PHARMACOLOGY
TEAM 439

MED439
KING SAUD UNIVERSITY

Editing file

# Drugs In Gout

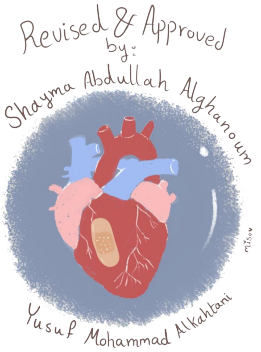
## OBJECTIVES:

- To know the pathophysiology of gout.
- To outline the stages of gout and the therapeutic objectives in each stage.
- To describe drug and non-drug treatment of gout.
- To classify drugs used for treatment of gout.
- To identify the mechanism of action of drugs used for treatment of gout.
- To study in detail the pharmacology of drugs used for treatment of gout.

**We highly recommend that you study The Biochemistry lecture (Purine Degradation & Gout) before studying this lecture**

- Important
- In male and female slides
- Only in male slides
- Only in female slides
- Extra information

Helpful video



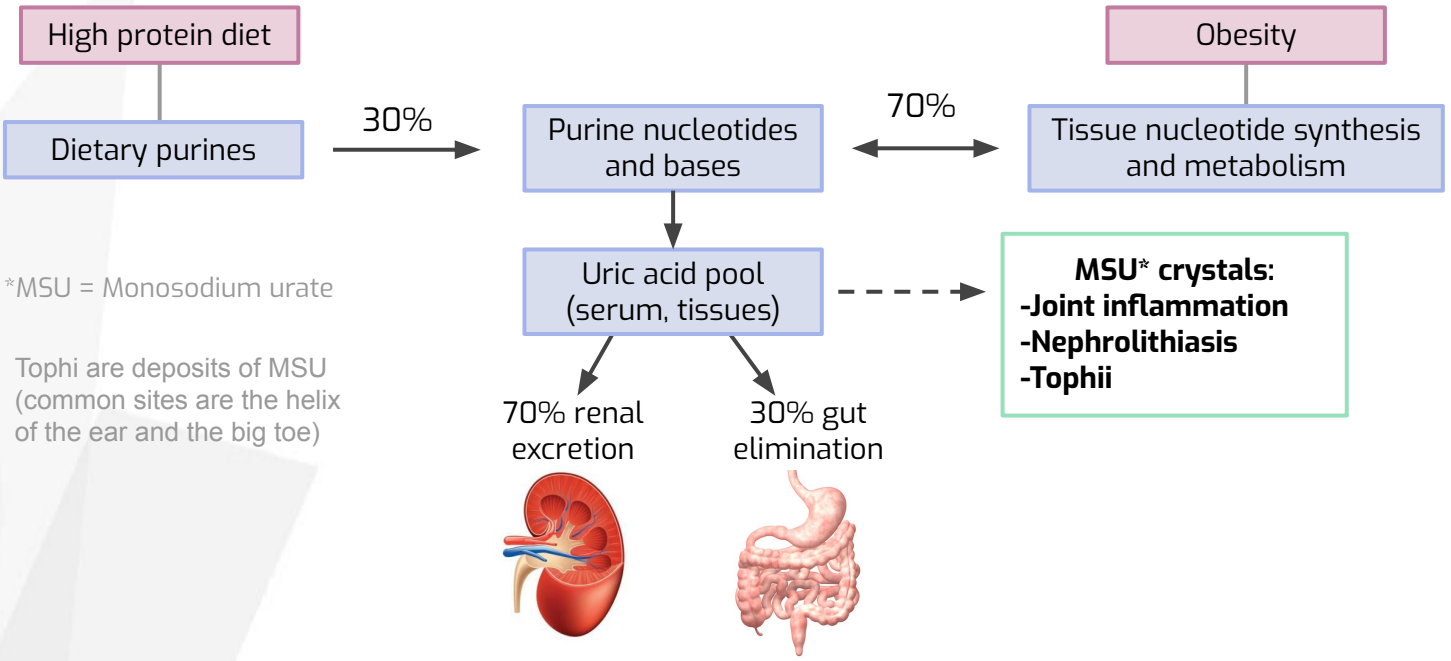
# Overview of GOUT

## What is GOUT?

- 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  in articular, periarticular, and subcutaneous tissues.
- May be **primary** or **secondary**:
  - **Primary-** hereditary error of purine metabolism
  - **Secondary-** drugs that inhibit uric acid excretion or increase rate of cell death or another acquired disorder

## Pathogenesis

Untreated Gout may lead to **tophaceous** masses of MSU* crystals in cartilage and **joints**, **renal stones**, and **urate nephropathy**.




*MSU = Monosodium urate

Tophi are deposits of MSU (common sites are the helix of the ear and the big toe)

**Cause:** elevated uric acid levels-hyperuricemia (above 7 mg/dl).

Normally, 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). Hyperuricemia may or may not precipitate GOUT.

# Overview of GOUT

## Epidemiology

- Gout was historically known as the "disease of kings" or "rich man's disease." (bc. they ate meat)
- Prevalence of hyperuricemia 5%
- Prevalence of gout 0.2%
- Male to female ratio 10:1 (more common in males)

## Pathophysiology

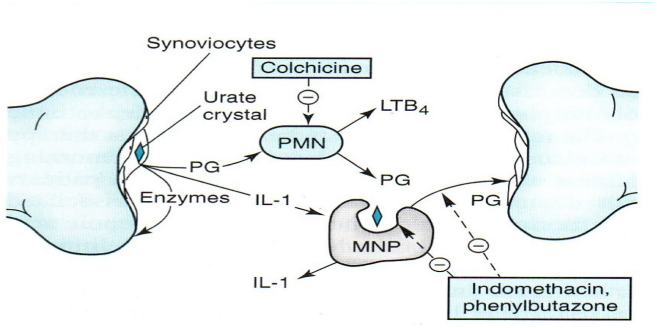



**Figure 36–5.** Pathophysiologic events in a gouty joint. Synoviocytes phagocytose urate crystals and then secrete inflammatory mediators, which attract and activate polymorphonuclear leukocytes (PMN) and mononuclear phagocytes (MNP) (macrophages). Drugs active in gout inhibit crystal phagocytosis and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

- **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.

## 4 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

**Elevated serum urate** (>7mg/dl in males & >6mg/dl in females) **with no clinical manifestations of gout**.

cause

-Hypertension
-CV disease
-Stroke
-Renal disease
-Metabolic Syndrome

### 2 Acute Flares (Acute intermittent)

Acute inflammation in joint caused by the free crystals.

**-Management: terminate the attack.**

### 3 Intercritical Gout

The intervals between acute flares.

**-Management: prevent recurrent attacks.**

### 4 Chronic gout

Long-term gout complications.
Management:

-Prevent complications
-Lower serum uric acid

# Treatment of Gout

## Non-Pharmacologic

**Lifestyle modifications:**

- **Loss of weight**
- Exercise
- Diet control
- Smoking cessation
- **Drink plenty of fluids, especially water** (if the body has more water precipitation of MSU will decrease)
- Choose low-fat or fat-free dairy products
- Consume complex carbohydrates
- Reduce saturated fat consumption
- Limit fish, meat, and poultry
- Avoid eatables sweetened with high fructose corn syrup
- **Avoid alcohol**

## Pharmacologic

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

## Drugs in Gout

### Acute Gouty Arthritis:

#### A. Anti-inflammatory

**Inhibit PGs:**

-NSAIDS
-Steroids

#### B.Tubulin Inhibitors

**Inhibit leukocyte entry into the affected joint:**

-colchicine

### Prevent recurrent attacks:

#### A.Uricostatic

**Interfere with uric acid synthesis:**

-allopurinol

-febuxostat

#### B.Uricosuric

**Increase uric acid excretion:**

-probenecid

-sulfinpyrazone

#### C.Mammalian Uricase

Pegloticase

# Acute Gouty Arthritis

## A. Anti-Inflammatory:

### 1- NSAIDS

**Overview**

- They 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 (Avoid NSAIDS; use corticosteroids insteads)**

- **GI ulcer**
- **Bleeding or perforation**
- **Renal insufficiency**
- **Heart failure**
- **Use of oral anticoagulants**

### 2- Steroids

**Overview**

- Corticosteroids are a good alternative where NSAIDs and colchicine cannot be used or in refractory cases (resistant to treatment)
- Studies showed equal efficacy between corticosteroid and NSAIDs. With no reported side-effects with short-term use of corticosteroids
- Used with elderly people, patients with liver or hepatic impairment, IHD (ischemic heart disease), PUD, hypersensitivity to NSAIDs.

**Pharmacokinetics**

**Administration:**

- Intra articularly **(preferred route if one or two joints affected** to reduce unwanted systemic effects**)**
- Orally
- Intramuscularly
- Intravenously

**ADRs**

- No significant short-term ADRs
- Long-term ADR: **Atrophy of the adrenal cortex** (**very serious**) because the body relies on the corticosteroid injections and stops secreting them from the adrenal cortex causing atrophy

# Acute Gouty Arthritis

## B. Tubulin Inhibitors

B- Colchicine

### Overview

- Alkaloid obtained from autumn crocus (a type of flower)
- Minimal effect on uric acid synthesis, excretion, and is not analgesic

### Mechanism ( very important)

- Binds to microtubules in neutrophils
- Inhibits cell division
- inhibits chemotactic factors
- inhibits inflammasome and IL-1 production

### Pharmacokinetics

**Administration**: oral

**Absorption**: rapidly absorbed from the GI tract

-Reaches peak plasma levels within 2 hours

**Excretion:** recycled in the bile and is excreted unchanged in the faeces or urine

### Contraindications

- 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 mediterranean fever (because it also has fever and arthritis)

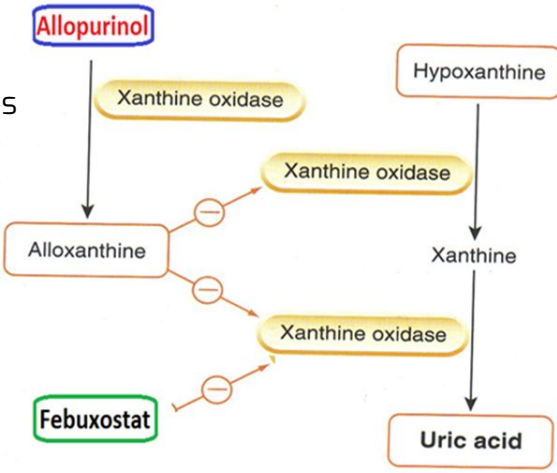
### ADRS

- **Diarrhea (sometimes severe)**
- Nausea
- Vomiting
- Abdominal cramps
- Dehydration
- Bone marrow depression
- Cardiac toxicity, arrhythmia
- Vascular collapse
- Hepatotoxicity, alopecia (hair loss)

# Prevention Of Recurrent Attacks

## Uricostatics

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




## 1- 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 glucouronic acid.
- **Protein binding:** 99% Protein bound.
- Given to patients who do NOT tolerate **allopurinol**.
- **$t^{1}/_{2}$** = 8 hours.

### Clinical Uses

- Indicated for the chronic management of hyperuricemia in patients with gout (as it reduces serum uric acid levels).
- Can be used in patients with renal disease.

### ADRS:

- Increases number of **gout attacks** during the first few months of treatment.
  Sometimes during treatment of gout, levels of **urate** *fluctuate*
- **Increases level of liver enzymes.**
- Nausea, Diarrhea
- Headache.
- Numbness of arm or leg.

2- Allopurinol

## Pharmacokinetics

- **Absorption:** 70%
- **Protein binding:** negligible (only 5%)
- **Hepatic metabolism**: 70%, metabolized by xanthine oxidase into 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.

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

## Clinical Use

- Management of hyperuricemia of **GOUT** (Mainly).
- Management of hyperuricemia **associated with chemotherapy**.
  (when cells are destroyed, a lot of purine is diffused).
- Prevention of recurrent calcium oxalate kidney stones, Uric acid stones, or nephropathy. (which can cause acute renal failure)
- 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.

## 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 and 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*

## ADRS

- Diarrhea, nausea, abnormal liver tests.
- Acute attacks of gout. *Fluctuation* effect at the start of treatment.
- ***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.
- ***DRESS syndrome:*** Drug Reaction (rash) with Eosinophilia and Systemic Symptoms.
  20% mortality rate Eosinophilia: an increase in the number of eosinophils in the blood, occurring in response to some allergens, drugs, and parasites.

# Prevention Of Recurrent Attacks

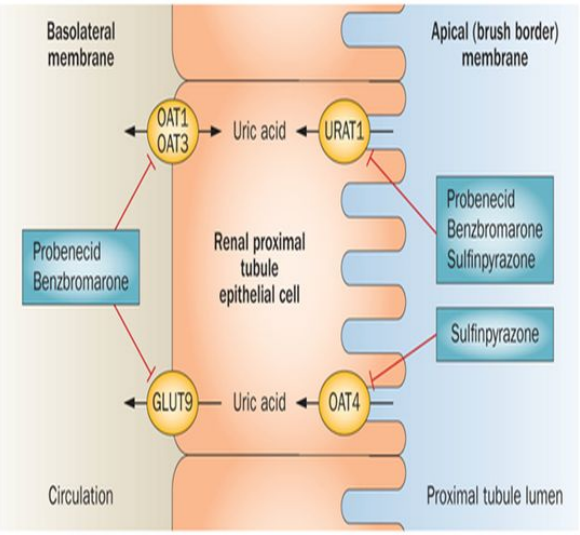
B

## Uricosuric

- Uricosuric drug **Blocks** tubular reabsorption of uric acid & enhances uric acid excretion in urine.
  Thus **Control** hyperuricemia and **prevent** tophus formation.

- **Increases risk of nephrolithiasis**.

- Some drugs reduce efficacy (e.g., aspirin).




| | Probenecid | Sulfinpyrazone |
|---|---|---|
| M.O.A | • Inhibits **Urate Transporters** (URAT1) in the apical membrane of the proximal tubule.<br>• Inhibits **organic acid transporter** (OAT), which mediates excretion of drugs from the plasma to the urine.<br>→ ↑ plasma concentration of penicillin.<br>(drug interaction between penicillin and uricosurics) | Inhibits URAT1 & OAT4. |
| Effect | Moderately effective | Enhances the action of certain antidiabetic drugs.<br>(Lower blood glucose). |
| Contraindications | • History of nephrolithiasis.<br>• Existing renal disease. (Or previous diagnosis of kidney stones)<br>• Recent **acute gout**.<br>• Less effective in elderly patients. | Patients with **renal disease.** |
| Drug Interactions | Drug interaction between penicillin and uricosurics | **Aspirin** reduces efficacy of sulfinpyrazone |
| ADRS | • GIT upset<br>• Exacerbation of acute attack<br>• Risk of uric acid stone<br>• Allergic rash | Can aggravate peptic ulcer disease. ( verryyy important) |

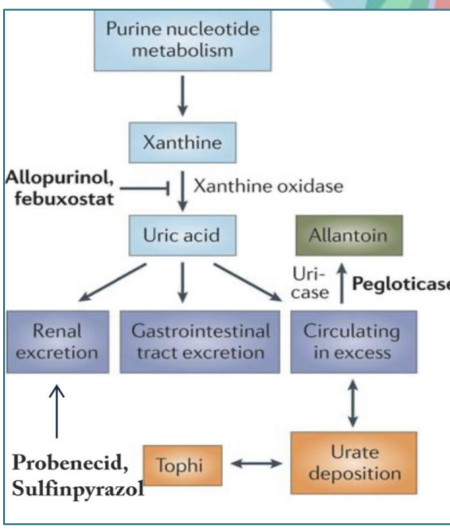
# Prevention Of Recurrent Attacks

C

## Recombinant Mammalian Uricase (Pegloticase):

**Recombinant mammalian uricase:** is a uric acid specific enzyme which is a recombinant modified.

(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...) )




# Pegloticase

### Pharmacokinetics

When Given by I.V, they produce → peak **decline** ↓ in uric acid level **within 24-72 hours.**

### M.O.A

- It enzymatically Converts **uric acid** to allantoin, which is **more soluble** and readily excreted in the urine.

### Clinical Uses

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

### ADRS

- Infusion reactions. (Fever and skin rash)
  (drugs administered by I.V may cause an infusion reaction).
- Anaphylaxis. (Life threatening)
  (more aggressive pattern of hypersensitivity).
- Gout flare. (due to fluctuation in urate levels during treatment)
- Arthralgia. (arthra=joint, algia= pain)
- Muscle spasm.
- Nephrolithiasis. (kidney stone)

# MCQ

**1- Which of these drugs is uricostatic?**

| | | | |
|---|---|---|---|
| A-Probenecid | B-Allopurinol | C-Sulfinpyrazone | D-Aspirin |

**A 32 y.o. patient 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 |

**3-Which of the following is a uricosuric?**

| | | | |
|---|---|---|---|
| A-Allopurinol | B-Aspirin | C- Colchicine | D-Sulfinpyrazone |

**4-Which of the following drugs used to treat gouty arthritis inhibits cell division?**

| | | | |
|---|---|---|---|
| A-Colchicine | B- Penicillin | C- Pegloticase | D- Probenecid |

**5- Which of the following converts uric acid to allantoin?**

| | | | |
|---|---|---|---|
| A-Probenecid | B-Allopurinol | C-Pegloticase | D-Sulfinpyrazone |

## ANSWERS

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| B | C | D | A | C |

# SAQ

1) What is the mechanism of action of colchicine?

2) Patient with gout was given a drug that led to bleeding due to interaction with Warfarin and Dicumarol by inhibiting their metabolism.
-Name the drug?

3) Explain the Mechanism of the previous drug? And name the active metabolite?

4) Give another important drug interaction for the previous drug?

5) Mention three side effects of the previous drug?

## ANSWERS

A1) It inhibits cell division by binding to microtubules.

A2) Allopurinol.

A3) xanthine oxidase metabolizes **allopurinol** to produce **alloxanthine**. Then the active metabolite (alloxanthine) inhibits xanthine oxidase.

A4) Reduce the metabolism of Anti-cancer drugs.

A5) ***Allopurinol Hypersensitivity Syndrome – DRESS syndrome – Toxic epidermal necrolysis***

# GOOD LUCK!

> *Failure is the condiment that gives success its flavor.*
>
> TRUMAN CAPOTE

## Team leaders

- طرفة الشريدي
- حمود القاضب

## Girls team members

منيرة السدحان
لينا المزيد
سديم الحازمي
نورة المسعد
وسام ال حويس
رانيا المطيري
الجوهرة البنيان
شادن العبيد
سديم آل زايد
روان باقادر
ميس العجمي
نورة السالم
نوف السبيعي
ندى بابللي
دانة نائب الحرم

## Boys team members

عبداللطيف المشاط
بسام الاسمري
ماجد العسكر
باسل فقيها
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