Drugs in Gout

Lecture no.5

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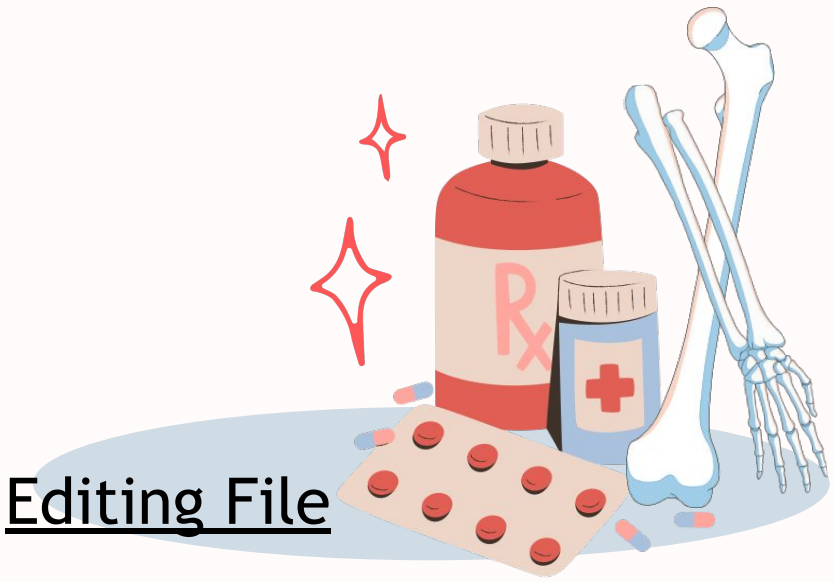

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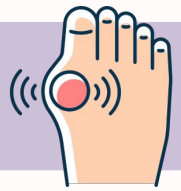
Objectives

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

★ You are highly recommended to first study biochemistry lecture “Purine Degradation & Gout” for complete understanding

Overview of Gout

Gout Disease



- It is usually characterized by recurrent attacks of acute inflammatory arthritis with red, tender, hot and swollen joints.
- Etiology of the inflammatory process: Sodium urate crystals are deposited in articular, periarticular, and subcutaneous tissues.

Epidemiology:

- Gout was historically known as the “disease of kings” or “rich man’s disease.” (bc. they ate a lot of meat)
- Prevalence of hyperuricemia 5% (not all patients with hyperuricemia have gout)
- Prevalence of gout 0.2% (of the 5% that have hyperuricemia)
- Male to female ratio 10:1

May be primary or secondary:

Primary	Secondary
Hereditary error of purine metabolism	Drugs (like small dose of aspirin) that inhibit uric acid excretion or increase the rate of cell death (chemotherapy drugs) or another acquired disorder

Distinct Stages of Gout

In most cases, diagnosis of gout is based on clinical presentation, which is quite characteristic: severe pain developing within hours, tenderness, warmth, swelling and erythema, e.g. in the first metatarsophalangeal or metacarpophalangeal joint.

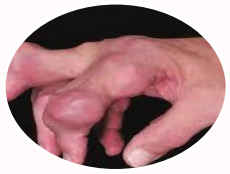
1- Asymptomatic Hyperuricemia	2- Acute Flares (Intermittent Gout)	3- Intercritical Gout	4- Chronic Gout (complication)
Elevated serum urate with no clinical manifestations of gout. Treat or not treat?	Acute inflammation in joint caused by the free crystals. **Management:** terminate the attack.	The intervals between acute flares. **Management:** prevent recurrent attacks.	Long-term gout complications. **Management:** -Prevent complications -Lower serum uric acid

Asymptomatic Hyperuricemia
>7 mg/dl (M)
>6 mg/dl (F)

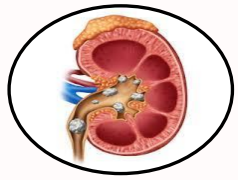
causes

- Hypertension.
- CV disease.
- Stroke.
- Renal disease.
- Metabolic syndrome.

Complications of Gout



Urate Nephropathy
(renal failure)



Osteoarthritis:
joint inflammation

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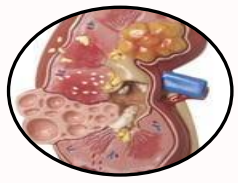
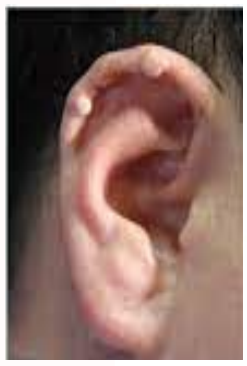
Tophaceous:
Masses of monosodium urate crystals in cartilage & joints.



Nephrolithiasis:
Renal stones.



Tophi

Osteoarthritis

Nephrolithiasis

- Cause: elevated uric acid levels
- hyperuricemia (above 7 mg/dl).
- Normal: the amount of uric acid produced (by the breakdown of purine bases) is the same as the amount excreted in urine. In hyperuricemia, increased production/decreased excretion results in raised levels of uric acid .
- Hyperuricemia may or may not cause GOUT.

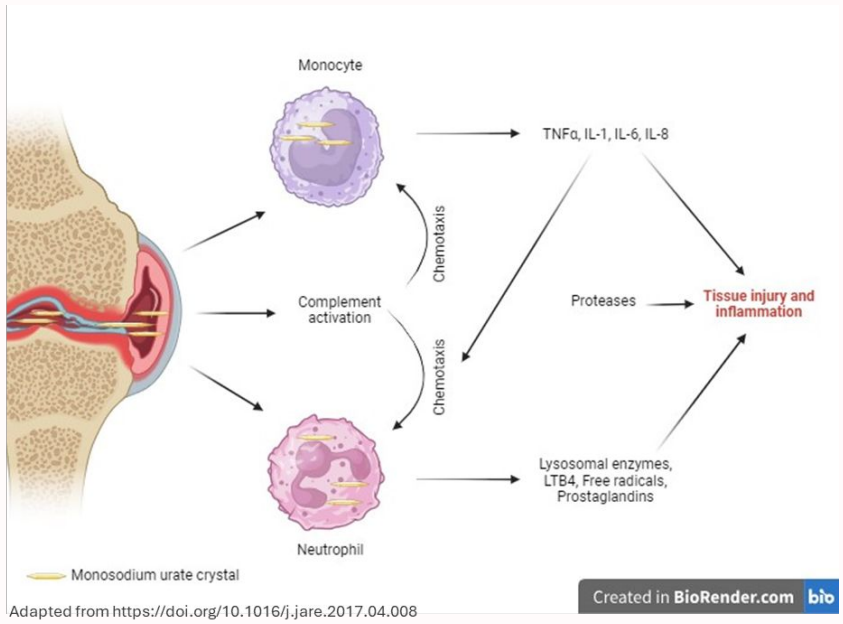
Tophaceous mass / Tophi: deposits of MSU (common sites are the helix of ear and big toe)

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. *Med435

- 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 after rich meals and alcohol consumption, and in the middle of the night.

443 note :
Two main reasons for gout:
1- increased uric acid synthesis 2- decreased uric acid excretion



Treatment of Gout

➔ **Non-pharmacological :**

Lifestyle modifications such as:

- Loss of weight
- Exercise
- Diet control
- Smoking cessation

➔ **Pharmacological :**

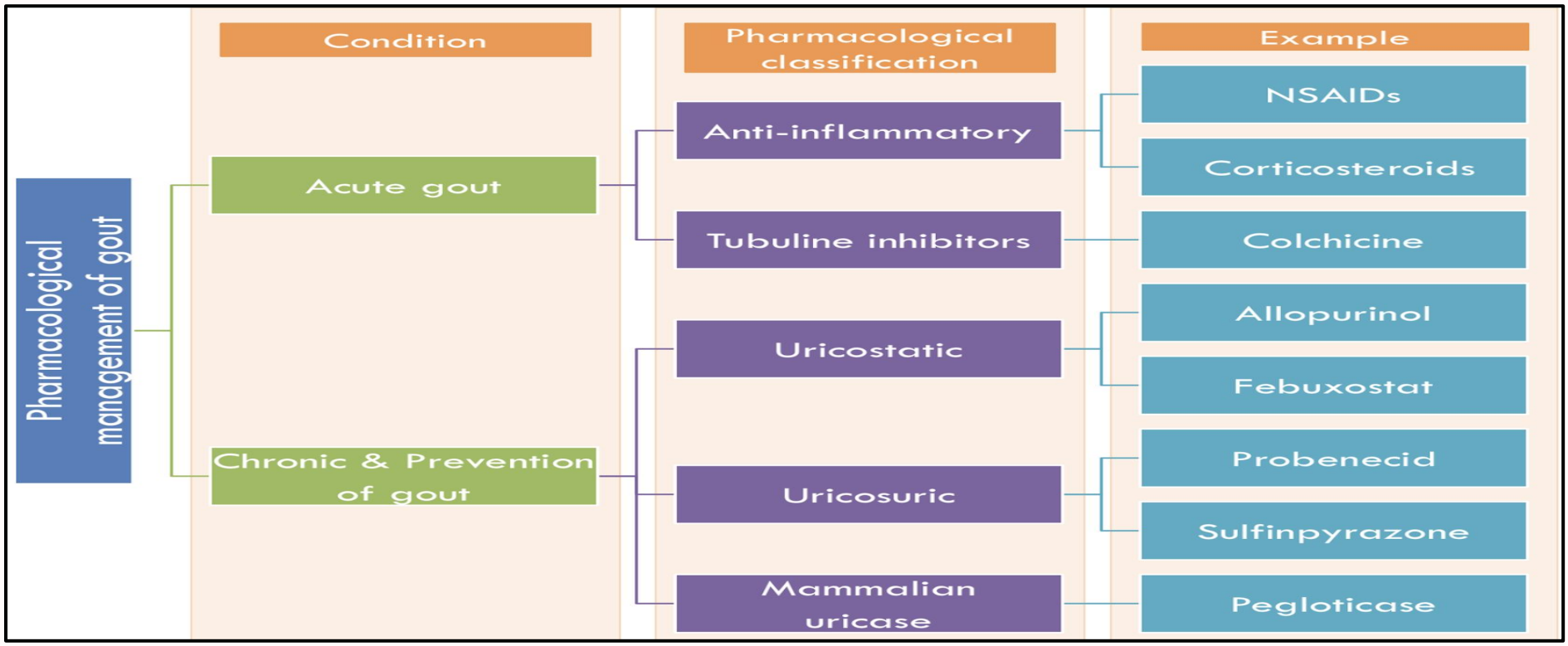
- Uricostatic
- Uricosuric
- Anti-inflammatory
- Tubulin inhibitors

Aim of Pharmacotherapy

Most therapeutic strategies for gout involve <u>lowering the uric acid level below the saturation point **(<6 mg/dL),**</u> thus preventing the deposition of urate crystals.

<u>This can be accomplished by:</u>

1. Interfering with uric acid synthesis with **Allopurinol, Febuxostat**.
2. Increasing uric acid excretion with **Probenecid** or **Sulfinpyrazone**.
3. Inhibiting leukocyte entry into the affected joint with **Colchicine**.
4. Administration of **NSAIDs**.



Drugs in Gout

Acute Gouty Arthritis	Preventing Recurrent Attacks
A. Anti-inflammatory: (inhibits PGs) -NSAIDs -Corticosteroids	**A. Uricostatic:** Inhibits with uric acid synthesis - Allopurinol - Febuxostat
B. Tubulin inhibitors: Inhibits leukocyte entry into the affected joint - Colchicine	**B. Uricosuric:** Increases uric acid excretion - Probenecid - Sulfinpyrazone
	C. Mammalian Uricase: - Pegloticase

in next slide

TEAM 443 NOTE:
What are the drugs that are used in acute attacks ?
What are the drugs that used in prevention of recurrent attack?

*الuricosuric and uricooststatic كلهم راح يسببون acute gout attack لكن ال uricosuric تكون بشكل أقوى لذلك ما يفضل أستخدمها بعد ال acute attack مباشرة، أستخدم uricostatic

Acute Gouty Arthritis : A.Anti-inflammatory

Corticosteroids

Indications:

★ **Alternatives where NSAIDs cannot be used:**

• In elderly people, patients with hepatic impairment, peptic ulcer disease,ischemic heart disease, and hypersensitivity to NSAIDs.

★ **Alternatives where colchicine cannot be used:**

•Renal or hepatic impairment in patients receiving a p-gp inhibitor (e.g.amiodarone, clarithromycin) in the last 14 days.

• Renal or hepatic impairment in patients receiving an agent that strongly reduces CYP3A4 availability (e.g. Clarithromycin, Ketoconazole) in the last 14 days.

★ **Refractory gout cases.**

-Studies showed equal efficacy between corticosteroids and NSAIDs, with fewer side effects with short-term use of corticosteroids.

Caution:

• Heart failure
• Uncontrolled hypertension
• Glucose intolerance

Route of administration:

• Intra articularly (preferred route if one or two joints affected)
• Orally.
• Intramuscularly or intravenously.

NSAIDs

• NSAIDs are the most commonly used first-line treatment.

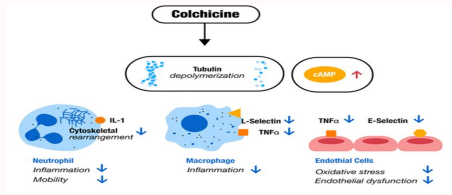
• Head-to-head studies show few differences between drugs.

• **Full doses** of NSAIDs should be initiated immediately and tapered after resolution of symptoms.

Contraindications:

• GI ulcer
• Bleeding or perforation
• Renal Insufficiency
• Heart failure
• Use of oral anticoagulants

Acute Gouty Arthritis : B. Tubulin Inhibitors (Colchicine)

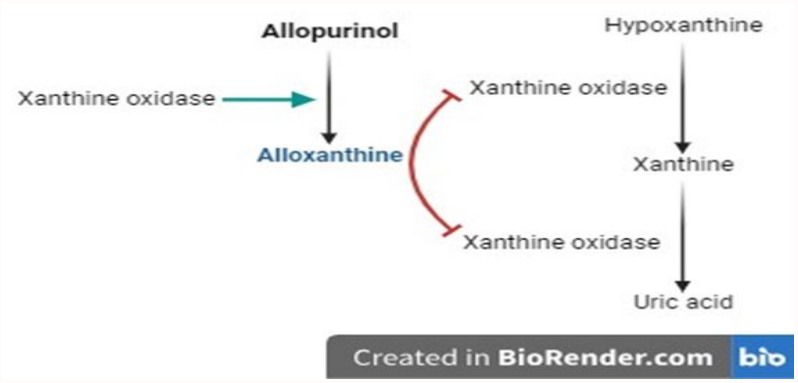
Overview	-Alkaloid obtained from autumn crocus. -Minimal effect on uric acid synthesis, excretion and is not analgesic.
Mechanism	-Binds to microtubules in neutrophils. -Inhibits cell division. -Inhibits chemotactic factors. -Inhibits inflammasome and IL-1 production. -Causes delayed wound healing. 
Pharmacokinetics	-Administered orally, rapidly absorbed from the GI tract. -Reaches peak plasma levels within 2 hours. -Recycled in the bile and is excreted unchanged in the faeces or urine.(can't be used for patients with liver or kidney problems or it can be used but after dose adjustments based on the class of the drug) -Use should be avoided in patients with a creatinine clearance of less than 50 ml/min
Clinical uses	-Treatment of gout flares. -Prophylaxis of gout flares. -Treatment of Familial Mediterranean Fever (FMF).
ADRs	-Diarrhea (sometimes severe)(most common), nausea and vomiting. -Abdominal cramps, Dehydration. -Bone marrow depression. -Cardiac toxicity, arrhythmia,vascular collapse. -Hepatotoxicity, alopecia.

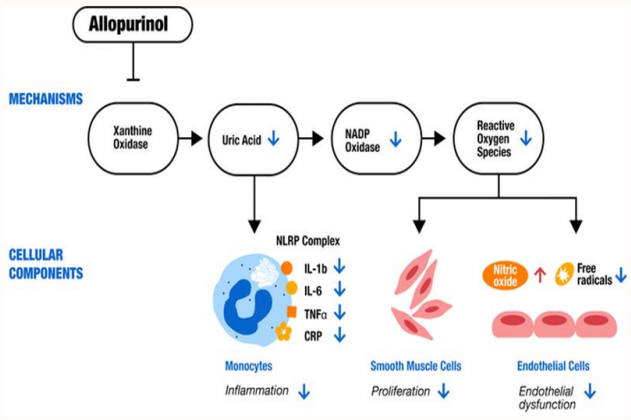
Prevention Of Recurrent Attacks

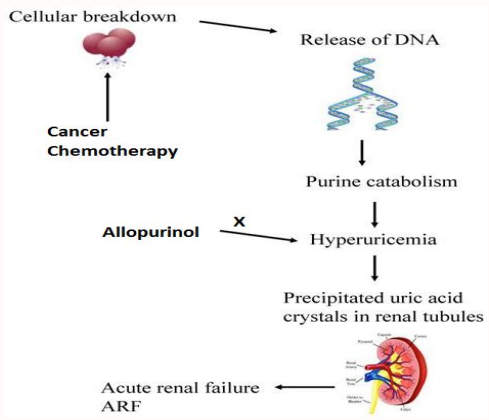
A. Uricostatics(Inhibitors of uric acid synthesis)

Inhibit uric acid synthesis via inhibition of xanthine oxidase (include: allopurinol & febuxostat). (in next slide)

• Allopurinol is metabolized by xanthine oxidase into alloxanthine which is pharmacologically active that inhibits xanthine oxidase.







B. Uricosurics(Increase uric acid secretion)

Include probenecid & sulfinpyrazone

Mechanism:

• Blocks tubular reabsorption of uric acid & enhances urine uric acid excretion.

• Probenecid inhibits Urate Transporters (URAT 1) in the apical membrane of the proximal tubule.

• It also inhibits organic acid transporter (OAT 1 & 3)→↑plasma concentration of penicillin.

• It inhibits glucose transporter 9.

• Sulfinpyrazone inhibits URAT1 & OAT4.

Effect:

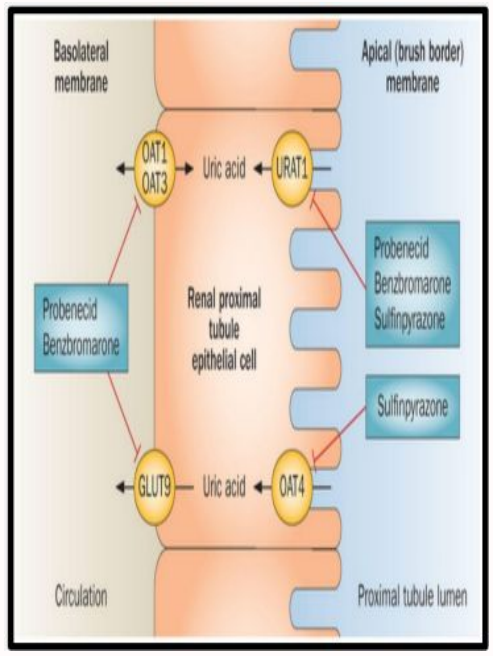
• Control hyperuricemia and prevent tophus formation

• Probenecid is moderately effective

• Increases risk of nephrolithiasis (kidney stones)

• Not used in patients with renal disease

• Some drugs reduce efficacy of uricosuric drugs (e.g. aspirin)



➔ Probenecid

ADRs:

• Exacerbation of acute attack.

• Risk of uric acid stone.

• GIT upset.

• Allergic rash.

Contraindications:

• History of nephrolithiasis.

• Recent acute gout.

• Existing renal disease.

• Less effective in elderly patients

➔ Sulfinpyrazone

ADRs:

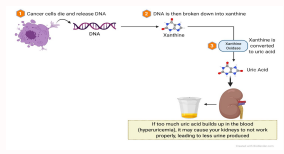
• Aggravates peptic ulcer disease

Drug Interactions:

• Aspirin reduces efficacy of sulfinpyrazone.

• Sulfinpyrazone enhance the action of certain anti-diabetic drugs.

1-Allopurinol

Pharmacokinetics	-Absorption: 70% -Protein binding: negligible (only 5%) -Hepatic metabolism: 70% converted to active metabolite (oxypurinol) -Oxypurinol is eliminated unchanged in urine
Mechanism	Metabolized by xanthine oxidase into the active metabolite alloxanthine (oxypurinol), which is pharmacologically active. The active metabolite inhibits the enzyme (Xanthine oxidase). Note that xanthine oxidase metabolizes allopurinol to produce alloxanthine. Then alloxanthine inhibits xanthine oxidase.
Clinical Uses	-Management of hyperuricemia of **GOUT** (Mainly). -Uric acid stones, or nephropathy. **- It is a drug of choice in patients with both gout & ischemic heart disease.** -Severe tophaceous deposits (uric acid deposits in tissues). -Management of hyperuricemia **associated with chemotherapy.** (when cells are destroyed, a lot of purine is diffused). -Prevention of recurrent calcium oxalate kidney stones, (which can cause acute renal failure) 
ADRs	-Diarrhea, nausea, abnormal liver tests. -Acute attacks of gout. -Fever, rash, toxic epidermal necrolysis, hepatotoxicity, marrow suppression, vasculitis. **-DRESS syndrome** (20% mortality rate): **D**rug **R**eaction, **E**osinophilia, **S**ystemic **S**ymptoms: skin rash, fever, lymphadenopathy, & inflammation of the liver, lung, and heart. -Allopurinol can cause: Allopurinol Hypersensitivity Syndrome, Toxic Epidermal Necrolysis and DRESS Syndrome as a result of its metabolite (Oxypurinol)
Drug Interactions	• Inhibits metabolism of warfarin & dicumarol (anticoagulants) Leading to a longer half-life which causes prolonged bleeding. • With ampicillin: Increases frequency of skin rash. • Reduce the metabolism of 6-mercaptopurine-azathioprine (anti-cancer drugs) 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. Med435* 

2- Febuxostat

Overview	- Oral specific xanthine oxidase inhibitor. - Chemically distinct from allopurinol (non-purine). - more efficacious than Allopurinol in reducing uric acid levels
Pharmacokinetics	- Administration: given orally once daily. - Absorption: well absorbed (85%). - Metabolism: in the liver-mainly conjugated to glucuronic acid. - Protein binding: 99% Protein bound. - Given to patients who do NOT tolerate allopurinol. - t½ = 8 hours.
Indications / clinical uses	- Management of hyperuricemia in patients with gout (as it reduces serum uric acid levels). - **Can be used in patients with renal disease.** - Given to patients who don't tolerate allopurinol
ADRs	- Increases frequency of gout attacks during the first few months of treatment. - Increases level of liver enzymes. - Nausea, Diarrhea - Headache. - Numbness of arm or leg.

C.Recombinant Mammalian Uricase (Pegloticase)

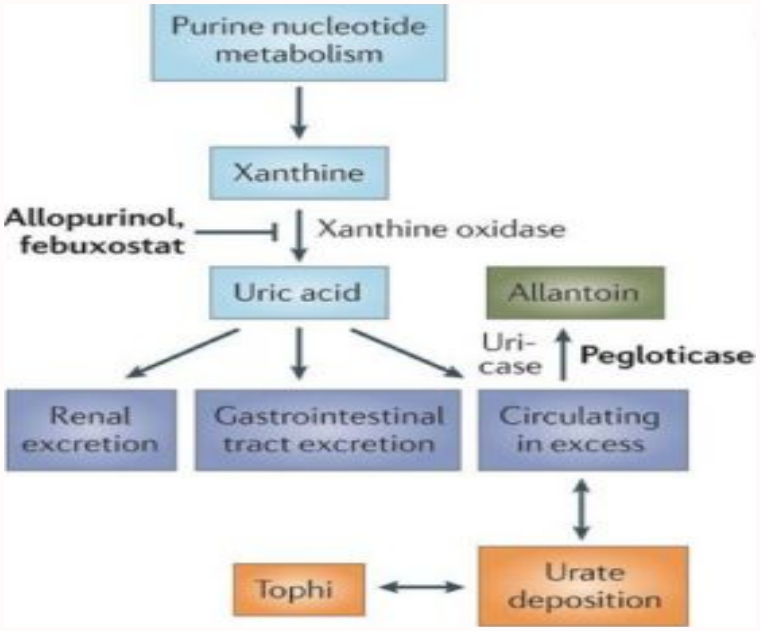
- It is a recombinant modified mammalian uricase enzyme
- Indication: Chronic refractory gout in adult
- P.K : Given I.V. peak decline in uric acid level within 24-72 hours.

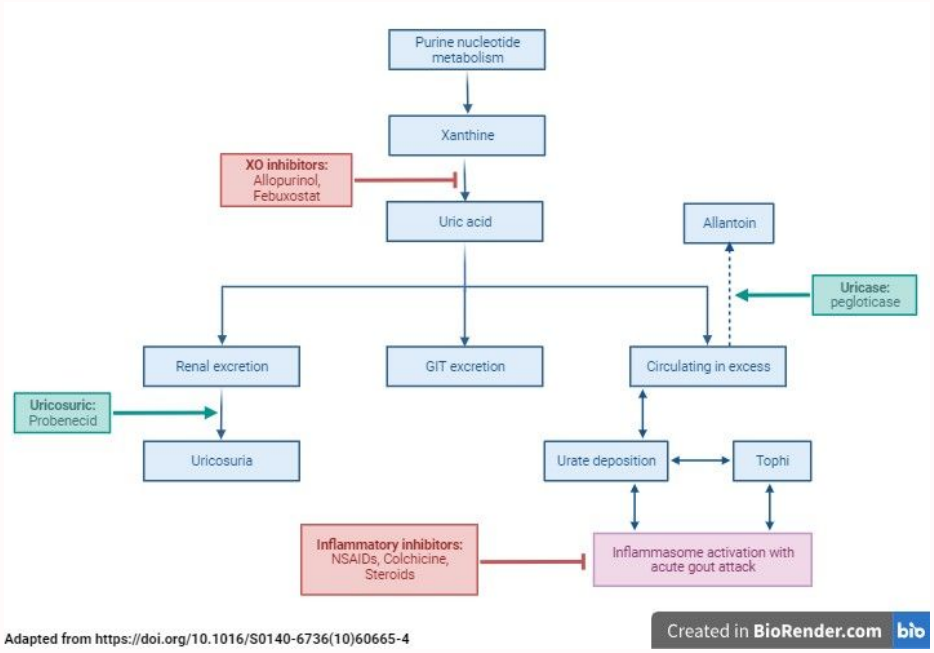
M.O.A:

- Enzymatically convert urate to allantoin, which is more soluble and readily excreted in the urine.

ADRs:

- Infusion reactions.
- Anaphylaxis.
- Gout flare.
- Arthralgia, muscle spasm.
- Nephrolithiasis.





MCQs

Q1. A patient suffers from gouty arthritis and ischemic heart disease. What is the drug of choice for his case?			
a) Allopurinol	b) Febuxostat	c) Colchicine	d) Probenecid

Q2. Which of the following converts uric acid to allantoin?			
a) Probenecid	b) Allopurinol	c) Pegloticase	d) Sulfinpyrazone

Q3. Allopurinol with Ampicillin causes ?			
a) Reduce metabolism	b)Increase metabolism	c) Skin rash	d) Bleeding

Q4. A 32 y.o. patient is diagnosed with chronic gout & refractory condition to gout drugs. The doctor decided a treatment plan that indicate the excretion of uric acid in a soluble form which is allantoin, a drug was administered and the uric acid levels peaked decline in only 2 days. Which drug was given?			
a) Allopurinol	b) Penicillin	c) Pegloticase	d) Probenecid

Q5.Which one is a uricostatic drug ?			
a)Colchicine	b)Allopurinol	c)Corticosteroids	d)NSAIDs

Answers:
1)a
2)c
3)c
4)c
5)b

SAQs

1 **What are the classifications of treatments for acute gout? and give an example for each .**

[anti-inflammatory]e.g. NSAIDs [Tubulin inhibitors]e.g. colchicine

2 **What are the complications of gout?**

slide 5

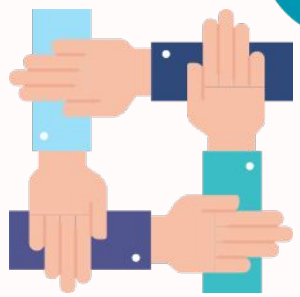
3 **What are the types of pharmacological managements of gout?**

1-acute 2- chronic and prevention

4 **What is used to treat refractory gout cases ?**

Corticosteroids

Team Leaders:



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