MED438
KING SAUD UNIVERSITY

pharmacology
Team 438

- Red : important
- Black : in male / female slides
- Pink : in female's slides only
- Blue : in male's slides only
- Green : Dr's notes
- Grey: Extra information, explanation

Editing File

LECTURE 5: DRUGS IN GOUT

NOTE:

In this lecture anything that's written in red or green is the female's Dr. notes
Anything written in purple is the male's Dr. notes

OBJECTIVES:

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

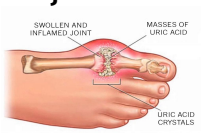
Overview of Gout

What causes gout?

Gout

definition

Gout is usually characterized by recurrent attacks of <u>acute inflammatory arthritis</u> with red, tender, hot and swollen joints.



Pathogenesis

Deposition of **sodium urate crystals** in articular, periarticular, and subcutaneous tissues. (not to confuse it with pseudogout which is characterized by deposits of calcium pyrophosphate)

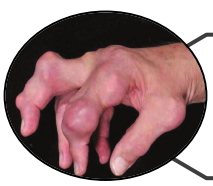
Types

Primary Gout (genetic): hereditary error of purine metabolism.

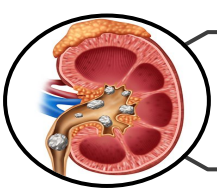
Secondary Gout (acquired): **drugs that inhibit uric acid excretion or increase rate of cell death e.g. chemotherapy or another acquired disorder.**

(Chemotherapy works by killing cells using cytotoxic agents, this causes the release of purines such as Adenine and Guanine, the end product of their catabolism is uric acid).

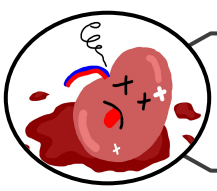
Untreated Gout leads to:



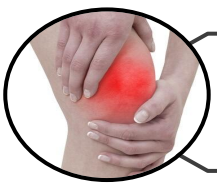
Tophaceous:
Masses of MSU crystals (Tofi) (Monosodium urate) in cartilages , joints , subcutaneous tissues .



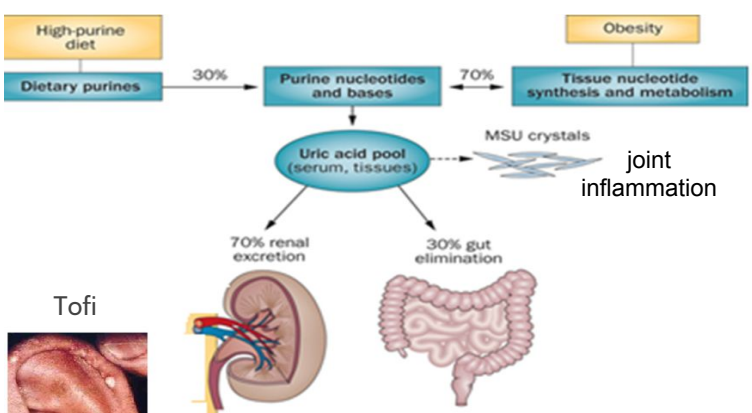
Nephrolithiasis:
Renal stones caused by the 70% Uric acid excreted by the kidney and 30% by gut elimination



Urate Nephropathy :
Renal failure caused by high levels of uric acid



Joint inflammation
and cardiovascular damage in advanced stages



Tofi

Nephrolithiasis

❖ Epidemiology :

Gout was historically known as "the disease of kings" or "rich man's disease."

- Prevalence of hyperuricemia 5% . Not all of them will develop the disease.
- Prevalence of gout 0.2%
- Male to female ratio 10:1

❖ Pathophysiology :

- gout is due to:

1- overproduction of uric acid (Uricostatic) 2- underexcretion (Uriocosuric)

- Urate crystals are initially phagocytosed by synoviocytes, which then release prostaglandins, lysosomal enzymes, and interleukin-1 (inflammatory mediators) which attracts and activates polymorphonuclear leukocytes (PMN) and mononuclear phagocytes (MNP) (macrophages). This is why we use NSAIDs.
- Attracted by these chemotactic mediators, polymorphonuclear leukocytes and mononuclear phagocytes migrate into the joint space and amplify the ongoing inflammatory process.
- In the later phases of the attack, increased numbers of mononuclear phagocytes (macrophages) appear, ingest the urate crystals, and release more inflammatory mediators

❖ Stages of gout:

1 Asymptomatic hyperuricemia

Elevated serum urate with no clinical manifestation of gout .

Treat or not to treat ?

2 Acute flares (intermittent gout)

Acute inflammation in joint caused by free urate crystals

Management: Terminate the attack.

(Symptoms start at this stage).

3 Intercritical Gout

The interval between acute flares

Management: prevent recurrent attack

4 chronic gout (complication)

Long-term gout complication

Management:

-Prevent complications

Tophi,deposition of crystals in kidney"

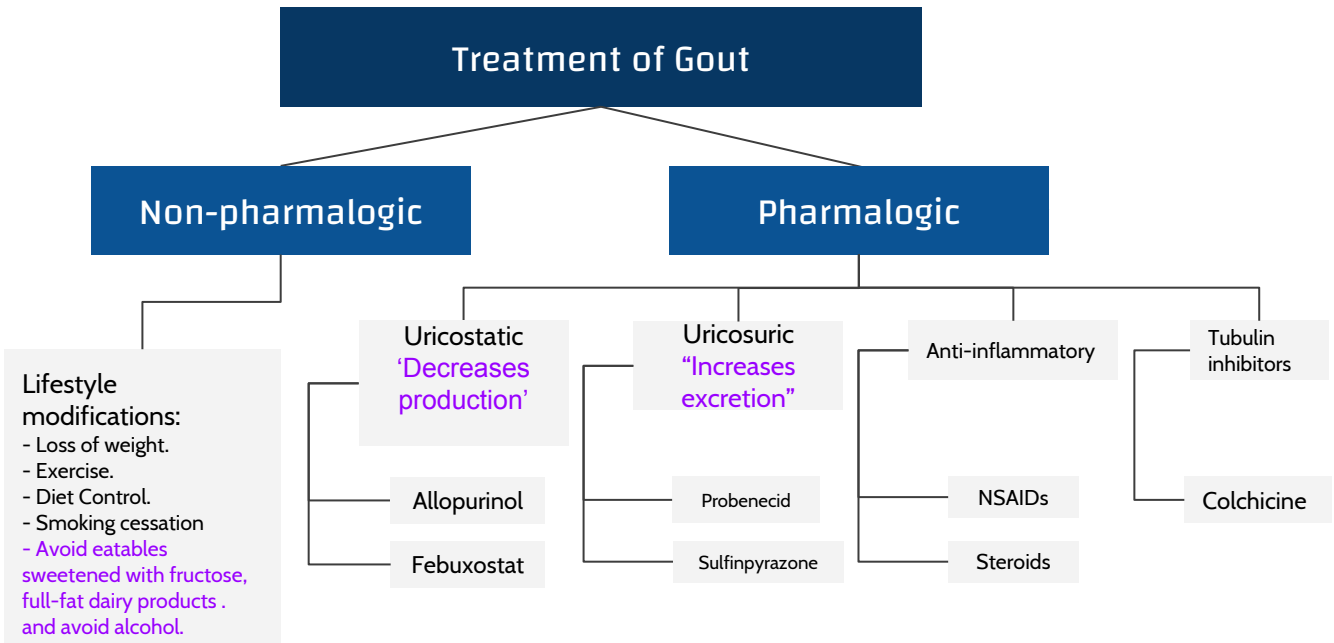
-lower serum uric acid

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

causes

- Hypertension
- CV Disease
- Stroke
- Renal Disease
- Metabolic Syndrome

Treatment of Gout:



What is the management of gout? or any disease.
1- Non-pharmacological treatment first 2- pharmacological treatment second

- **Aim of Pharmacotherapy:**

Most therapeutic strategies for gout involve **lowering the uric acid level below the saturation point (<6 mg/dL),** thus preventing the deposition of urate **crystals**.
This can be accomplished by: (how these drugs work)
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.** such as naproxen and ibuprofen in HIGH doses (Anti-inflammatory and analgesic effects)

Treatment of Acute Gout:

"Classification of drugs", it's important to know the drug and the group it belongs to

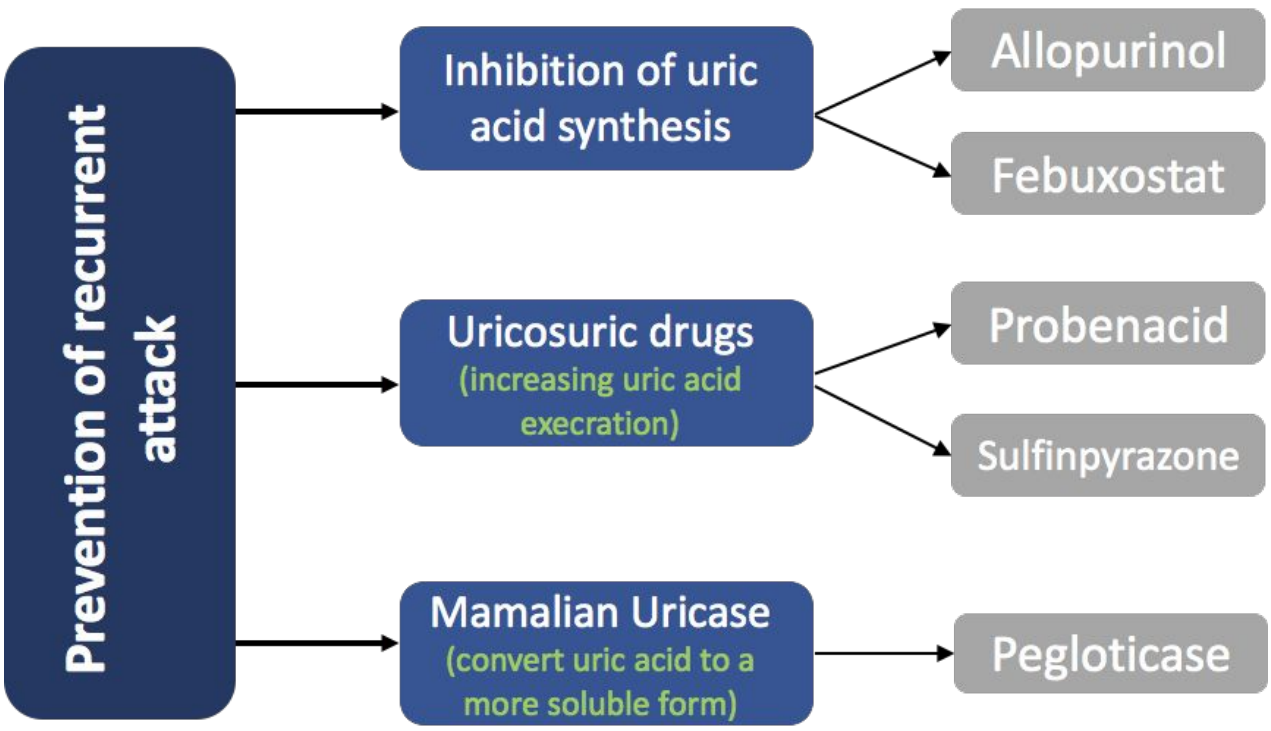
NSAIDs	• To stop inflammation • The most commonly used first-line treatment.(because they relieve pain) • Head-to-head studies show few differences between drugs. (Drugs of this class are similar). • Full Doses of NSAIDs should be initiated immediately and tapered after resolution of symptoms. (we do not start with small doses) (keep in mind that one of the ADRs of aspirin is acute gouty arthritis when given in low doses)
Contraindicated	1- GI ulcer. 2- Bleeding or perforation. 3- Renal insufficiency. 4- Heart Failure. 5- Use of oral anticoagulants. (Increases bleeding). *Recall Lecture 2 NSAIDs

Cont.

Steroids (Stronger than NSAIDs)	• Corticosteroids are a good alternative where NSAIDs and colchicine cannot be used or in refractory cases. (Resistance case) • Studies showed equal efficacy between corticosteroids and NSAIDs, **with no reported side-effects with short-term use of corticosteroids.**
Uses	• In elderly people, patients with with liver or hepatic impairment, IHD (Ischemic heart disease), PUD (Peptic ulcer disease), Hypersensitivity to NSAIDs.
Route of Administration	• Intra articularly (preferred route if one or two joints are affected). long use causes joint damage and increased risk of infections leading to severe arthritis. • Orally. • Intramuscularly or intravenously.

Cont.

Colchicine (Very important)	• **Origin**: Alkaloid obtained from autumn crocus (flowering plant). • **The effect: Minimal effect on uric acid synthesis, excretion & is not analgesic.**
Mechanism What is the Main mechanism ? Microtubules inhibitor (Antimitotic drug)	• **Binds to microtubules in neutrophils.** • **Inhibits cell division by:(Mitosis)** • **Inhibits chemotactic factors.** • **Inhibits inflamosomes & IL-1 production. (inflamosomes are inflammatory proteins)** Colchicine relieves a painful gouty attack by going to work right in the joint (localized). It can have you running smoothly again.
Pharmacokinetic	• **Route of Administration:** orally.(I.V causes diarrhea,bone marrow suppression increase) • **Absorption:** rapidly absorbed from the GI tract. • **Half-life:** reaches peak plasma levels within 2 hours. • **Recycling:** in the bile. (Enterohepatic circulation). • **Excretion:** unchanged in the faeces or urine. • **Should be avoided in:** patients with a creatinine clearance of less than 50 mL/min. (Renal diseases patients).
Clinical Uses	1. Treatment of gout flares.(Acute) 2. Prophylaxis (Prevention) of gout flares. (In between attacks) 3. Treatment of Mediterranean fever.
Side Effects important	1. **Abdominal:** Diarrhea (sometimes severe and bloody, the patient stops taking the drug), Nausea, Vomiting, Abdominal Cramps, Dehydration. 2. **Immune:** Bone marrow depression. (may cause hair fall like in chemotherapy)."because they are anti-mitotic drugs" 3. **Cardiac (large doses):** Cardiac toxicity, arrhythmia, Vascular collapse, Hepatotoxicity, alopecia.



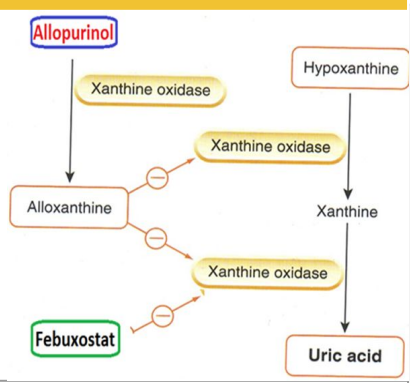
Uric acid synthesis inhibitors: Allopurinol, Febuxostat

Mechanism of Action

- Inhibit Xanthine oxidase.

Hypoxanthine → Xanthine → Uric acid

- Allopurinol not active is metabolized by xanthine oxidase into alloxanthine (oxypurinol) which is pharmacologically active



P.K
Pharmacokinetics

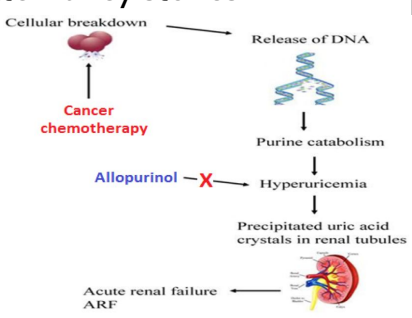
- Absorption 70%
- Protein Binding negligible 5%
- Hepatic metabolism, 70% converted to active metabolite (Oxypurinol) which is eliminated unchanged in the urine.

ADRS
These side effects are due to the active metabolite **Alloxanthine (Oxypurinol)**

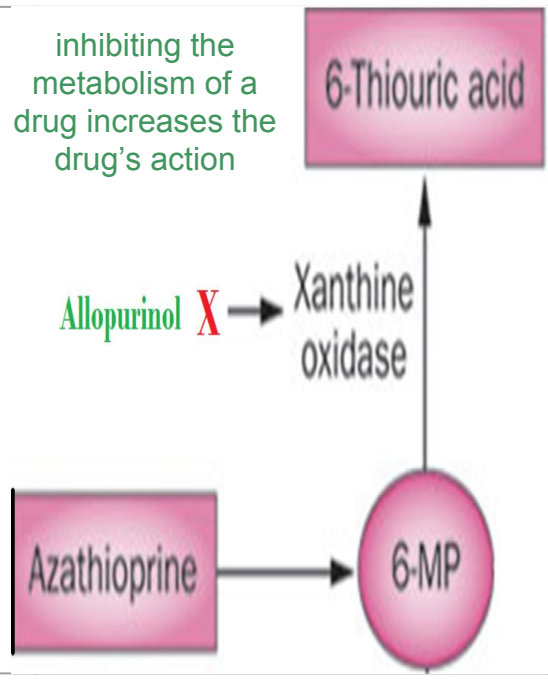
1-Diarrhea,nausea,abnormal liver tests.
2-Acute attacks of gout. explained in the green note below
3-Fever,rash,*toxic epidermal necrolysis (Severe ADRS), hepatotoxicity, marrow suppression vasculitis.
4-DRESS syndrome (Drug reaction, Eosinophilia,Systemic Symptoms).
5-20% mortality rate.
6- Allopurinol hypersensitivity syndrome

*Toxic epidermal necrolysis causes ulcers which leads to infections.

بداية العلاج ممكن تحصل هجمات ليش ؟ لأن آلية عمل الأدوية انها تقلل من اليوريك أسيد الليّ بالدم ف اليوريك أسيد الليّ في ال tissue راح يحصل له **mobilization** ويرجع يدخل الدم من جديد فتحصل الهجمات

Drug	Allopurinol	Febuxostat
Clinical Uses	• Management of hyperuricemia of gout. Mainly • Uric acid stones or nephropathy. • **It is a drug of choice in patients with with both gout & ischemic heart disease** • Severe tophaceous deposits.(uric acid deposits in tissues). • Management of hyperuricemia associated with chemotherapy. • Prevention of recurrent calcium oxalate kidney stones. (when cells are destroyed, lots of purine is diffused). 	• Indicated for the management of hyperuricemia in patients with gout (as it reduces serum uric acid levels). • Chemically distinct from allopurinol (non purine). • **Can be used in patients with renal disease.** • Oral specific xanthine oxidase inhibitor. More specific than allopurinol
P.K	• Metabolism: it is metabolized by xanthine oxidase into alloxanthin which is pharmacologically active (The active metabolite inhibits the enzyme). • Absorption 70% • Protein Binding negligible 5% • Hepatic metabolism, 70% converted to active metabolite(Oxypurinol) which is eliminated unchanged in the urine.	• **Route of administration :** Given orally once daily. • **Absorption:** well absorbed(85%). • **Metabolism:** Metabolized in liver,mainly conjugated to glucuronic acid • **Protein BInding: 99%.** • **Half life:** (Girls slide:8 hrs, Boys slide :4-18 hrs) • Given to patients who do not tolerate allopurinol. • High dose of febuxostat have a lesser effect than the lowest dose of allopurinol.
ADRs	The side effects are due to the active metabolite which are: • Allopurinol Hypersensitivity Syndrome • Toxic Epidermal Necrolysis • DRESS Syndrome (Drug Reaction Eosinophilia Systemic Symptoms) 20% mortality rate. • Fever, rash, marrow suppression,diarrhea,nausea, abnormal liver tests & vasculitis, acute gout attacks and hepatotoxicity	• Increases number of gout attacks the first few months of treatment. • Increases level of liver enzymes. • Nausea, diarrhea. • Numbness of arm or leg. • Headache

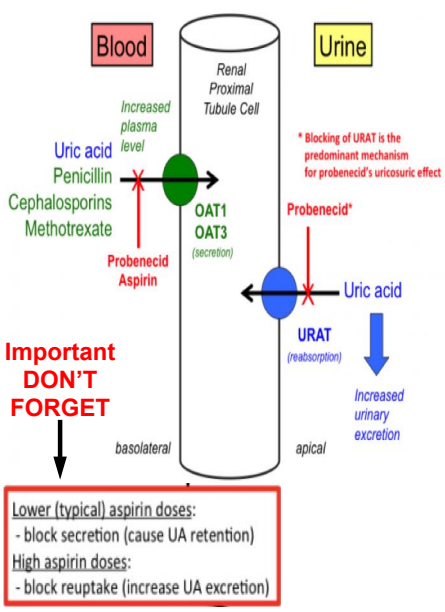
Cont..

Drug interactions For Allopurinol only	•Warfarin & dicumarol: inhibits their metabolism (Bleeding) •6-mercaptopurine and azathioprine (anti-cancer drugs): Reduces their metabolism •Ampicillin : Increases frequency of skin rash	inhibiting the metabolism of a drug increases the drug's action 

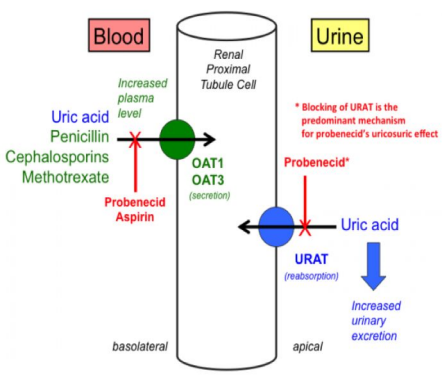
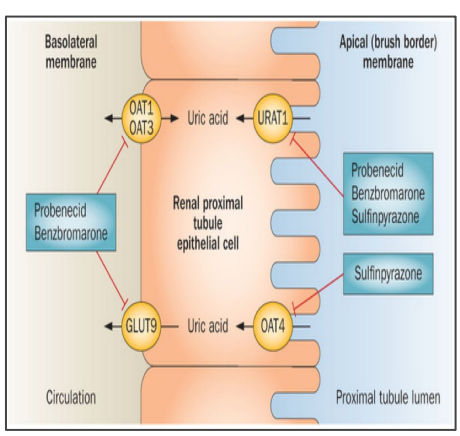
What is the drug of choice for a patient with ischemia and gout ?
Allopurinol

What is the drug of choice for a patient with a renal disease?
Febuxostat

Uricosuric Drugs

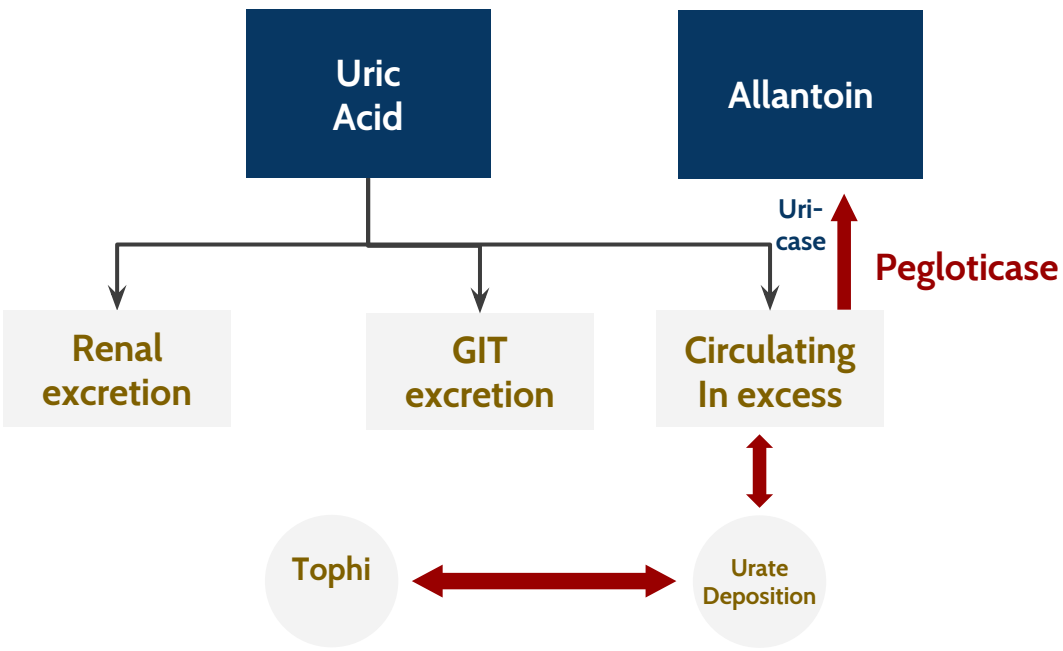
Mechanism of action	Effect	Contradiction
• Blocks tubular reabsorption of uric acid and enhances urine uric acid excretion. 	1-Control hyperuricemia and prevents tophus formation. 2-Increases risk of nephrolithiasis. the excreted urine is high in uric acid which leads to the formation of kidney stones that's why some of these drugs cannot be given to patients with renal disease. 3-Some drugs reduce efficacy (e.g, aspirin).	1-Patients with renal disease. 2-History of nephrolithiasis. 3-Recent acute gout 4-Less effective in elderly patients.

TYPES OF URICOSURIC DRUGS

Drugs	Probenecid	Sulfinpyrazone
Features	**ADRS (side effect):** •Exacerbation of acute attack •Risk of uric acid stone • GIT upset • Allergic rash.	**•Can aggravate peptic ulcer disease.** • Aspirin reduces efficacy of sulfinpyrazone. • Enhances the action of certain anti-diabetic drugs.Lower blood glucose
MOA (Mechanism of action)	Probenecid inhibits Urate Transporters (URAT) in the apical membrane of the proximal tubule It also inhibits organic acid transporter(OAT) → ↑ **plasma concentration of penicillin** 	Sulfinpyrazone inhibits URAT1 & OAT4. (Organic acid transporter 4) (responsible for reabsorption of uric acid) 
Effect	1-Moderately effective.	

Pegloticase

Mechanisms	•A uric acid specific enzyme which is a recombinant modified mammalian uricase enzyme through genetic engineering • Enzymatically converts uric acid to allantoin, which is more soluble and readily excreted in the urine. كأنها الن تلينين فتلين وتصير سايلة وتطلع من الجسم
Clinical use	Used for the treatment of **chronic gout** in adult patients refractory to conventional therapy. Expensive therapy
P.K (Pharmacokinetics)	• Route of administration: IV • peak decline in uric acid level within 24-72 hours (Rapid decrease, and this is an advantage)
ADRS Adverse drug reactions	•Infusion reactions. Fever and skin rash •Anaphylaxis. Life threatening •Gout flare •Arthralgia (arthra: joints, algia: pain) •Muscle spasm. During infusion and after it •Nephrolithiasis



SUMMARY

Summary table from team 437

<table>
<tr><td rowspan="5">Treatment of gout</td><td>Nonphar-macologic</td><td colspan="4">Lifestyle modifications
- Loss of weight
- Exercise
- Diet control
- Smoking cessation and avoid alcohol</td></tr>
<tr><td rowspan="4">Pharmacological</td><td rowspan="3">Treatment of acute gout</td><td>NSAIDs</td><td colspan="2">First line treatment
Contraindicated : heart failure</td></tr>
<tr><td>steroids</td><td colspan="2">-Stronger than NSAIDs
-Uses in elderly people or hypersensitivity to NSAIDs</td></tr>
<tr><td>Colchicine</td><td colspan="2">Treatment of Mediterranean (inflammatory) fever</td></tr>
<tr><td rowspan="3">Prevention of recurrent attacks</td><td>Inhibition of uric acid synthesis</td><td>Allopurinol
drug of choice in patients with both gout & ischemic heart disease.</td><td>Febuxostate
Patients with renal disease</td></tr>
<tr><td>Uricosuric drugs</td><td>Probenecid
↑plasma concentration of penicillin.</td><td>Sulfinpyrazone
inhibits URAT1 & OAT4.</td></tr>
<tr><td>Mamalian uricase</td><td colspan="2">Pegloticase : convert urate to allantoin</td></tr>
</table>

QUIZ

MCQs

1-Which of the following causes the inflammatory process in Gout?
A-Deposits of Sodium Urate Crystals
B-High serum Uric acid
C-Cytokines

2-A 50 years old man came to the ER complaining from severe pain in his toes joints with hotness on them. Blood sample was taken from him and it revealed high uric acid with creatine clearance rate of 23 mL/min. Which of the following should be avoided in treating his Gout?
A-NSAIDs
B-Colchicine
C-Febuxostat

3-Allopurinol is metabolized into Alloxanthin by
A-Aspirin
B-Xanthine oxidase
C-Pegloticase

4-Jamal is a 35 years old man with known history of Gout was diagnosed with bacterial infection and was prescribed penicillin. Which drug of Gout his doctor must stop it in this case due to interaction ?
A-Probenecid
B-Febuxostat
C-Steroids

5-If a Gout patient has ischemic heart disease, what is the drug of choice?
A-Pegloticase
B-Allopurinol
C-Colchicine

1-A 2-B 3-B 4-A 5-B

QUIZ

SAQ

A- What are the stages of Gout?

Four distinct stages:
a) asymptomatic hyperuricemia
b) acute intermittent gout
c)Intercritical stage
d) chronic gout

B-How to manage each stage?

Asymptotic: Life style modification
Acute: terminate the attack
Intercritical: Prevent the recurrent attacks
Chronic: prevent complication and lower serum uric acid

C-In Gout we have acute treatment and prophylactic therapy. According to the previous statement, answer the following:

- Write Colchicine mechanism of action and clinical uses:

Slide 6 in Colchicine part.

- Mention one class that is used a preventive therapy with two ADRs:

Any class with its ADRs

D- Give a short answer about the metabolism of allopurinol.

It is metabolized by xanthine oxidase into alloxanthin which is pharmacologically active.

pharmacology

Team 438

GOOD LUCK

Team Leaders:

Nouf Alshammari

Zyad Aldosari

Team Members:

Alwaleed Alsaleh

Talal Abozaid

Muhannad Makkawi

Sources:

Team 435

Team 437