LEC.2 DRUGS USED FOR THE TREATMENT OF GOUT

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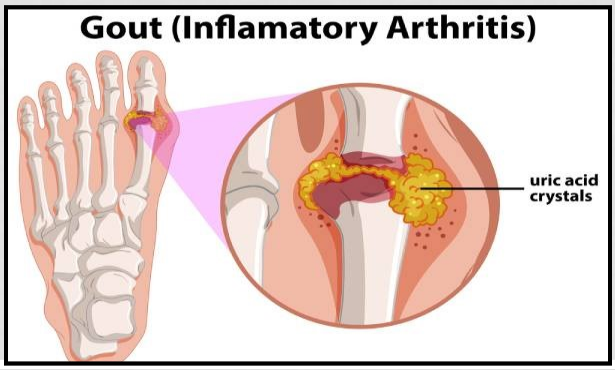
GOUT

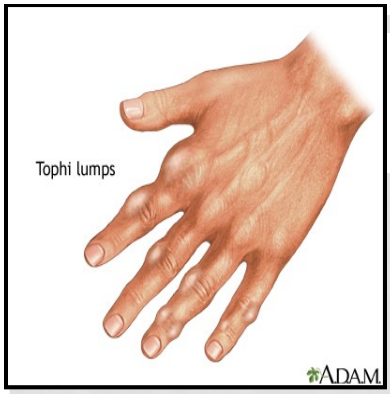
- Gout is a metabolic disorder characterized by high levels of uric acid in the blood (hyperuricemia).
- Hyperuricemia can lead to deposition of sodium urate crystals in tissues, especially the joints and kidney.
- The deposition of urate crystals initiates an inflammatory process involving the infiltration of granulocytes that phagocytize the urate crystals.
- Acute flares of gout usually present as pain, swelling, tenderness, and redness in the affected joints (for example, big toe, knees, ankles, wrists, or elbows).

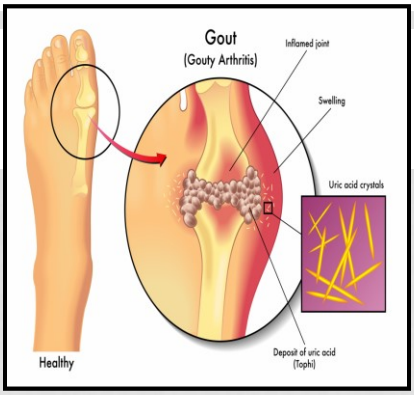
- The cause of hyperuricemia in gout is an imbalance between overproduction of uric acid and/or the inability to excrete uric acid renally.
- **Most therapeutic strategies for gout involve lowering the uric acid level below the saturation point (6 mg/dL).**
- This can be accomplished by interfering with uric acid synthesis or increasing uric acid excretion.

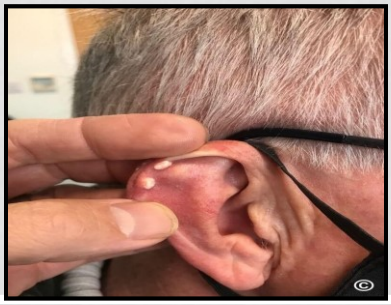


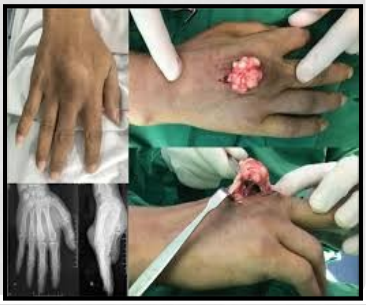
TREATMENT OF ACUTE GOUT

- Acute gout attacks can result from a number of conditions, including excessive alcohol consumption, a diet rich in purines, and kidney disease.
- **NSAIDs, corticosteroids, and colchicine are effective agents for the management of acute gouty arthritis.**
- Patients are candidates for prophylactic urate-lowering therapy if they have more than two attacks per year or they have chronic kidney disease, kidney stones, or tophi (deposit of urate crystals in the joints, bones, cartilage, or other body structures).





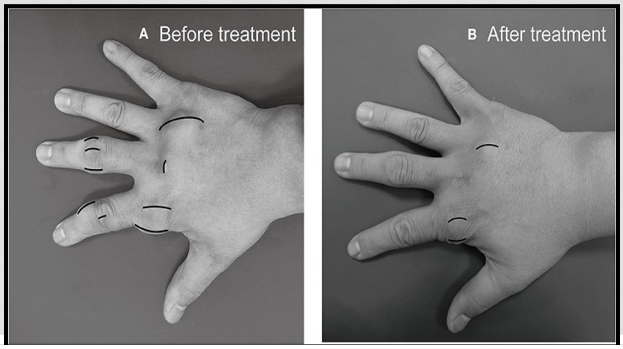




TREATMENT OF CHRONIC GOUT

- Urate-lowering therapy for chronic gout aims to reduce the frequency of attacks and complications of gout.
- **Treatment strategies include the use of xanthine oxidase inhibitors to reduce the synthesis of uric acid or use of uricosuric drugs to increase its excretion.**
- Xanthine oxidase inhibitors (allopurinol, febuxostat) are first-line urate lowering agents.
- **Uricosuric agents (probenecid) may be used in patients who are intolerant to xanthine oxidase inhibitors or fail to achieve adequate response with those agents.**

- [Note: Initiation of urate-lowering therapy can precipitate an acute gout attack due to rapid changes in serum urate concentrations.
- **Medications for the prevention of an acute gout attack (low-dose colchicine, NSAIDs, or corticosteroids) should be initiated with urate-lowering therapy and continued for at least 6 months.**



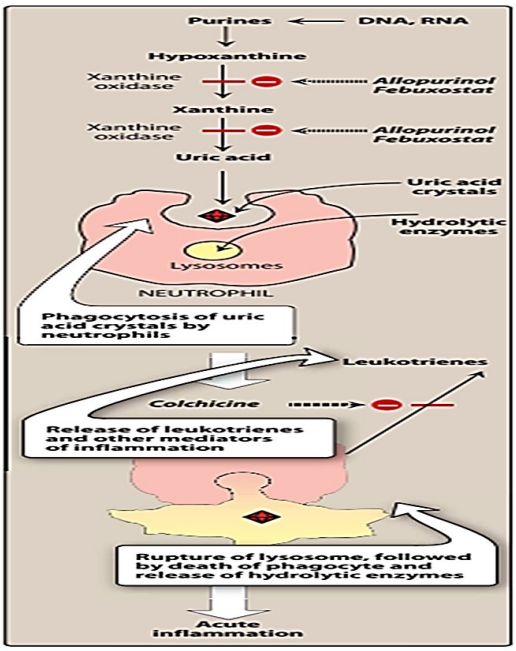


Figure 38.20
Role of uric acid in the inflammation of gout.

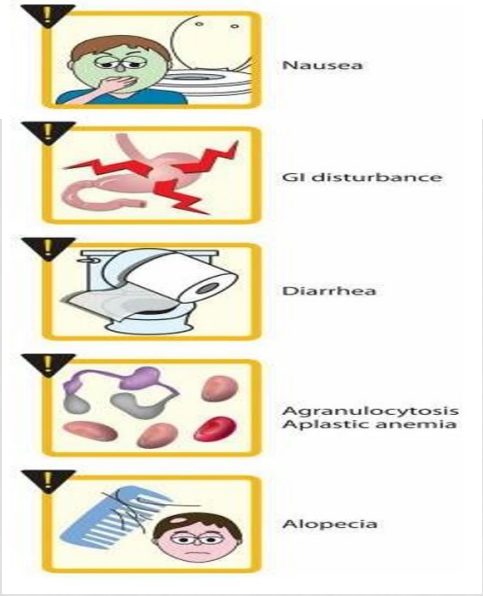
COLCHICINE

- Colchicine, a plant alkaloid, is used for the treatment of acute gouty attacks.
- It is neither a uricosuric nor an analgesic agent, although it relieves pain in acute attacks of gout.
- Mechanism of action:
- Colchicine binds to tubulin, a microtubular protein, causing its depolymerization.
- This disrupts cellular functions, such as the mobility of neutrophils, thus decreasing their migration into the inflamed joint.
- Furthermore, colchicine blocks cell division by binding to mitotic spindles.

- Therapeutic uses:
- The anti-inflammatory activity of colchicine is specific for gout, usually alleviating the pain of acute gout within 12 hours.
- (Note: Colchicine must be administered within 36 hours of onset of attack to be effective).
- NSAIDs have largely replaced colchicine in the treatment of acute gouty attacks for safety reasons.
- Colchicine is also used as a prophylactic agent to prevent acute attacks of gout in patients initiating urate-lowering therapy).

- **Pharmacokinetics:**
- Colchicine is administered orally and is rapidly absorbed from the GI tract.
- **Colchicine is metabolized by hepatic CYP450 3A4 and other tissues.**
- It undergoes enterohepatic recirculation and exhibits high interpatient variability in the elimination half-life.
- **A portion of the drug is excreted unchanged in the urine.**

- **Adverse effects:**
- Nausea, vomiting, abdominal pain, and diarrhea.
- Chronic administration may lead to myopathy, neutropenia, aplastic anemia, and alopecia.
- The drug should not be used in pregnancy and should be used with caution in patients with hepatic, renal, or cardiovascular disease.
- Dosage adjustments are required in patients taking CYP3A4 inhibitors (for example, clarithromycin and itraconazole) or P-glycoprotein efflux pump inhibitors (for example, amiodarone and verapamil) and those with severe renal impairment.



Adverse effects of cholchicine

ALLOPURINOL,

- **Allopurinol, a xanthine oxidase inhibitor, is a purine analog. It reduces the production of uric acid by competitively inhibiting the last two steps in uric acid biosynthesis that are catalyzed by xanthine oxidase.**
- **Therapeutic uses:**
- **Allopurinol is an effective urate-lowering therapy in the treatment of gout and hyperuricemia secondary to other conditions, such as that associated with certain malignancies (those in which large amounts of purines are produced, particularly after chemotherapy) or in renal disease.**

- **Pharmacokinetics:**
- Allopurinol is completely absorbed after oral administration.
- **The primary metabolite alloxanthine (oxypurinol) is also a xanthine oxidase inhibitor with a half-life of 15 to 18 hours. Thus, effective inhibition of xanthine oxidase can be maintained with once-daily dosing.**
- The drug and its active metabolite are excreted in the urine.
- **Dose adjustment is needed if estimated glomerular filtration rate is less than 30 mL/min/1.73 m2.**

- **Adverse effects:**
- Allopurinol is well tolerated by most patients.
- Hypersensitivity reactions, especially skin rashes, are the most common adverse reactions.
- The risk is increased in those with reduced renal function.

FEBUXOSTAT

- Febuxostat is an oral xanthine oxidase inhibitor structurally unrelated to allopurinol.
- Its adverse effect profile is similar to that of allopurinol, although the risk for rash and hypersensitivity reactions may be reduced.
- Febuxostat does not have the same degree of renal elimination as allopurinol and thus requires less adjustment in those with reduced renal function.
- Febuxostat should be used with caution in patients with a history of heart disease or stroke, as this agent may be associated with a greater risk of these events as compared to allopurinol.

PROBENECID

- Probenecid is an oral uricosuric drug. It is a weak organic acid that promotes renal clearance of uric acid by inhibiting the urate-anion exchanger in the proximal tubule.
- At therapeutic doses, it blocks proximal tubular reabsorption of uric acid.
- Probenecid should be avoided if the creatinine clearance is less than 50 mL/min.
- Adverse effects include: nausea, vomiting, and dermatologic reactions, and, Rarely, anemia or anaphylactic reactions.

PEGLOTICASE

- Pegloticase is a recombinant form of the enzyme urate oxidase or uricase.
- It acts by converting uric acid to allantoin, a water-soluble nontoxic metabolite that is excreted primarily by the kidneys.
- Pegloticase is indicated for patients with gout who fail treatment with standard therapies such as xanthine oxidase inhibitors.
- It is administered as an IV infusion every 2 weeks.
- Infusion-related reactions and anaphylaxis may occur with pegloticase, and patients should be premedicated with antihistamines and corticosteroids.