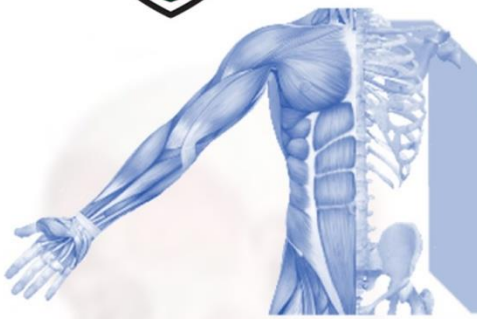

MSS

Musculoskeletal System

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NO.

Pharmacology

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Drug Therapy of Gout

(00:00-10:00)

What Is Gout?

a type of complex ARTHRITIS that affects joints suddenly (maybe in the middle of night), characterized by severe pain, swollen in the joint, redness and tenderness, it could happen to one or more joints, the big toe is the most commonly to be affected. It starts when the big toe is on fire, the joint will be hot, swollen and painful and it happened because an inflammatory reaction in that side. It also caused by metabolic disease, it happens because arthritis, this is due to deposition of uric acid crystals in the joints and cartilage.

-we can see some of the deposited uric acid in kidney, so we call it renal calculi (stones in the kidney), and in intestinal nephritis as well.

Main characteristics of gout

- ✅ sudden onset
- ✅ affect mainly middle-aged males
- ✅ severe pain
- ✅ distal joints like in the big toe
- ✅ Intense inflammation
- ✅ recurrent episodes at any time
- ✅ influenced by diet
- ✅ the appearance of bony erosions on Xray

the cascade of events induces this inflammation.

Hyperuricemia ⏩ crystal deposition ⏩ protein binding ⏩ receptor binding ⏩ cytokine release influx of PMN's ⏩ crystals engulfed ⏩ inflammation

--more clarification:

- Uric acid is a poorly soluble substance that is the major end product of purine metabolism.
- Most mammalian have the enzyme uricase that converts uric acid to more soluble allantoin. Human does not process this enzyme, so we must control the level of uric acid by excretion throw the kidney. Any imbalances between the uptake and the elimination of uric acid, might elevate the uric acid level in serum, then the deposition in joints, kidney, intestine and cartilages as well.
- This substance will bind to receptors laying on the cells that lining the joints, which called synoviocytes. Synoviocytes will engulf the uric crystals and release cytokines, prostaglandin, lysosomal enzyme and IL-1 (this causes the severe pain). The release of these products will bring the attraction of many cells like polymorph nuclear cells and leucocytes which will migrate to the joint space and amplify the inflammation process. The PMNs is a critical compound of crystal-induced inflammation.
- Later stages, mononuclear phagocyte will increase in number and start the ingestion of urate crystal and release more inflammatory mediators.

🔎🔬 Diagnosis: by hyperuricemia and bony erosions on Xray.

Anyway, why hyperuricemia occurs?

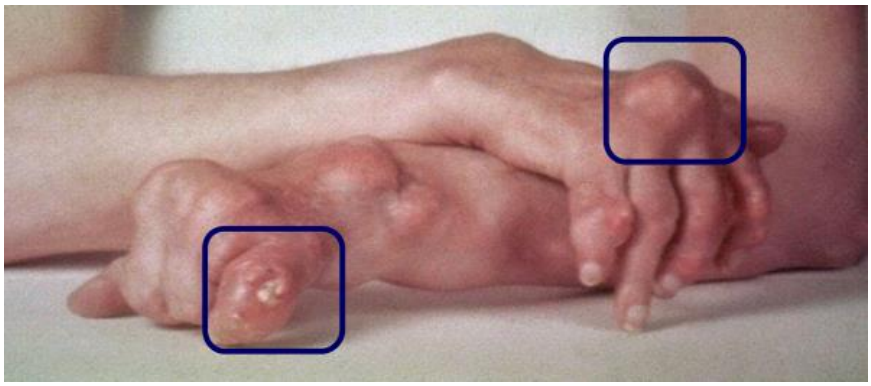
-the production of uric acid exceeds than the excretion.

-when the excretion is loss because kidney doesn't excrete enough, this will end up with increasing the blood stream level of uric acid and again we will have hyperuricemia.

We must maintain the balance, e.g., the intake a lot of substances that converted in our body to uric acid like red meat (which will be digested to

purine the metabolized to uric acid), people with gout must be careful of taking too much red meat otherwise they will suffer from hyperuricemia.

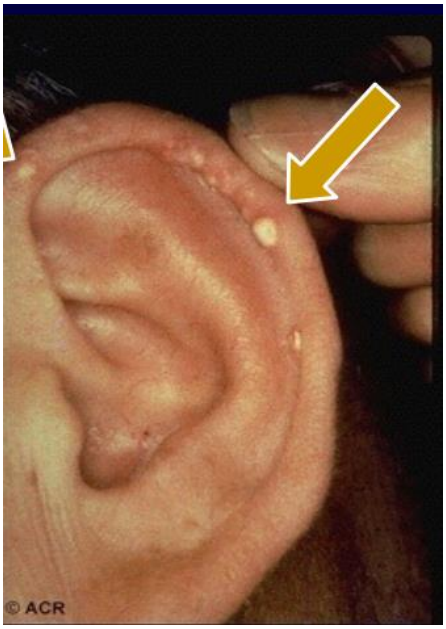
Chronic tophaceous gout



It is chronic form of gout when we see nodular masses because urate crystal is deposited in different tissue in the body, most commonly around the figures and toes, this is very painful inflammatory process, but also disfiguration of patients.

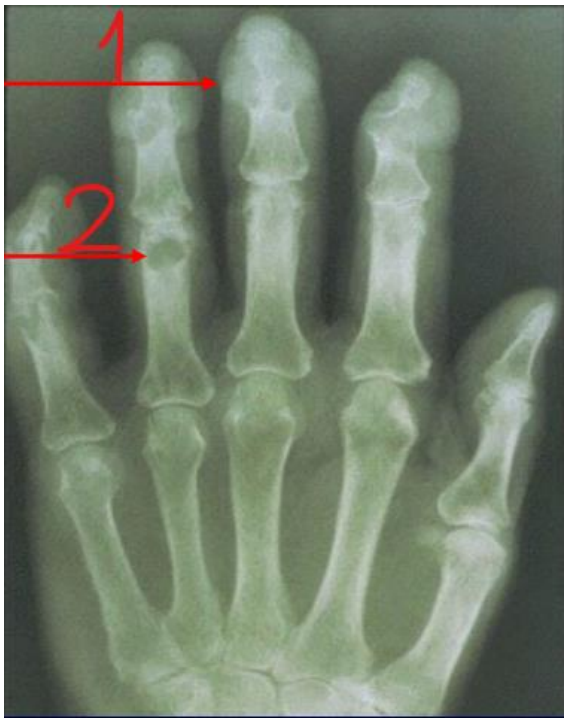
-Tophus is localized deposit of monosodium urate crystals.

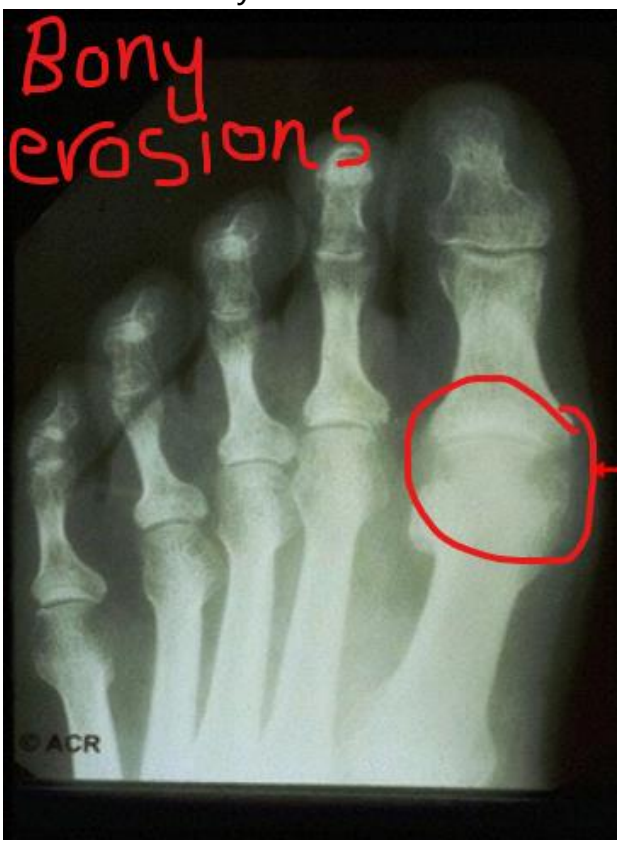
-tophi can be found in toe, finger, elbow and helix of the ear.



Gout - X-ray changes

We can see joint destruction in the 1- Distal interphalangeal joint (DIJ) and 2- formation of cysts in the bone.





(10:00-20:12)

-Clinical gout episodes usually associated with hyperuricemia, most patients with hyperuricemia mightn't develop clinical events from urate crystal deposition, so before starting the chronic urate lowering therapy of gout patient where hyperuricemia is associated with gout and urate stones, we need to distinguish between patients with only hyperuricemia and patients with gouty episodes because the efficacy of long-term therapy of asymptomatic hyperuricemia isn't proven to be effective, so some individual with very high uric acid can live their whole lives without adverse consequences.

Gout - cardinal manifestations

The manifestations that make a person characterized with gout and need pharmacological treatment (all of them associated with increasing the level of uric acid in blood stream):

1. Arthritis-> can be acute or chronic.
2. Tophi
3. Nephrolithiasis (kidney stone)
4. nephropathy

Drug therapy of gout

-we said that the diet affect the level of uric acid which will ultimately affect the condition of gout.

* Uric acid metabolism

dietary intake ⏩ purine bases ⏪ cell breakdown

⏬

hypoxanthine

⏬

Xanthine

⏬

uric acid

- xanthine oxidase catalyzes hypoxanthine to xanthine & xanthine to uric acid

Renal handling of uric acid

The net effect of all different events that's been throughout the kidney glomeruli is excretion of uric acid. We start with :

1. glomerular filtration which will lead to decrease the concentration of uric acid CO. In the plasma.

2. The proximal convoluted tubule reabsorption
3. Tubule excretion
4. post-secretory reabsorption

If we want to control this process we can prevent the reabsorption or post-secretory reabsorption by some pharmacological events.

Gout - problems

• excessive total body levels of uric acid

• deposition of monosodium urate crystals in joints & other tissues

• crystal-induced inflammation

Drugs used to treat gout:

-acute gouty arthritis

• colchicine: isn't the first line drug in treatment, but used to be the primary one for many years

• NSAID's (non-steroidal anti-inflammatory drugs)

• steroids

• rest, analgesia, ice, time

-Urate Lowering Drugs

- allopurinol
- probenecid
- Febuxostat

The treatment course includes the drug+ rest+ analgesia + time.

Now let's get into details:

1- NSAID's

The mechanism of action is inhibiting the production of prostaglandin by inhibiting the enzyme cyclooxygenase. This family is inti inflammatory and painkiller.

- Indomethacin (Indocin): it inhibits urate crystal phagocytosis; this mechanism occurs also in most NSAIDs, except for aspirin. It is used in the initial treatment of gout and as a replacement of colchicine. Administrated as 25 to 50 mg four times daily, usually for(5- 7) days.

-Aspirin isn't used to treat acute gouty arthritis, because it leads to renal retention of uric acid when used in low dose (<2.6 gram per day), on the other hand, the higher dose (>3.6 gram per day) is **uricosuric.**

الدكتورة ما حكت شي عن الادوية ال٤ الي تحت ,بس احتياطا **احفظوهم**

- Naproxen (Naprosyn) 500 mg two times daily
- buprofen (Motrin) 800 mg four times daily
- Sulindac (Clinoril) 200 mg two times daily
- Ketoprofen (Orudis) 75 mg four times daily

2- Colchicine - plant alkaloid

Is taken from plant called colchicum autumnale (autumn crocus or meadow saffron).

• “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, how does this drug help in the treatment of gouty arthritis?

By inhibition microtubule polymerization by binding to tubulin, one of the main constituents of microtubules, and prevents the polymerization of these subunits of tubulin to form the microtubule.

-remember when we said that phagocytes have a rule in inflammatory process and gouty arthritis, so for these cells to engulf the urate crystal to move around and perform phagocytosis, they need to have continuous formation and polymerization microtubule. Thus, if we inhibit the synthesis of microtubule, we will inhibit the phagocytosis process and decrease inflammatory response to

these deposited crystals. It can also diminish PMN phagocytosis of crystals, and this leads to block cellular response to deposited crystals, blocking the inflammation and cytokines release. The end results are reducing the signs and symptoms of this disease.

^go back to page no.1 and the cascade of which induce the inflammation, Colchicine work takes place in the second step by preventing the synoviocytes from binging to urate crystals, thus, preventing all the following steps.

(20:12-30:00)

Colchicine – indications

-high dose-> treatment of acute gouty arthritis

-low dose-> prevention of recurrent gouty arthritis, this is a maintenance therapy to prevent further flare-ups of attack of gout.

Side effect

• gastrointestinal (nausea, vomiting, cramping, diarrhea, abdominal pain)

• hematologic (agranulocytosis, aplastic anemia, thrombocytopenia)

• muscular weakness, this is because colchicine prevents the polymerization if microtubules which are important for the formation mitotic spindles, so in highly replicating cells colchicine can affects the replication process, so it affects the blood forming cells such as platelets, RBCs and WBCs.

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

- more useful for daily prophylaxis because it is used at low dose (0.6 mg/2 times a day), it prevents recurrent attacks.

-now, we can notice a declining use in acute gout arthritis which require high dose and more replaced with NSAIDs as the first line drug.

***remember**: gout is mainly caused by hyperuricemia which is caused by excessive production of uric acid or inadequate excretion. So obviously, to fix this problem we should either blocking the production or enhance the excretion, the net effect is reduction in total body pool of uric acid.

🔷 Gout - urate-lowering therapy: its drug that prevents arthritis, tophi & stones by lowering total body pool of uric acid so it isn't indicated after first attack, actually it might worsen the attack if given immediately after the first attack, so we must wait some time before administrating it, this is because when we use these drugs this will result in urate crystals to be shed from the cartilage or joint into the joints space and increase the serum level of uric acid. this will flareup an acute inflammation.

1- Drugs That Block Production of Uric Acid--->

1. Allopurinol (Zyloprim™)

- inhibitor of xanthine oxidase which catalyzes hypoxanthine to xanthine & xanthine to uric acid so it effectively blocks formation of uric acid.
- Administrated orally as tablets and found in two concentration (100 mg & 300 mg tablets)
- pregnancy category C, which is used in case of benefits overweighs the risk. It can interfere with the synthesis of uric acid in infants, affecting the purine metabolism and cause some risk to the fetus.

- usage indications:

• management of hyperuricemia of gout

• management of hyperuricemia associated with chemotherapy

• prevention of recurrent calcium oxalate kidney stones

-common reactions:

• diarrhea, nausea, abnormal liver tests

• acute attacks of gout

•rash and allergic skin reaction

• necrotizing fasciitis

• Bone marrow suppression

• Very rarely aplastic anemia

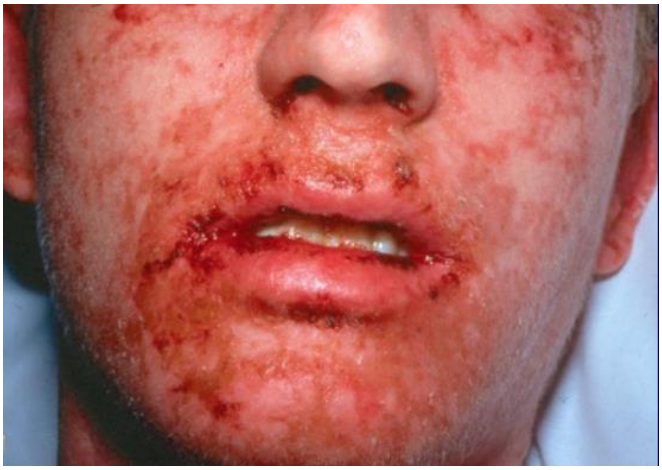
• Hepatic toxicity

• Interstitial nephritis

• allergic skin reaction that develops from skin rash into **maculopapular** lesions, can happen almost at 3% of the patients.

• Exfoliative dermatitis

• In very rare cases, Allopurinol can bind to the Lense and cause cataracts.



-serious reactions occurs by allopurinol is called steven Johnson syndrome or epidermal necrolysis. The symptoms are target skin lesions with mucous membrane erosions, epidermal necrosis with skin detachment, its very rare(<2%).

-Other serous reactions:

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

- Allopurinol hypersensitivity is an extremely serious problem that must be recognized early, the first sign is rash which can be developed into impaired renal function which also will progress to toxic epidermal necrolysis & death.

2. Febuxostat

recently approved by FDA in 2009, structurally different from allopurinol but act as the same mechanism as xanthine oxidase inhibitor. It reduces the amount of urate acid to <6.0 mg/dl which is the thing we aim for, for about 94% of people. It has minimal adverse effects comparing to allopurinol.

- adverse effects:

- Diarrhea
- headache
- Nausea

But it seems to be more tolerated for those who have sensitivity or intolerance to allopurinol, so it is a good alternative for allopurinol.

3. PEGLOTICASE

The newest found urate lowering therapy drug, recently approved by FDA 2010 for the treatment of refractory chronic gout (doesn't respond to any other treatment). It's a recombinant mammalian uricase that covalently binds to methoxy polyethylene glycol MPEG. This drug is recombinant form of enzyme urates that found in pig or porcine.

*remember that the drug name comes from the chemical compound (PEG) not pig the animal. The addition of pig or porcine enzyme and PEG is to increase the half-life of the drug.

-it helps by lowering the immune response for this this enzyme (that comes from animal source not human), the addition of polyethylene glycol is decreasing the antigenicity for this enzyme.

-administrated IV and works fast within the first (24-72) hours to reach its peak concentration. It stays in the body for (6-13) days, usually the clearance of this body is by antibody response.

-adverse effects:

- Infusion reaction
- Flare up of the gout, especially During the first 3 months of treatment)
- Nephrolithiasis (kidney stones)
- Arthralgia
- Muscle pain and spam
- Headache
- Anemia
- Nausea
- Frequent sides effects including respiratory tract infection,
- Peripheral edema
- Diarrhea
- Urinary tract infection

‼️This drug must be avoided with patients who suffer from glucose-6-phosphate dehydrogenase deficiency because of the production of hydrogen peroxide by the enzyme uricase.

2- Drugs That Enhance Excretion of Uric Acid-->

1. Uricosuric therapy like probenecid:

These drugs block tubular reabsorption of uric acid and can enhance urine uric acid excretion, this will increase uric acid level in urine and decreases serum uric acid level.

These agents are moderately effective, mainly used for tophaceous gout and frequent gout attack treatment.

‼️ **contraindication:** not used in patients with renal disease, patients with history of nephrolithiasis and who excrete huge amount of uric acid. Its less effective in elderly patients because they usually have deteriorated kidney function.

-side effects are mild like GI irritation.

💡 how I choose the best urate-lowering drug?

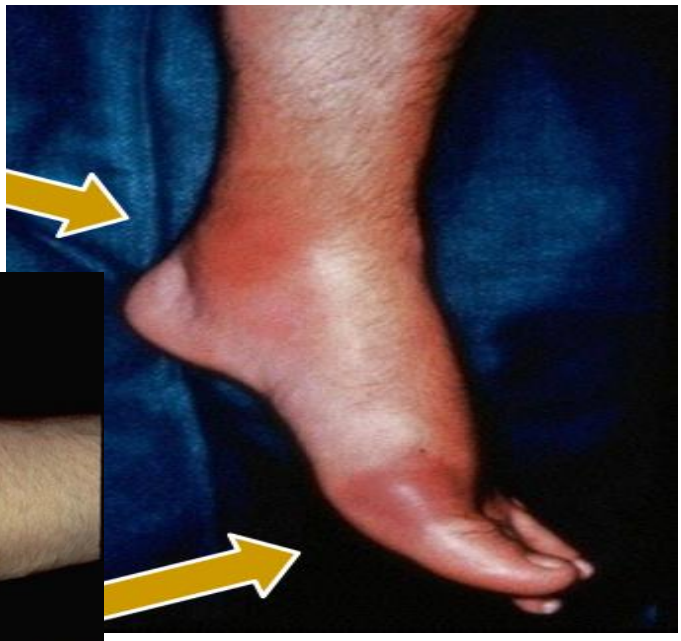
excessive production of uric acid ---> use xanthine oxidase inhibitor as allopurinol

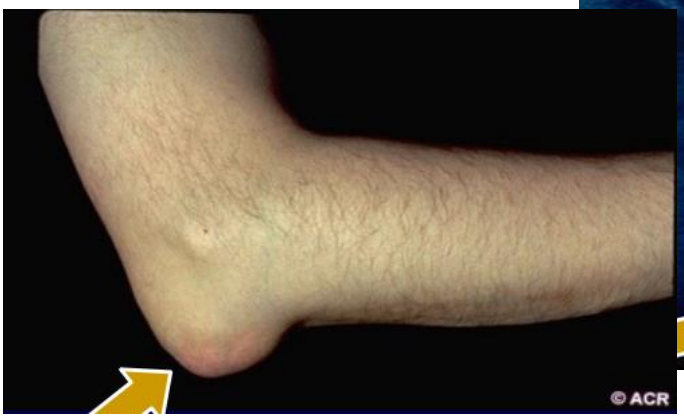
inadequate excretion--> use uricosuric agent such as probenecid

🔎 Case Presentation

55 y/o male came to the hospital complaining about pain in his big toe & ankle 12 hours ago, he went to bed last night feeling fine but in the morning felt as if he had broken toe. The past medical history (PMH) of similar problems in right ankle & left wrist.

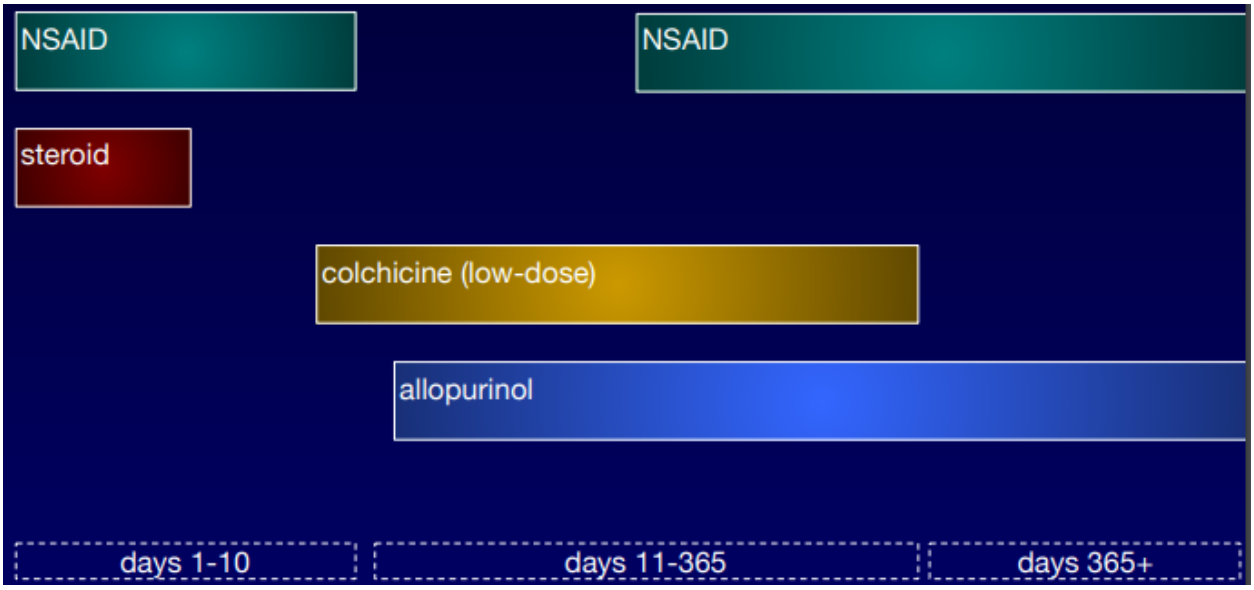
*this is acute synovitis, ankle & first MTP joints (metatarsophalangeal articulations) which are the joints between the metatarsal bones of the foot and the proximal





** patient presented with acute olecranon bursitis, which is inflammation of the fluid-filled sac (bursa) that lies between a tendon and skin, or between a tendon and bone.

Case presentation – therapy



The treatment starts with NSAID which is the first line treatment, we can also give the patient steroid and this last for about (1-10 days). Before we stop the NSAID we can give low doses of colchicine as a maintenance therapy to prevent any future attack of this case. Again, we can't give allopurinol at the first attack so we wait a period and continuo with colchicine and NSAID, then we stop NSAID and

give allopurinol to the patient as a maintenance of low uric acid level in the serum. After the attack is subsided, we maintain the patient on colchicine and allopurinol, although nowadays colchicine isn't recommended because its numerous side effects if we have flareup again we can give the patient NSAID in that period.

We have another group of drugs to mention:

- Interleukin 1 receptor antagonist--> Anakinra, Canakinumab and Rilonacept. Used to treat rheumatoid arthritis and currently for gout these drugs target IL-1 pathway thus, inhibiting the inflammation. We use them when patient doesn’t response to NSAID and colchicine.\
- Glucocorticotiods--> like Prednisone, used during acute gouty arthritis attack. Can be administered orally, Intra-articular and Subcutaneous, this depends on the degree of pain, inflammation and the degree of acute attack.

واسألك كلمة الحق في الرضا والغضب