Pharmacology
Team 437

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Drugs in Gout

Objectives:

- ✓ Know the pathophysiology of Gout
- ✓ Outline the stages of Gout and the therapeutic objective 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

Editing File

Important Notes Extra

Overview of Gout

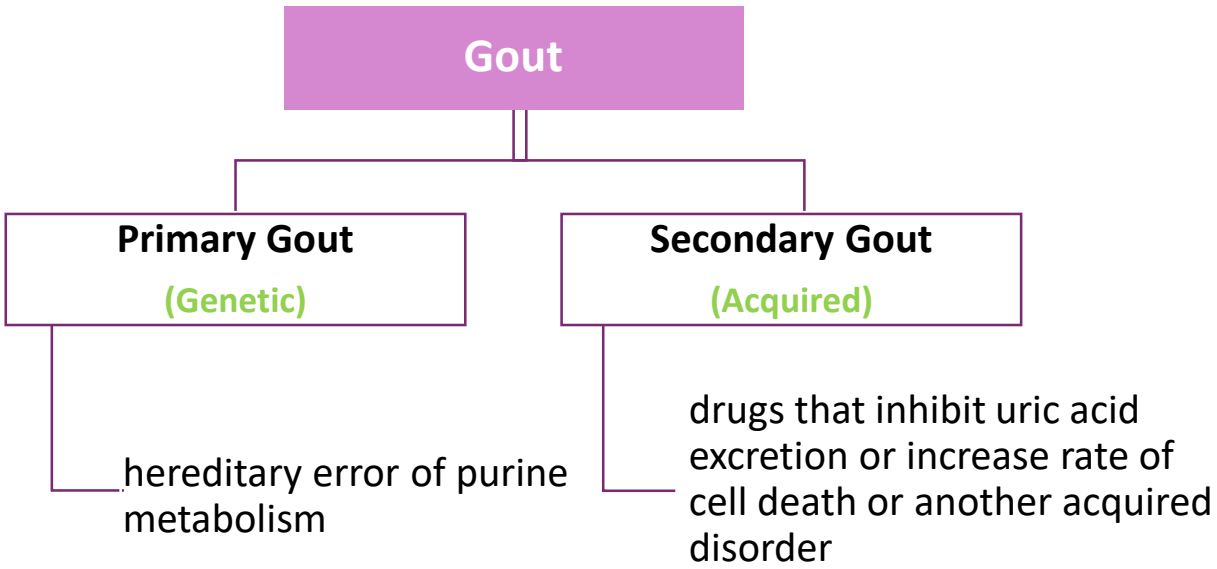
What is Gout?

Gout is usually characterized by recurrent attacks of acute inflammatory arthritis with red, tender, hot and swollen joints. It usually happens in small joints specially foot.

❖ Pathogenesis (cause) of Gout:

Deposits of **sodium urate crystals** in articular, periarticular, and subcutaneous tissues. This is what causes the inflammatory process in Gout.

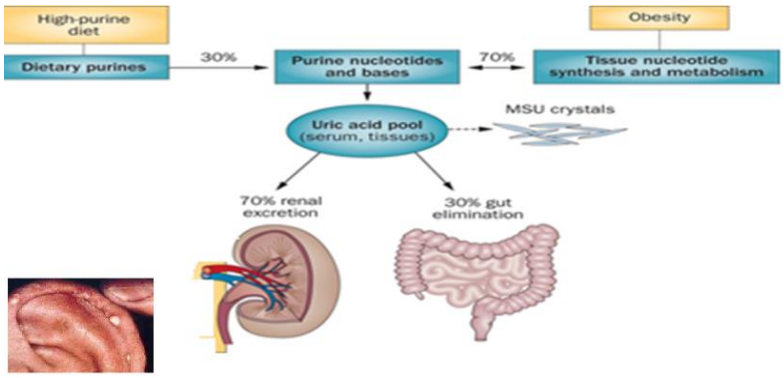
❖ Types of Gout:



❖ Untreated Gout leads to:

- Tophaceous: Masses of MSU (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.

❖ Continue of untreated gout:



❖ 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: Prof.Yeldez explained it.

- Urate crystals are initially phagocytosed by synoviocytes, which then release prostaglandins, lysosomal enzymes, and interleukin-1 which attract and activate 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.

❖ Diagnosis:

- 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. Frequently, gout flares up following rich meals and alcohol consumption, in the middle of the night.

❖ Stages of Gout:

Symptoms start at this stage

Asymptomatic hyperuricemia *

Elevated serum urate with no clinical manifestation of gout

Treat or not to treat?

Acute intermittent gout

acute inflammation in joint caused by free urate crystals

Management: Terminate the attack

Intercritical stage

The interval between acute flares

Management: Prevent recurrent attacks

Chronic gout

Complications

Long-term gout complication

Management: - Prevent complications **-** Lower serum uric acid

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

Cause

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

Treatment of Gout:

*If we found out that the patient is having Hyperuricemia during routine blood test then we have to start an early treatment at the asymptomatic stage.

Treatment of Gout

Non-pharmacologic

Lifestyle modifications
- Loss of weight
- Exercise
- Diet control
- Smoking cessation and avoid alcohol

Pharmacologic

Uricostatic
- Allopurinol
- Febuxostat

Uricosuric
- Probenecid
- Sulfinpyrazone

Anti-inflammatory
- NSAIDs
- Steroids

Tubulin inhibitors
- **Colchicine**

❖ 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 those 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. Anti-inflammatory and analgesic effects.

Treatment of acute gout

NSAIDS

- the most commonly used first-line treatment.
- Head-to-head studies show few differences between drugs. Drugs of this class are similar.
- Full doses of NSAID should be initiated immediately and tapered after resolution of symptoms لا نبدأ بجرعات صغيرة .

Contraindicated	1-GI ulcer 2- Bleeding or perforation. 3-Renal insufficiency leads to congestive HF 4- **Heart failure**. 5-Use of oral anticoagulants. increases the bleeding Recall: lecture 2 NSAIDs – ASPIRIN ADRs

Steroids Stronger than NSAIDs

- Corticosteroids are a good alternative where NSAIDs and colchicine cannot be used or in refractory cases.
- Studies showed equal efficacy between corticosteroid and NSAIDs, **with no reported side-effects with <u>short-term</u> use of corticosteroids**.

Uses	• In elderly people, patients 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 affected).long use causes joint damage and increases risk of infections leading to sevre arthritis • Orally. • Intramuscularly or intravenously.

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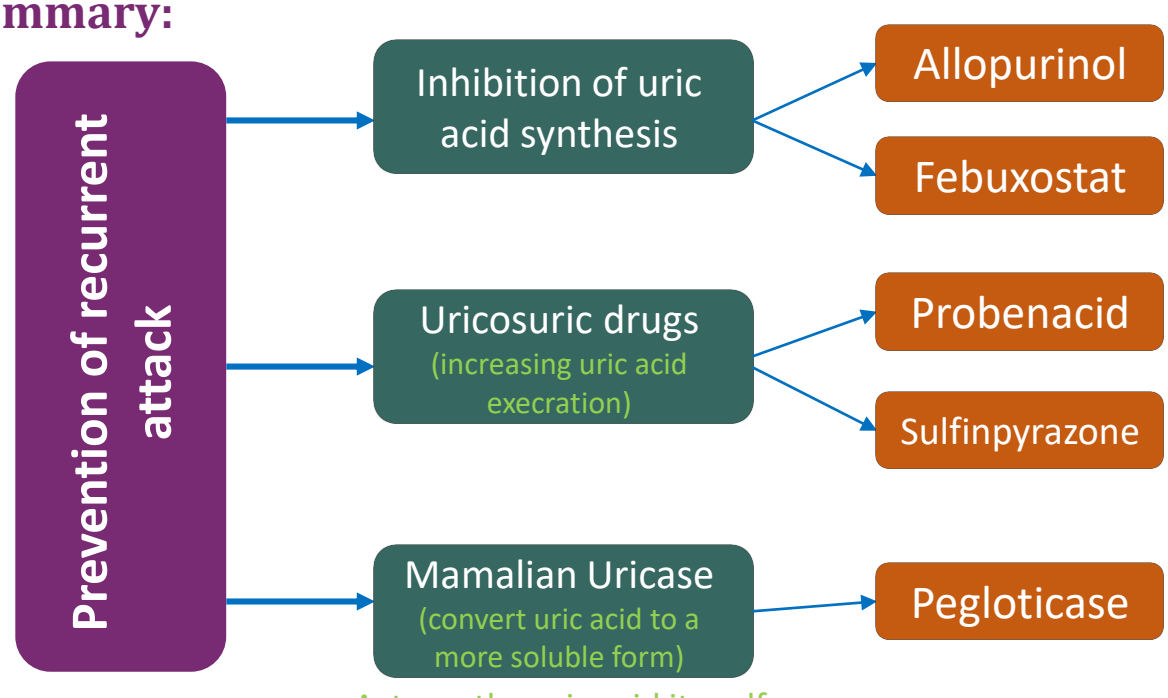
Colchicine VERY IMPORTANT!

Origin	Alkaloid obtained from autumn crocus (flowering plant) The effect: **Minimal effect on uric acid synthesis , excretion & is not analgesic**
Mmechanism	**Binds to microtubules in neutrophils** **Inhibits cell division by:** **1- Inhibits chemotactic factors.** **2- Inhibits inflammasomes & IL-1 production.**
Pharmacokinetic	• **Route of administration:** orally. • **Absorption:** rapidly absorbed from the GI tract. • **Half-life:** Reaches peak plasma levels within 2 hours. • **Rrecycling:** in the bile. Enterohepatic circulation • **Excretion:** unchanged in the faeces or urine. • **Should be avoid in :** patients with a creatinine clearance of less than 50 mL/min. (Renal failure patients) ممكن يجي عليها سؤال!
Clinical Uses	1- Treatment of gout flares 2- Prophylaxis (الوقاية) of gout flares in between attacks 3- Treatment of Mediterranean (inflammatory) fever with arthritis, polyserositis.
Side effect	**1- abdominal:** **Diarrhea** (sometimes severe), Nausea, Vomiting, Abdominal cramps, Dehydration. **2- immune:** Bone marrow depression. may cause hair fall like in chemotherapy **3- cardiac**(in toxic doses)**:** Cardiac toxicity, arrhythmia, Vascular collapse, Hepatotoxicity , alopecia

Prevention of Recurrent attacks

❖ **Summary:**



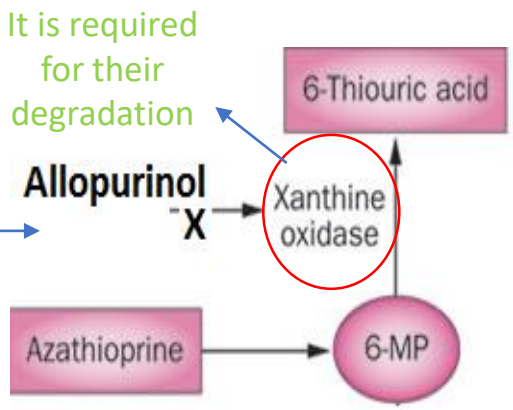
Acts on the uric acid its self.

Inhibitors of Uric acid synthesis:

UAS Inhibitors

MOA	• Inhibit the xanthine oxidase which catalyzes its formation from xanthine and hypoxanthine.	
P.K	• Absorption 70% • Protein Binding neglible 5% • **Hepatic metabolism, 70% converted into active metabolite (Oxypurinol) which is eliminated unchanged in the urine.** *Toxic epidermal necrolysis causes ulcers which leads to infections	
ADRS	Those side effects are due to the active metabolite 1- Diarrhea, nausea, abnormal liver tests. 2- Acute attacks of gout. Fluctuation effect at the start of treatment 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-Hypersensitivty.	
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 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	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 .

Cont..

P.K	**Very important!** • Metabolism: it is metabolized by xanthine oxidase into alloxanthin which is pharmacologically active. The active metabolite inhibits the enzyme.	• **Route of administration:** Given orally once daily. • **Absorption:** well absorbed (85%). • **Metabolism:** Metabolized in liver , mainly conjugated to glucouronic acid. • **Protein binding:** 99%. • **Half-life:** (girl's slide: 8 hours) , (boy's slide: 4-18 hours) • **Given to patients who do not tolerate allopurinol.**
ADRS	The side effects are due to the active metabolite which are: • Allopurinol Hypersensitivity Syndrome • Toxic Epidermal Necrolysis • Dress Syndrome	• Increases number of gout attacks during the first few months of treatment. • **Increases level of liver enzymes.** • Nausea, Diarrhea. • Numbness of arm or leg. • Headache.
Drug Interaction	• Warfarin & dicoumarol: inhibits their metabolism (Bleeding) • 6-mercaptopurine and azathioprine (anti-cancer drugs):Reduce their metabolism • ampicillin : Increases frequency of skin rash	

Uricosuric Drugs:

*Increases stone formation.

Mechanism of action	Effect	Contraindication
• Blocks tubular reabsorption of uric acid & enhances urine uric acid excretion.	1-Control hyperuricemia and **prevent tophus formation.** 2-Increases risk of nephrolithiasis. *** 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.**

Drug	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. • enhance the action of certain antidiabetic drugs.Lower blood glucose
MOA	Probenecid inhibits Urate Transporters (URAT1) in the apical membrane of the proximal tubule It also inhibits organic acid transporter(OAT)→↑**plasma concentration of penicillin.**	Sulfinpyrazol inhibits URAT1 & OAT4.
Effect	1-moderately effective.	–

Recombinant mammalian uricase:

Pegloticase	
Mechanism	• A uric acid specific enzyme which is a recombinant modified mammalian uricase enzyme through genetic engineering • Enzymatically convert urate to allantoin, which is more soluble and readily excreted in the urine. كانها الن تلينين فتلين وتصير سايلة وتطلع من الجسم. **VERY IMPORTANT!**
Clinical use	Used for the treatment of **chronic gout** in adult patients refractory to conventional therapy. Expensive therapy
P.K	• peak decline in uric acid level within 24-72 hours • Route of administration: IV

Cont..

ADRS (side effect)

- Infusion reactions. Fever and skin rash
- Anaphylaxis. Life threating
- Gout flare
- Arthralgia (arthra: joints, algia: pain)
- Muscle spasm. During infusion and after it
- Nephrolithiasis

Picture regarding the non drug treatment:

We add it because Prof.Yeldez commented on it.

Summary:

Treatment of gout	**Non pharmacologic**	**Lifestyle modifications** **- Loss of weight** **- Exercise** **- Diet control** **- Smoking cessation and avoid alcohol**			
	Pharmacologic	**Treatment of acute gout**	**NSAIDs**	**First line treatment** **Contraindicated : heart failure**	
			steroids	-Stronger than NSAIDs -Uses in elderly people or hypersensitivity to NSAIDs	
			Colchicine	**Treatment of Mediterranean (inflammatory) fever**	
		Prevention of recurrent attacks	**Inhibition of uric acid synthesis**	**Allopurinol** drug of choice in patients with both gout & ischemic heart disease.	**Febuxostate** Patients with renal disease
			Uricosuric drugs	Probenecid ↑plasma concentration of penicillin.	Sulfinpyrazone inhibits URAT1 & OAT4.
			Mamalian uricase	**Pegloticase :** convert urate to allantoin	

Questions

MCQ:

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

Questions

SAQ:

- **Based on your study of Gout and its treatment, answer the following:**

A- What are the stages of Gout?

Four distinct stages:
a)asymptomatic hyper-uricemia
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

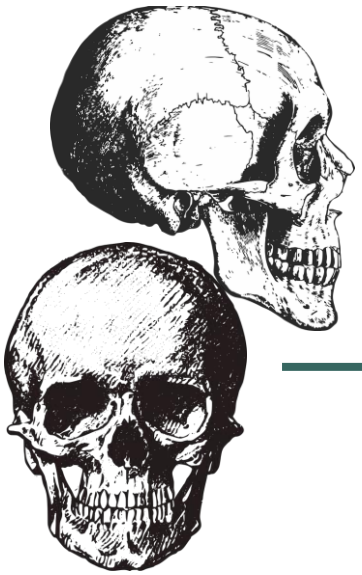
C-In Gout we have acute treatment and prophylactic therapy. According to the previous statement, answer the following:

- 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



"It is not hard, you just made it to the end!"

Team Leaders:

Yazeed Al-Harbi & Aseel Ba Dukhon

Thanks for those who worked on this lecture:

Renad Al-Gharebi
Alanoud Al-Essa
Nourah Bin Hassan
Alfahdah Al-Saleem

References:

- ✓ Team436
- ✓ Doctors' notes and slides

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