

## Antirheumatic Drugs

Chandan Shrestha, PhD

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## Rheumatoid Arthritis

- Autoimmune disease in which there is joint inflammation, synovial proliferation and destruction of articular cartilage.
- Systemic inflammatory diseases that primarily affect the joints.
- RA may also affect the skin, eyes, lungs, heart, blood, or nerves.

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## Signs and Symptoms

- Low grade fever
- muscle and joint aches
- morning stiffness (> hour)
- fatigue
- lack of appetite.



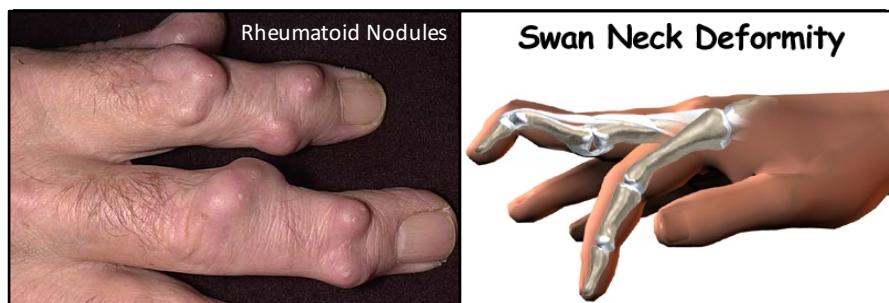
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## Diagnosis

**Blood Test** RF, ACPAs  
Others: CBC, Hb, ESR

**Imaging** X ray  
Ultrasound/ MRI



Rheumatoid factor (RF)  
Anti-citrullinated protein antibodies (ACPAs)

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## Treatment

- No known cure for RA.
- The goal of treatment is to
  - ✓ reduce joint inflammation and pain,
  - ✓ prevent joint damage, and
  - ✓ maximize joint function.
- Aggressive and Individualized Treatment
- **Exercise / Medication / Surgery**

Medications used in treating rheumatoid arthritis:

- A. fast-acting "first-line drugs" (NSAIDs and Corticosteroids) and
- B. slow-acting "second-line drugs" (also referred to as disease-modifying antirheumatic drugs or DMARDs)

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## Antirheumatoid Drug

### A. Disease modifying antirheumatic drugs (DMARDs)

1. Immunosuppressants: **Methotrexate**, Azathioprine, Cyclosporine
2. Sulfasalazine
3. Chloroquine or Hydroxychloroquine
4. Leflunomide
5. Gold
6. D-Penicillamine

### B. Biologic response modifiers (BRMs)

- TNF $\alpha$  inhibitors: Etanercept, Infliximab, Adalimumab
- IL-1 antagonist: Anakinra

### c. Adjuvant drugs: Corticosteroids (Prednisolone and others) 6

## NSAIDs

- Aspirin, Ibuprofen, Naproxen, Diclofenac, Piroxicam, Etoricoxib
- For symptomatic Treatment.
  - Reduce tissue inflammation, pain and swelling by inhibiting PGs synthesis.
  - Do not alter course of the disease.
  - Chronic use should be minimized.
  - Most common side effect related to GI tract
- Best- taking after the evening meal and then again on awakening.

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## Corticosteroids

- Potent immunosuppressant and anti-inflammatory activity
- Work rapidly to control inflammation and pain.
- More potent than NSAIDs in reducing inflammation and in restoring joint mobility and function.
- used in combination with DMARDs, which significantly enhances the benefits of DMARDs.
- Daily, low-dose needed in some patients to control their rheumatoid arthritis symptoms. (However, even low-dose oral steroids have adverse effects on bone density, blood sugar, and weight.)
- sometimes injected directly into joints for relief of flare-ups when only one or a few joints are affected.

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## Disease Modifying AntiRheumatic Drugs

- NSAIDs and corticosteroids can relieve joint inflammation and pain, they do not necessarily prevent joint destruction or deformity.
- RA requires medications to stop progressive damage to cartilage, bone, and adjacent soft tissues.
- DMARDs: Standard treatments for RA and may take weeks to months to become effective.
- used for long periods of time, even years, at varying doses.
- The most commonly used agent is **methotrexate** with other frequently used agents including **sulfasalazine** and **leflunomide**.

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## Methotrexate

- First DMARD of choice in the treatment of RA
- Methotrexate is an immunosuppressive drug and also have anti-inflammatory properties.
- **Inhibits dihydrofolate reductase**; the enzyme that converts folic acid to its active, coenzyme form, tetrahydrofolic acid (FH4).
- beneficial effects in RA are probably related to inhibition of cytokine production, chemotaxis and cell mediated reaction.
- **Adverse effect**: nausea and vomiting, rash, mild hair loss, headache, mouth sores, and muscle aches.
- **Contraindication**: Pregnancy, breast feeding, liver disease, leucopenia and peptic ulcer.

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**Azathioprine**

- Acts through its major metabolite, **6-thioguanine**.
- Suppress B cell and T cell function, immunoglobulin (Ig) production
- Used at a dosages of 2mg/kg/d in RA.
- Adverse effect: bone marrow suppression, GI disturbances. Rarely, fever, rash, and **hepatotoxicity**

**Cyclosporine**

- It is used for people with RA who have not responded to other drugs.
- Used at a dosages of 3-5mg/kg/d divided into two doses.
- The most serious and common side effects of cyclosporine are hypertension and **nephrotoxicity**.

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## Sulfasalazine

- traditionally used in the treatment **Ulcerative colitis**.



- sulfapyridine is probably the active moiety when treating RA (5-aminosalicylic acid is active moiety in ulcerative colitis).
- Suppress generation of superoxide radicals and cytokine release by inflammatory cells.
- **Adverse Effect:** Well tolerated. Common side effect includes GI upset, skin rash, headache.
- Because of fewer adverse effects it is a good alternative to methotrexate for milder / early cases.

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## Leflunomide

- An immunomodulatory drug.
- Relieve the symptoms and halt the progression of the disease.
- As effective as methotrexate; suitable alternative to methotrexate or sulfasalazine in RA.
- Rapidly converted in the intestine and in the plasma to its active metabolite, A77-1726.
- This metabolite inhibits dihydroorotate dehydrogenase and **pyrimidine synthesis** → ↓ synthesis of DNA and RNA
- Adverse effects: nausea, diarrhea, headache, hair loss, rashes, thrombocytopenia, leucopenia.
- It is not used in children and pregnant/ lactating women.

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## Chloroquine or Hydroxychloroquine

- These are originally used for preventing malaria and are now also used for mild, slowly progressive rheumatoid arthritis.
- Their mechanism of action is not known, however, they have been found to reduce monocyte IL-1, consequently inhibiting B lymphocytes.
- *Adverse Effect:* Rashes, graying of hair, irritable bowel syndrome, myopathy and neuropathy. **Ocular toxicity** may occurs at high doses. Ophthalmologic monitoring every 6-12 months is advised.

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## Biologic response modifier

- novel approach to the treatment of RA and are products of modern biotechnology.
- Have rapid onset of action and can have powerful effects on stopping progressive joint damage by targeting specific components of the immune system.
- In general, their methods of action are also more directed, defined, and targeted.

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## Biologic response modifier

### **Anti-TNF Drugs (Etanercept, Infliximab, Adalimumab)**

- They block TNF, which is a cytokine involved in the inflammatory process.

### **Interleukin-1 (IL-1) receptor antagonist (Anakinra)**

- blocks the biologic activity of IL-1 including inflammation, cartilage degradation associated with RA.
- by binding to a IL-1 to its receptor.

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## Antigout Drugs

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## Gout

- A **metabolic disorder characterized** by recurrent attack of acute inflammatory arthritis caused by **elevated levels of uric acid in the blood (hyperuricemia)**.
- Deposit in the form of monosodium urate crystal in joints and cartilage.
- Formation of uric acid calculi in the kidney also occur.
- affects 1–2% of adults in developed countries
- Big toe is the most commonly affected (50% of the cases); Podagra
- historically known as  
    "**the disease of kings**"  
    **OR**  
    "**rich man's disease**".

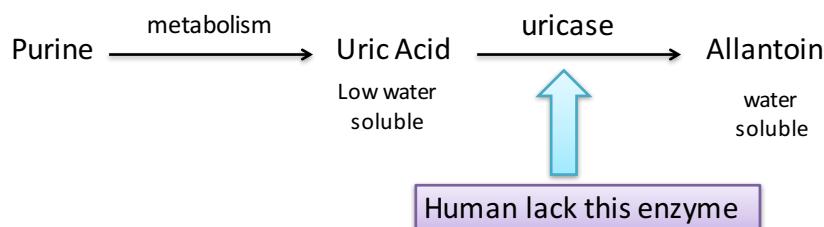


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## What is Uric Acid?

- Uric acid, a product of purine metabolism, has low water solubility, especially at low pH.



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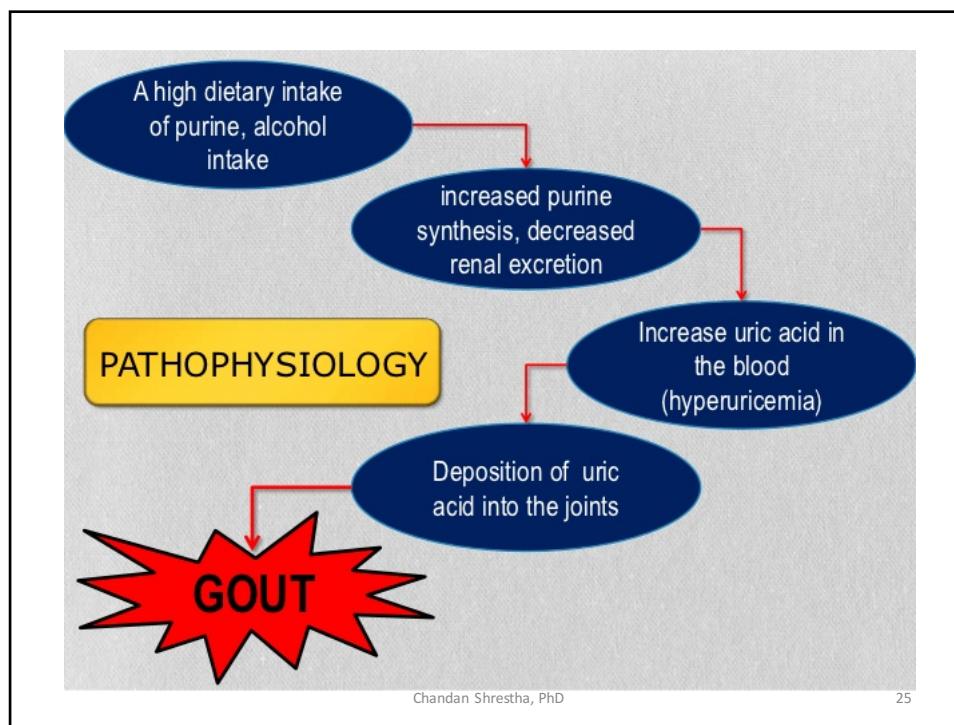
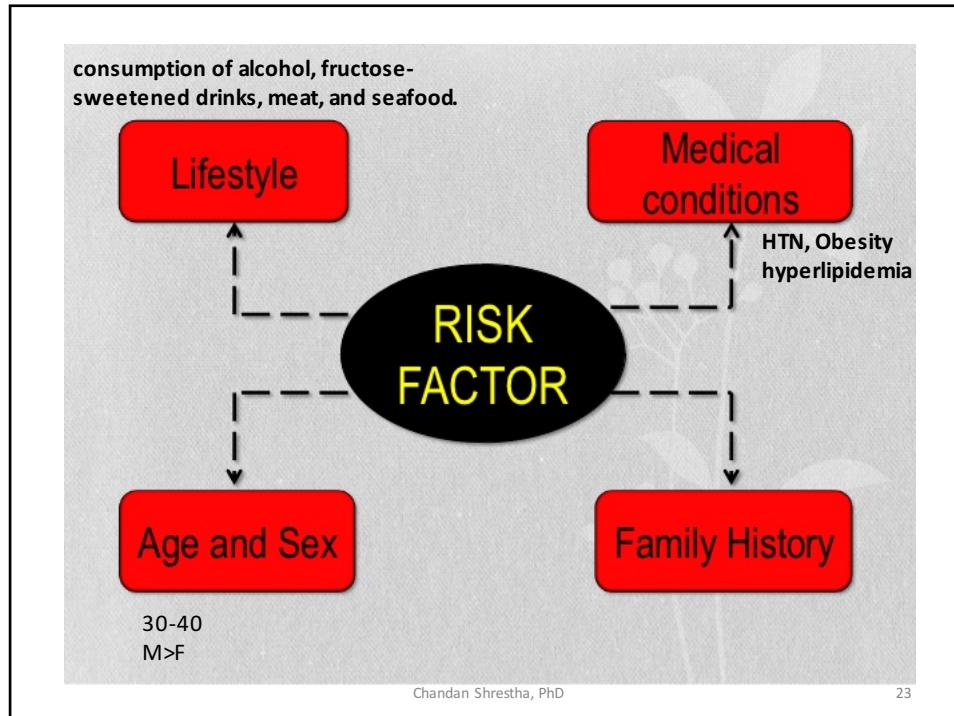
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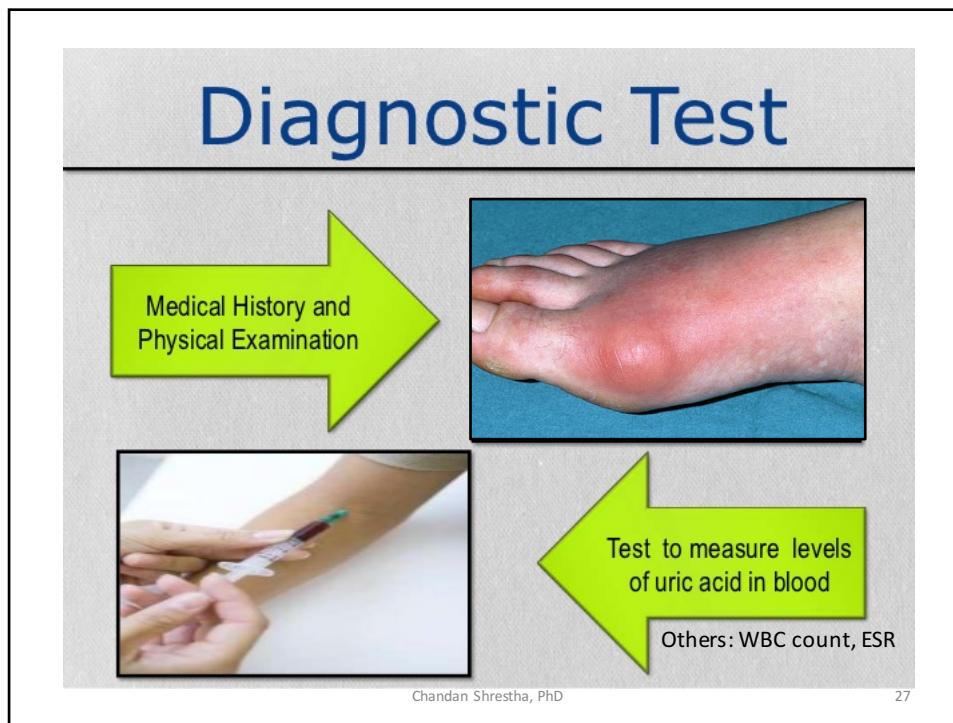
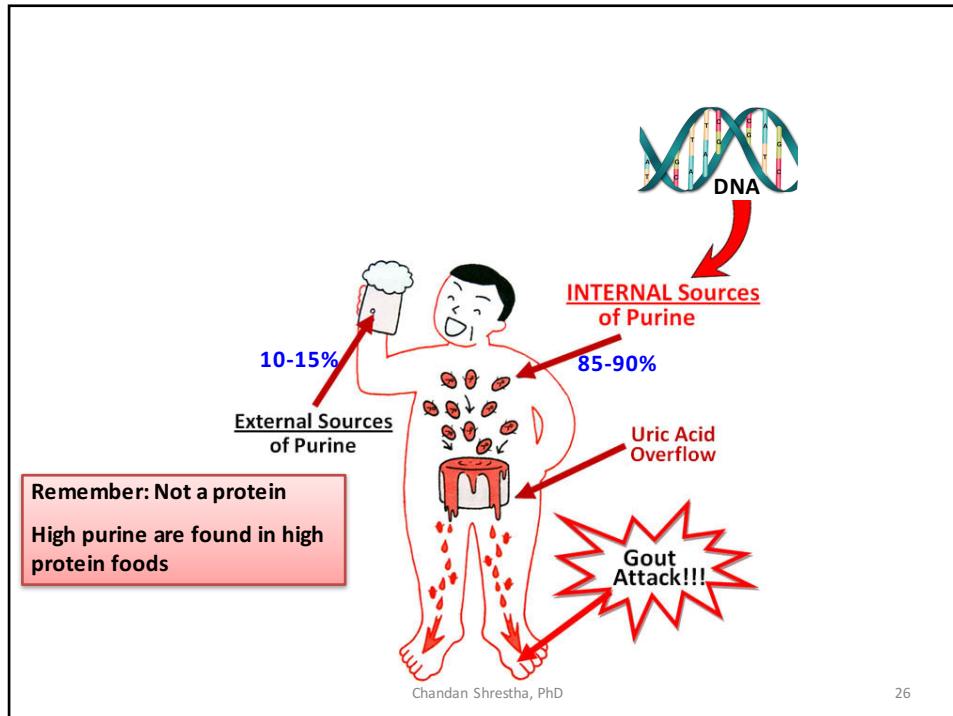
## Gout

- When blood levels are high, it precipitates and deposits in joints, kidney and subcutaneous tissue.
- The deposition of urate crystals initiates an inflammatory process involving the infiltration of granulocytes that phagocytize the urate crystals.
- This process generates oxygen metabolites, which damage tissues, resulting in the release of lysosomal enzymes that evoke an inflammatory response.
- In addition, there is increased production of lactate in the synovial tissues. The resulting local decrease in pH increases deposition of urate crystals.

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## Diagnostic Test con't

Test to measure levels of uric acid in urine

Female urinary system    Male urinary system  
Urine sample taken

Urine is tested for uric acid levels

ADAM

Normal foot    Gout in toe

Figure 1    Figure 2

Extremity X-ray

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## Diagnostic Test con't

Joint fluid analysis

Synovial Fluid  
KNEE JOINT

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## Antigout Drug

### A. For acute gout

1. NSAIDs
2. Colchicine
3. Corticosteroids

### B. For chronic gout/ hyperuricaemia

1. Uricosurics: Probenecid, Sulfinpyrazone
2. Synthesis inhibitor: Allopurinol, Febuxostat

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## NSAIDs

- strong antiinflammatory action but not uricosuric action.
- Indomethacin, Naproxen, piroxicam or diclofenac at high and quickly repeated doses.
- Effective in terminating the attack but response is slower (12-24 hr) than colchicine
- Majority of patients prefer NSAIDs over colchicine.
- Long term therapy is not recommended because of risk of toxicity.

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## Colchicine

- An alkaloid obtained from *Colchicum autumnale*
- *Neither analgesic nor antiinflamamtory* BUT Relieves pain and inflammation of gouty arthritis.
- Does not inhibit the synthesis or promote the excretion of uric acid.
- Colchicine binds to tubulin, a microtubular protein, causing its depolymerization → Inhibit leukocytes migration. It also inhibits the synthesis and release of the leukotrienes

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## Colchicine

- Adverse effect: nausea, vomiting, abdominal pain, watery or bloody diarrhea.  
In high doses, it produces kidney damage, CNS depression, intestinal bleeding.
- Contraindication: Hypersensitivity, Anaemic Patient, Patient with agranulocytosis.

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## Corticosteroids

- Refractory cases and those not responding or tolerating NSAIDs/ Colchicine.
- Intraarticular injection suppress symptoms of acute gout.
- Systemic steroid are rarely needed. They are very effective and produce rapid response as colchicine but are reserved for patients with renal failure/ history of peptic ulcer in whom NSAIDs are contraindicated or not responding or not tolerating to NSAIDs.
- Prednisolone 40-60mg may given in one day, followed by tapering dose over few weeks.

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## Uricosuric Agents

(increase excretion of uric acid)

### Probenecid

- Completely blocks active transport of organic acid by organic anion transporter (OAT) at all sites (renal tubules)
- Uric acid is largely reabsorbed by active transport while less of it is secreted; only 1/10 of filtered load is excreted in urine.
- Probenecid promotes excretion and reduces its blood level.

**Adverse Effect:** well tolerated. Dyspepsia (Common). Rash (rare)

### Contraindication

- Hypersensitivity to probenecid.
- Not recommended in persons with known blood dyscrasias or uric acid kidney stones.

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## Uricosuric Agents

### Sulfinpyrazone

- Have uricosuric action but is neither analgesic nor anti inflammatory.
- At therapeutic doses, inhibits tubular reabsorption of uric acid

**Adverse Effect:** Gastric irritation(common). Rash (rare)  
Contraindicated in patient with peptic ulcer.

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## Uric acid synthesis inhibitor

### Allopurinol

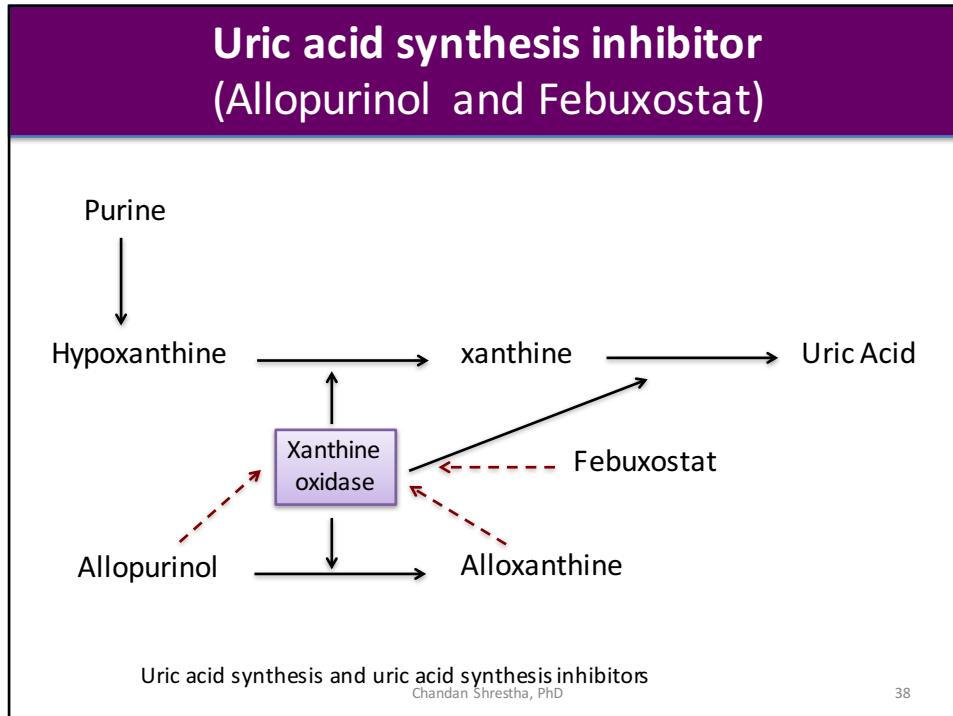
- Reduce the synthesis of uric acid by inhibiting xanthine oxidase.
- Xanthine oxidase oxidize both hypoxanthine and xanthine to uric acid. Hence inhibiting xanthine oxidase therefore reduces production of uric acid.
- Allopurinol is metabolized by xanthine oxidase to alloxanthine.
- Alloxanthine retains the capacity to inhibits xanthine oxidase and a long duration of action.

**Adverse Effect:** rashes, fever, malaise and muscle pain. Gastric irritation, headache, nausea and dizziness are infrequent.

**Contraindication:** Hypersensitivity, pregnancy and lactating mother

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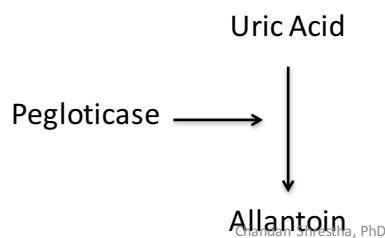


### Febuxostat

- Novel XOI, thus lower urate concentrations in the body.
- indicated for use in the treatment of chronic gout and hyperuricemia
- 80-120 mg/d are more effective than allopurinol 300mg/d
- Adverse effect: nausea, diarrhea, headache, rash, increased hepatic enzyme activity and a small increase in rate of serious cardiovascular events.

## Pegloticase

- A recombinant porcine like uricase, metabolize uric acid to allantoin.
- Reduces the risk of precipitates, since allantoin is 5-10 times more soluble than uric acid.
- Treatment of severe, refractory, chronic gout
- FDA Approved in september 2010
- Drug is administered by iv (infusion)



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