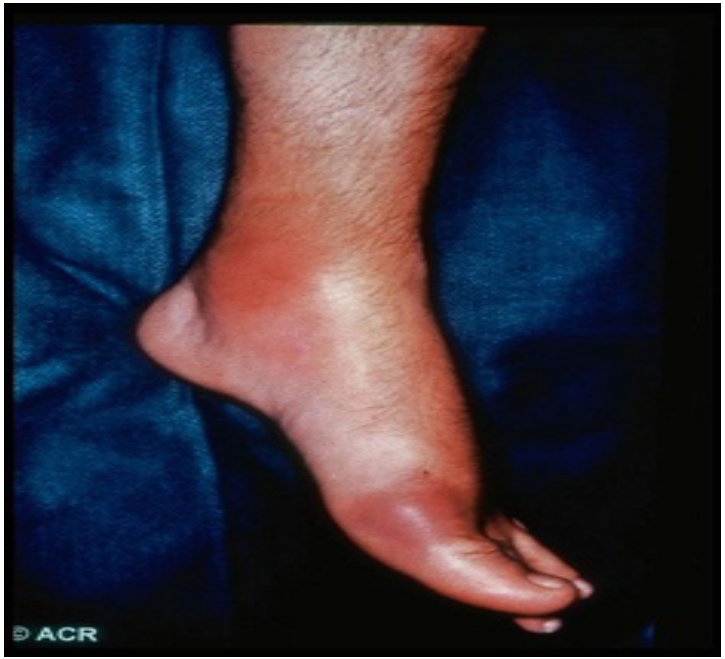
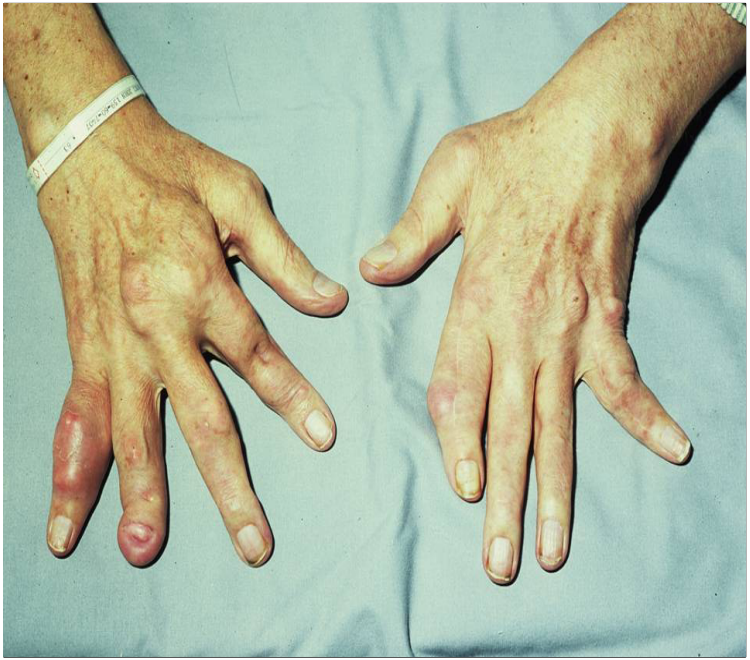
Drugs used for treatment of gout

Gout disease





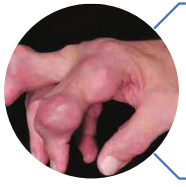
Outlines

- 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 treatment of gout.
- Identify the mechanism of action of drugs used for treatment of gout.
- Study in detail the pharmacology of drugs used for treatment of gout.

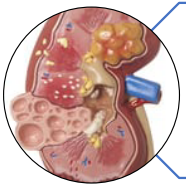
What is Gout?

- Gout is usually characterized by recurrent attacks of **acute inflammatory arthritis with red, tender, hot and swollen joints.**
- Deposits of sodium urate crystals in articular, peri-articular, 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.

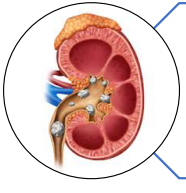
Untreated gout may Lead to…



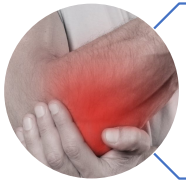
Tophaceous: Masses of monosodium urate crystals in cartilage & joints.



Urate nephropathy: Renal failure.



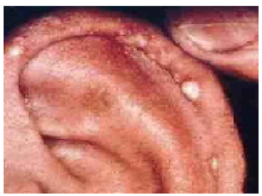
Nephrolithiasis: Renal stones.

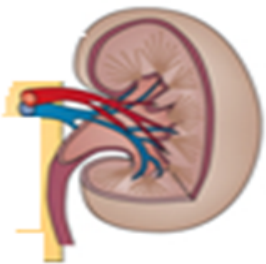


Joint inflammation.

Untreated gout may Lead to…

Tofi





Nephrolithiasis

Epidemiology

- Gout was historically known as "**the disease of kings**" or "**rich man's disease**."
- Prevalence of hyperuricemia 5%.
- Prevalence of gout 0.2%.
- Male to female ratio 10:1.

Pathophysiology

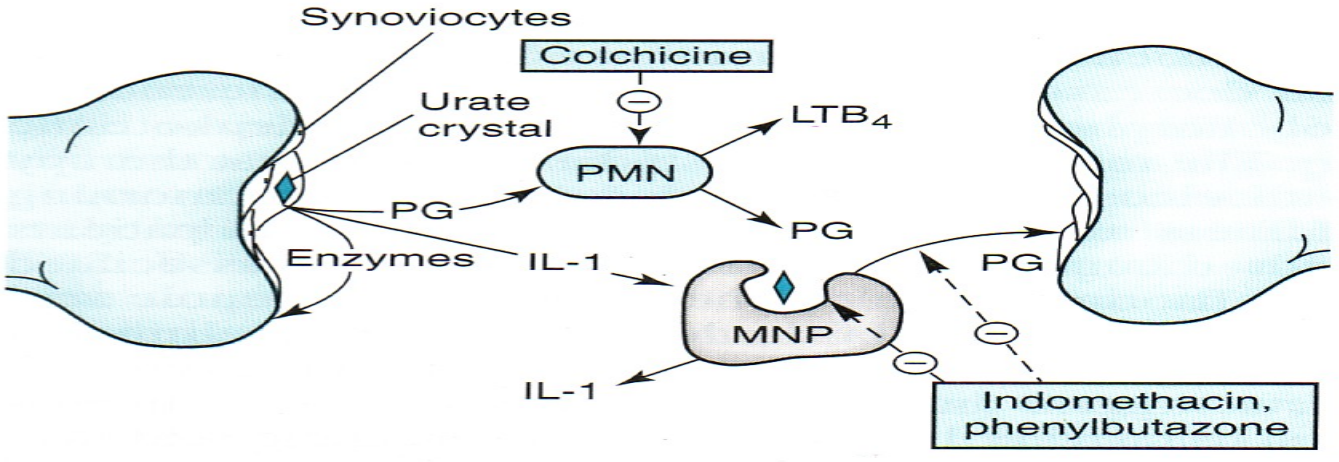


Figure 36–5. Pathophysiologic events in a gouty joint. Synoviocytes phagocytose urate crystals and then secrete inflammatory mediators, which attract and activate polymorphonuclear leukocytes (PMN) and mononuclear phagocytes (MNP) (macrophages). Drugs active in gout inhibit crystal phagocytosis and polymorphonuclear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

Stages of gout

1

Asymptomatic hyperuricemia

Elevated serum urate with no clinical manifestations of gout

Treat or not treat?

2

Acute flares (intermittent gout)

Acute inflammation in joint caused by free urate crystals

Management: terminate attack

3

Intercritical Gout

The interval between acute Flares

Management:

Prevent recurrent attack

4

Chronic gout (complication)

Long term gout complications

Management:

-Prevent complications

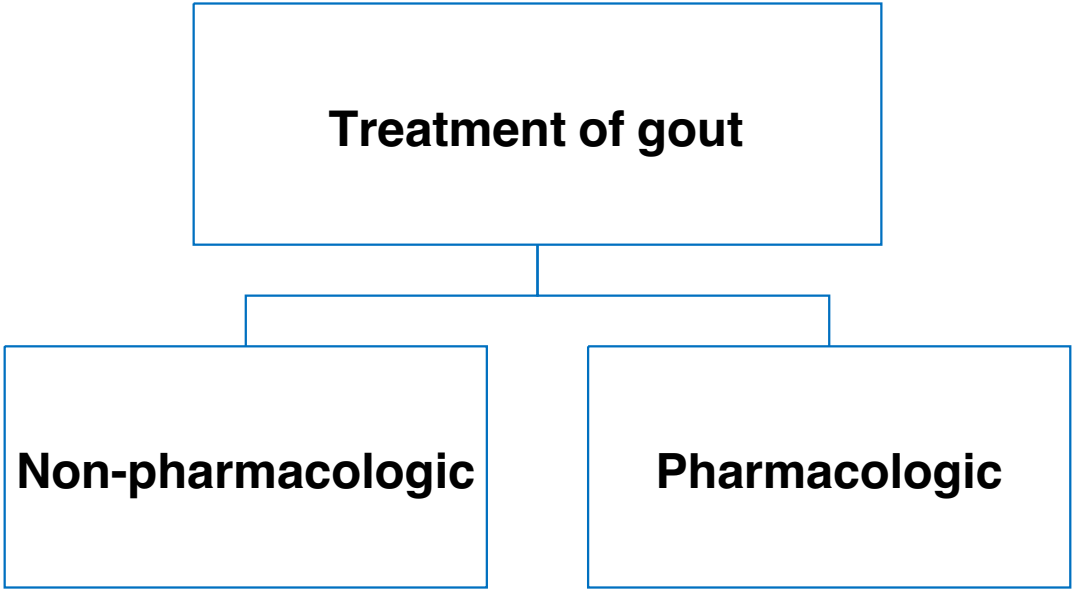
-lower serum uric acid

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

causes

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

Drugs in gout



Non-pharmacologic Therapy

Lifestyle modifications such as:

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

Aim of pharmacotherapy

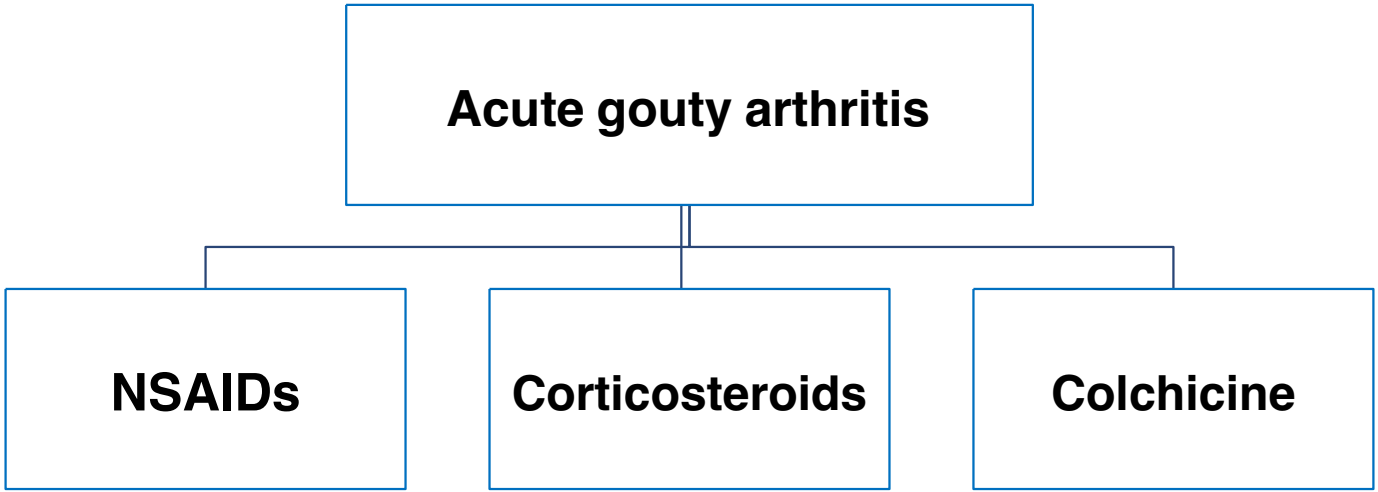
- Most therapeutic strategies for gout involve lowering the uric acid level below the saturation point **(<6 mg/dL),** thus preventing the deposition of urate crystals.
- This can be accomplished by:

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

Uricostatic	Allopurinol Febuxostat
Uricosuric	Probenecid Sulfinpyrazone
Anti- inflammatory	NSAIDs Steroids
Tubulin inhibitors	Colchicine

Treatment of acute gout



NSAIDS

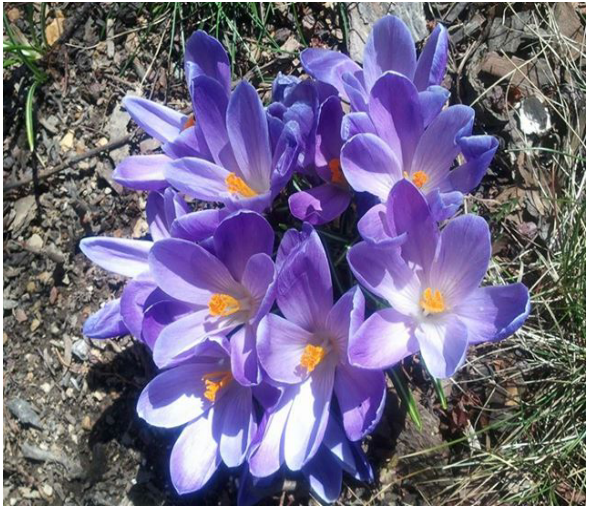
- **NSAIDs** are the most commonly used **first-line treatment**.
- Head-to-head studies show few differences between drugs.
- Full doses of NSAIDs should be initiated immediately and tapered after resolution of symptoms.
- Avoid NSAIDs:
  - **GI ulcer.**
  - **Bleeding or perforation.**
  - **Renal insufficiency.**
  - **Heart failure.**
  - **Use of oral anticoagulants.**

Steroids

- **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 short-term use of corticosteroids.
- In elderly people, patients with hepatic impairment, peptic ulcer disease, ischemic heart disease, hypersensitivity to NSAIDs.
- Route administration:
  - Intra articularly (preferred route if one or two joints affected)
  - Orally.
  - Intramuscularly or intravenously.

Colchicine

- Alkaloid obtained from autumn crocus.
- Minimal effect on uric acid synthesis, excretion and is not analgesic.



Colchicine

Mechanism:

- Binds to microtubules in neutrophils.
- Inhibits cell division.
- Inhibits chemotactic factors.
- Inhibits inflamosomes and IL-1 production.

Colchicine

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
- Use should be avoided in patients with a creatinine clearance of less than 50 ml/min.

Colchicine

Clinical uses:

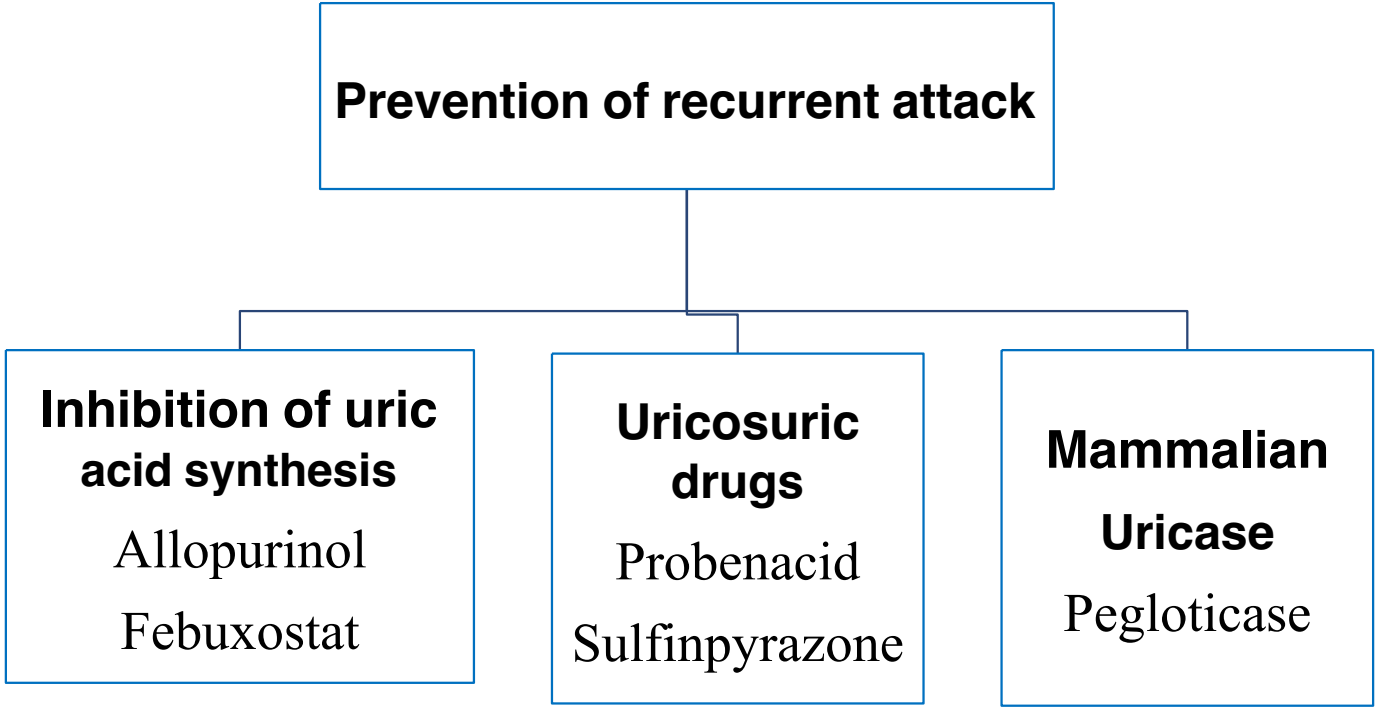
- Treatment of gout flares.
- Prophylaxis of gout flares.
- Treatment of Mediterranean fever.

Colchicine

ADRs:

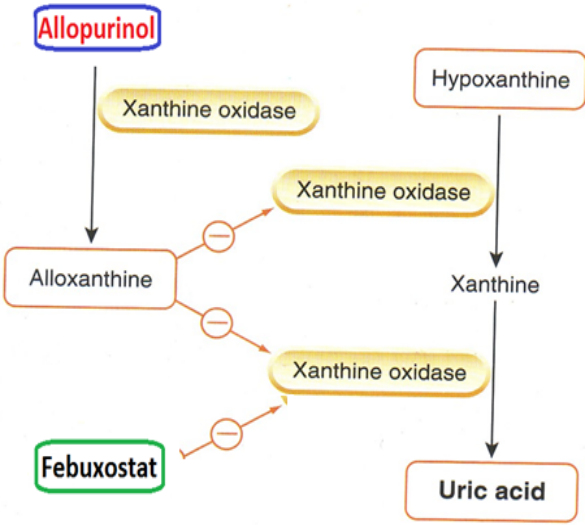
- Diarrhea (sometimes severe).
- Nausea and Vomiting.
- Abdominal cramps, Dehydration.
- Bone marrow depression.
- Cardiac toxicity, arrhythmia.
- Vascular collapse.
- Hepatotoxicity, alopecia.

Prevention of recurrent attack



Inhibitors of uric acid synthesis

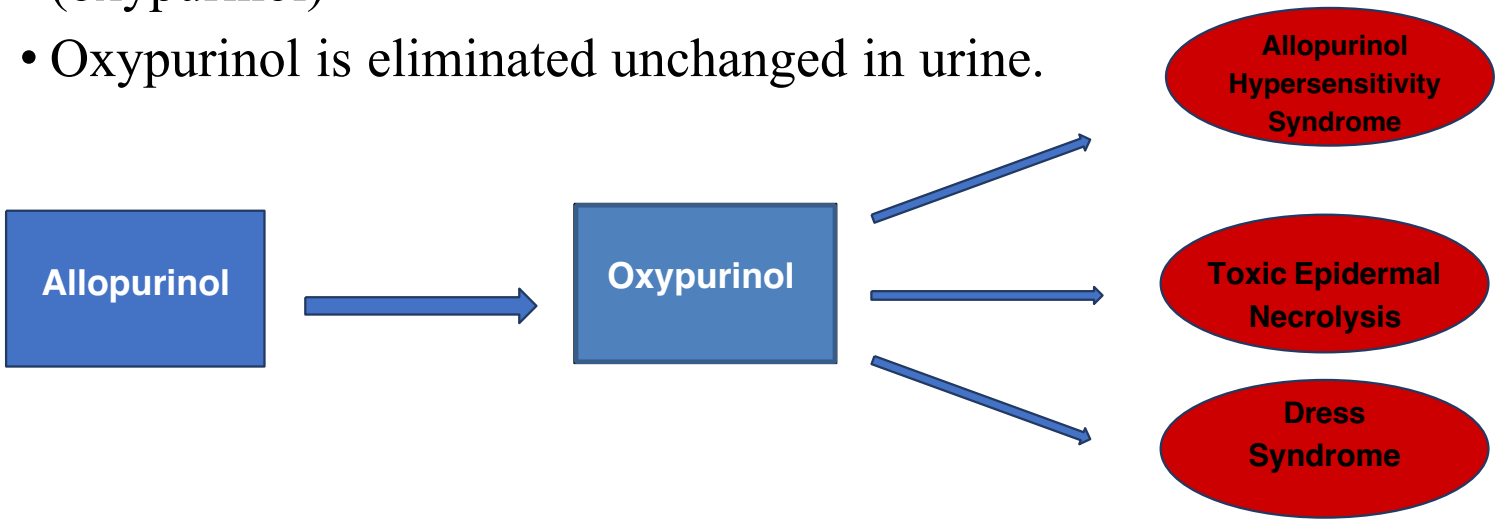
- Inhibit xanthine oxidase (include: allopurinol & febuxostat).
- Allopurinol is metabolized by xanthine oxidase into alloxanthine which is pharmacologically active.



Inhibitors of uric acid synthesis

Pharmacokinetics:

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



Inhibitors of uric acid synthesis

ADRs:

- Diarrhea, nausea, abnormal liver tests.
- Acute attacks of gout.
- Fever, rash, **toxic epidermal necrolysis,** hepatotoxicity, marrow suppression, vasculitis.
- **DRESS** syndrome: 20% mortality rate

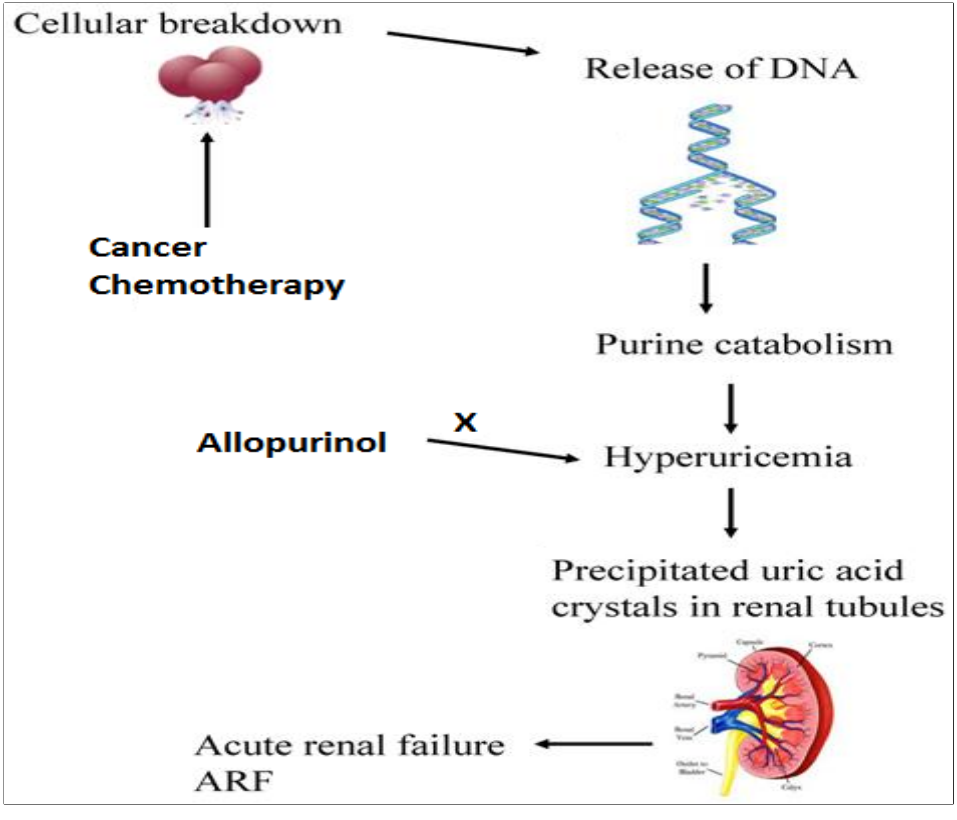
Drug Reaction, Eosinophilia, Systemic Symptoms: skin rash, fever, lymphadenopathy, and inflammation of the liver, lung, and heart.

Allopurinol

Clinical uses:

- Management of hyperuricemia of gout.
- 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.
- Prevention of recurrent calcium oxalate kidney stones.

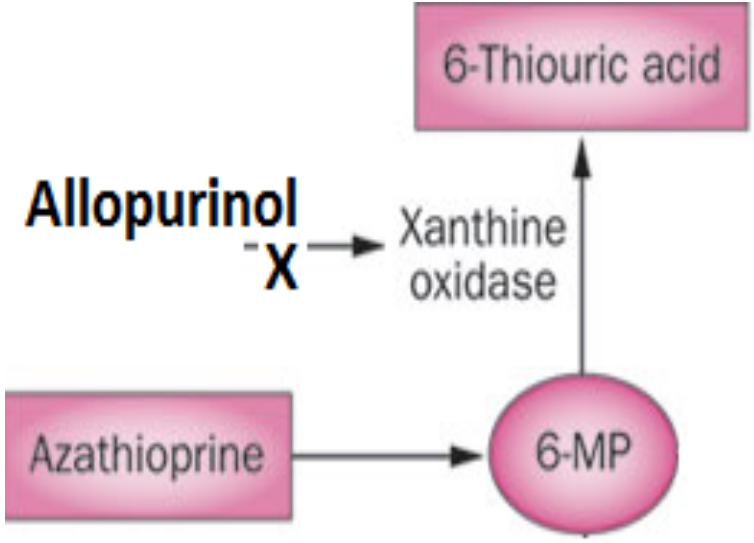
Allopurinol



Allopurinol

Drug Interactions:

- **Warfarin** & **dicumarol** **(**inhibits their metabolism).
- Reduce the metabolism of **6-mercaptopurine** and **azathioprine**.
- With **ampicillin**: Increases frequency of **skin rash.**



Febuxostat

- Oral specific xanthine oxidase inhibitor.
- 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.

Febuxostat

Pharmacokinetics

- Given orally once daily, well absorbed (85%).
- Metabolized in liver , mainly conjugated to glucouronic acid.
- Given to patients who do not tolerate allopurinol.
- 99% protein bound.
- ½ 8 hours.

Febuxostat

ADRs

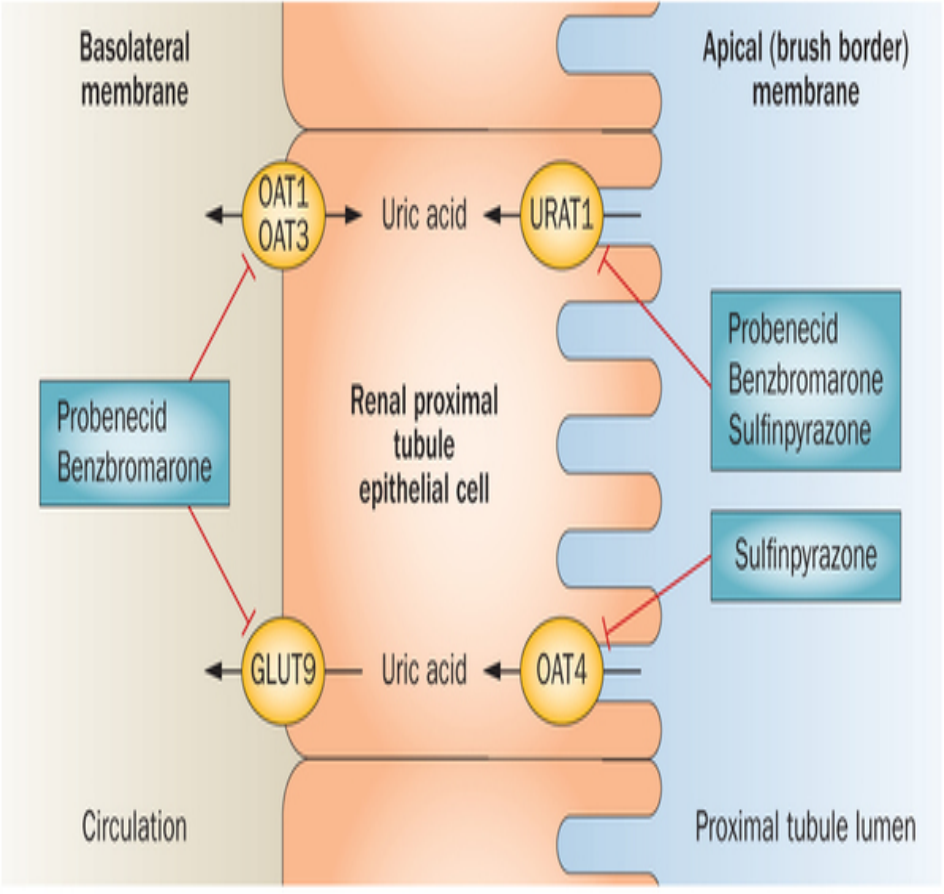
- Increases number of gout attacks during the first few months of treatment.
- Increases level of liver enzymes.
- Nausea, Diarrhea.
- Headache.
- Numbness of arm or leg.

Uricosuric drugs

Mechanism

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

Uricosuric drugs



Uricosuric drugs

Effect

- Control hyper-uricemia and prevent tophus formation.
- Probenecid is moderately effective.
- Increases risk of nephrolithiasis…
- Not used in patients with renal disease
- Some drugs reduce efficacy (e.g., aspirin)

Probenecid

ADRs

- Exacerbation of acute attack.
- Risk of uric acid stone.
- GIT upset.
- Allergic rash.

Probenecid

Contra-indications

- History of nephrolithiasis.
- Recent acute gout.
- Existing renal disease.
- Less effective in elderly patients.

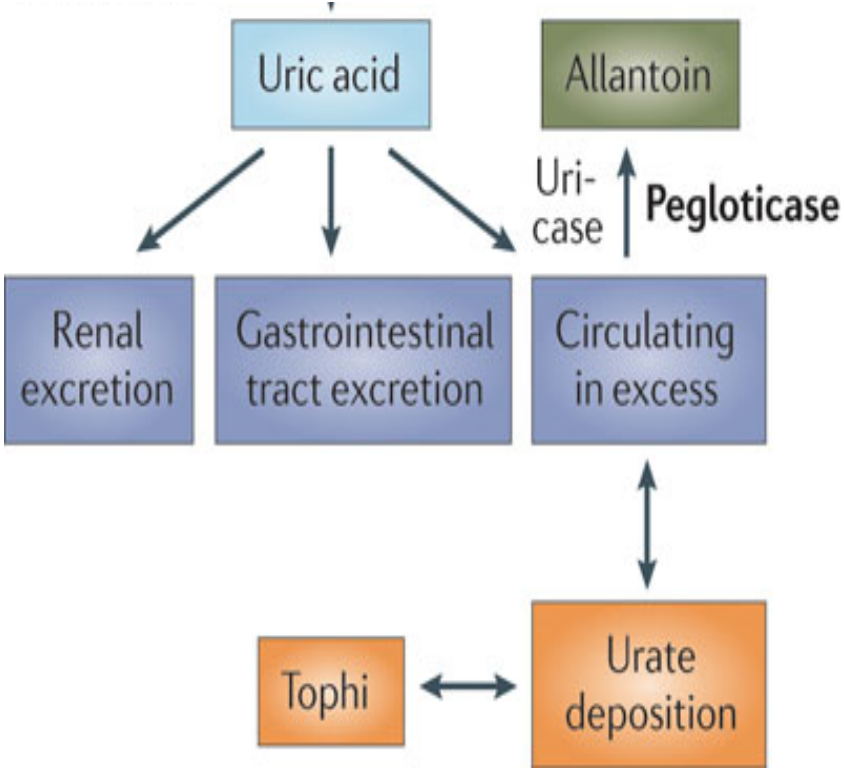
Sulfinpyrazone

- Sulfinpyrazone can aggravate peptic ulcer disease.
- Aspirin reduces efficacy of sulfinpyrazone.
- Sulfinpyrazone enhance the action of certain anti-diabetic drugs.

Recombinant mammalian uricase
Pegloticase

- A uric acid specific enzyme which is a recombinant modified mammalian uricase enzyme.
- enzymatically convert urate to allantoin, which is more soluble and readily excreted in the urine.
- Given I.V. peak decline in uric acid level within 24-72 hours

Recombinant mammalian uricase
Pegloticase



Recombinant mammalian uricase
Pegloticase

- Used for the treatment of chronic gout in adult patients refractory to conventional therapy.

ADRs:

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