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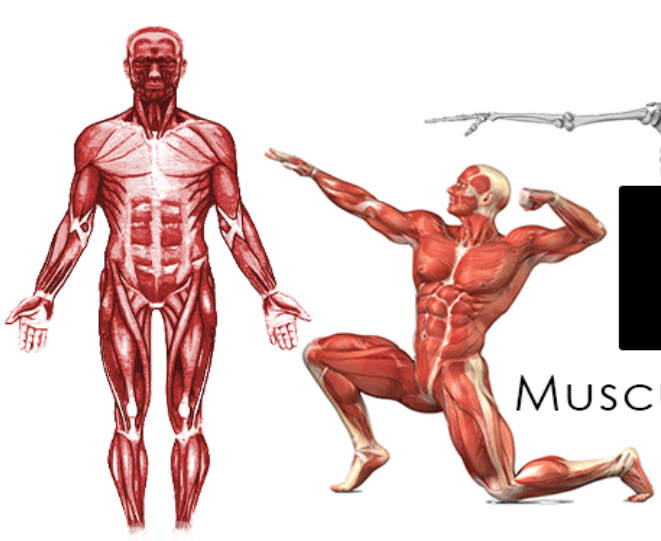

MSS

Musculoskeletal System

Pharmacology

Doctor 2018 | Medicine | JU

Done by

Sarah Basel & Batool Bdour

Contributed In The Scientific Correction

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Contributed In The Grammatical Correction

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Doctor

Alia Shatanawi

This will be the last sheet of the pharmacology material explained, drugs for GOUT, we hope the MSS journey treated you well and we wish you the best of luck in the final exam 😊

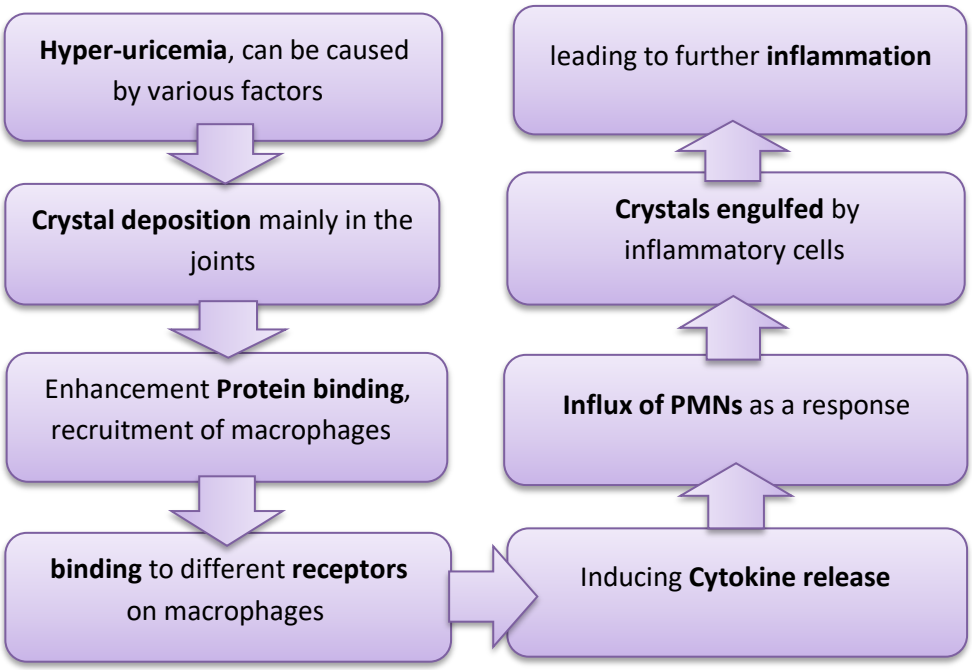
Defining GOUT: what is it?

It's an inflammatory disease, a type of ARTHRITIS that affects joints mainly and is caused by deposition of uric acid crystals in certain locations.

- Main characteristics of gout:

- Sudden onset
- Middle aged males
- Severe pain
- Distal joints
- Intense inflammation
- Recurrent episodes
- Influenced by diet → high protein diets, specifically.
- Bony erosions on X-ray. These bone and cartilage changes are associated with long term morbidity.

Gout is a crystal induced inflammation, that has a path of progression (pathogenesis)



Key element: PMNs are a critical component of crystal-induced inflammation

♈ A treatment approach:

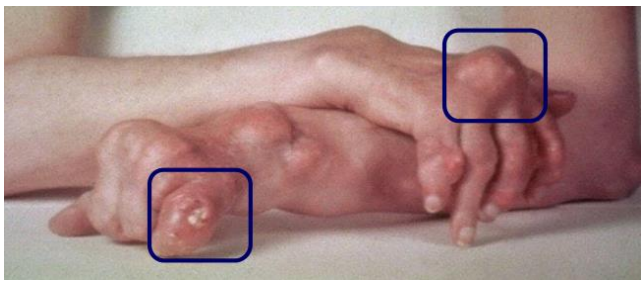
Hyperuricemia is the **hottest point to target** in the treatment of gouty arthritis, because it's the distinguishing point between gout and other types of arthritis.

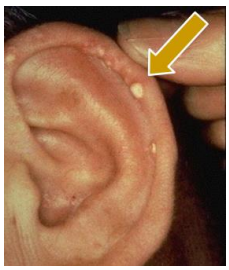
- It's caused by an imbalance between the **production** and the **excretion** of uric acid. This can be either over production, or under excretion of uric acid.

So to treat hyper uricemia, we can choose to **increase the excretion of uric acid**, or **decrease the production of uric acid** in the body.
These are actually modalities followed to treat this disorder.

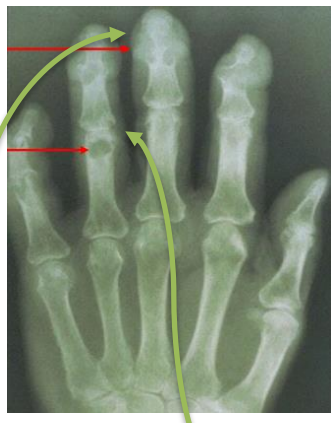
- Presentations of the disease and X-ray changes:

› Tophi: are a characteristic of chronic gout. They are defined as localized deposition of monosodium urate crystals in different parts of the body including joints, cartilage or skin. Tophi can be disfiguring not only painful.





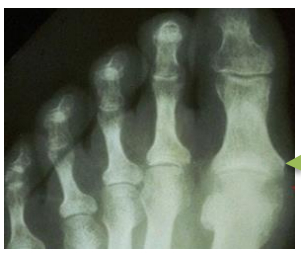
Helix of the ear (very cartilaginous area) is a common site for tophous formation



› changes in the bone can be observed, here for example: DIP (Distal interphalangeal joint) joint destruction.
And a radiolucent spot on a distal phalangeal bone [phalangeal bone cysts]

↳ Deposition in the distal inter phalangeal joints, which lead to joint destruction and phalangeal bone resorption.

› Bony erosions in the foot.



cardinal manifestations of gout are:

Arthritis (acute and chronic), tophi, nephrolithiasis (stones in the kidney) and nephropathy.

They are the doing of Hyperuricemia.

- About uric acid: The metabolism.

Uric acid can be **synthesized** by normal pathways in the body (cell breakdown) or **obtained from diet**.

Dietary intake: after the protein gets digested it'll generate **purine bases** or when the cells are broken down we have **endogenous synthesis** of these purine bases

Purine bases can form **hypoxanthine**

Xanthine oxidase

hypoxanthine can form **xanthine**

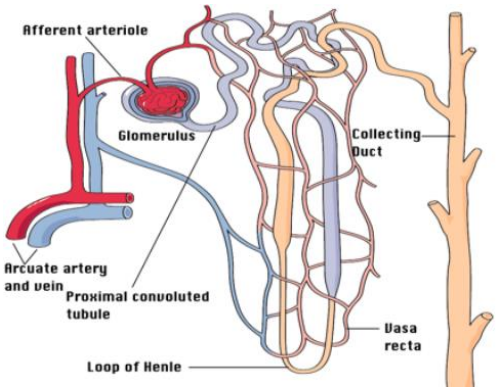
which is converted into **uric acid**

- There are different enzymes acting on this pathway, we'll only focus on one enzyme. Which is xanthine oxidase
  - Xanthine oxidase catalyzes the conversion of hypoxanthine to xanthine & xanthine to uric acid.

this is another target for the treatment of gout (decreasing the synthesis)

Another modality we mentioned is increasing the excretion, what to target?

- Renal handling of uric acid:



- uric acid gets excreted by **glomerular filtration.** part of it gets reabsorbed by tubular reabsorption, and part will be excreted in the tubule
- Then it goes through secondary (post secretory) reabsorption

- The net normal effect of uric acid it needs to be excreted in the urine, and only a small amount of it needs to be circulating in the plasma

- If we have high concentration of uric acid in the plasma, due to various conditions, this could lead to uric acid crystals deposition, in the joints mainly and other body locations mentioned before, and this consequently induces inflammation leading to gout.

- Gout – problems associated with it
  - excessive total body levels of uric acid
  - deposition of monosodium urate crystals in joints & other tissues
  - crystal-induced inflammation

- Different treatment modalities:
  - Drugs reducing uric acid production, so we have drugs interfering with the pathway producing uric acid
  - Drugs Increasing the excretion of uric acid
  - Anti-inflammatory drugs (to reduce the inflammation and the symptoms accompanying it, and the **macrophages** that get activated in this disease which are a key component of further inflammatory processes' activation by generation of other cytokines

↳ macrophages stimulate the cytokines release which will stimulate PMNs activation.

- Drugs of Gout:
  - Acute attack drugs:
  - Colchicine
  - NSAIDs can be helpful for the inflammation
  - Steroids (anti-inflammatory properties)
  - rest, analgesia, ice, time (indicated as supportive therapy)
  - chronic and prophylactic drugs: urate lowering drugs

↳ used to balance the uric acid pool in the body which helps as a preventive measure for the recurrence of acute gouty attacks.

  - Allopurinol
  - Probenecid
  - Febuxostat (a new drug, just released to the market)
  - rest, analgesia and time

- NSAIDs briefly: (focusing on the important points)

Mechanism of action: inhibition of COX enzyme of the PGs synthesis pathway (they aren't selective, yet they show some affinity towards COX-2)

↳ Although they're **not selective** they show an increased incidence of cardiovascular conditions such as **thrombosis**

Why? It occurs because the activity of COX-1 overwhelms the inhibition with an increase in its products, especially (thromboxane) which would lead to this thrombotic effect.

The only exception for that is aspirin, which binds irreversibly to the platelets inducing inactivation of platelet COX for a long period of time.

- Indomethacin (Indocin)

Notes: It is indicated in pregnancy for the closure of patent ductus arteriosus.

Ibuprofen have recently been used for the same indication.

- Naproxen (Naprosyn)
- Ibuprofen (Motrin)
- Sulindac (Clinoril)
- Ketoprofen (Orudis)

All of them can be used to inhibit the inflammatory processes or further activation of cytokines and neutrophils that happen in gout.

A note the doctor wants you to remember: aspirin is pregnancy category C, and becomes D in the 3rd trimester. but it can be indicated in the first trimester of pregnancy in patients performing IVF to increase the vascularization to the fetus, to enhance the implantation of it.

our first drug is a drug targeting these macrophages

- colchicine

- originates form a plant called *Colchicum automnale (autumn crocus or meadow saffron)*
- Mechanism of action: disruption of microtubules, inhibits microtubule polymerization by binding to tubulin, one of the main constituents of microtubules.
  - Indicated in gouty arthritis. Especially, the acute conditions of it because it **suppresses the inflammation**.
- It doesn't have a direct analgesic activity, but it decreases inflammation and the production of cytokines which would lead to a form of analgesia.
- Does NOT affect renal excretion of uric acid
- Does NOT alter plasma solubility of uric acid (neither raises nor lowers serum uric acid)

- Effects of colchicine:

- reduces inflammatory response to deposited crystals, which would stop the activation of migration of these inflammatory cells to the site of inflammation
- diminishes PMN phagocytosis of crystals
- blocks(reduces) inflammatory cellular response to deposited crystals

Depending on the dose we have different indications:

High dose → acute gouty arthritis
Low dose → prevent the recurrence of these conditions

However, we're **always** reluctant to use it in high doses because it has many side effects. These are because it affects actively replicating cells, it blocks this replication. So, it'll show side effects associated with its mechanism of action.

- Main side effects:
  - Gastrointestinal (nausea, vomiting, cramping, diarrhea, abdominal pain), because the lining of the GI system is highly replicative.
  - Hematologic (agranulocytosis, aplastic anemia, thrombocytopenia) because blood cells are also highly replicative cells.
  - Muscular weakness

↳ adverse effects are dose-related & more common when the patient has **renal or hepatic disease.**

why? Because metabolism of colchicine occurs in the liver, so if a patient has a liver problem, not the same metabolic activity rate will exist.
Also, excretion of this drug happens by the enterohepatic circulation in the liver through the biliary route and in the feces or it can get excreted unchanged in the urine.

Exam tip: In the **muscle relaxants** course the doctor wants you to focus on the differences between half-lives of different drugs, especially neuro-muscular blocking agents, and why there is difference between them, causes like site of metabolism (liver or blood).

It's all explained in the lecture, it'll be very easy and very simple, so just study it thoroughly and all will be well

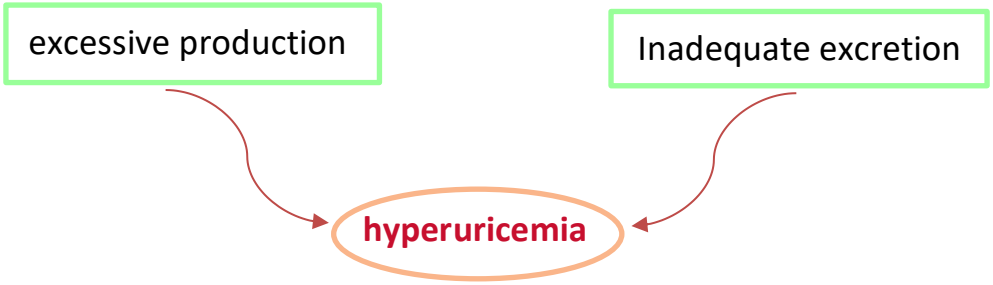
Gout - colchicine therapy:

- **more useful for daily prophylaxis (low dose).**
- **Colchicine** is used as a prophylactic agent to prevent acute attacks of gout in patients initiating urate-lowering therapy (treatment of chronic gout).
- Prevents recurrent attacks.
- colchicine 0.6 mg qd-bid
    - qd (quaque die…which means once a day in Latin)
    - bid (bis in die… twice a day in Latin).
- **declining use in acute gout (high dose):**

- **NSAIDs** have largely replaced colchicine in the treatment of acute gouty attacks for safety reasons (taking is consideration its SE).

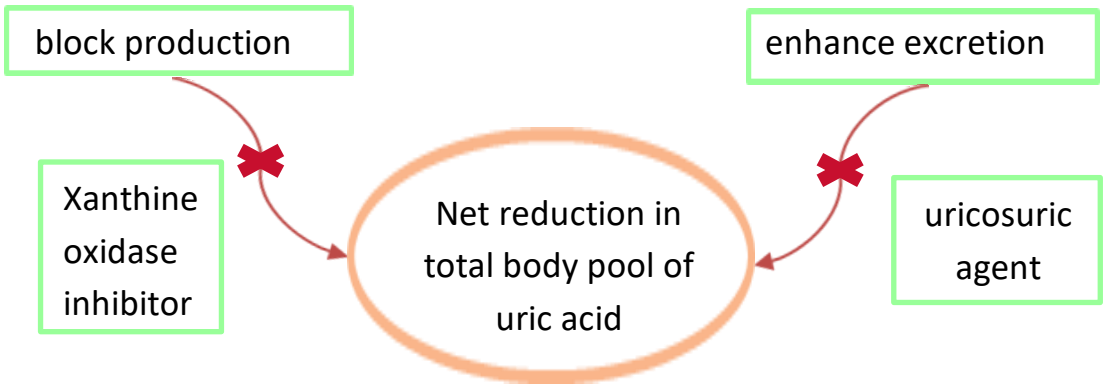
Hyperuricemia – mechanisms:

The cause of hyperuricemia in gout is an imbalance between overproduction of uric acid and/or the inability to excrete uric acid renally.



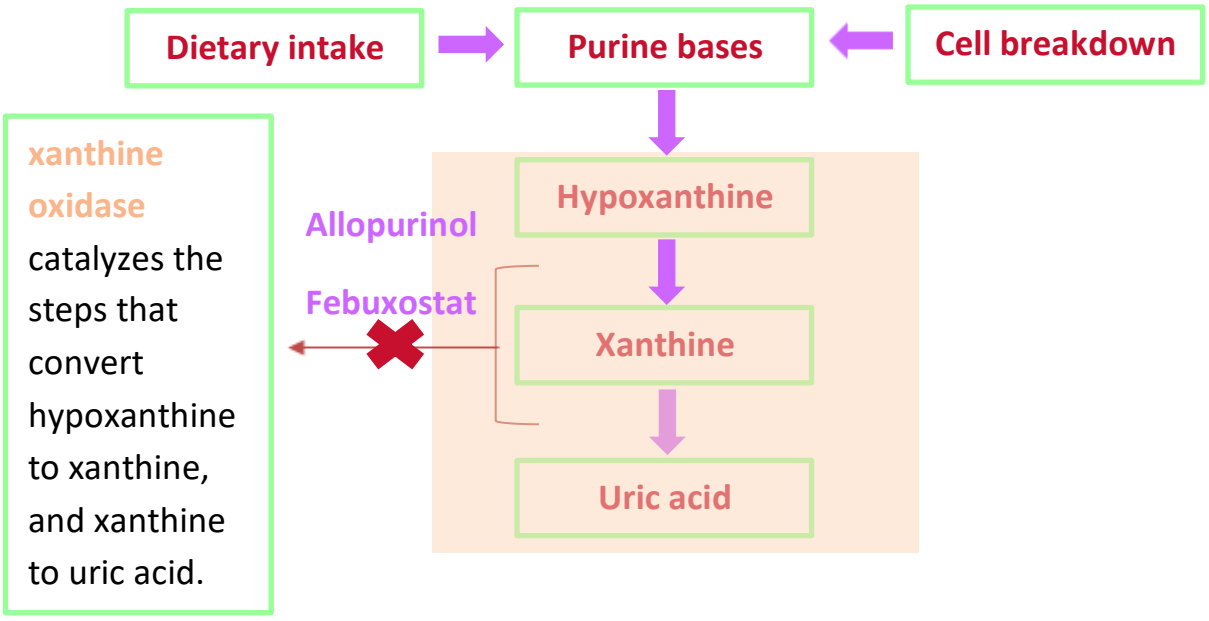
Treatment of chronic gout:

- Urate-lowering therapy for chronic gout aims to reduce the frequency of attacks and complications of gout.
- Treatment strategies include the use of drugs that reduce the synthesis of uric acid or drugs that increase its excretion.



- **Gout-urate-lowering therapy:**
  - **Xanthine oxidase inhibitors:**
    These drugs act by inhibiting the enzyme that catalyzes the last two steps in uric acid biosynthesis (end product of purine metabolism in humans), **Xanthine oxidase**.
  - Xanthine oxidase inhibitors (**Allopurinol, Febuxsotat**) are first-line urate-lowering agents.
  - These drugs prevent arthritis, tophi and stones by lowering total body pool of uric acid.
  - Urate-lowering therapy is **not indicated** after first attack.
    EXTRA: patients are candidates for prophylactic urate-lowering therapy if they have more than two attacks per year or if they have tophi.
  - **No role** to play in managing **acute gout**.
  - **IMPORTANT NOTE: initiation of therapy can worsen or bring on acute gouty arthritis.** Initiation of urate-lowering therapy can precipitate an acute gout attack due to rapid changes in serum urate concentrations. Medication for the prevention of an acute gout attack (low-dose colchicine, NSAIDs, or corticosteroids) should be initiated with urate-lowering therapy and continued for a period of time.

Drugs That Block Production of Uric Acid:



Allopurinol (Zyloprim™), inhibitor of xanthine oxidase:

- effectively blocks formation of uric acid
- how supplied - 100 mg and 300 mg tablets
- **pregnancy category C** (Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks).
- **Therapeutic uses:**

Management of hyperuricemia of gout.
management of hyperuricemia secondary to other conditions, in which large amount of purines are produced, particularly **after chemotherapy**.
prevention of recurrent calcium oxalate **kidney stones**.

- **Pharmacokinetics:**
- Allopurinol is absorbed after oral administration by the GI tract, it then functions at the target sites (after distribution).
- It get metabolized by the liver.

- **Excreted renally in the urine, or in the feces through the enterohepatic circulation** (excreted by the liver into bile, and then into intestinal tract, finally eliminated from the body in the feces).

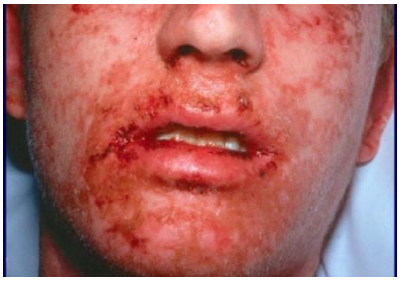
Allopurinol - common reactions:

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

Allopurinol - serious reactions:

- Fever, rash, toxic epidermal necrolysis. Hypersensitivity reactions, especially skin rashes, are the most common adverse reactions.
- Steven Johnson syndrome and toxic epidermal necrolysis **(SJS-TEN).**

Stevens-Johnson syndrome:



1. Target skin lesions.
2. Mucous membrane erosions.
3. Epidermal necrosis with skin detachment**.**
4. Extremely serious problem.
5. Prompt recognition is required.
6. First sign usually skin rash.
7. More common with impaired renal function.
8. Progression to toxic epidermal necrolysis and death.

- Hepatotoxicity, marrow suppression.
- Vasculitis.
- Drug interactions (ampicillin, thiazides, mercaptopurine, azathioprine).
- Death.

Febuxostat:

- Recently approved by FDA.
- Xanthine oxidase inhibitor, structurally and chemically unrelated to allopurinol reducing the risk of rash and hypersensitivity reactions.
- 94% of patients reached urate < 6.0 mg/dl.
- Minimal adverse events.
- Can be used in patients with renal disease because it does not have the same degree of renal elimination as allopurinol and thus requires less adjustment in those with reduced renal function.

PEG-uricase:

- **Recombinant form** of the enzyme urate oxidase or uricase (EXTRA: this enzyme converts uric acid to a water-soluble nontoxic metabolite that is excreted by the kidneys).
- investigational drug.
- PEG-conjugate of recombinant porcine (obtained from pigs) uricase.
- Treatment-resistant gout, **pegloticase** is indicated for patients with gout who fail treatment with standard therapies such as xanthine oxidase inhibitors.
- Uricase speeds resolution of tophi.
- Further research needed.

Drugs That Enhance Excretion of Uric Acid:

- **Uricosuric therapy:**
- **Uricosuric drugs:** Drugs that increase the excretion of uric acid in the urine, thus reducing the concentration of uric acid in blood plasma.

Probenecid:

- Blocks tubular reabsorption of uric acid.
- Enhances urine uric acid excretion.
- Increases urine uric acid level.
- Decreases serum uric acid level.

Probenecid is sometimes used along with penicillin antibiotics because it interferes with their renal secretion increasing their half-life and thus elevating their plasma concentration. This increase makes the antibiotic work better in treating certain infections.

Uricosuric therapy:

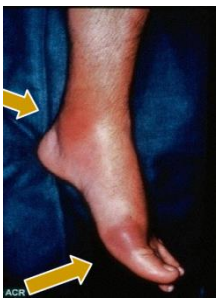
- Moderately effective.
- Increases risk of nephrolithiasis (kidney stones).
- Not used in patients with renal disease.
- Frequent, but mild, side effects (nausea, vomiting…).

♈ Contra-indications:

- History of nephrolithiasis.
- Elevated urine uric acid level, because urine cannot handle more and more uric acid. (**EXTRA:** urine uric acid levels are already elevated ⟶ urine is acidic, the high acid concentration of urine makes it easier for uric acid stones to form).
- Existing renal disease.
- Less effective in elderly patients (compromised renal function).

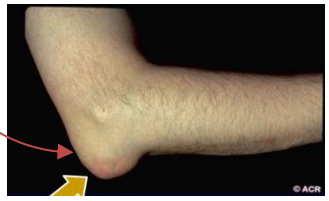
♈ Case Presentation:

A 50-year-old alcoholic man not known to have any medical illnesses, came to ER complaining of severe dull pain in his right big toe and ankle, describing it as if his toe was suddenly broken or dislocated. The patient's previous medical history showed that he had experienced several episodes with similar symptoms in his right ankle and left wrist.



- **Clinical presentation:**

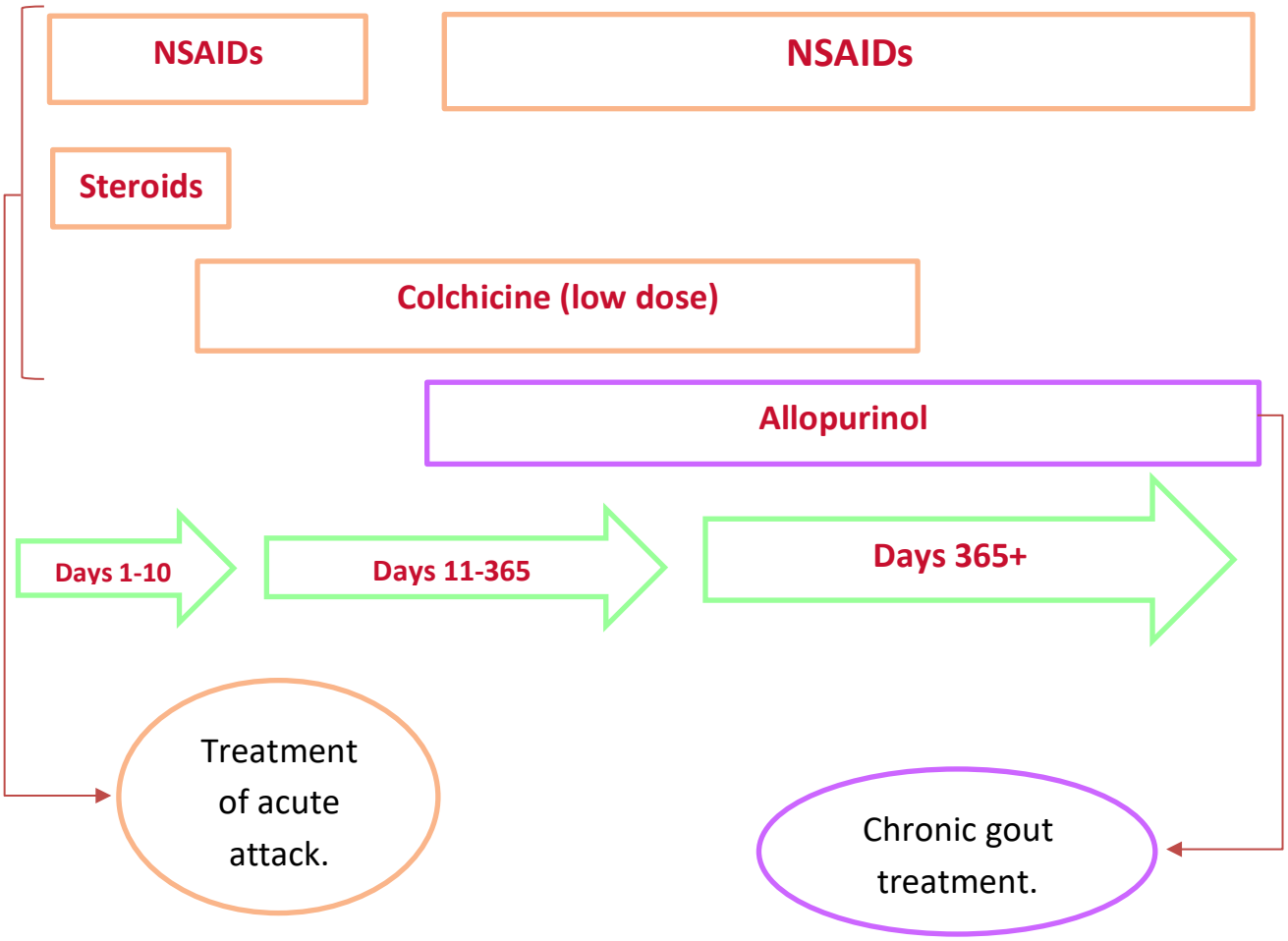
The initial manifestation of gout is usually an acute attack of synovitis affecting a single peripheral joint, most commonly the first **(metatarsophalangeal MTP),** other commonly affected joints include the **ankle joint** and elbow joint (**acute olecranon bursitis**: inflammation of the fluid-filled sac (bursa) that lies between a tendon and skin, or between a tendon and bone) .



- **Acute Gout attack.**

Such attacks are characterized by sudden onset of excruciating joint pain typically lasting for less than 24 hours.

♈ Therapy:



♈ Important notes:

- NSAIDs, corticosteroids, and colchicine are first-line therapy to treat acute gout attacks.
- Allopurinol and other urate-lowering drugs are indicated for treating chronic gout but not acute attacks.
- Colchicine (at low doses) should be initiated with urate-lowering drugs to prevent the onset of an acute gout attack.

Good luck ❤