(2) PHARMACOTHERAPY OF GOUT (CHRONIC)

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CLINICAL PHARMACOLOGY

DR SHAMS SULEMAN

LEARNING OBJECTIVES

- Classify drugs used to treat gout
- Describe the role of NSAIDs in the treatment of gout
- Describe the role of Glucocorticoids in the treatment of gout
- Describe the mechanism of action of various drugs (Colchicine, Probenecid, Allopurinol, Febuxostat) used in the treatment of Gout

LEARNING OBJECTIVES

- Discuss the adverse effects of anti-gout drugs
- Describe the drug interactions of Allopurinol and Probenecid
- Enlist the drugs causing hyperuricemia
- Discuss the mechanism by which drugs causes hyperuricemia

DRUGS FOR CHRONIC GOUT

- **Uricosuric Agents**

  (increase urinary excretion of uric acid)

  - Probenecid
  - Sulfinpyrazone
  - Benzobramone
  - Lesinurad
  - ***Adjuvant drugs: not used primarily for gout***
    - ***Losartan***
    - ***Fenofibrate***
    - ***Atorvastatin***
    - ***Vitamin C***
    - ***Rilonacept***

DRUGS FOR CHRONIC GOUT

- **Uricostatic agents**

  (Decreasing Production Of uric acid)

  - Allopurinol
  - Oxypurinol
  - Febuxostat

- **Uricolytic agents**

  - Rasburicase
  - Pegloticase
  - Polyethylene glycol uricase

TREATMENT

MANAGEMENT OF CHRONIC GOUT:

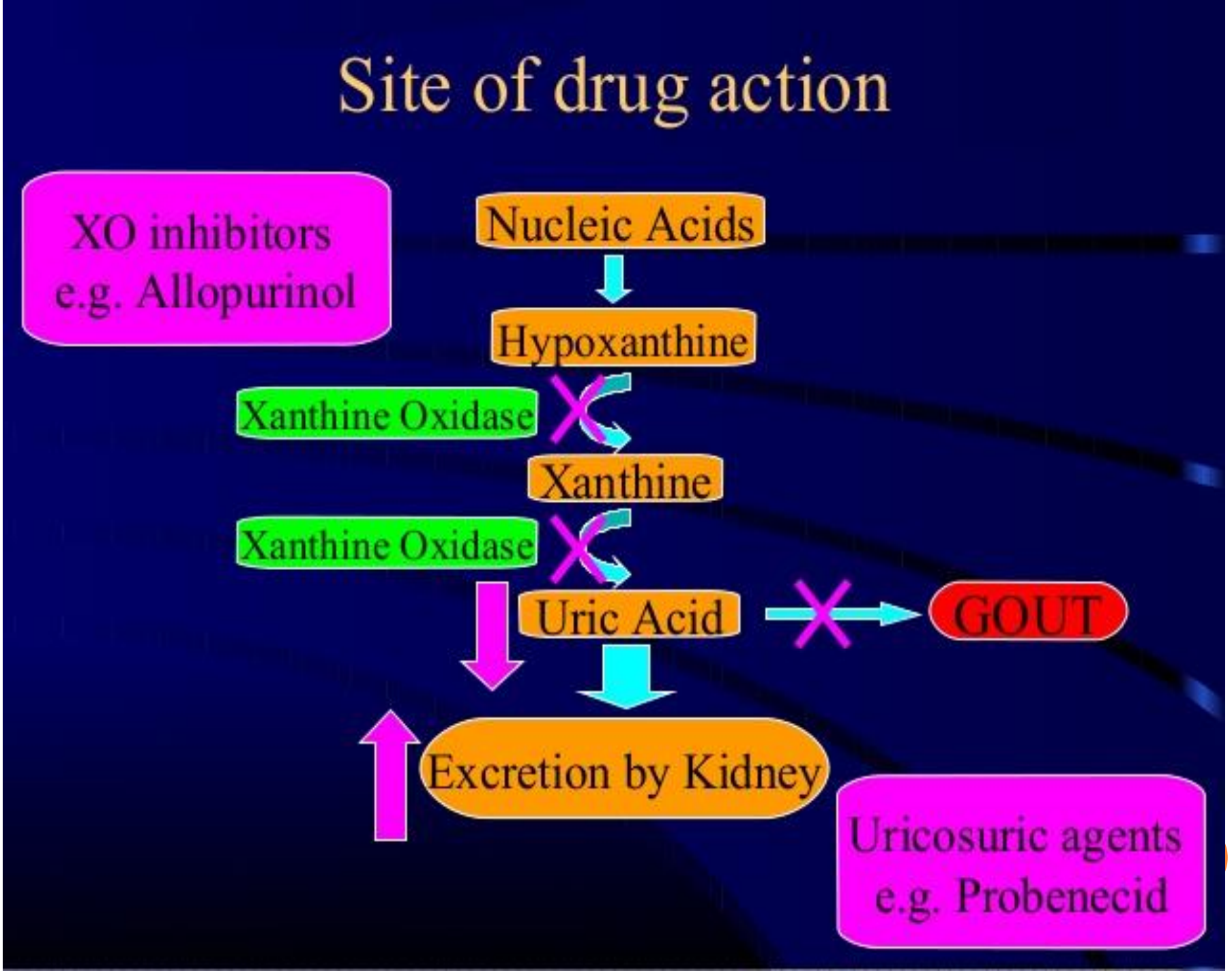
CLASS	DRUGS	MOA	DOSE	SIDE EFFECTS
Uricostatic agents	Allopurinol (ALOPRIM®) Febuxostat (FABULAS®)	Inhibition of xanthine oxidase enzyme ↓ Decreased production of uric acid	100mg\day 80mg\120mg	•Rashes •GIT disturbances •Hepatotoxicity •Fever
Uricosuric agents	Benzbromarone (BENZRONE®) Sulphinpyrazone (ANTURANE®) Probenecid (BENEMID®)	inhibits post-secretary tubular absorption of uric acid from filtered urate in the kidney. ↓ increase uric acid excretion	50-200mg 200-800mg per day 0.5 -2 gm\day	•GIT disturbance •Ulceration •Blood disorders
Uricolytic agents	Rasburicase (ELITEK®) Poly ethylene glycol (MIRALAX®)	They convert the uric acid to more soluble allontoin and increased its excretion through kidneys	0.2mg\day for 5-7 days 3500mg	•GIT disturbances •Rashes •Headache

Choosing Among Urate Lowering Therapies (ULTs)

URICOSURICS	XANTHINE OXIDASE INHIBITORS	URICASE
Probenecid Sulfinpyrazone Losartan Fenofibrates	Allopurinol Febuxostat	Pegloticase

Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 ACR Guidelines for Management of Gout. Part 1. Arth Care & Res 2012; 64 (10): 1431-46.

Site of drug action



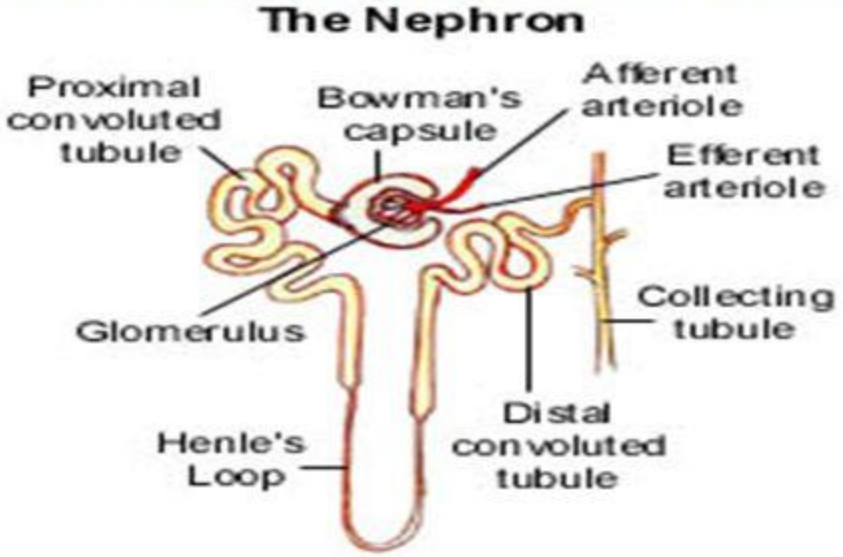
Management of Chronic Gout: Key facts	
First line treatment	**Second line treatment**
Allopurinol	Sulphinpyrazone Febuxostat Benzbromarone
Increase allopurinol by 100mg every 4 weeks until target reached	Uricosuric agents should be avoided in those with renal stones
Target uric acid 0.3 mmol/L. Monitor uric acid every 4 weeks until target reached	
Colchicine 0.5 mg twice daily is used for the first 6-12 months after initiating urate lowering therapy	

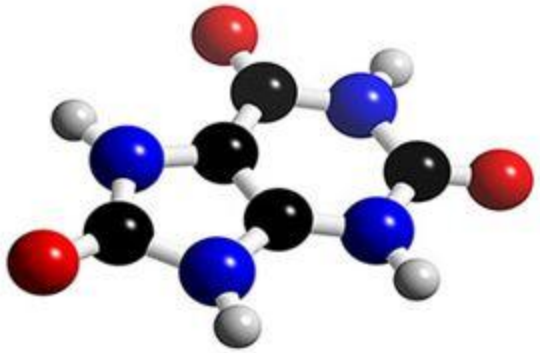
(NHS Fife, Gout Management Guidelines, 2010)

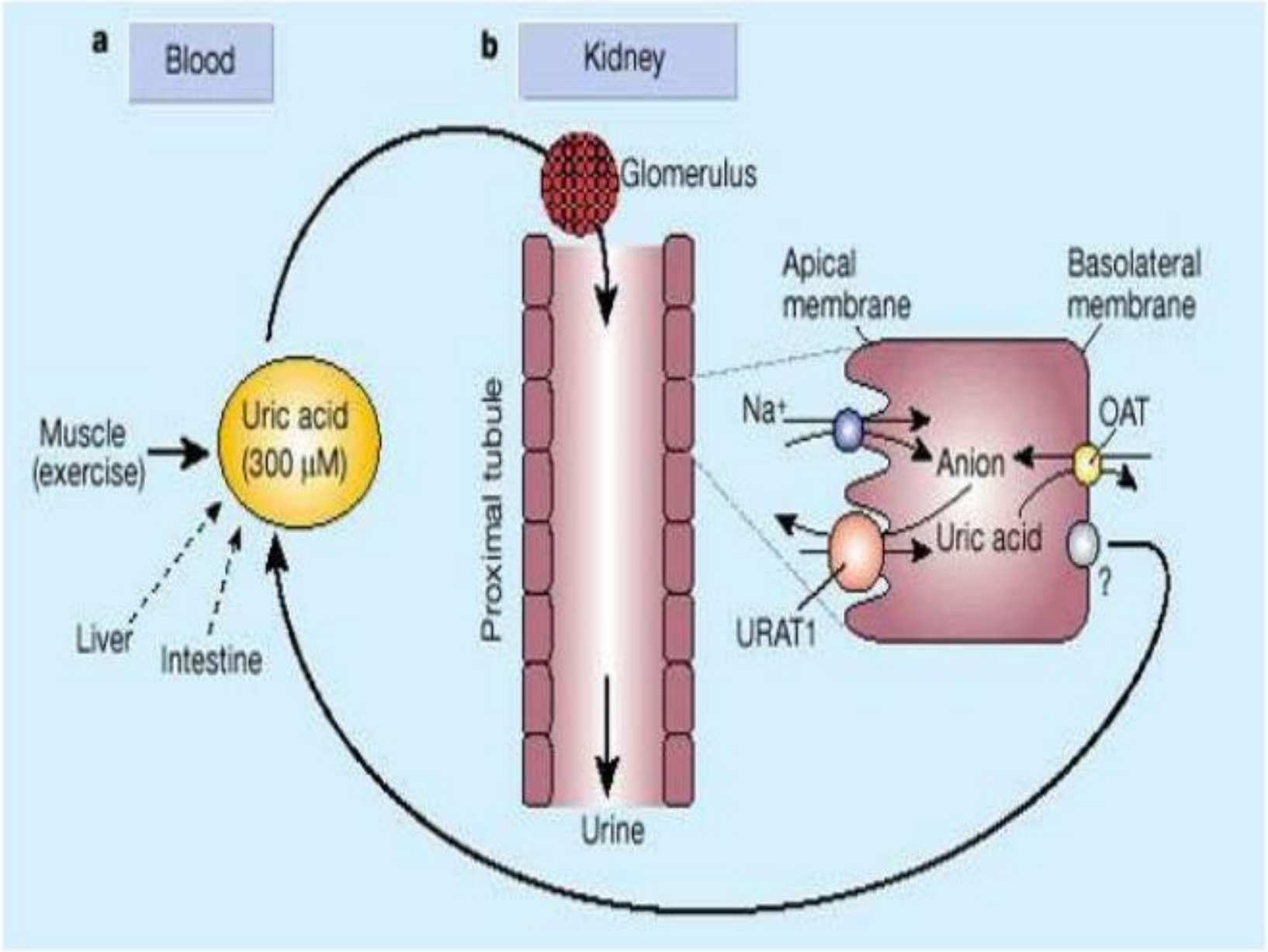
URICOSURIC DRUGS

Mechanism of action

- **Uricosuric drugs** (probenecid, sulfinpyrazone, large dose of aspirin)
- block the active transport sites of the proximal tubules(middle segment , decrease the reabsorption of uric acid & increase the amount excreted






a
Blood
b
Kidney
Glomerulus
Apical membrane
Basolateral membrane
Muscle (exercise)
Uric acid (300 μM)
Proximal tubule
Na+
OAT
Anion
Uric acid
?
URAT1
Liver
Intestine
Urine

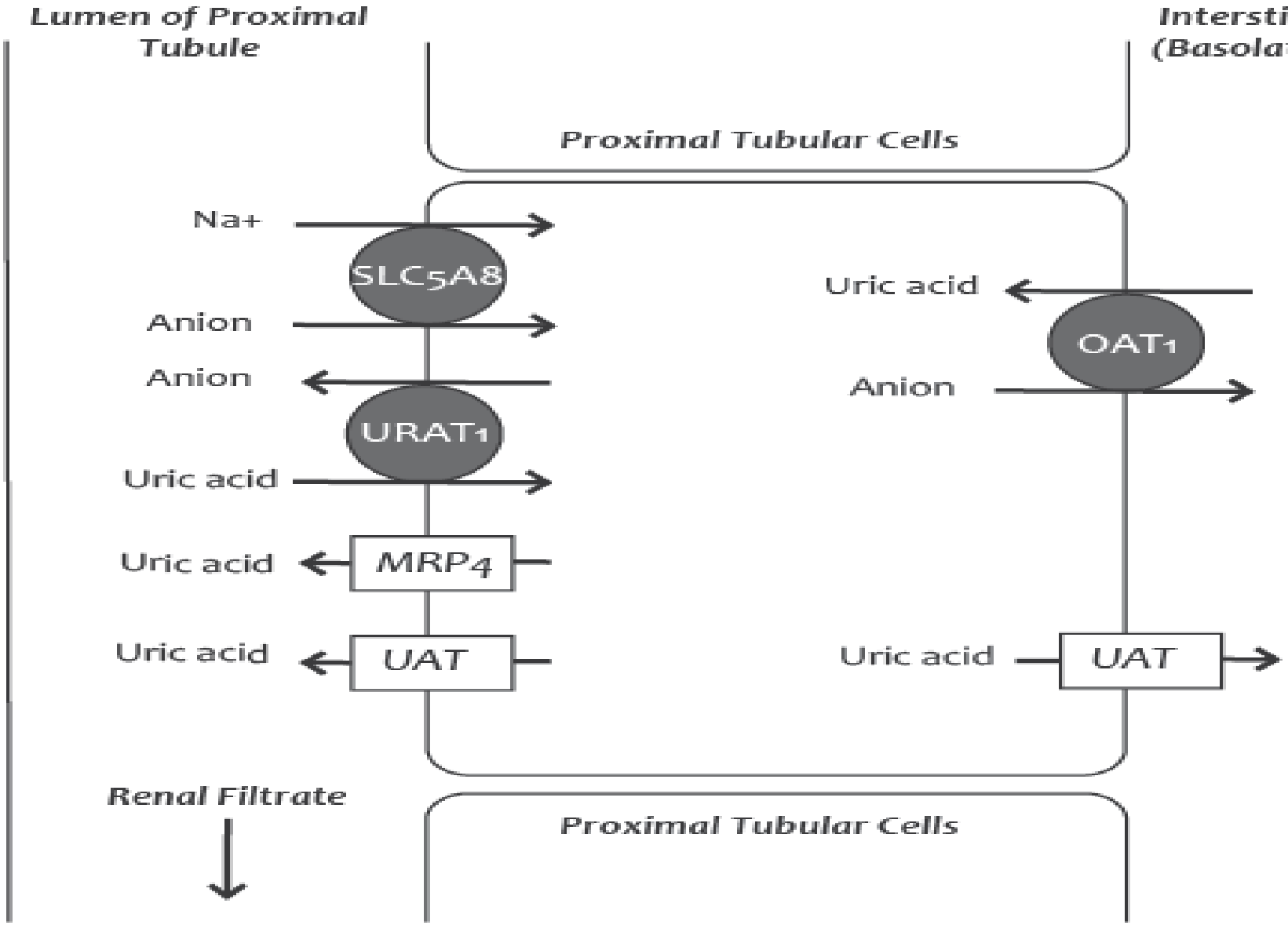


Figure 1. Normal renal physiology of uric acid elimination.

URICOSURIC DRUGS

- *In PCT uric acid is reabsorbed, metabolized and then secreted at ionic transporter sites*
- Proenecid; allopurinol & febuxostat intolerant
- Sulfinpyrazone
- Aspirin in higher doses; 2.6 gm/day
- Alkali and high urine volume = to prevent nephropathy
- 2-3 weeks after acute attack

URICOSURIC AGENTS

- The **uricosuric drugs** (or urate diuretics) are anions that are somewhat similar to **urate** in structure; therefore, they can compete with uric acid for transport sites.
- ***Small doses of uricosuric agents*** will actually **decrease** the total excretion of urate by inhibiting its tubular secretion.
- And ***at high dosages these same drugs increase*** uric acid elimination by inhibiting its proximal tubular reabsorption.

- The initial phase of therapy == dangerous period.
- Drug levels should be build up sufficiently
- Equilibrium between reabsorption and secretion is essential
- The risk of an acute gouty attack and renal stone formation due to rise in urinary uric acid concentrations is more
- Ideally start with the administration of small amounts of NSAID/Colchicine before adding a uricosuric drug to the therapeutic regimen.

Uricosuric drugs: (probencid)

- Highly lipid soluble benzoic acid.

- It blocks reabsorption of urate in proximal tubule by blocking transport (Bidirectional transport)

- PK: Dose dependent t1/2 life

- Dose -250- 500mg b.d. with plenty of fluids, alkalinization of urine.

Uses :

chronic gout along with NSAIDs / colchicine for initial 1-2 months.

PROBENECID

PHARMACOKINETICS

- Orally == completely absorbed
- plasma protein binding == 90%
- Metabolism == very slowly, Conjugated in liver
- Plasma half life == 8-10 hours
- Excretion == by kidney

PROBENECID

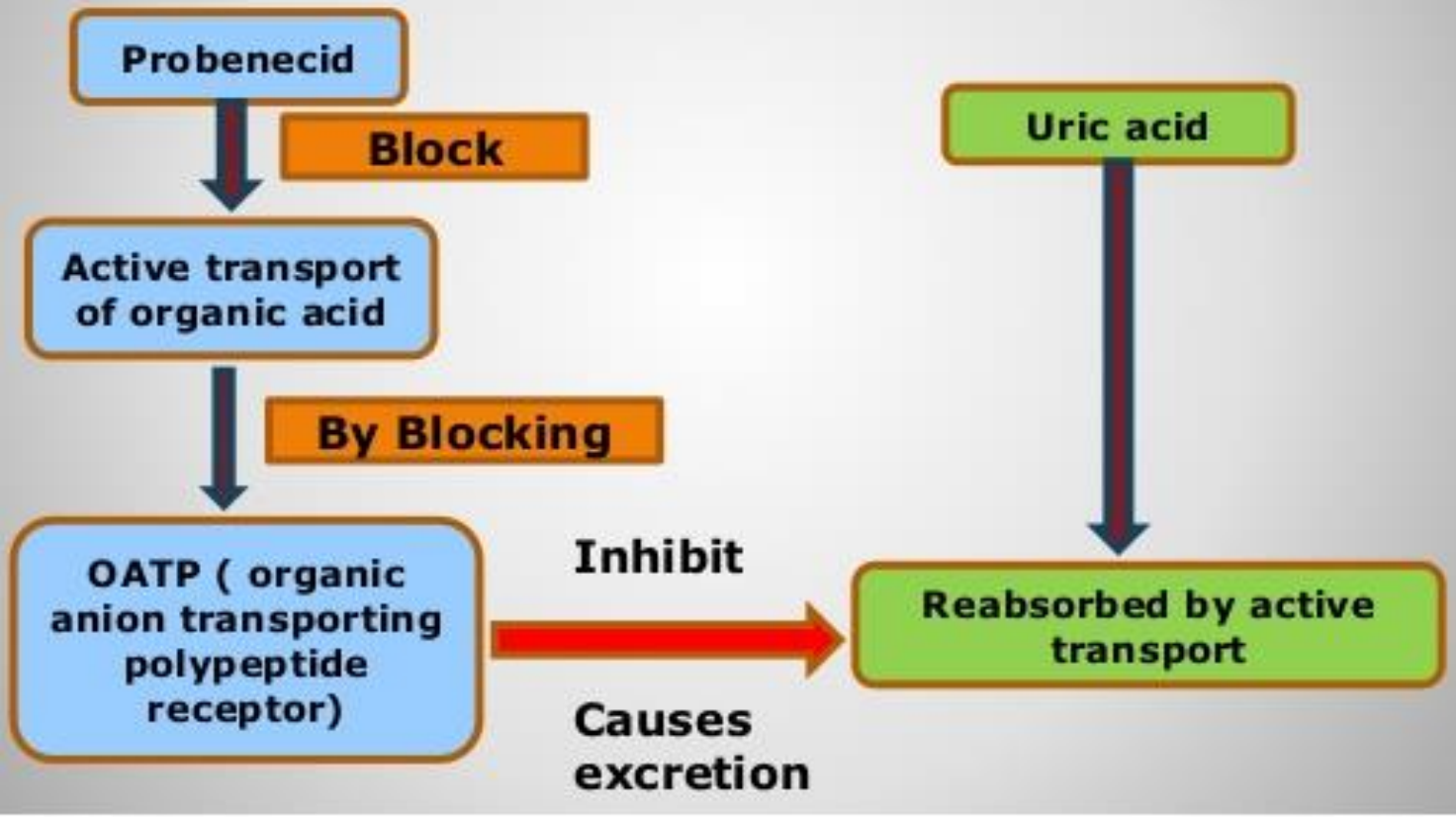
MOA

- Uric acid is freely filtered at the glomerulus.
- Reabsorbed by Organic anion transporters in the middle segment of the proximal tubule
- Then secreted by the same transporter
- Uricosuric drugs— Probenecid, Sulfinpyrazone, and large doses of aspirin blocks these transporters
- Net reabsorption of uric acid in the proximal tubule is decreased.

4. Probenecid

- Lipid soluble organic acid developed in 1951.

***Mechanism of action Probenecid:**



PROBENECID

CONTRAINDICATIONS

- Renal calculi
- It is essential to maintain a large urine volume to minimize the possibility of stone formation.

INTERACTIONS

- Probenecid was originally developed to prolong penicillin blood levels.
- Aspirin competes with the transporter in PCT

*Pharmacokinetics:

- **Absorption:** Rapid orally.
- **Distribution:** 90% bound to plasma protein
- **Metabolism:** Liver
- **Elimination:** Urine.

***Drug interaction with other drug:** Probenecid shows interaction with;

Sr . No.	Category of drug	Example from class	Interaction
1.	Antibiotics	penicillins, cephalosporins, sulfonamides,	Inhibits the urinary excretion
2.	NSAID's	Indomethacin, salicylates	
3.	Antibiotics	rifampicin.	Biliary excretion
4.	Antimicrobial	nitrofurantoin	Inhibits tubular secretion of drug

PROBENECID

DOSAGE

- 0.5 g orally daily in divided doses
- Progressing to 1g daily after 1 week.

Sulfinpyrazone : 200 mg orally daily, progressing to 400–800 mg daily.

It should be given in divided doses with food to reduce adverse gastrointestinal effects.

Sulfinpyrazone

- It is a Pyrazolone derivaties related to Phenylbutazone.
- Inhibits tubular reabsorption of uric acid at therapeutic doses.
- Its action is additive with probenecid.
- Use -chronic gout
- Dose :100-200mg BD gradually increase according to the response.

Benzbromarone

- It is newer and more potent uricosuric drug
- Used in patients allergic to probenecid or sulfinpyrazone
- It is reversible inhibitor of tubler reabsorption
- Effective dose 60-80mg/day
- With allopurinol more effective

XANTHINE OXIDASE INHIBITORS

Decreases uric acid production

- Allopurinol
- Oxypurinol
- Febuxostat

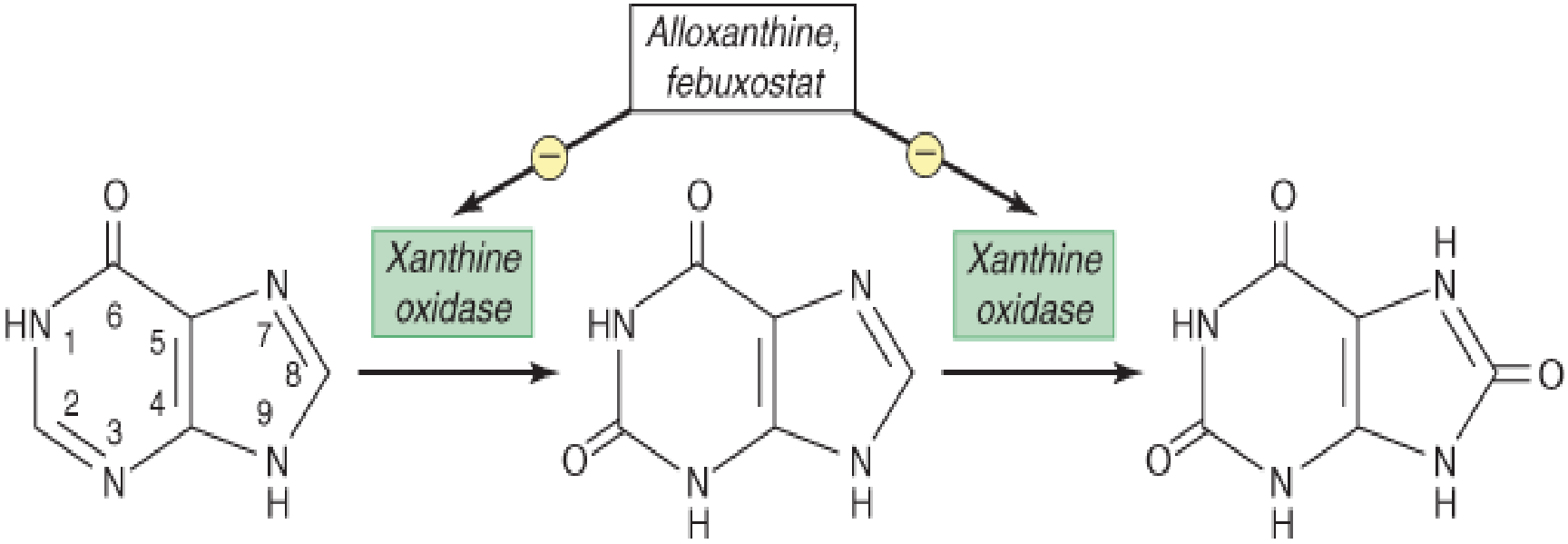
ALLOPURINOL

- Isomer of hypoxanthine, metabolized to alloxanthine
- Acts both as a substrate and metabolite of xanthine oxidase….
- Results in increased levels of soluble xanthine and hypoxanthine

  & Decreased levels of insoluble uric acid
- Metabolite Alloxanthine is long acting: $t_{1/2}$ = 24 hours
- Started 6-7 days after colchicine/ NSAIDs
- May precipitate urate stones initially

Mechanism of Action

- Xanthine oxidase metabolizes purines in the food to hypo-xanthine, then xanthine and finally oxidize to uric acid.
- Allopurinol causes **competitive inhibition** of this xanthine oxidase
- As a result the urinary and blood concentrations of uric acid are greatly reduced
- Simultaneous increase in the excretion of the more soluble uric acid precursors i.e. xanthine and hypoxanthine.



Source: Trevor AJ, Katzung BG, Masters SB: *Pharmacology Examination & Board Review, 9th Edition:* www.accesspharmacy.com

Dosage

- The initial dosage of allopurinol is 100 mg/d.
- Titrated upward till serum uric acid is below 6 mg/dl.
- This level is commonly achieved at 300 mg/d

ALLOPURINOL

- Start low 50-100 mg qd
- Increase by 50-100mg every 2-3 weeks according to symptoms
  - "Average" dose 300 mg daily
  - lower dose if renal/hepatic insufficiency
  - higher dose in non-responders
  - prophylactic colchicine until allopurinol dose stable

- Indications:
- Chronic gout
- In patients 24 hrs urinary acid excretion exceeds 1.1g
- For recurrent renal ureate stones.

Uses of allopurinol

- **Allopurinol is prescribed to**
- prevent chronic gout attacks,
- manage high uric acid levels caused by cancer medications (**Secondary Hyperuricaemia**), and
- to treat kidney stones.

ALLOPURINOL…

ADVERSE EFFECTS

- Peripheral neuritis
- Bone marrow depression/aplastic anemia
- Necrotizing vasculitis
- Interstitial nephritis
- Maculopapular rash
- Cataract

ALLOPURINOL…

DRUG INTERACTIONS

- 6 Mercaptopurine
- Azathioprine
- Cyclophophamide
- Probenecid
- Oral anticoagulants
- Iron

* Pharmacokinetics:

- **Absorption:** Rapid orally.
- **Distribution:** Not bound to plasma protein.
- **Metabolism:** During chronic administration inhibit self metabolism.
- **Elemination:** 1/3 excreted as unchanged form in urine.

***Drug interaction with other drug:** Allopurinol shows interaction with;

Sr . No.	Category of drug	Example from class	Interaction
1.	Anticancer	f 6-mercaptopurin & azathioprine	Allopurinol prevent degradation of all drugs
2.	Uricosurics	Probenecid	kidney or liver disease
3.	Anti asthmatic	theophylline	skin rashes
4.	Haematinics	Iron therapy	mobilization of hepatic iron stores

ALLOPURINOL

Allopurinol side effects

- GI upset, alopecia, cataract.

- Allopurinol Hypersensitivity:

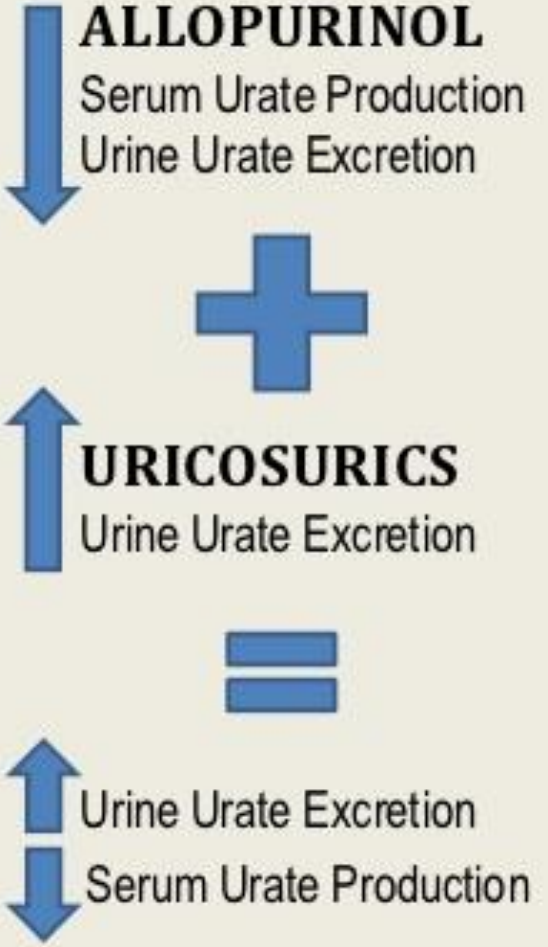
  Pruritic papular skin rash, fever, hepatitis, eosinophilia, renal impairment

- CI:-
  - Chidrens
  - Elderly patients
  - Pregnancy
  - Lacation
  - Liver and kidney diseases.

FEBUXOSTAT

- Non purine selective inhibitor of xanthine oxidase = FDA approved
- Oral and potent = 80 - 120 mg /day
- Chronic gout; inter critical period
- After colchicine and NSAIDs
- Allopurinol intolerant cases
- Adverse = hepatitis, diarrhea, headache

COMBINATION THERAPY



Combination of Allopurinol and Sulfinpyrazone

- Diminution of SUA
- Rapid softening & dissolution of tophi
- Cessation of renal stone formation

Kuzell W, et al. Ann Rheum Dis 1966

Combination of Allopurinol and Benzbromarone

- Lowered SUA in patients with renal dysfunction
- Lower doses of both drugs were used
- Reduced serum Oxypurinol levels

Ohno I, et al. Nippon Jinzo Gakkai. 2008

Newer Drugs

➢ URICASE ENZYMES:

- Catabolize urate to allantoin:

  More soluble, excretable form
- Currently approved for hyperuricemia in tumor lysis syndrome
- Some concerns: fatal immunogenicity & unknown long-term effects

3. URICOLYTIC AGENTS:

MOA: They convert the uric acid to more soluble allantoin and increase its excretion through urine.

ADRs: Haemolysis, GI disturbances, hypersensitivity reactions like skin rashes may occur.

Dose: Rasburicase-0.2mg/day for 5-7days

Poly ethylene glycol-uricase-3.5gm/day

Urate-lowering drugs: Rasburicase

- Off –label monthly infusions of rasburicase have been eff ective in patients with severe gout not treatable with allopurinol.
- A pegylated uricase—less antigenic& longer half-life—is under development.
- FDA-approved for Tumor Lysis Syndrome
- High cost.

Table – Summary of drugs recently available or in development for gout

Drug	Effect in gout	Mechanism of action	Summary of trial results
Rilonacept	Prevents recurring attacks	Soluble IL-1 receptor Fc fusion protein	Phase 2 study: Weekly injections (160 mg SC) lower risk of recurring attacks vs placebo
Canakinumab	Resolves acute attacks, prevents recurring attacks	Monoclonal antibody to IL-1ß	Phase 2 study: Single 150 mg SC injection superior to triamcinolone 40 mg IM injection in resolving acute gouty attacks, highly effective at preventing recurring gouty attack for remainder of study (2 months)
Febuxostat	Lowers serum uric acid level	Decreases uric acid production by inhibiting xanthine oxidase	Febuxostat 80 mg/d superior to allopurinol 300 mg/d in 3 large phase 3 studies
RDEA594	Lowers serum uric acid level	Increases renal excretion of uric acid via inhibition of URAT1 in the proximal tubule	Phase 2 study demonstrated urate-lowering effects to be comparable to those of allopurinol, 300 mg/d
Pegloticase	Lowers serum uric acid level	Pegylated uricase, enzymatically breaks down uric acid	Two phase 3 studies demonstrated superiority to placebo

IL, interleukin; URAT1, urate transporter 1.

Tumor Lysis Syndrome

- Large numbers of tumor cells are destroyed rapidly, resulting in intracellular contents being released into the bloodstream faster than the body can eliminate them.
- Collaborative management includes:
  - Prevention
  - Hydration
  - Drug therapy

Treatment Algorithm

Acute attack

↓

- Rest for 1-3 days and Topical ice application
- Review medication and life style
- Resolve pain with NSAIDs/ Colchicine/ Corticosteroid

Chronic attack

↓

- Uricostatic agents-Allopurinol/ Febuxostat
- Uricosuric agents-Probenacid/ Sulfinpyrazone
- Uricolytic agents- Rasburicase/ PEG-Uricase

Low-Purine Diet for Gout

Eat More


Fruits


Vegetables


Whole grains


Low-fat dairy


Legumes


Nuts

Eat Less


Shellfish


Organ meats (liver)


Alcoholic beverages


Soft drinks

Avoid Foods that Cause Gout

Gout commonly strikes between the ages of 30 and 50, usually occurring in men and, less often in women in menopause. Avoiding certain foods high in purine and keeping weight down are controllable risk factors.

Risky foods

Anchovies, herring/sardines

Mushrooms

Asparagus, peas and beans

Mussels

Kidney, liver, heart and brain, gravies, sweetbreads, broths and consomme

Alcohol increases production of urate acid and interferes with elimination

Other risk factors include sudden severe illness, crash diets, joint injury and chemotherapy

Low Purine DIET GUIDE

Group I: Select from these Foods	
Cheese	Fruits (except those in group III)
Eggs	Gelatine
Cereals/ cereal products	Milk
Bread	Coffee and tea
Butter/ margarine	Vegetables
Beverages	Syrups
Group II: Use in Moderation	
Fish (expect those in group III)	Chicken (poultry products)
Legumes (beans)	Seafoods (crabs, shrimps, oysters)
Meat (meat soup and broth)	Vegetables (spinach, mushrooms, asparagus, cauliflowers)
Oatmeal	
Group III: Avoid these Foods	
Gravies	Nuts-Peanuts, cashew nuts . . .
Mackerel/Sardines	Fruits (avocado)
Mussels	Sweet beans
Meat Extracts	Fish (Tuna)
Internal organs	
Yeast	

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