Drug Therapy for gout and management of hyperuricemia

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Objectives

- Contrast the treatment of acute and chronic gout
- Drugs used for management of an acute attack of gout (e.g. colchicine, certain NSAIDs & glucocorticoids).
- Drugs used for the long-term management of gout (uricosuric agents & allopurinol)
- Mechanism of action, toxicities of the different groups of drugs used in the management of gout
- List the drugs that can precipitate gout

What is gout?

- **Inflammatory arthritis**
- **Due to monosodium urate crystals deposition** in tissues (joints & kidney)
- Presents with acute self-limiting attacks of severe **agonising** pain
- Chronic – causes **tophi** (masses of uric acid crystals) deposits, joint damage and chronic pain
- **The normal reference range for uric acid is:**
- 1.5 – 6.0 mg/dL for adult female
- 2.5 to 7.0 mg/dL for adult male
- uric acid crystals start to form at **6.8 mg/dL**.

Gouty arthritis

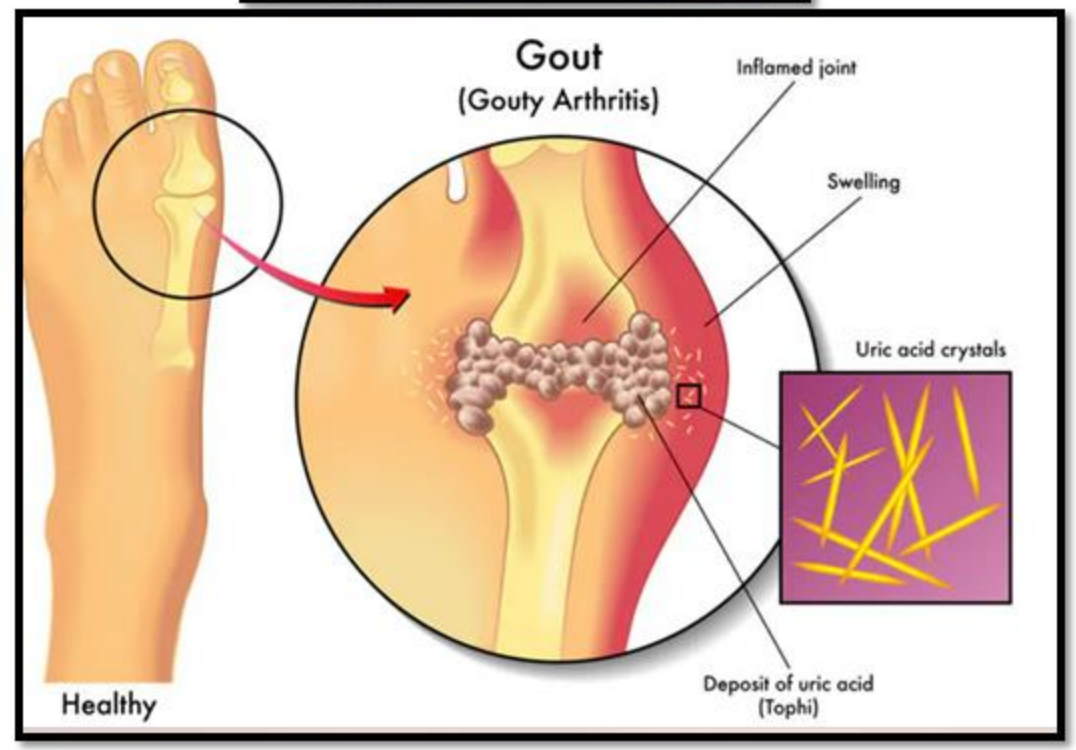
- Gouty arthritis affects **only one joint at a time** – often the toes, ankle, or knees.
- **Phases:**

➢ **Flares (flare up):** when symptoms worsen. An acute attack of gout typically lasts between 5 and 7 days.

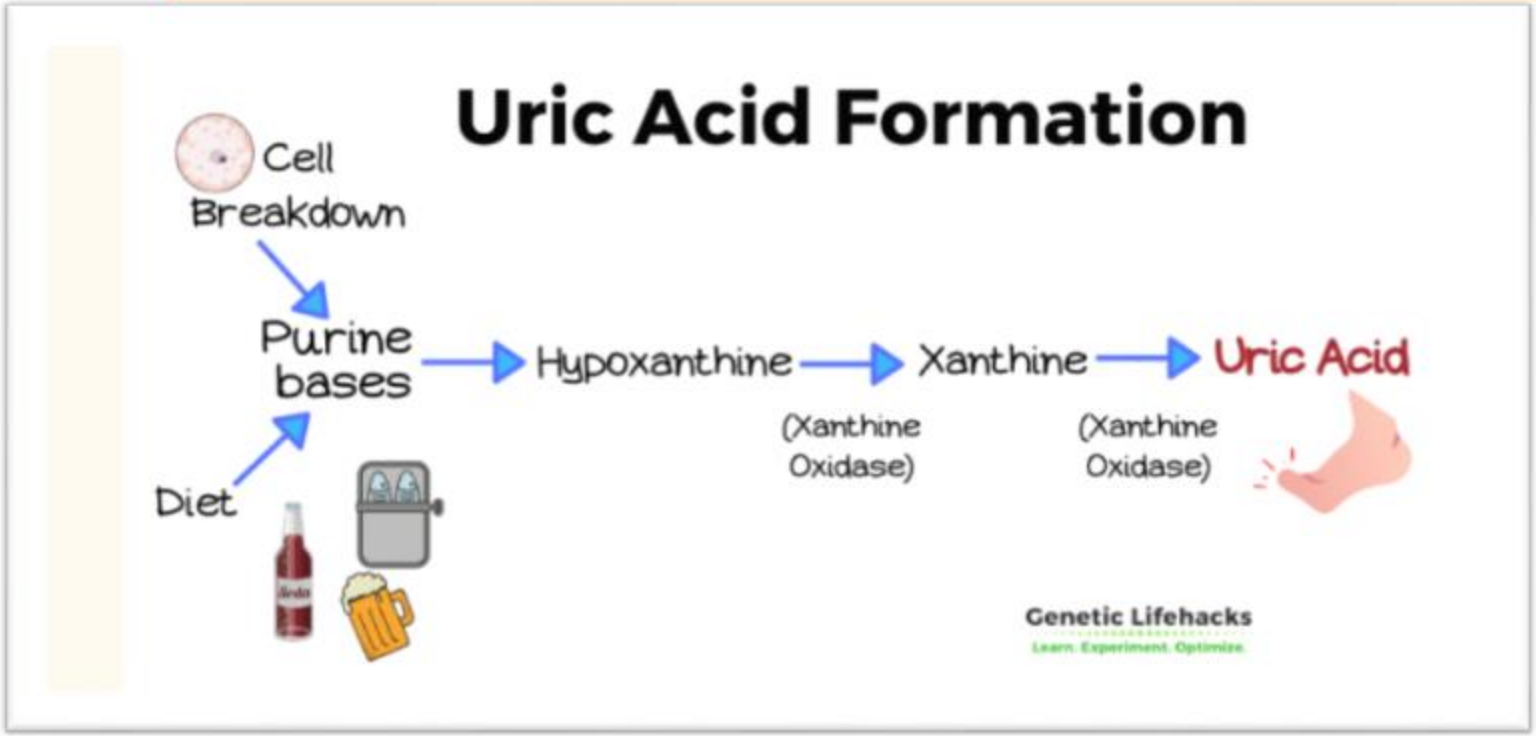
➢ **Remission**: when there are little or no symptoms

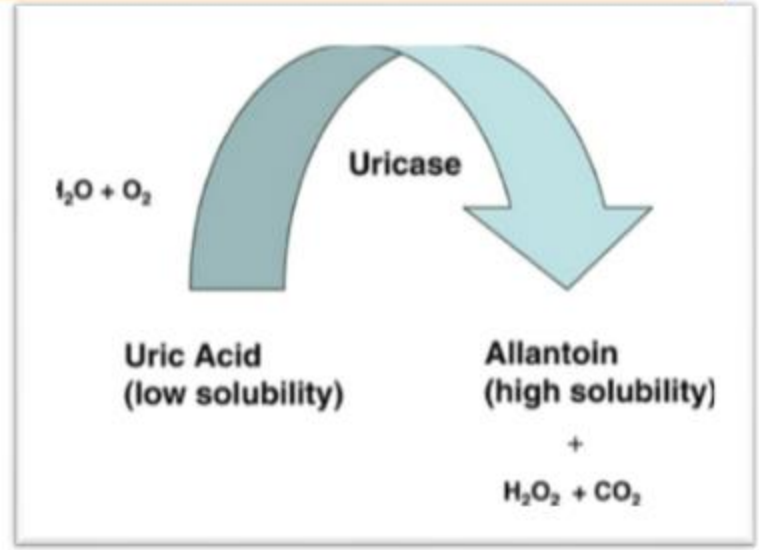
- **Symptoms of gout:**

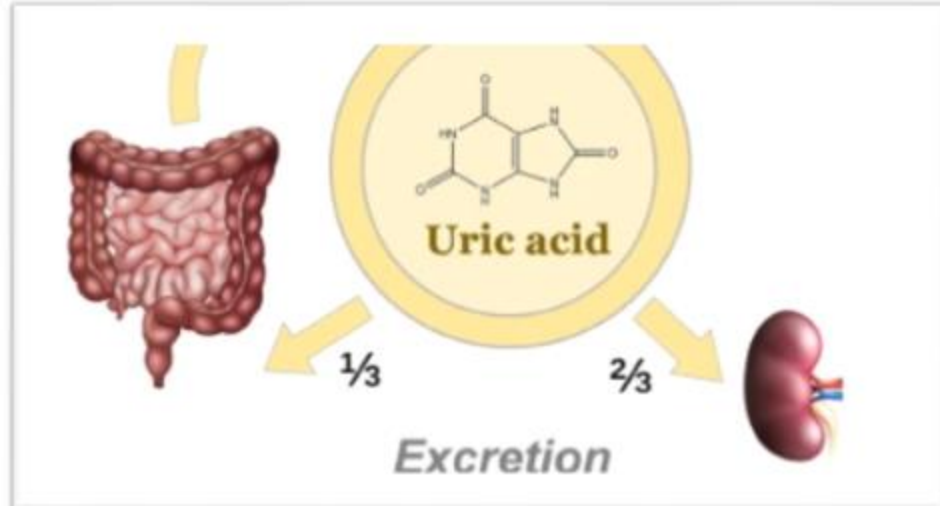
❖ Redness
❖ Swelling
❖ Sever pain
❖ Heat
❖ Limitation of movement



Uric acid formation and kinetics







Aetiology

- **1- Overproduction of uric acid: (10%): secondary hyperuricemia**
- **Diet**: high purine intake: alcohol, fructose, seafood: (mussels, tuna, sardines) , red meat, organ meat
- **Increased cell turnover (malignant tumours): tumour lysis syndrome**
- **Genetic predisposition**: **Lesch Nyhan syndrome**

2- Decreased uric acid excretion (90%): primary hyperuricemia

- **Risk factors:**
- High purine diet
- Rapid weight loss- obesity
- Family history- males
- Drugs: thiazide diuretics
- Diabetes type 2- blood tumours

Idiopathic decrease in uric acid excretion 90%

Management of gout

Non-pharmacological

Pharmacological

Non- pharmacological treatment of gout

- **Patients should be educated about**: the importance of lifestyle changes.
- **In overweight patients:** dietary modification to achieve ideal body weight should be recommended
- **Reduction of high purine foods and red meat**

Drugs for Treatment of Gout (pharmacological)

- Hyperuricemia does **NOT** always lead to gout, but **gout is always preceded by hyperuricemia.**
- **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.

Drugs for treatment of gout

Hypouricemic drugs

In chronic gout

Uric acid levels> 7 mg/dl

To prevent future gout attacks

- **1- Decreasing uric acid synthesis:**
- **selective inhibitor of the terminal steps in the biosynthesis of uric acid: inhibitor of xanthine oxidase**
- **2- Increasing uric acid metabolism uricase enzyme: pegloticase**
- **3- Increasing uric acid excretion: uricosuric drugs**

Anti-inflammatory drugs

In acute attack

To relieve symptoms of acute attack

- **NSAIDs**
- **Corticosteroids**
- **Colchicine: slow onset**

Pain subside within 1 hour

Drug therapy of acute gouty attack

- Acute attacks are treated with **indomethacin**

- **Benefits:**

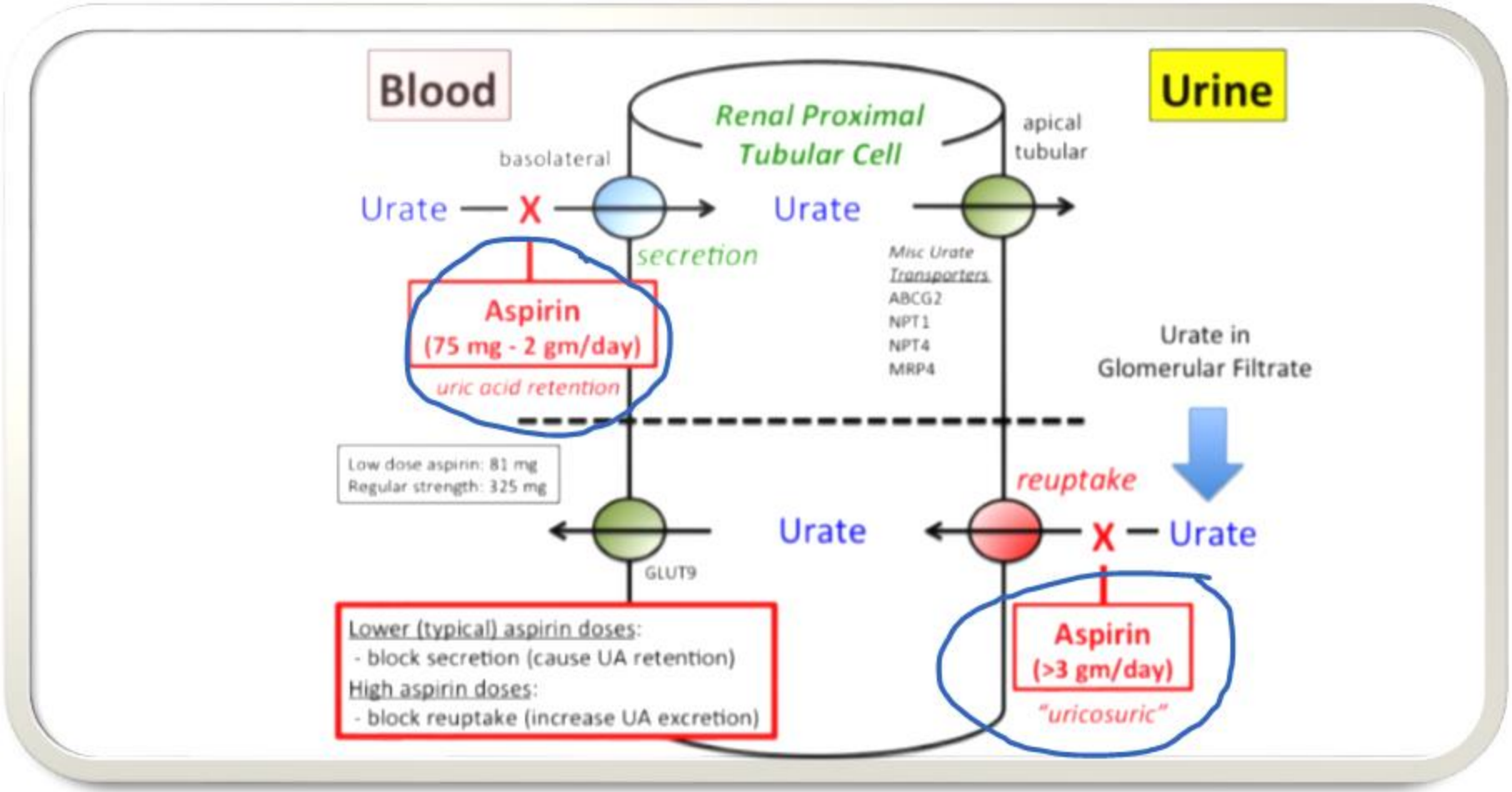
- 1- **Anti-inflammatory**: decreasing migration of macrophages into the affected area

- 2- **Analgesic:** relieving pain.

- NSAIDs other than indomethacin are also effective

- **Aspirin is contraindicated, because it competes with uric acid for the organic acid secretion mechanism (excretion) in the proximal tubule of the kidney.**

Aspirin in management of gout



Colchicine

- **Source:** plant alkaloid
- Colchicine is an **anti-inflammatory drug** primarily used in the management of acute gouty arthritis, familial Mediterranean fever, and sometimes in pericarditis and Behçet's disease (off-label)
- It is **NOT** an analgesic or uric acid–lowering agent, but it inhibits leukocyte activity, which is key to managing gout flare-ups.

Colchicine

- **Mechanism of action:**
- **Mitotic blocker:** Colchicine blocks cell division by binding to mitotic spindles (microtubules):
- inhibition of mitotic division in macrophages: inhibition of release of cytokines (IL-1β)
- Blocks neutrophil migration and activation (key to manage gout flare-ups)
- **Dose:** Colchicine tablet: 0.6 mg One Tablet, after one hour: one tablet, after 12hrs.: one tablet /12 hrs.(till improvement or toxicity)
- **Disadvantages:** (2nd choice in acute gouty attacks)
- 1- **Slow onset**: alleviates pain within 12 h
- 2- **Sever side effects**
- **3- Narrow therapeutic index**

Colchicine

- **Therapeutic uses of colchicine in gout:**
- Colchicine must be administered within 24 to 48 hours of onset of acute attack to be effective.
- **Pharmacokinetics:**
- **Absorption**: rapid absorption from the GI tract after oral administration.
- **Metabolism**: liver (**CYP3A4**)
- **Excretion**: fecal or renal.

Adverse effects of colchicine:

- **Most common**: nausea, vomiting, and **diarrhea**.
- **Most rare:** Chronic administration may lead to myopathy, and **alopecia.**
- **Most dangerous**: **aplastic anemia**: bone marrow depression 50% mortality

- **PRECAUTIONS**:
- 1- Contraindicated in **pregnancy**
- 2- Should be used with caution in patients **with hepatic, renal (creatinine clearance of less than 50 ml/min), or cardiovascular** disease.
- **3- Narrow therapeutic index: The fatal dose has been reported as low as 7 to 10 mg.**
- **4- Concurrent administration with enzyme inhibitors (CYP3A4): Clarithromycin potentiates colchicine toxicity**

Comparative Analysis: Colchicine vs NSAIDs in Gout

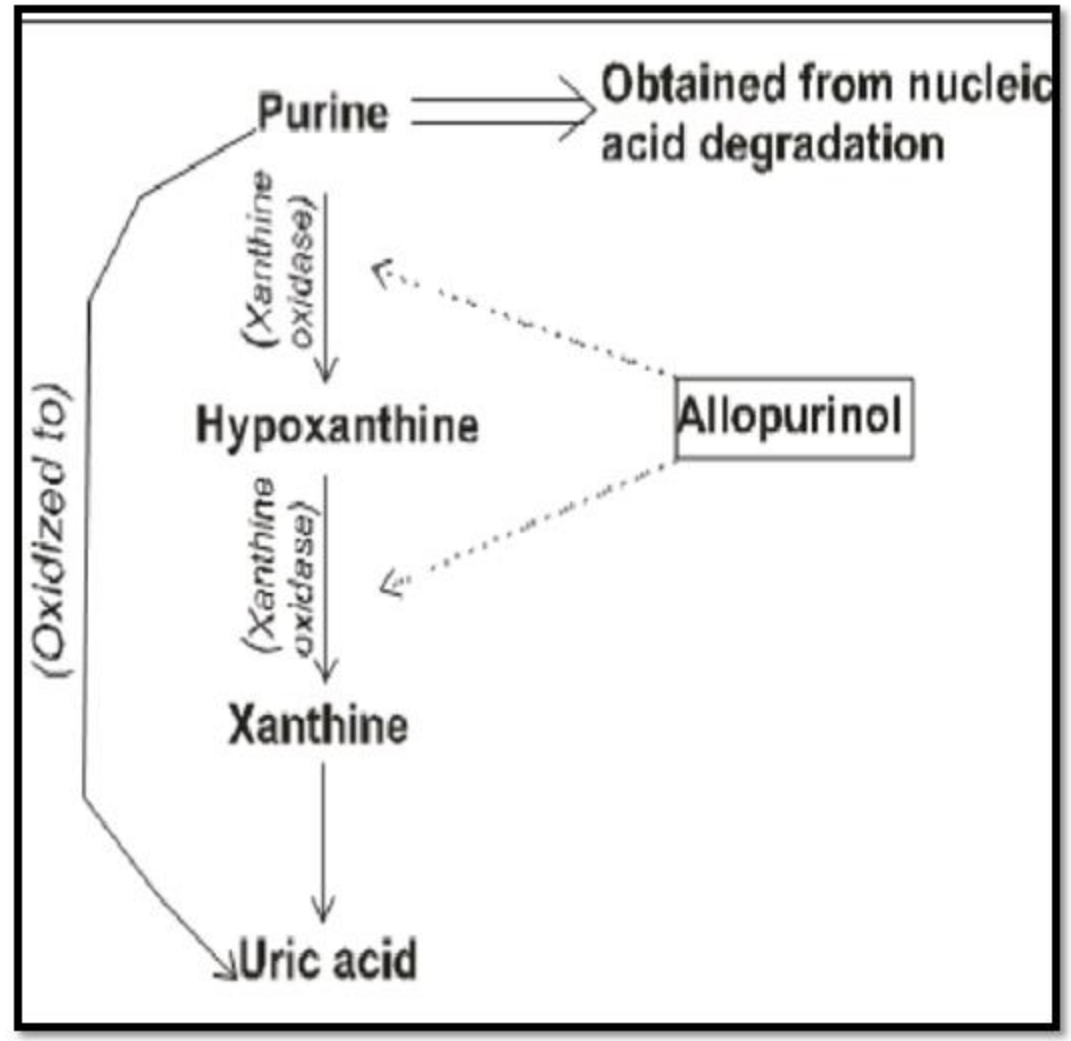
Feature	Colchicine	NSAIDs
Mechanism	Blocks neutrophil activity	Inhibits COX enzymes (prostaglandins)
Onset of action	Slower (within hours)	Rapid (minutes–hours)
Uric acid effect	No effect	No effect
Adverse effects	GI, myopathy, marrow suppression	GI bleeding, renal toxicity
Preferred use	When NSAIDs are contraindicated	First-line (in absence of contraindication)

Drugs used for chronic gout /hyperuricemia

Allopurinol & (febuxostat)

- Allopurinol is a **purine analogue**
- **Mechanism of action:** potent inhibitor of xanthine oxidase (competitive): **reducing Uric Acid Synthesis**
- **By decreasing uric acid production: relieves the symptoms of gout, which may include painful tophi, joint pain, inflammation, redness, decreased range of motion, and swelling**
- **Therapeutic uses**:
- **chronic hyperuricemia**
- 1- Primary hyperuricemia of gout (UA excretion)
- 2- Secondary hyperuricemia: tumor lysis syndrome, Lesch-Nyhan syndrome (UA production)
- **Chronic gout**: > 2 attacks of acute gout/ year
- **Dose**: single daily dose or divided doses: 100-300 mg/ day

- **Pharmacokinetics of allopurinol:**
- **Absorption:** Completely absorbed after oral administration.
- **Metabolism:** The primary metabolite is oxipurinol: t ½ is up to 24 hours; the half-life of allopurinol is 2 hours (rapid renal clearance).
- **Excretion:** The drug and its active metabolite are excreted in the feces (20%) and urine (80%).



Mechanism of action of allopurinol

Adverse effects of allopurinol

- 1- Hypersensitivity (skin rash): may be fatal: **Stevens-Johnson syndrome (SJS)**
- 2- Nausea, vomiting, diarrhea
- **Precautions:**
- 1- **NEVER** use in acute gouty arthritis
- 2- Allopurinol interferes with the metabolism of the **anticancer agent 6-mercaptopurine** and the **immunosuppressant azathioprine, theophylline** requiring a reduction in dosage of these drugs.
- 3- Allopurinol decreases excretion of abacavir (increasing serum levels)
- 4- Avoid in pregnancy use with **caution during lactation**
- 5- Take with a full glass of water.
- 6- Take with food (to avoid stomach irritation), Avoid alcohol.
- **N.B. febuxostat**: **a potent, non-purine selective xanthine oxidase**
- It is often used when allopurinol is ineffective or not tolerated

Uricosuric drugs

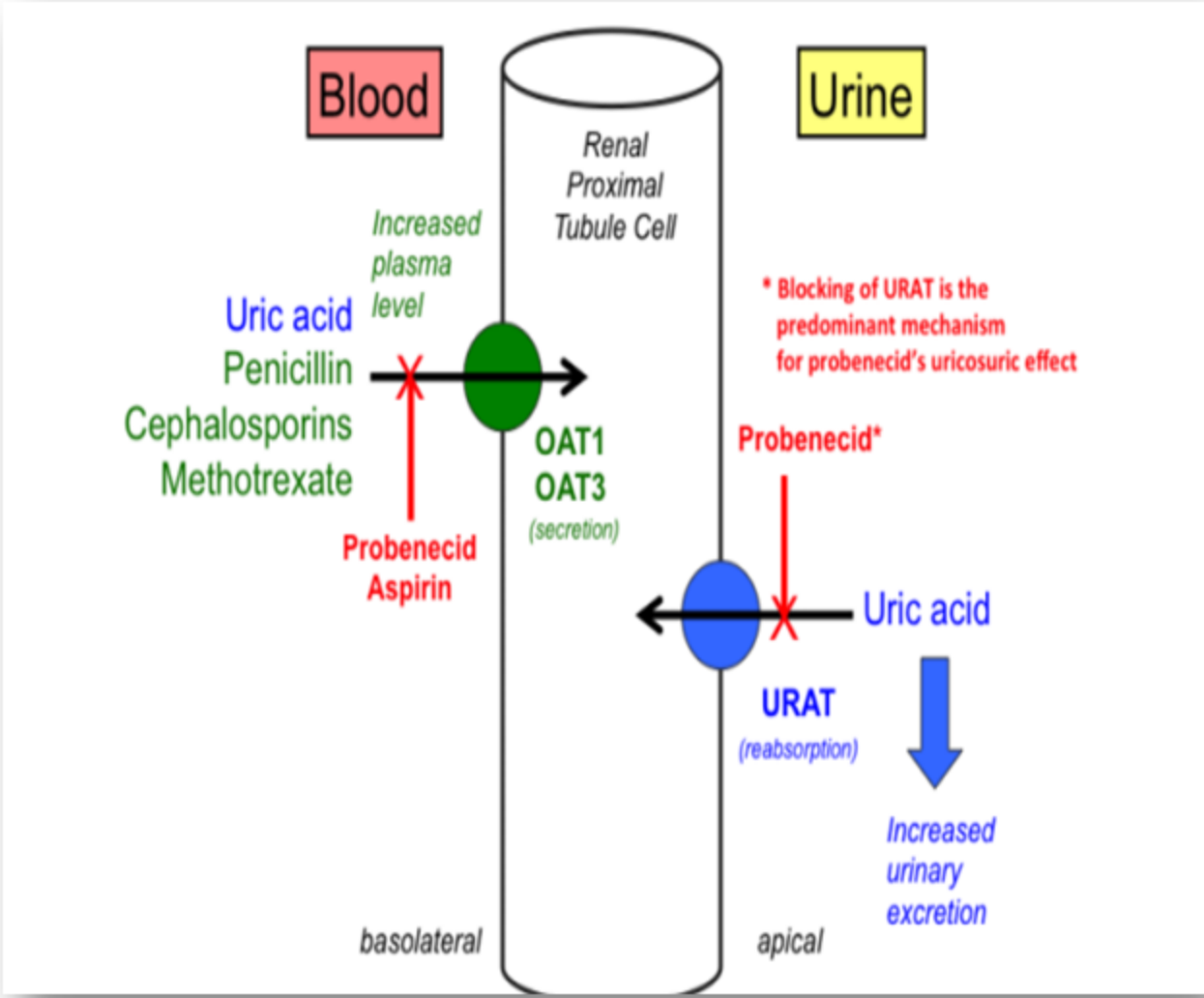
- Substances that **increase the rate of uric acid excretion in the urine** by reducing its reabsorption in the renal proximal tubules, typically by inhibiting the URAT1 transporter which is responsible for reabsorbing uric acid from the urine back into the blood.
- **Probenecid and sulfinpyrazone:**
- These drugs are **weak organic acids** that promote renal clearance of uric acid by inhibiting the transporter of reabsorption in the proximal tubule that mediates urate reabsorption.
- **Clinical tip:** At the proximal tubules, **probenecid competitively inhibits the secretion (excretion) of many weak organic acids** including penicillins, most cephalosporins, and some other β-lactam antibiotics.
- This results in an increase in the plasma concentrations of these drugs. Thus, the drug can be used for therapeutic advantages to increase concentrations of certain β-lactam antibiotics in the treatment of gonorrhea, neurosyphilis, or pelvic inflammatory disease
- **Dose:** high dose: tablet 500mg : 2-3 tab./day
- Dose used to increase antibiotic concentration: 500 mg/ day

- **Lesinurad** (a newer uricosuric drug) is a URAT1 inhibitor approved in 2015 to treat high blood uric acid (hyperuricemia) associated with gout.
- **Daily dose**: 200 mg tablet alongside a xanthine oxidase inhibitor as using it alone increases the risk of acute renal failure.
- **Precautions during uricosuric therapy:**

1- Never use in acute attack

2- Increase fluid intake (preventing formation of uric acid kidney stones)

3- Alkalization of urine (preventing stone formation and dissolve existing stones)



Pegloticase

•**Pegloticase** is a **PEGylated enzyme** containing a recombinant form of **mammalian uricase enzyme** derived from a genetically modified strain of E. coli.

•Pegloticase lowers uric acid by **promoting the oxidation of uric acid to allantoin, which is excreted by kidney**.

• Pegloticase was initially approved in the U.S. in 2010.

•**T1/2**: 12 days

•**Dose**: 8mg IVI/2 weeks

•Onset: 24 h

•**Indication**: In chronic gout: sever and complicated cases: sever gouty tophi, gouty nephropathy.

Drugs contraindicated in gout

- These drugs may precipitate an acute attack of gout by blocking the renal tubular secretion of uric acid, and raising serum uric acid concentrations.
- **During a gout flare, it is recommended to avoid certain medications that can worsen the condition**:
- **1- NSAIDs** like ibuprofen, naproxen, and indomethacin in patients with kidney disease, heart failure, or a history of stomach ulcers
- **2- Aspirin** even in low doses, as it can worsen a gout attack by inhibiting uric acid excretion
- **3- Diuretics** : hydrochlorothiazide and furosemide, which can raise uric acid levels
- **4- Alcohol**: which can increase uric acid production and worsen inflammation
- **Never start** uricosuric treatment during an acute flare as they can initially worsen symptoms; however, if the patient is already on these medications, should continue taking them.

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Thank you