PHARMACOLOGY

Lecture 5: treatment of gout

OBJECTIVES:

- Describe drug and non drug treatment of gout
- Identify the mechanism of action of drugs used for treatment of gout
- Outline the stages of gout and the therapeutic objectives in each stage
- Classify drugs used for treatment of gout
- Study in detail the pharmacology of drugs used for treatment of gout

Epidemiology of gout

- Prevalence of hyperuricemia 5%
- Prevalence of gout 0.2% .
  not everyone with hyperuricemia develops gout
- Male to female ratio 10:1

PHARMACOLOGY
435

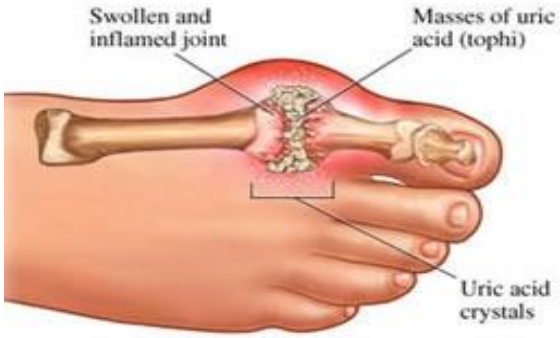
Before studying this lecture, we advise you to study lecture4 in biochemistry “purine degradation-gout”, And lecture4 in pathology “arthritis”.

- Important.
- Extra notes.

Gout

❖ What is gout?

Gout is usually characterized by recurrent attacks **of acute inflammatory arthritis** with severe sudden attacks of pain, in addition to red, tender, hot and swollen joints.

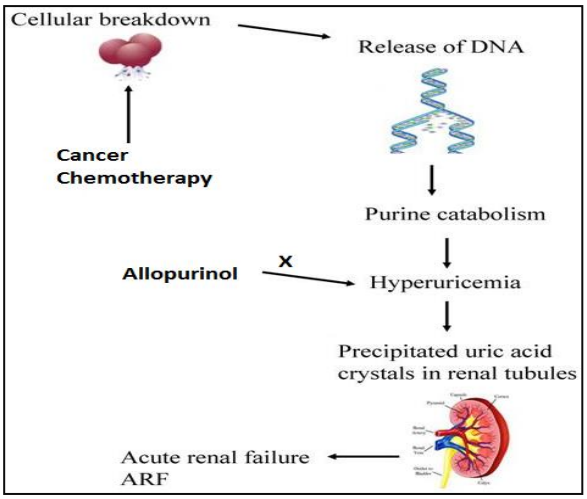


❖ Pathophysiology:

- Uric acid is a waste product formed from the breakdown of purines into xanthine, xanthine is then oxidized into uric acid by **Xanthine oxidase** .
- Unbalance between urate produced and urate excreted leads to deposits of **monosodium urate crystals** (MSU) in articular, periarticular, and subcutaneous tissues, which initiate an inflammatory response, eventually causing gout.
- Frequently, gout **flares up** following rich meals and alcohol consumption, in the middle of the night.

❖ Gout can be divided to:

- **Primary gout**: hereditary error of purine metabolism.
- **Secondary gout**: drugs that inhibit uric acid excretion or increase rate of cell death* or another acquired disorder.
  * cell death → breakdown of DNA → increased amounts of purine → uric acid accumulation (e.g. chemotherapy)



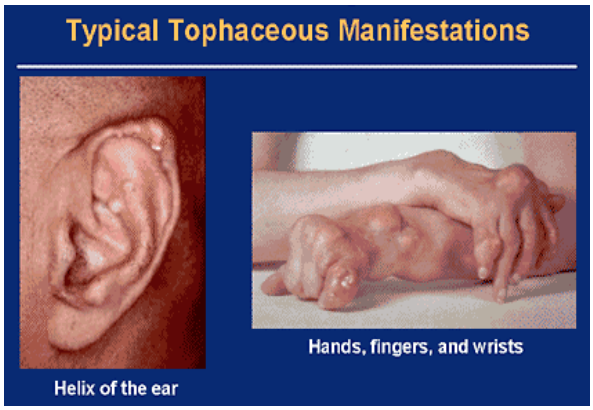
NOTE: Only 30% of uric acid is obtained dietary (e.g. from meat), the rest 70% is obtained by catabolism of purine in the body.

video: gout

Stages of gout

❖ Stages of gout		Characteristics	Management
Stage 1:	Asymptomatic hyperuricemia Hyper= increased Uric= urate Emia= in blood	Elevated serum urate with no clinical manifestations of gout	**Urate should be reduced to Saturation level** (no more than 6 mg/dl). If not managed, hyperuricemia causes hypertension, CV disease, strokes, renal disease, metabolic disorders (obesity), and of course, gout.
Stage 2:	Acute flares	Acute inflammation in joint caused by free urate crystals	Terminate the attack, mostly by anti-inflammatory drugs.
Stage 3:	Intercritical gout	The intervals between acute flares	Prevent recurrent attacks
Stage 4:	Advanced gout	Long-term gout complications	Prevent complications and lower serum uric acid

❖ Untreated gout may lead to:



1. Tophaceous (masses of Monosodium Urate crystals (MSU) in cartilage & joints, and sometimes in Subcutaneous tissue).
2. Nephrolithiasis (uric acid is 70% excreted by the kidney, sometimes it precipitate causing renal stones).
3. Urate nephropathy. **(renal insufficiency that is caused by high levels of uric acid in the urine (hyperuricosuria)**

YouTube Hyperuricemia ... A closer look

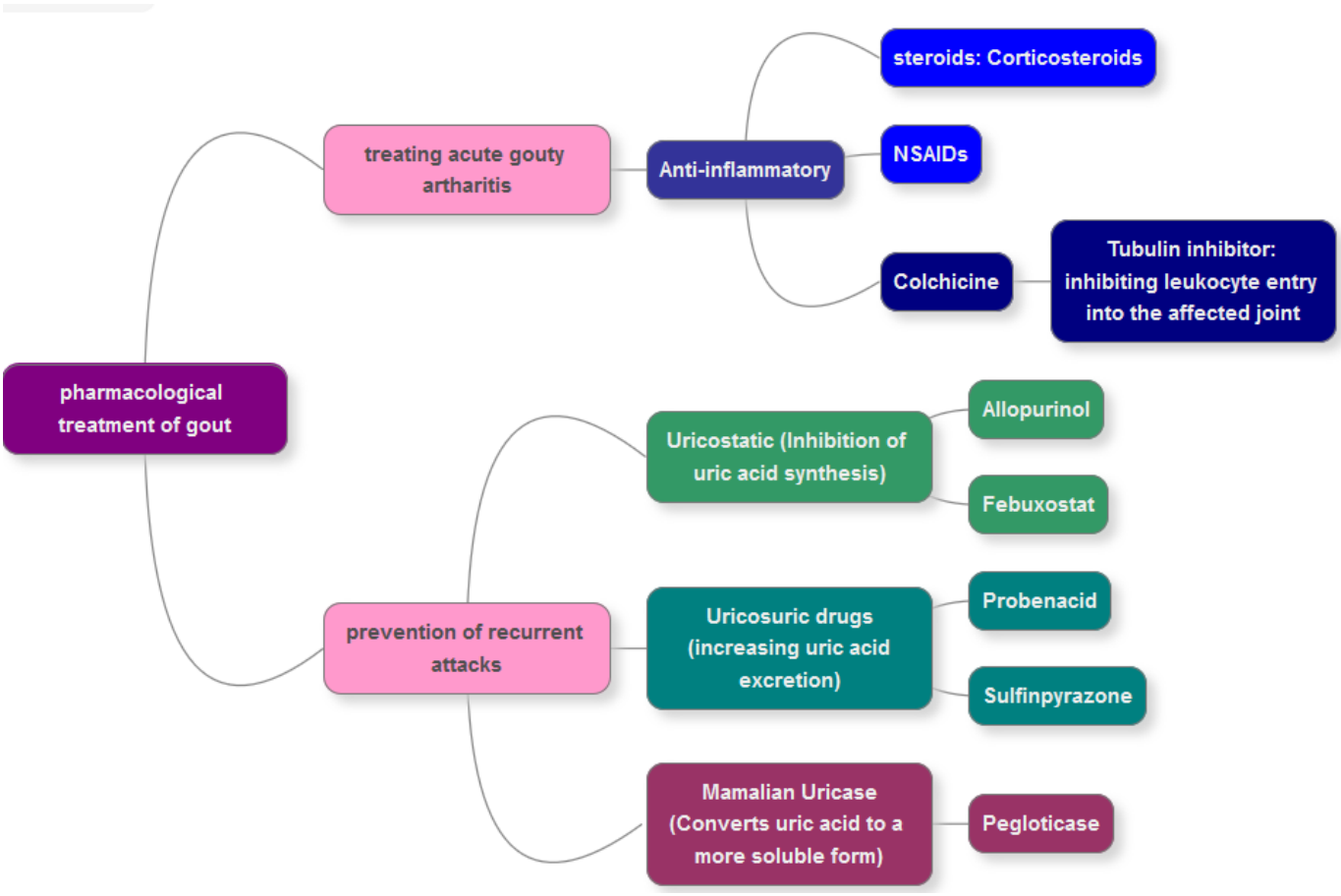
Treatment of gout :

1. Non-pharmacological treatment of gout, with :

Lifestyle modifications : Loss of weight , Exercise, Smoking cessation, And Diet control:

- Drink plenty of fluids (water)
- Choose low-fat or free-fat dairy products, reduce saturated-fat consumption.
- Eat complex carbohydrates
- Limit purine-rich foods, such as: fish ,meat, poultry «الدواجن» .
- Avoid eatable sweetened with high fructose corn syrup and alcohol

2. Pharmacological treatment of gout, with :



Treatment of acute gouty arthritis:

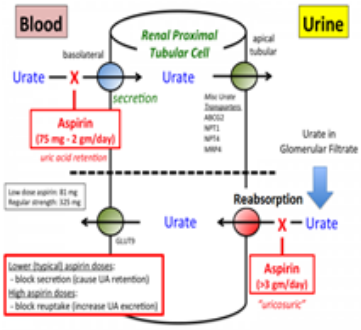
Pharmacological treatment of gout:
Treatment of acute gouty arthritis

1-NSAIDS (e.g. large doses of aspirin, diclofenac, celecoxib)

- Most commonly used first-line treatment
- Head-to-head studies* show few differences between drugs
  *Head-to-head studies— A direct comparison in a clinical trial between two or more medicines.
- Full doses of NSAID should be initiated immediately and tapered after resolution of symptoms.
- **NSAIDs should be avoided in these cases (Contraindications):**
  - G-I ulcer, Bleeding or perforation
  - Renal insufficiency, Heart failure
  - Use of oral anticoagulant

Recall: lecture 2 NSAIDs - ASPIRIN

Adverse effect of aspirin in low dose



- **Acute gouty arthritis:**
- SMALL dose of Aspirin:
  Blocks secretion of urate to urine, leading to its accumulation in blood CAUSEING Gout.
- LARGE dose of Aspirin:
  Blocks reuptake of urate and leads to its excretion in urine CURING Gout.

2- STEROIDS :

- **Corticosteroids** are a good **alternative** drugs for NSAIDs when they are not tolerated (The contraindications mentioned above) , such as elderly people, patients with kidney or hepatic impairment, IHD (Ischemic Heart Disease), PUD (Peptic Ulcer Disease).
- Studies showed **equal Efficacy** between steroidal and non steroidal drugs if the steroidal drugs used for **a short period**. (they cause many adverse effects with chronic use) .
- It can be given orally, intravenously, Intramuscularly **or Intra-articularly** (by injection directly into the joint. This is very effective when only one or two joints are affected, not in systemic cases).

Treatment of acute gouty arthritis:

3- Colchicine:

Colchicine is a Natural alkaloid product, obtained from **autumn crocus.**

❖ Major Characteristics :

It does not reduce uric acid production, increase uric acid excretion, and is not analgesic (painkiller).
Thus has to be taken with drugs reducing urate levels.

❖ Mechanism of Action..

Colchicine will Bind to microtubules in neutrophils, therefore inhibit **cell division.** Because microtubules are one of the major components of the cytoskeleton, and function in many processes, including structural support, intracellular transport, and DNA segregation (mitosis).
It also inhibits **chemotactic factors** (migration of leukocyte to the affected area), **inflammasomes & IL-1 production (inflammatory mediators).**

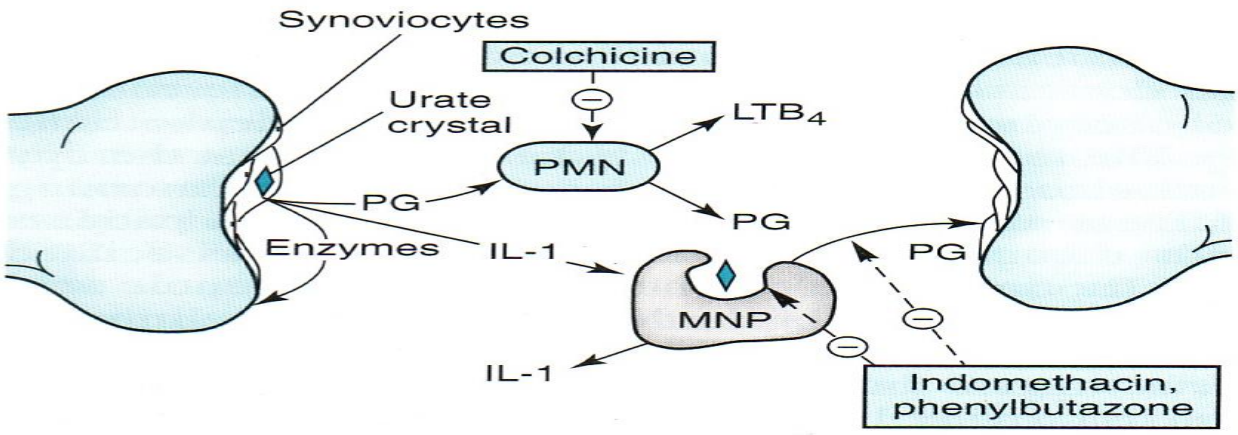


Figure 36–5. Pathophysiologic events in a gouty joint. Synoviocytes phagocytose urate crystals and then secrete inflammatory mediators, which attract and activate polymorphonuclear leukocytes (PMN) and mononuclear phagocytes (MNP) (macrophages). Drugs active in gout inhibit crystal phagocytosis and polymorphonuclear leukocyte and macrophage release of inflammatory mediators. (PG, prostaglandin; IL-1, interleukin-1; LTB4, leukotriene B4.)

Treatment of acute gouty arthritis:

3- Colchicine (cont.) :

❖Pharmacokinetics :

- Given **orally**, rapidly absorption from the GI tract (It is rarely given Parenterally because it causes **Bone Marrow Suppression)**.
- Reaches peak plasma levels within 2 hours
- Drug undergo enterohepatic recycling (back into systemic blood circulation) and is **excreted unchanged in the feces or urine.**

❖ Contraindications:

We should not use it when the kidney function is **Impaired** :
creatinine clearance is a test for renal function, so if the creatinine clearance is less than 50 mL/min, we should avoid colchicine. (normal = 120 mL/min)

❖ Clinical uses :

1. Treatment of gout flares (acute gout attacks).
2. Prophylaxis of gout flares. (Prophylaxis «الوقاية»: the prevention of disease or control of its possible spread)
3. Treatment of Mediterranean fever (an inflammatory disorder that causes recurrent fevers and painful inflammation of abdomen, lungs and joints)

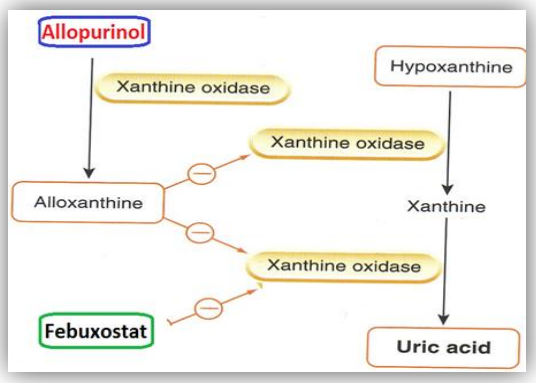
❖ Adverse drug reactions (side effects):

- **Diarrhea**, sometimes **severe**, which results in **Dehydration**.
- Nausea, Vomiting and Abdominal cramps (المغص)
- **Bone marrow depression** (lowest point of colchicine-induced bone marrow suppression occurs a week after the drug administration)
- Cardiac toxicity ,Arrhythmia
- Vascular collapse (cardiovascular collapse: Sudden loss of blood flow to the brain and other organs)
- Hepatotoxicity, since it is **metabolized** in liver.
- **Alopecia** (loss of hair)

Prevention of gout recurrent attacks:

1. Uricostatics:

- They act by **inhibiting xanthine oxidase** which catalyzes the oxidation of xanthine into uric acid (also the oxidation of hypoxanthine to xanthine).
- By doing so, they reduce production of uric acid.
- They include **Febuxostat & Allopurinol**



❖ Febuxotat :

Overview:

- **Oral** specific xanthine oxidase inhibitor
- Indicated for the **chronic management of hyperuricemia** in patients with gout (as it reduces serum uric acid levels)
- Chemically distinct from allo**purin**ol (non **purine**)
- **can be used in patients with renal disease**
- more efficacious than Allopurinol in reducing uric acid levels.

Pharmacokinetics:

- Given **orally** once daily, well absorbed(85%)
- Metabolized in **liver** , mainly conjugated to **glucuronic acid**
- Given to patients who do **not tolerate allopurinol**
- 99% protein bound
- t½ = 8 hours

ADRS:

- Increase number of **gout attacks** during the first few months of treatment. (sometimes during treatment of gout, levels of urate fluctuate «تتقلب», causing increased amounts and sudden gouty flares)
- Increase level of liver enzymes
- Nausea, Diarrhea, Headache
- **Numbness** of arm or leg

Prevention of gout recurrent attacks:

❖ Allopurinol

Clinical uses

-Management of **hyperuricemia** of gout, especially if associated with chemotherapy
-Prevention of recurrent **calcium oxalate kidney stones**, **Uric acid stones, or nephropathy**
-severe **tophaceous** deposits (uric acid deposits in tissues)
-It is a drug of choice in patients **with both gout & ischemic heart disease**
-Allopurinol has a **cardioprotective** effect.

Pharmacokinetics :

- Absorption 70%
- Protein binding negligible (only 5%).
- Hepatic metabolism. 70% is metabolized **by xanthine oxidase** into the active metabolite **alloxanthine (oxyourinol)**.

Note that **xanthine oxidase metabolizes allopurinol to produce alloxanthine. Then alloxanthine inhibits xanthine oxidase.**

- Oxypurinol is eliminated unchanged in urine.

ADRS

- Diarrhea, nausea, abnormal liver tests.
- Acute attacks of gout (reason is mentioned in Febuxotat)
- **Allopurinol Hypersensitivity Syndrome:** Fever, rash, hepatotoxicity, marrow suppression, vasculitis **toxic epidermal necrolysis.** (TEN) is a dermatologic disorder characterized by erythema, necrosis, and bullous **detachment** of the **epidermis** and mucous membranes, resulting in exfoliation and possible sepsis and/or death.
- DRESS syndrome (**D**rug **R**eaction (rash) with **E**osinophilia and **S**ystemic **S**ymptoms)

Eosinophilia: an increase in the number of eosinophils in the blood, occurring in response to some allergens, drugs, and parasites.

- 20% mortality rate

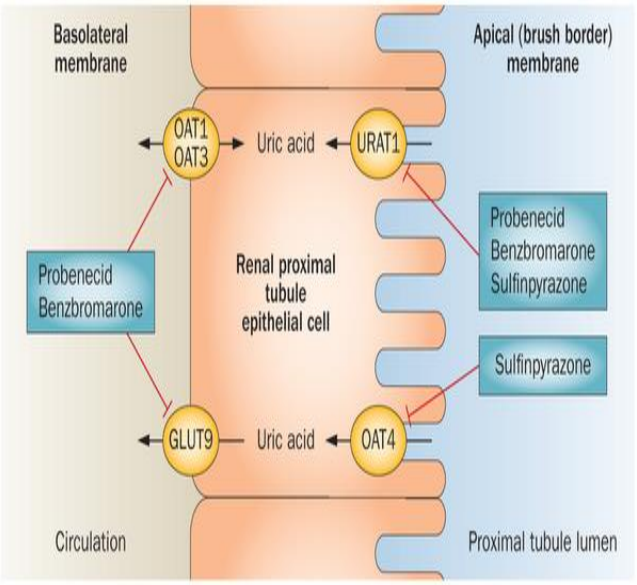
Drug Interactions

- Inhibits metabolism of Warfarin & dicumarol (anticoagulants)
- Reduce the metabolism of 6-mercaptopurine and azathioprine (anti-cancer drugs)
- With ampicillin : Increases frequency of skin rash

Xanthine oxidase metabolizes two things:
1st : uric acid . so if we inhibit xanthine oxidase → there is no accumulation of uric acid so there is no gout..
2nd : anticancer drugs, so if we inhibit it → the toxicity of the anticancer drugs will increase ..
So if we want to give allopurinol and anticancer drugs at the same time we have to reduce the dose of one of them.

Prevention of gout recurrent attacks:

2. Uricosuric drugs :



Mechanism of Uricosuric drugs:

Blocks tubular reabsorption of uric acid
& enhances uric acid excretion in urine.
Thus Control hyperuricemia and prevent tophus formation
They inhibit:

1. Urate Transporters (URAT) in the apical membrane of the proximal tubule.
   Which helps in reabsorption of urate from urine to the blood.

When inhibited, ↑urate in urine

2. organic acid transporter(OAT), which mediates excretion of drugs from the plasma to the urine .

When inhibited, ↑ penicillin in plasma.
(drug interaction between penicillin and uricosurics)

Uricosuric drugs

1. Probenecid
(moderately effective)

ADRs:
GIT upset
Exacerbation of **acute** attack
Risk of uric acid stone
Allergic rash

Contraindications:
History of nephrolithiasis
Existing renal disease
Recent **acute** gout
Less effective in elderly patients

2. Sulfinpyrazol

ADRs: can aggravate peptic ulcer disease and Increase risk of nephrolithiasis

Drug interaction:
- Aspirin reduces efficacy of sulfinpyrazone
- Enhance the action of certain anti-diabetic drugs

Contraindications: patients with renal disease

Prevention of gout recurrent attacks:

3. Recombinant mammalian uricase (pegloticase):

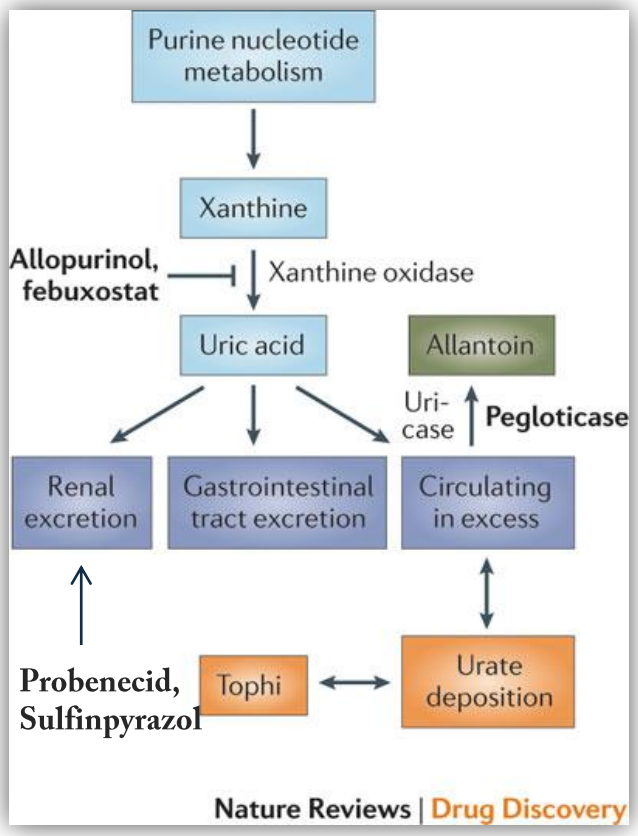
❖ **Recombinant mammalian uricase** is a uric acid specific enzyme (human's cannot further degrade uric acid since they don't have the enzymes which do that, but other animals have those enzymes. Those enzymes can be used as drugs in certain ways (recombination…))

- It enzymatically Converts uric acid to **allantoin**, which is more soluble and readily excreted in the urine.
- When Given by I.V, they produce peak **decline** in uric acid level within 24-72 hours

❖ **Used** for the treatment of chronic gout in adult patients refractory (resistant) to conventional urate-lowering therapy (uricosuric and uricostatic drugs) .

❖ **ADRS**

1. Infusion reactions (drugs administered by I.V may cause an infusion reaction)
2. Anaphylaxis (more aggressive pattern of hypersensitivity)
3. **Gout flare** (due to fluctuation in urate levels during treatment)
4. Arthralgia (arthra=joint, algia= pain)
5. **Muscle spasm.**
6. Nephrolithiasis (kidney stone)



Anti-Gout Drugs Mnemonics

Summery of drugs in gout

Treatment of acute gouty arthritis

Drug	Mechanism	Contraindications, ADRs , uses
NSAIDs	most commonly used **first-line treatment** Full doses of NSAID should be initiated immediately and tapered after resolution of symptoms .	ADRs GI ulcer, Bleeding or perforation, Renal insufficiency, Heart failure, Use of oral anticoagulant.
Steroids (Corticosteroid)	Pharmacokinetics It can be given orally, IV, IM, or Intra-articularly . Has equal Efficacy with NSAIDs if the steroidal drugs used for a short period.	Used when NSAIDs are contraindicated or not tolerated. such as elderly people, patients with kidney or hepatic impairment, IHD, PUD.
Colchicine	Natural product, obtained from autumn crocus. It was the first line of treatment of gout, but because it causes severe diarrhea, it limits its usage. It inhibits cell division, chemotactic factors, inflamosomes & IL-1 production. Pharmacokinetics: Given **orally**, Reaches peak plasma levels within 2 hours, Drug undergo enterohepatic recycling and is **excreted unchanged in the feces or urine.**	Uses: Treatment of gout flares Prophylaxis of gout flares. Treatment of Mediterranean fever Contraindications: renal impairment ADRs Diarrhea, Nausea, Vomiting, Alopecia, Abdominal cramps , Dehydration Bone marrow depression, Cardiac toxicity ,Arrhythmia Vascular collapse Hepatotoxicity

Prevention of gout recurrent attacks

Drug	Overview and Clinical uses	ADRS	Pharmacokinetics
Uricostatic drugs (inhibit uric acid synthesis by **inhibiting xanthine oxidase**)			
Allopurinol (purine)	• Management of hyperuricemia of gout (especially associated with chemotherapy) • Uric acid stones or nephropathy • It is a drug of choice in patients with both gout & ischemic heart disease • Severe tophaceous deposits • Prevention of recurrent calcium oxalate kidney stones • has a cardioprotective effect.	• Diarrhea, nausea, abnormal liver tests • Acute attacks of gout • Fever, rash, toxic epidermal necrolysis, hepatotoxicity, marrow suppression, vasculitis • **DRESS** syndrome • 20% mortality rate	**Drug Interactions** • ↑Warfarin , dicumarol & 6-mercaptopurine and azathioprine • With ampicillin : Increases frequency of skin rash • Absorption 70% • Protein binding negligible ,5%. • Hepatic metabolism, 70% metabolized by xanthine oxidase into **alloxanthine (oxyourinol) which is pharmacologically active**. eliminated unchanged in urine.
Febuxostat (non purine) more efficacious	• Indicated for the chronic management of hyperuricemia in patients with gout • can be used in patients with renal disease	• ↑ gout attacks during the first few months of treatment • ↑ liver enzymes • Nausea, Diarrhea • Headache • Numbness of arm or leg	• Given orally once daily, well absorbed(85%) • Metabolized in liver , mainly conjugated to glucuronic acid • Given to patients who do not tolerate allopurinol. • 99% protein bound • t½ = 8h

Uricosuric drugs (increase uric acid excretion by Blocking tubular reabsorption)

Clinical use: Control hyperuricemia and prevent tophus formation

Probenacid	ADRs: GIT upset, Exacerbation of acute attack, nephrolithiasis, Allergic rash.	Contraindications: History of nephrolithiasis, Recent acute gout, Existing renal disease, Less effective in elderly patients.
Sulfinpyrazone	ADRs can aggravate peptic ulcer disease Increase risk of nephrolithiasis. Not used in patients with renal disease	Drug Interactions: Aspirin reduces efficacy of sulfinpyrazone enhance the action of certain antidiabetic drugs.

Recombinant Mammalian uricase

pegloticase	Used for the treatment of chronic gout in adult patients refractory (resistant) to conventional urate-lowering therapy.	ADRs Infusion reactions, Anaphylaxis, Gout flare, Arthralgia, Muscle spasm, Nephrolithiasis	Pharmacokinetics Converts uric acid to allantoin, which is more soluble and readily excreted in the urine. When Given by I.V, they produce peak decline in uric acid level within 24-72 hours

QUIZ

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435