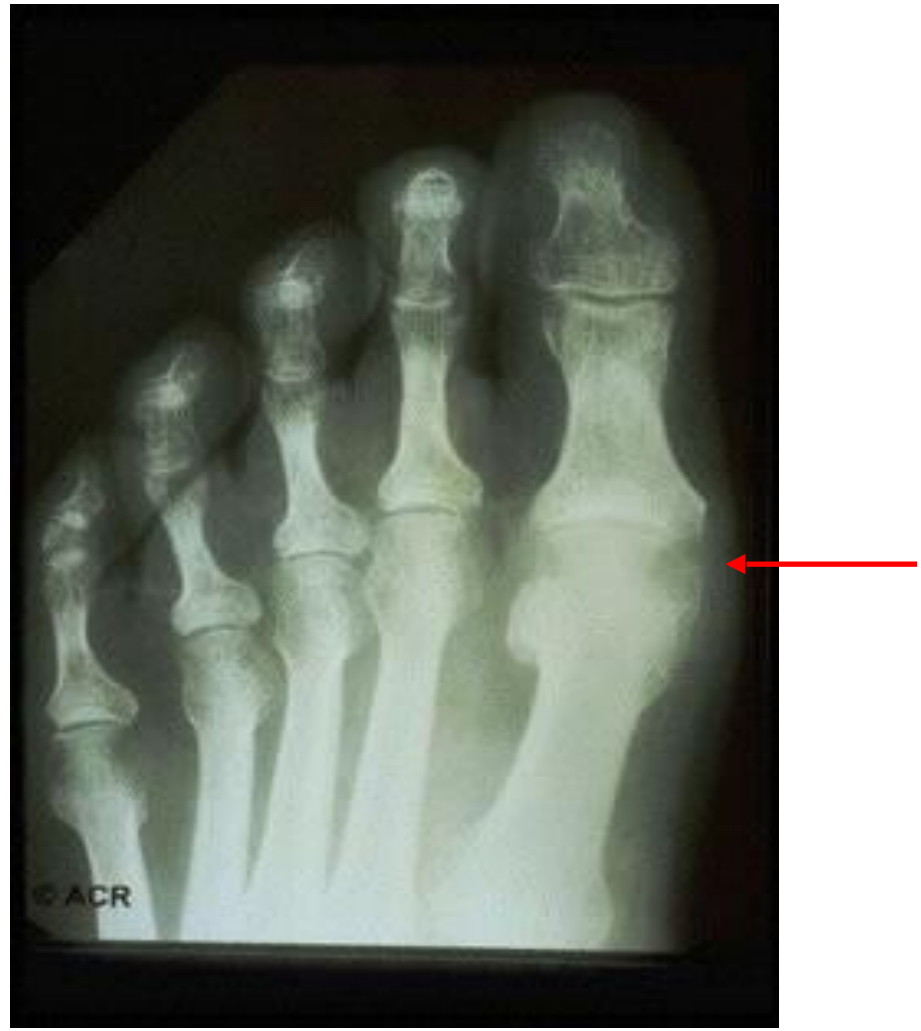


- Some of the clinical manifestations of gout in the body.

# Gout - X-ray changes

Bony erosions

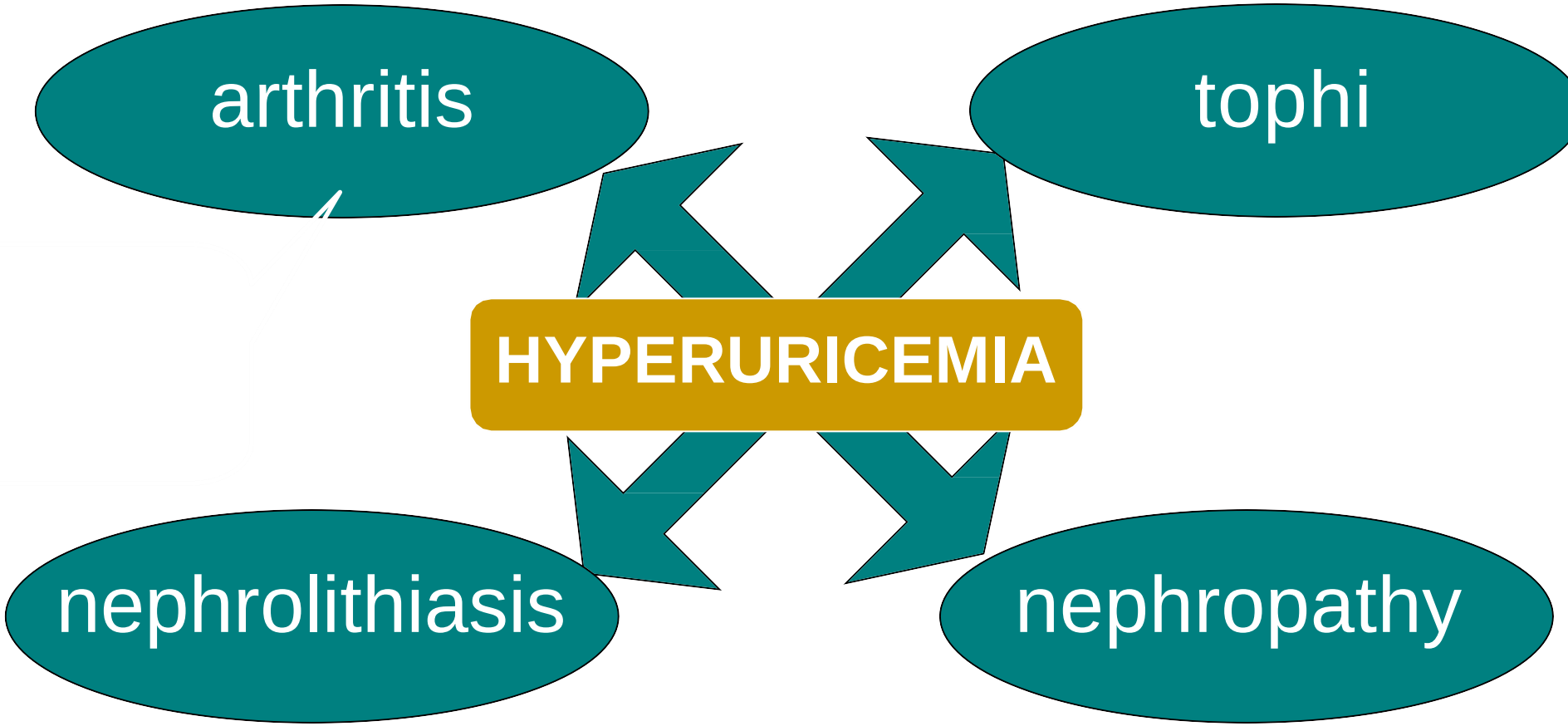
- Some of the clinical manifestations of gout in the body.
- It can also happen in other places in the body; we have uric acid renal caliculi, stones in the kidney.



# Extra information :)

- One important note we need to mention is that while clinical gouty episodes are associated with hyperuricemia, most individuals with hyperuricemia may never develop a clinical event from urate crystal deposition.
- Before starting chronic urate-lowering therapy for gout patients in whom hyperuricemia is associated with gout and urate lithiasis must be clearly distinguished from individuals with only hyperuricemia. The efficacy of long-term drug treatment in an asymptomatic hyperuricemic person is unproved.
- So even in some individuals where we see high levels of uric acid, maybe they could go through their whole life without having gouty manifestations.

# Gout - cardinal manifestations



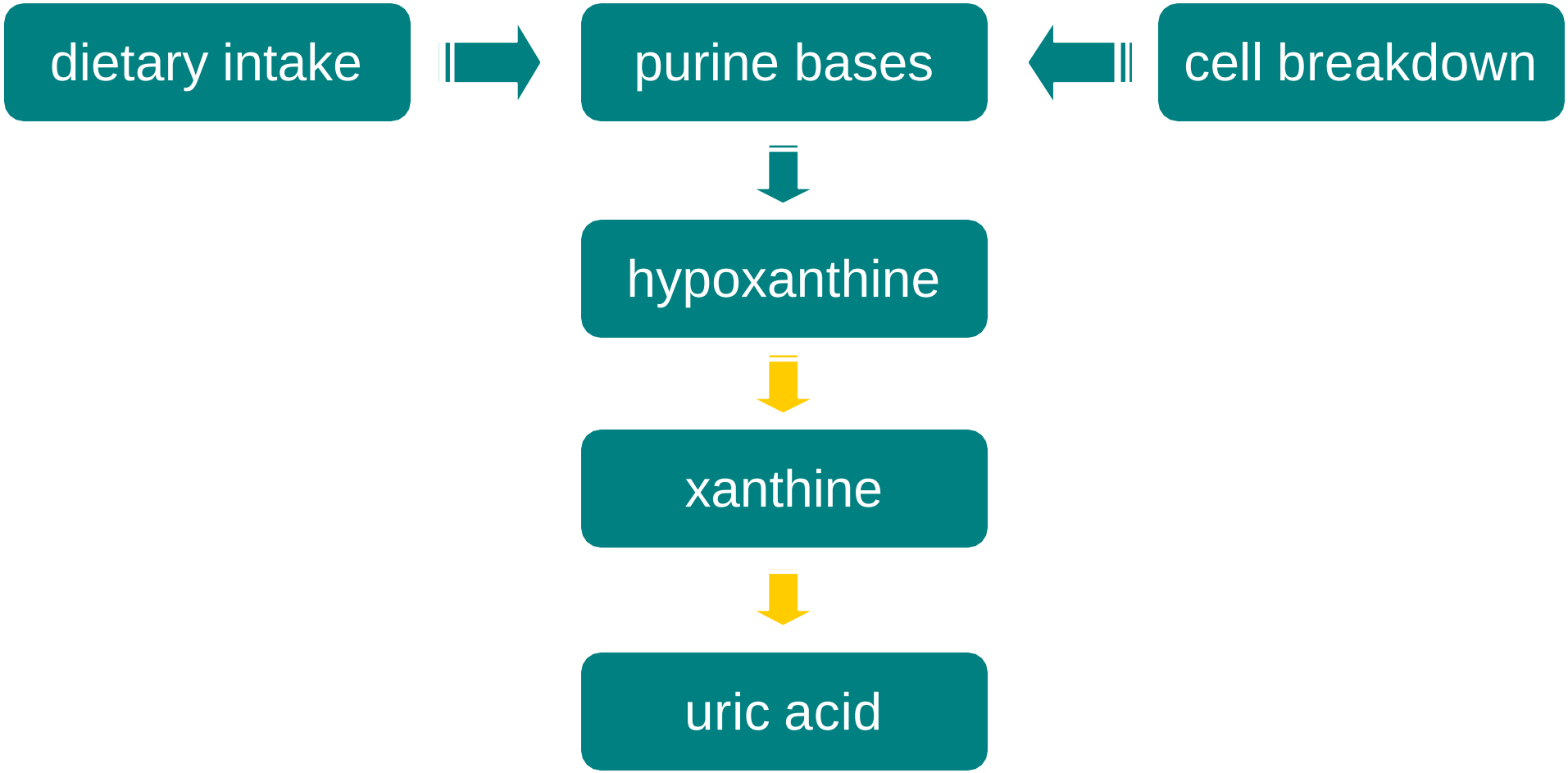
# Explanation of the previous slide

- What are the cardinal manifestations that make a person characterized by gout and in need of pharmacological treatment?
- The first cardinal manifestation is the presence of arthritis, so we have inflammation in this case. Arthritis can be either acute or chronic.
- Nephrolithiasis, which means the kidney stones.

# Drug therapy of gout

*The Role of*
*Uric Acid in Gout*

# Uric acid metabolism



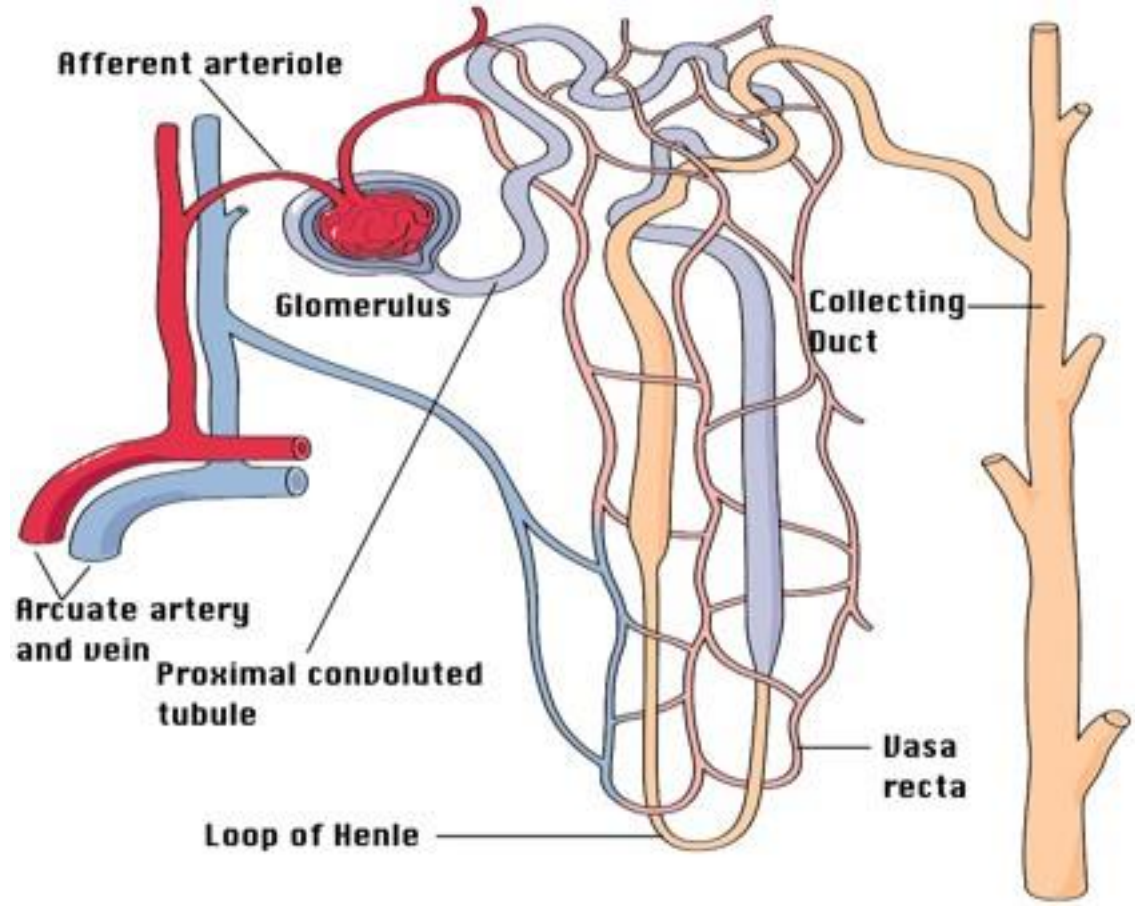
# Explanation of the previous figure

- *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 proteins, this will be metabolized in our body to purine bases. Also, when the cells in our body metabolize or break down, we are also going to have an increase in purine bases.

# Renal handling of uric acid

- Glomerular filtration ⬇
- Tubular reabsorption ⬆
- Tubular excretion ⬇
- Post-secretory reabsorption ⬆
- Net excretion



# Explanation of the previous slides

- In the kidneys, how is uric acid handled? What is 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. We start with glomerular filtration which will lead to the decrease of uric acid in the plasma, later on in the proximal renal tubule, we have reabsorption, then there is the stage of tubular excretion and finally the post-secretory reabsorption.
- Ultimately the total or net effect is excretion of uric acid. If you want to control this process, we can prevent the process of tubular reabsorption and the post-secretory reabsorption by the use of pharmacological agents.

# Gout - problems

To summarize, the problems associated with gout is that we have:

- Excessive total body levels of uric acid
- Which leads to deposition of monosodium urate crystals in joints & other tissues
- And this will lead to crystal-induced inflammation

# Treating acute gouty arthritis

- Colchicine
- NSAID's
- Steroids
- Rest, analgesia, ice, time

  - Although NSAIDs, corticosteroids, or colchicine are now first-line drugs for acute gout, colchicine was the primary treatment for many years.

# Drugs used to treat gout

## *Acute Arthritis Drugs*

- Colchicine
- Steroids
- NSAID's

## *Urate Lowering Drug*

- Allopurinol
- Probenecid
- Febuxostat?

- We also have steroids and then we have nonsteroidal anti-inflammatory drugs. Additionally, we can use some urate lowering drugs.
- In addition to all the drug treatments in the condition of acute gouty arthritis, rest, analgesia (pain relief), and time will help heal this condition.

# 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

# Explanation of the previous slide

- All of these drugs share a common mechanism of action which is inhibition of the synthesis of prostaglandin, by the inhibition of the enzyme cyclooxygenase.
- In addition to that, NSAIDs inhibit urate crystal phagocytosis. Aspirin is not used because it causes renal retention of uric acid at low doses (≤2.6 g/d). It is uricosuric at doses greater than 3.6 g/d.
- Indomethacin is commonly used in the initial treatment of gout as a replacement for colchicine, with a dosage of 25 mg three times daily for 5–7 days.

# Colchicine - plant alkaloid

*Colchicum autumnale*

(autumn crocus or meadow saffron)

# Colchicine

- “Only effective in gouty arthritis”
- It does not function as 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.

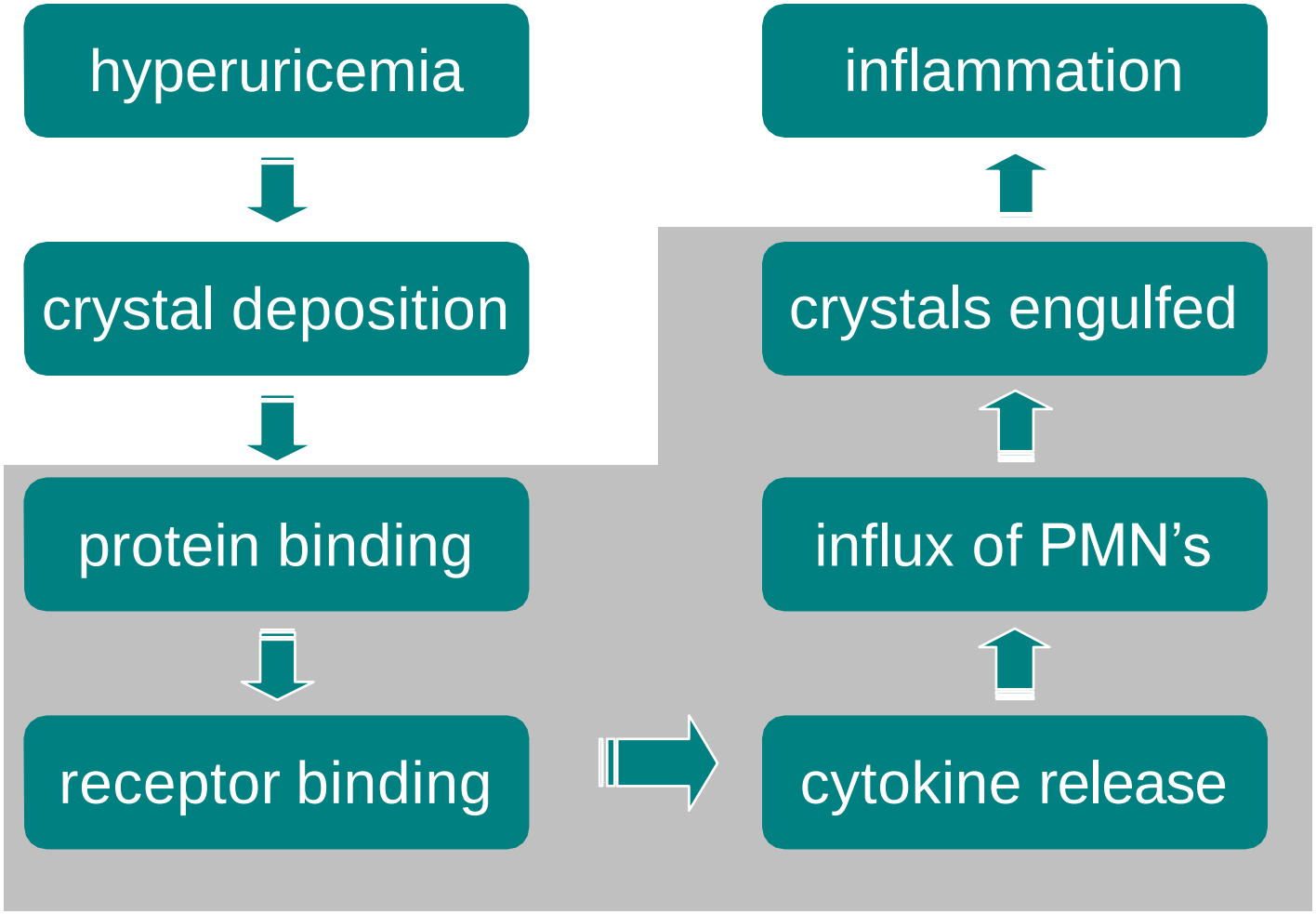
# Colchicine

- Colchicine inhibits microtubule polymerization by binding to tubulin, one of the main constituents of microtubules, and prevents the polymerization of the subunits of tubulin to form the microtubule.
- Phagocytosis is a main part of the inflammatory process associated with gout, so for the cells to engulf these urate crystals, for them to move around and to be able to perform the process of phagocytosis, they need to have continuous formation of microtubules.

# The rest of the previous slide

- Thus, if we inhibit the microtubule polymerization, we will inhibit this process or the activation of phagocytes, thus we will reduce the inflammatory response to deposited crystals.
- Diminishes PMN phagocytosis of crystals
- Blocks cellular response to deposited crystals, blocking the inflammation, the cytokine release, and this helps with 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 the cytokine release and the influx of PMN and 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 can be used either at a high dose or a low dose. For the treatment of acute gouty arthritis, we usually use a high dose and for the prevention of recurrent gouty arthritis we use a low dose, so this is a maintenance therapy to prevent further flare-ups or attacks of gout.

# Colchicine - toxicity

Side effects associated with Colchicine

- **Gastrointestinal problems** (nausea, vomiting, cramping, diarrhea, abdominal pain)
- **Hematological problems** (agranulocytosis, aplastic anemia, thrombocytopenia) Remember we said colchicine prevents the polymerization of microtubules and remember microtubules are very important for the formation of the mitotic spindles, 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 white blood cells. So, we must be careful about the use of colchicine because of these adverse effects.
- **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

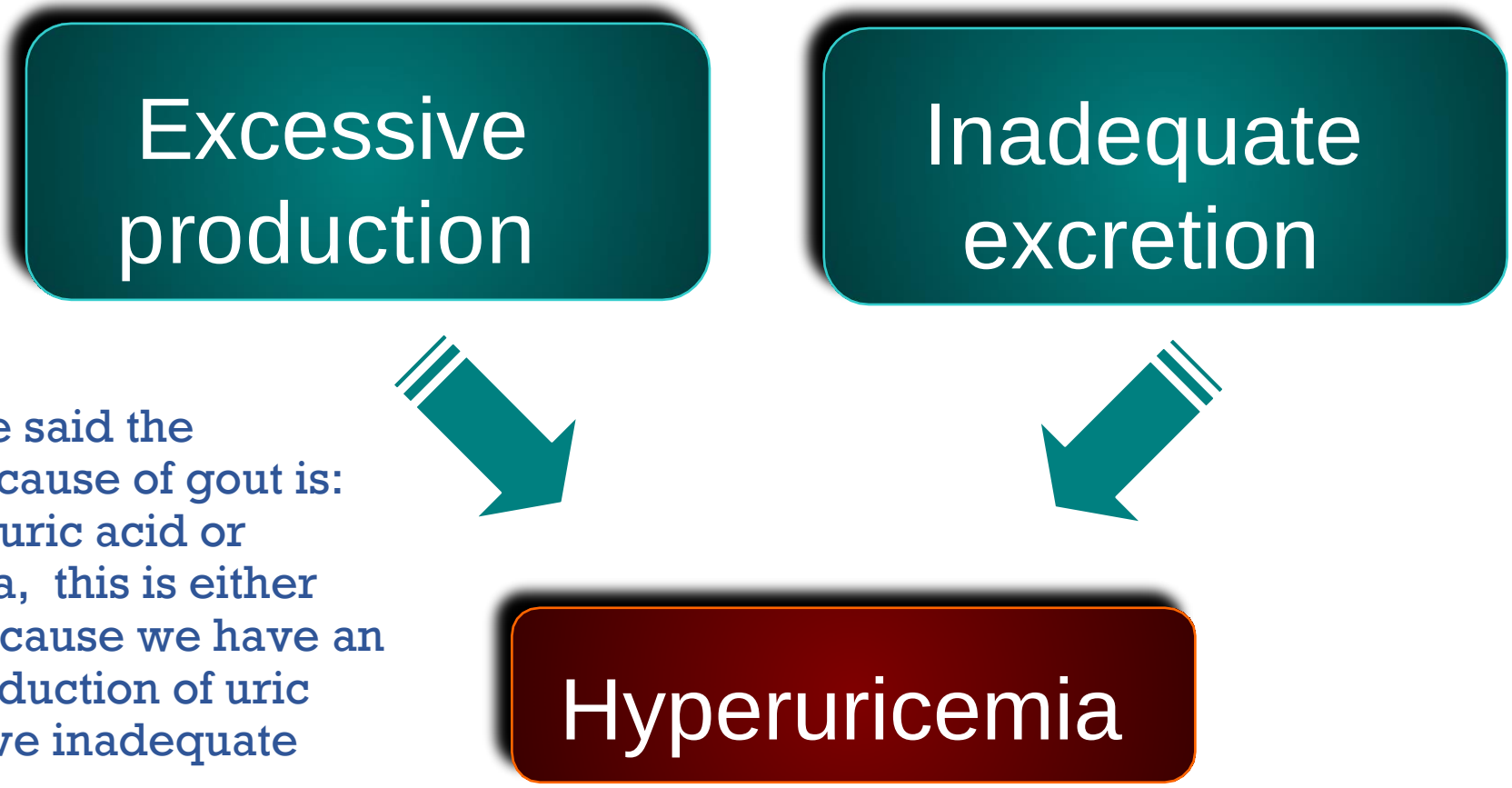
    It is used at a concentration of 0.6 milligram, two times a day.

So, because of the previous slide effects , it's better to use it for daily prophylaxis because we use a low dose.

- Declining use in acute gout (high dose)

We note that recently we've seen a decline in use of colchicine in acute gouty arthritis, which is the high dose that we mentioned. It's more replaced now by **non-steroidal anti-inflammatory drugs** as first line drugs for those acute conditions.

# Hyperuricemia - mechanisms

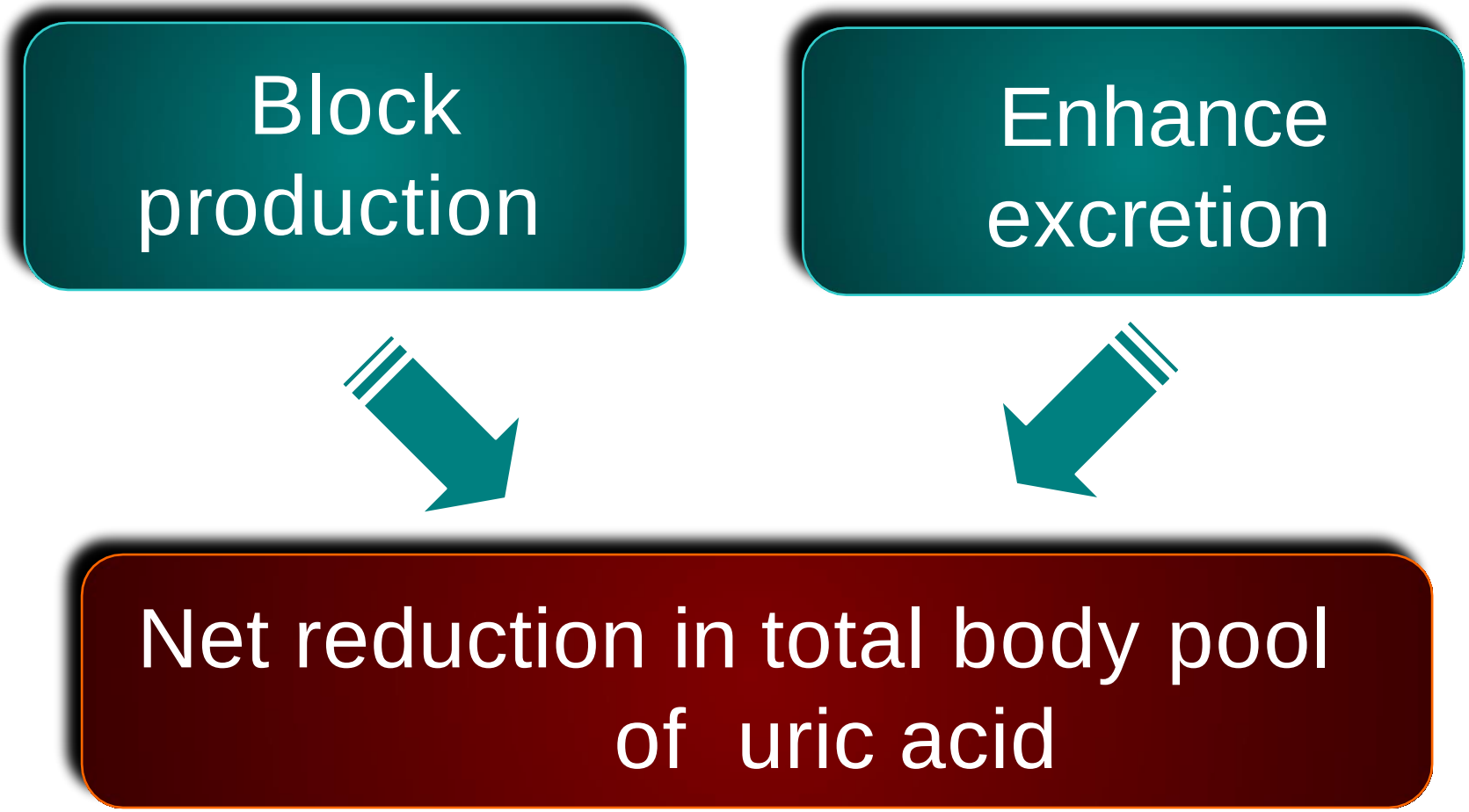



Remember we said the predisposing cause of gout is: high levels of uric acid or hyperuricemia, this is either happening because we have an excessive production of uric acid or we have inadequate execution.

Continue to next slide ,,

# Urate-lowering drugs

So, one way to address this problem is either by blocking the production or by enhancing the excretion and the net effect would be net reduction in the total body pool of uric acid.



# Gout - urate-lowering therapy

We have certain drugs that we call urate-lowering drugs, these drugs :

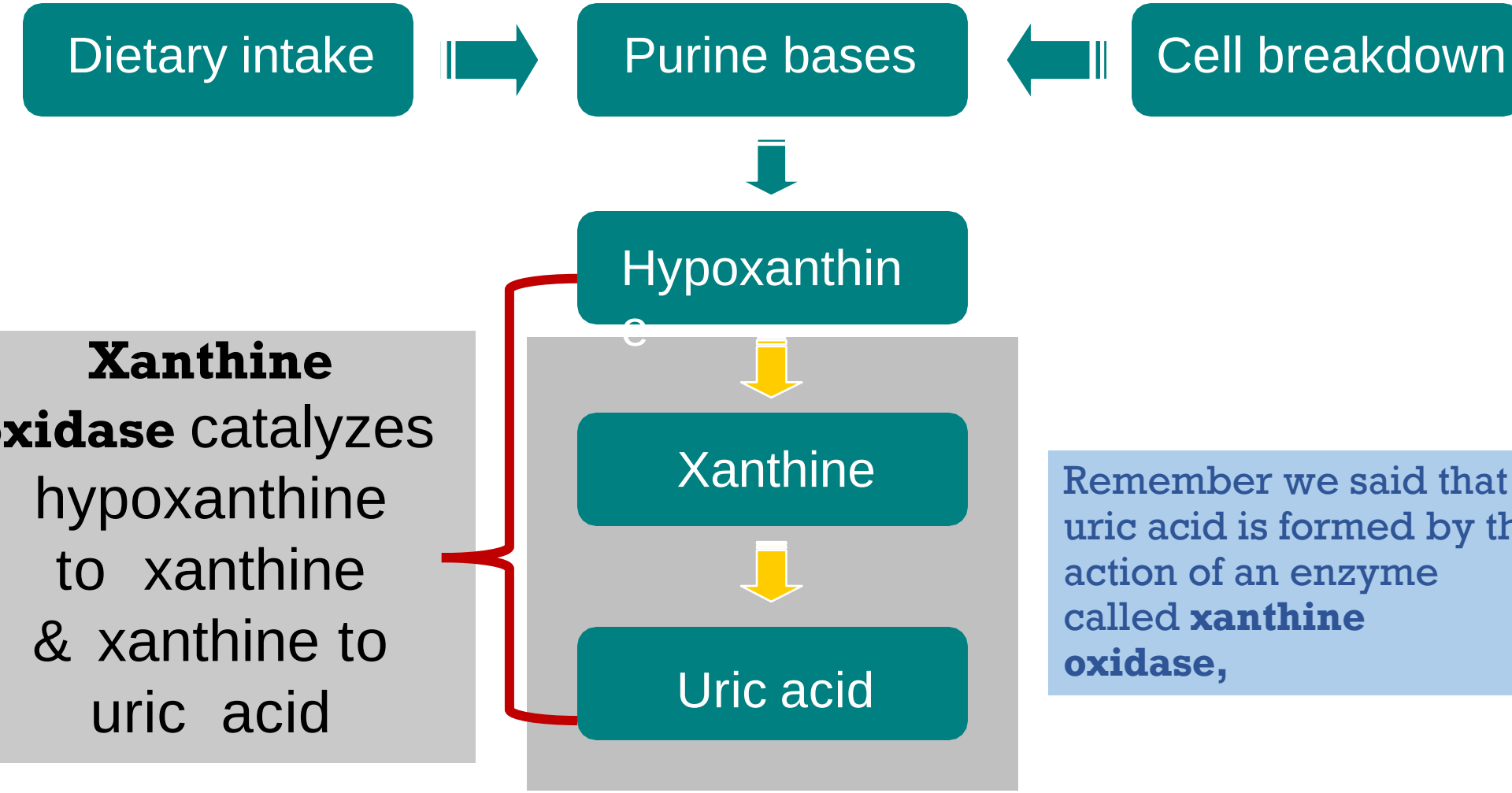
- Prevent arthritis, tophi & stones by lowering total body pool of uric acid.
- Not indicated after first attack, actually they might worsen the attack if they're used after the first attack.
- Initiation of therapy can worsen or bring on acute gouty arthritis, so we have to wait some time before administering these drugs. This is because when we use these urate-lowering drugs, this would result in urate crystals 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, so their use immediately after an attack can worsen or bring an acute gouty arthritis attack.

# Drug therapy of gout

This is the first group of drugs that we're going to talk about

*Drugs That Block Production of Uric Acid*

# Uric acid metabolism




**Xanthine oxidase** catalyzes hypoxanthine to xanthine & xanthine to uric acid

Remember we said that uric acid is formed by the action of an enzyme called **xanthine oxidase,**

# Allopurinol (Zyloprim™)

- Inhibitor of xanthine oxidase
- Effectively blocks formation of uric acid
- How it is supplied : usually administered orally in the form of tablets we have two concentrations; either 100 milligrams or 300 milligram tablets.
- Pregnancy category C, this means we can use this drug if the benefits of this drug outweigh the risk of its use. Of course, it would interfere with the synthesis of uric acid in the infants affecting the purine metabolism so it can cause some risks to the fetus.

# Allopurinol – usage indications

The indications for the use of allopurinol :

- Management of hyperuricemia of gout
- Management of hyperuricemia associated  with chemotherapy
- Prevention of recurrent calcium oxalate  kidney stones

# Allopurinol - common reactions

The common adverse effects associated with allopurinol :

- Diarrhea, nausea, abnormal liver tests
- Acute attacks of gout, as we said also briefly before, it can stimulate an acute attack of gout. This is because after initiation of allopurinol, we're going to have mobilization of urate crystals from their attached sites in the joint to the joint spaces and this results in acute changes in the serum uric, acid level which can predispose a gout attack.
- Rash **and** Allergic skin reactions starting from pruritus or rash into maculopapular lesions, which can happen in almost three percent of the patient
- Exfoliation of the skin called **exfoliative dermatitis,** in some patients
- Allopurinol can become bound to the lens resulting in **cataracts**, in very rare cases.

# Allopurinol – serious reactions

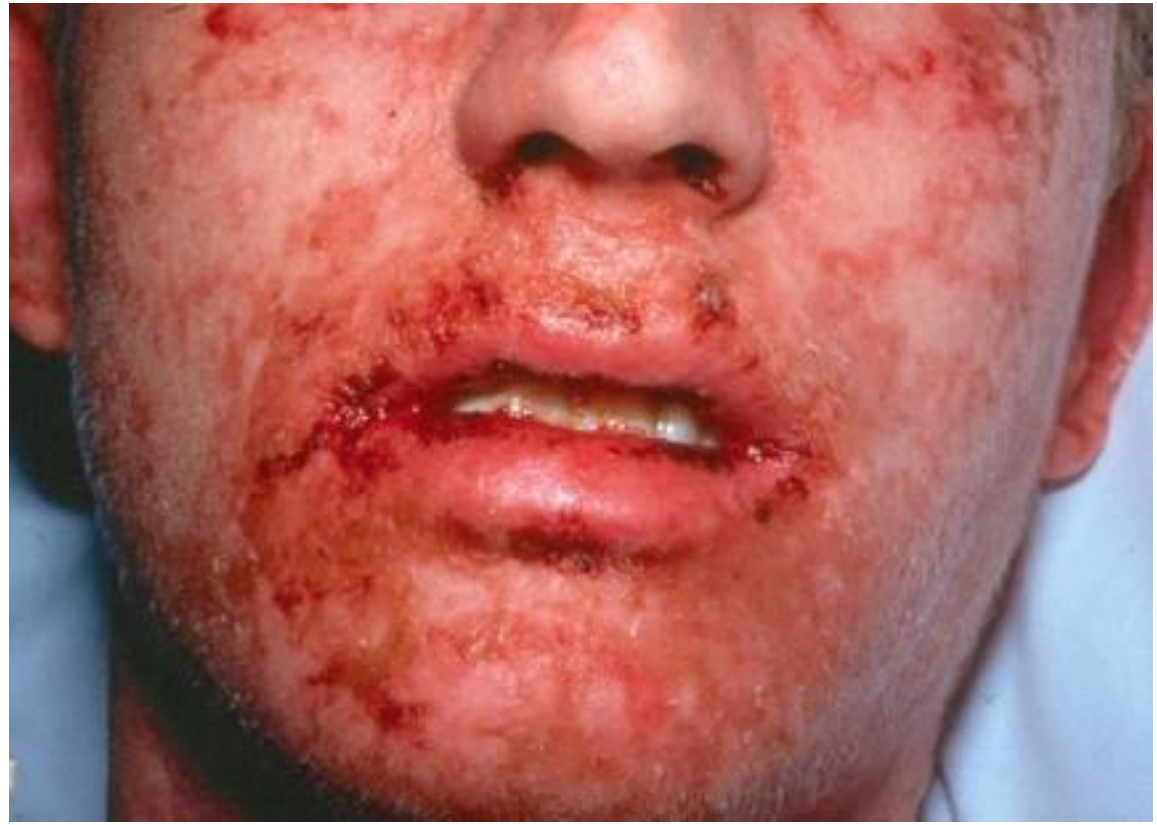
- Fever, rash, toxic epidermal necrolysis = SJS (next slide)
- Hepatotoxicity and interstitial nephritis*
- bone marrow suppression and rarely aplastic anemia
- Necrotizing Vasculitis
- Drug interactions (ampicillin, thiazides, mercaptopurine, azathioprine)
- Death

* Interstitial nephritis, also known as tubulointerstitial nephritis, is an inflammation of the area of the kidney known as the renal interstitium, which consists of a collection of cells, extracellular matrix, and fluid surrounding the renal tubules.

# Stevens-Johnson syndrome SJS

Another serious side effect

- Target skin lesions
- Mucous membrane erosions
- Epidermal necrosis with skin detachment



It's also called **epidermal necrolysis** where we have target skin lesions mucus, we said this is very rare and it can happen in less than two percent of the patients

# Allopurinol hypersensitivity

Some patients will develop allopurinol hypersensitivity as a side effect

- Extremely serious problem, which we have to recognize early
- Prompt recognition required with the first sign usually skin rash
- More common with impaired renal function
- Progression to toxic epidermal necrolysis & death

If developed later on, it may cause impairment of the renal function which can also progress to toxic epidermis necrolysis and death

# Febuxostat

Another new drug that's also from the same family

- Recently approved by FDA, it's actually been approved in 2009 for the treatment of gout
- Oral xanthine oxidase inhibitor
- Chemically distinct from allopurinol
- 94% of patients reached urate < 6.0 mg/dl
- minimal adverse events

Compared to allopurinol ,which can cause diarrhea, headache, and nausea, this drug seems to be more well tolerated in patients who have sensitivity or intolerance to allopurinol.

So, it's a good alternative to allopurinol in patients who cannot use that drug

It's structurally different from allopurinol although it does show the same mechanism of action.

It can cause reduction of urate levels, in about 94% of patients, to **below six milligram per deciliter** which is the amount we want or the level we aim for.

# PEGLOTICASE

The newest urate blocking therapy drug

- Recently approved by FDA 2010, for the treatment of **refractory** chronic gout, a refractory fracture means it is not responding to any other medication.
- Treatment of resistant gout
- PEG-conjugate of recombinant porcine uricase, it is a recombinant mammalian uricase that is covalently attached to methoxy polyethylene glycol or **m-peg.** **Note in next slide**
- Intravenously administered, it works **fast** within 24 to 72 hours to reach its peak concentration. Usually, it stays inside the body for days between 6 to 13 days and the clearance is by an antibody response. Here comes the importance of "pegulation" or adding polyethylene glycose to minimize this antibody response of the body.
- Uricase speeds resolution of tophi

- **Note:** 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 the **recombinant form** of the enzyme that's present in pigs or porcine (by pig we mean animal here, but the word peg in the name comes from the chemical compound polyethylene glycol) and the addition of peg or polyethylene glycol conjugation aims to increase the half-life of this drug.
- Also, it helps in diminishing or lowering the immune response for this enzyme which doesn't come from a human source but from an animal source, so we need to decrease the antigenicity of this enzyme or protein in our body and we do that by the addition of polyethylene glycol.

# Adverse effects

- Flare up of the gout especially during the first three months of treatment
- Nephrolithiasis, that means kidney stones
- Arthralgia, muscle pain, muscle spasm
- Headache, anemia and nausea .
- Frequent side effects include respiratory tract infection, peripheral edema, urinary tract infection and diarrhea.
- One major 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

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

## Probenecid Example of uricosuric drugs

- ✓ 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

- So, these agents are moderately effective, they are mainly used in patients who have fasciitis gout or patients who have frequent gouty attacks.
- In patients who usually excrete large amounts of uric acid, or patients with renal disease, thes e agents will not be used.

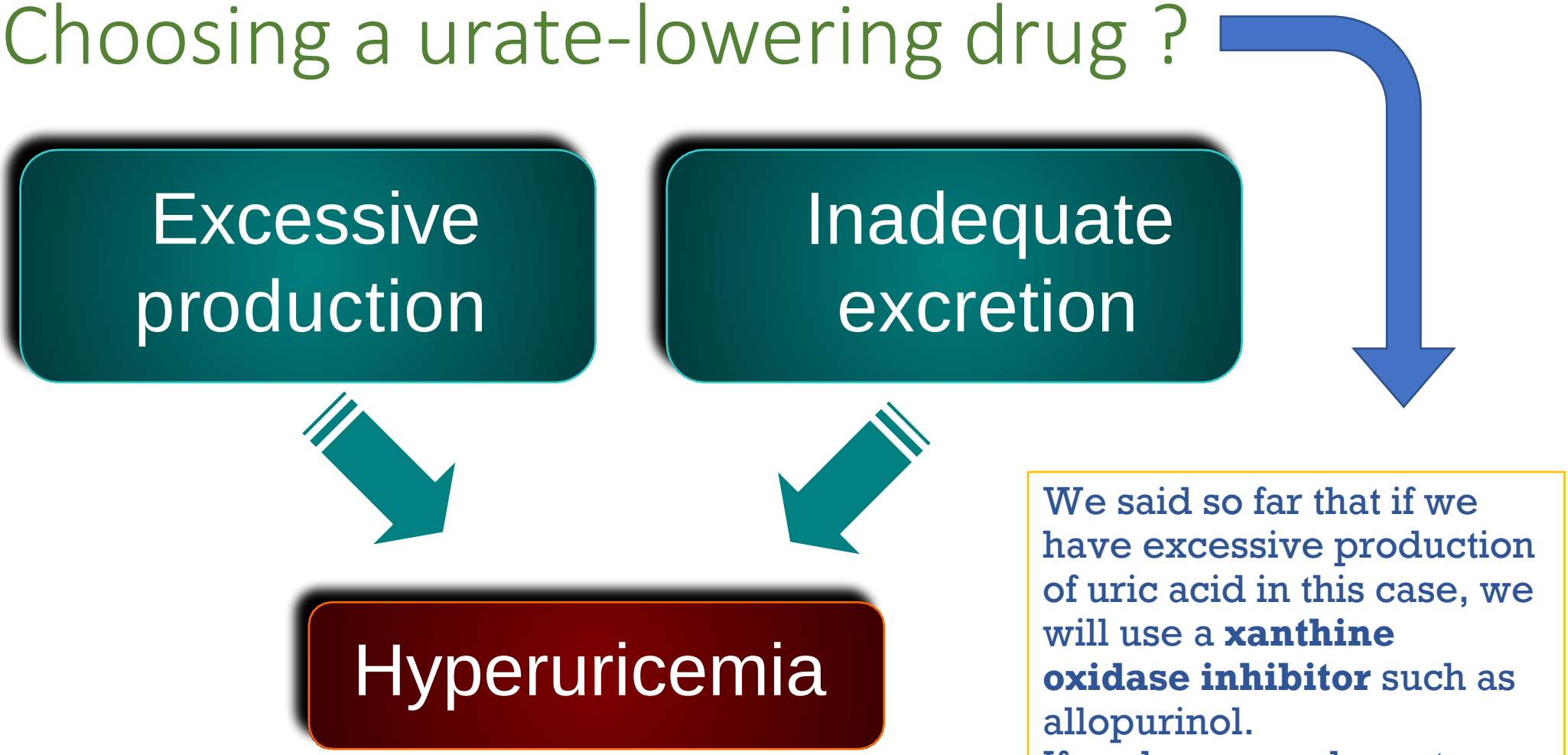
# Uricosuric therapy

- Contra-indications
  - ✓ History of nephrolithiasis
  - ✓ Elevated urine uric acid level
  - ✓ Existing renal disease
- Less effective in elderly patients, and this is because elderly patients usually have deteriorated kidney function.

So, their contraindication is patients who have history of nephrolithiasis = kidney stones, patients who have elevated urine uric acid levels and patients with an existing renal disease.

- Side effects associated with these drugs are mild such as GI irritation.

# Choosing a urate-lowering drug ?




We said so far that if we have excessive production of uric acid in this case, we will use a **xanthine oxidase inhibitor** such as allopurinol.
If we have an adequate excretion in this case, we will use a Uricosuric agent such as probenecid.

# Drug therapy of gout

*Case Presentation*

*Future doctors, get prepared (;*

# Case presentation

Here we have a 55-year-old male who has had pain in his big toe and ankle, so he described that he had this pain12 hours ago, he stated that he went to bed last night feeling fine but then felt **as if he had a broken toe this morning** . He also has past medical history (PMH) of similar problems in the right ankle and in the left wrist

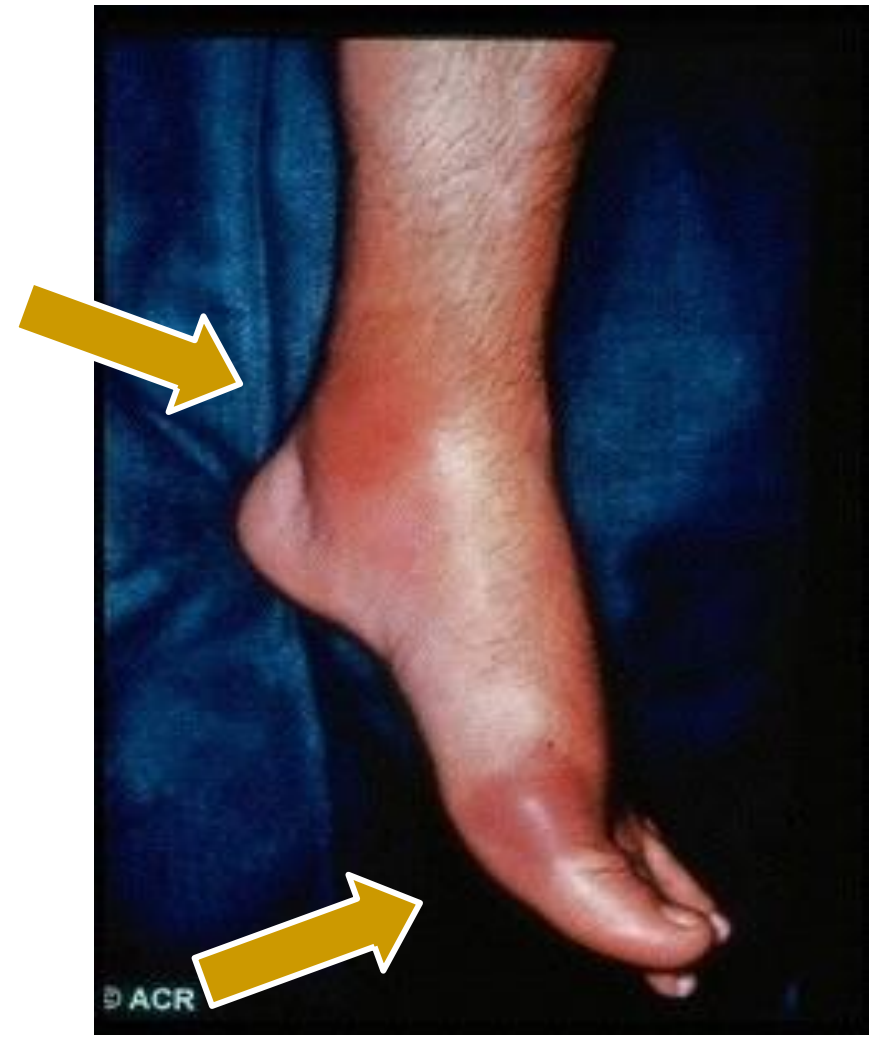
- ✓ 55 y/o male
- ✓ 12 hours “pain in my big toe &ankle”
- ✓ went to bed last night feeling fine
- ✓ Felt as if had broken toe this morning
- ✓ PMH of similar problems in right ankle & left wrist

*History is taken from the patient*

# Gout - acute arthritis

*Clinical examination*

Acute synovitis, ankle & first MTP joints

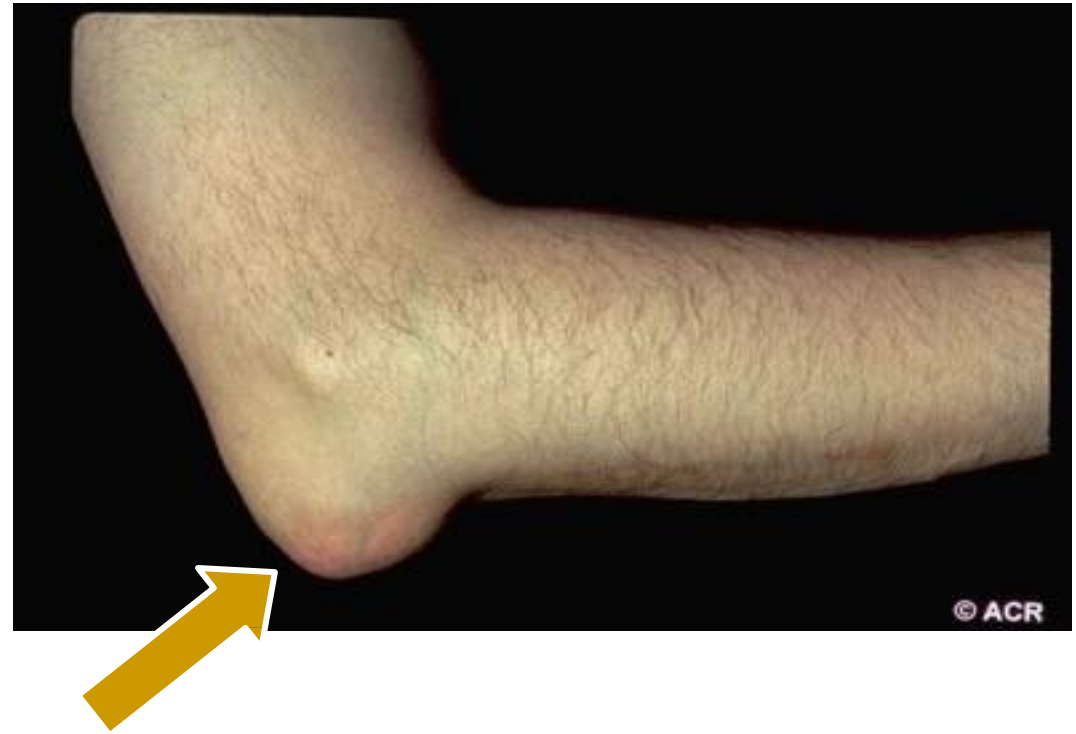



The metatarsophalangeal articulations are the joints between the metatarsal bones of the foot and the proximal bones.

# Gout - acute bursitis

Acute olecranon bursitis

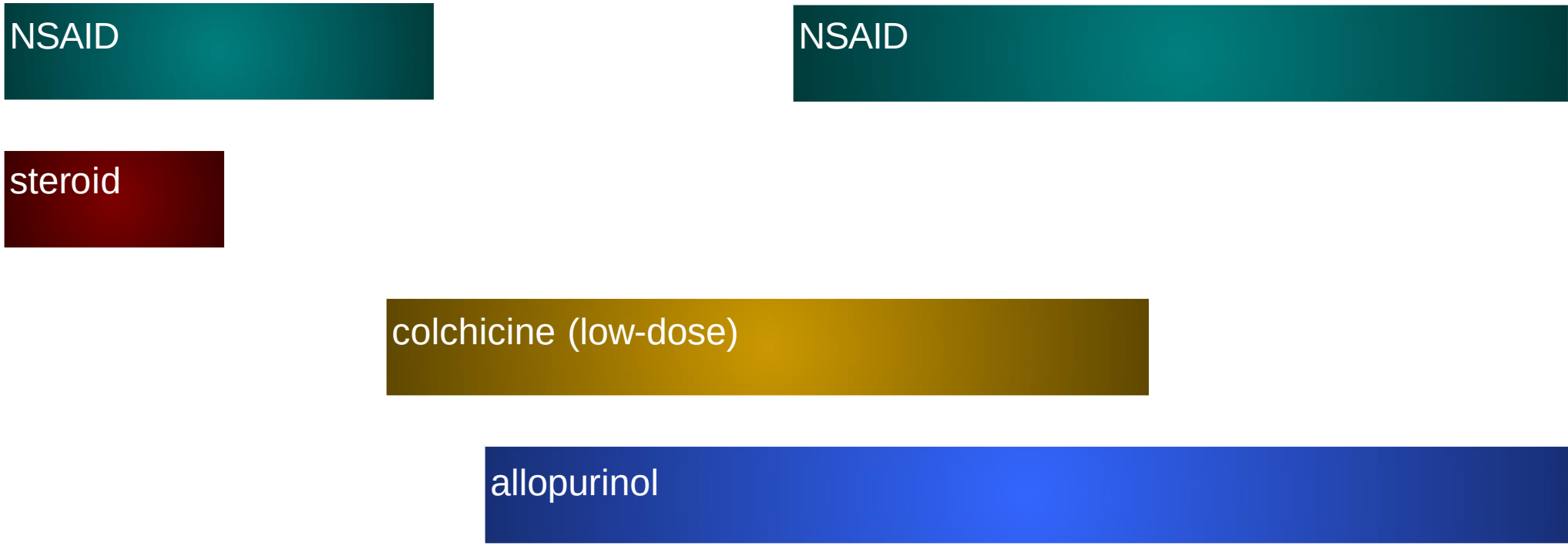
Bursitis is inflammation of the fluid-filled sac (bursa) that lies between a tendon and skin, or between a tendon and bone



# Case presentation - therapy

Next slide plz

Treatment :)



- We start the patient on **non-steroidal anti-inflammatory drug therapy,** as we said this is the first line treatment, we can also give the patient steroids at this stage starting from day one to day 10. Usually before we end up the non-steroidal anti-inflammatory drugs, we start the patient on a **low dose of colchicine as a maintenance therapy** to prevent further or any future attacks of this condition.
- We cannot start allopurinol immediately after an acute attack, so we wait for a period of time while the patient is still on NSAIDs and colchicine. After that, we can add allopurinol and we stop NSAIDs . So, we can add allopurinol as a maintenance therapy to maintain low levels of uric acid in the blood
- Then after the attack is subsided, we maintain the patient on colchicine and allopurinol, even though nowadays colchicine is not recommended because of the numerous side effects associated with it. If we have any flare up, we can go again and give the patient NSAID at any time during that period.

# Interleukin 1 receptor antagonist

Example:

- Anakinra
- Canakinumab
- Rilonacept

- Lastly just to mention two more groups of drugs we have interleukin one receptor antagonists. Examples of of these are listed here.
- 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 they do is that they target the **interleukin-1 pathway** thus they would **suppress the inflammation**.

➢ So, in conditions where we have patients not responding to NSAIDs or colchicine we would try using these drugs as a treatment.

# Glucocorticoids

Prednisone

- Oral
- Intra-articular
- Subcutaneous

The second group : Glucocorticoids we said we can use glucocorticoids during an acute gouty arthritis attack, one example of these drugs is **prednisone** it can be given orally or inside the joint "**intra-articularlly**" or subcutaneously and this depends on the degree of the acute attack, the degree of pain and the inflammation in the patient.

*Good Luck*