GOUT

BY

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GOUT

- Gout involves **hyperuricemia**, **recurrent attacks of acute arthritis** with monosodium **urate (MSU) crystals in synovial fluid leukocytes**, **deposits** of MSU crystals **in tissues in and around joints** (tophi), **interstitial kidney disease**, and **uric acid nephrolithiasis**.

PATHOPHYSIOLOGY OF GOUT

- -**Uric acid is the end product of purine degradation**. gout may result from **overproduction** or **underexcretion**.
- Purines originate from **dietary purine**, conversion of **tissue nucleic acid to purine** nucleotides, and **de novo synthesis of purine bases**.
- Overproduction of uric acid may result from **abnormalities in enzyme systems that regulate purine metabolism**. Uric acid may also be overproduced because of **increased breakdown of tissue nucleic acids,** as with myeloproliferative and lymphoproliferative disorders. Cytotoxic drugs can result in overproduction of uric acid due to **lysis and the breakdown of cellular matter**.

- **Dietary purines are insignificant** in generating hyperuricemia without some derangement in purine metabolism or elimination.
- **Two-thirds of uric acid produced daily is excreted in urine**. The remainder is eliminated through gastrointestinal (GI) tract after degradation by colonic bacteria. Decline in urinary excretion leads to hyperuricemia.
- **Drugs that decrease renal uric acid clearance include** diuretics, nicotinic acid, salicylates (<2 g/day), ethanol, pyrazinamide, levodopa, ethambutol, cyclosporine, and cytotoxic drugs.

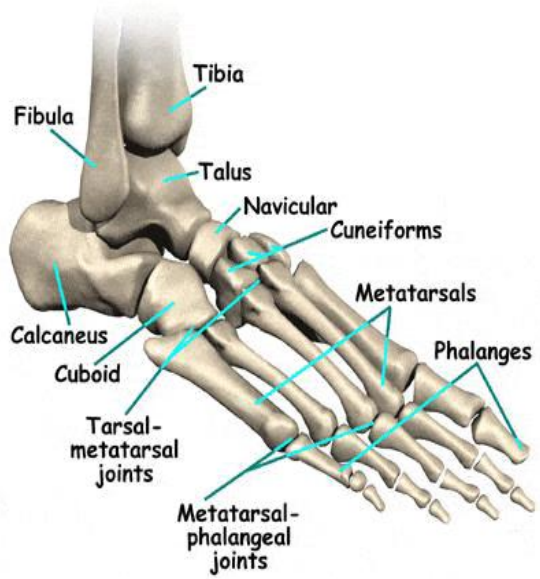
- Deposition of urate crystals in synovial fluid results in **inflammation**, **vasodilation**, increased vascular **permeability**, **complement activation**, and ch**e**motactic **activity** for polymorphonuclear leukocytes.
- **Phagocytosis of urate crystals** by **leukocytes** results in ra**pid lysis of cells and discharge of proteolytic enzymes** into cytoplasm. The ensuing **inflammatory reaction** causes intense joint pain, erythema, warmth, and swelling.
- **Uric acid nephrolithiasis occurs in ∼10% of patients with gout**. Predisposing factors include excessive urinary excretion of uric acid, acidic urine (pH <6), and highly concentrated urine.

- **In acute uric acid nephropathy**, acute kidney injury occurs because of blockage of urine flow from massive precipitation of uric acid crystals in collecting ducts and ureters. **Chronic urate nephropathy** is caused by long-term deposition of urate crystals in the renal parenchyma.
- **Tophi** (**urate deposits**) are uncommon and are a late complication of hyperuricemia. The most common sites are the base of the fingers, olecranon bursae, ulnar aspect of forearm, Achilles tendon, knees, wrists, and hands.

Clinical presentation

- **Acute gout attacks are characterized by** rapid onset of excruciating pain, swelling, and inflammation. The attack is typically monoarticular, most often affecting

the first metatarsophalangeal joint (podagra), and then, in order of frequency, the insteps, ankles, heels, knees, wrists, fingers, and elbows.



- Attacks commonly begin at **night**, with the patient awakening with excruciating pain. Affected joints are erythematous, warm, and swollen.

- **Fever** and l**eukocytosis** are common. Untreated attacks last from 3 to 14 days before spontaneous recovery.
- **Acute attacks may occur without provocation or be precipitated by** stress, trauma, alcohol ingestion, infection, surgery, rapid lowering of serum uric acid by uric acid-lowering agents, and ingestion of drugs known to elevate serum uric acid concentrations.

Diagnosis

- Definitive diagnosis requires **aspiration of synovial fluid from the affected joint** and identification of intracellular crystals of MSU monohydrate in synovial fluid leukocytes.
- When joint aspiration is not feasible, a presumptive diagnosis is based on **presence of characteristic signs and symptoms as well as the response to treatment.**

Treatment

- **Goals of Treatment**: **Terminate the acute attack**, **prevent recurrent attacks**, and **prevent complications** associated with chronic deposition of urate crystals in tissues.
- **Nonpharmacologic Therapy**
- **Local ice** application is the most effective adjunctive treatment.
- Dietary **supplements** (eg, flaxseed, cherry, celery root) **are not recommended.**
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For Acute attack Gout

- **Pharmacologic Therapy**

Most patients are treated successfully with

1-**NSAIDs**,

2- corticosteroids

3- colchicine.

Treatment should begin **as soon as possible after the onset of an attack**.

A-NSAIDS

- NSAIDs have **excellent efficacy and minimal toxicity** with short-term use. Indomethacin, naproxen, and sulindac have FDA approval for gout, **but others are likely to be effective**.
- Start therapy within 24 hours of attack onset and **continue until complete resolution** (usually 5–8 days). Tapering may be considered after resolution, especially if comorbidities such as impaired hepatic or kidney function make prolonged therapy undesirable.

- The **most common adverse effects involve the GI tract** (gastritis, bleeding, and perforation), **kidneys** (renal papillary necrosis, reduced glomerular filtration rate), **cardiovascular system** (increased blood pressure, sodium and fluid retention), and **central nervous system** (impaired cognitive function, headache, and dizziness).
- **Selective cyclooxygenase-2 inhibitors** (eg, celecoxib) **may be an option** for patients unable to take nonselective NSAIDs, but the risk-to-benefit ratio in acute gout is unclear, and cardiovascular risk must be considered.

B-Corticosteroids

- Corticosteroid efficacy is equivalent to NSAIDs; **they can be used systemically or by intra-articular (IA) injection**. If only one or two joints are involved, either IA or oral corticosteroids are recommended. **Systemic therapy is necessary for polyarticular attacks**.
- **Tapering** is often used to reduce the hypothetical risk of a rebound attack upon steroid withdrawal.

- **IA corticosteroids should be used with an oral NSAID**, **colchicine**, or **corticosteroid therapy**. Methylprednisolone (a long-acting corticosteroid) given by **a single intramuscular** (IM) **injection** followed by a short course of oral corticosteroid therapy is another reasonable approach.

- Alternatively, **IM corticosteroid monotherapy** may be considered in patients with multiple affected joints who cannot take oral therapy.
- **Short-term corticosteroid use is generally well tolerated**. Use with caution in patients with diabetes, GI problems, bleeding disorders, cardiovascular disease, and psychiatric disorders. **Avoid long-term use because of risk for** osteoporosis, hypothalamic–pituitary–adrenal axis suppression, cataracts, and muscle deconditioning.

C-Colchicine

- Colchicine is **highly effective** in relieving acute gout attacks; when it is started within the first 24 hours of onset, about two-thirds of patients respond within hours.
- **Use only within 36 hours of attack onset** because the likelihood of success decreases substantially if treatment is delayed.

- Colchicine causes **dose-dependent GI adverse effects** (nausea, vomiting, and diarrhea). **Non-GI effects include** neutropenia and axonal neuromyopathy, which may be worsened in patients taking other myopathic drugs (eg, statins) or with impaired kidney function.
- Use colchicine with **caution in patients taking P-glycoprotein or strong CYP450 3A4 inhibitors** (eg, **clarithromycin**) due to increased plasma colchicine levels and potential toxicity; colchicine dose reductions may be required.

Hyperuricemia in gout(recurrent attack)

- Recurrent gout attacks can be prevented by maintaining low uric acid levels,
- but adherence with nonpharmacologic and pharmacologic therapies is poor.

Nonpharmacologic Therapy

- **weight loss**
- **Alcohol restriction**
- **Dietary recommendations** include limiting consumption of high-fructose corn syrup and purine-rich foods (organ meats and some seafood) and **encouraging consumption of vegetables and low-fat dairy products**.
- The **DASH diet** (Dietary Approaches to Stop Hypertension) may lower serum uric acid by ~1.0 mg/dL
- **clinical outcomes such as reduction in gout flares.**

- **Evaluate the medication list for potentially unnecessary drugs that may elevate uric acid levels**. The American College of Rheumatology (ACR) guidelines recommend elimination of nonessential uric acid-elevating medications in patients with hyperuricemia when feasible (eg, thiazide and loop diuretics, calcineurin inhibitors, niacin**). Low-dose aspirin for cardiovascular prevention should be continued** because aspirin has a negligible effect on elevating serum uric acid.

Pharmacologic Therapy

- After the first attack of acute gout, **prophylactic pharmacotherapy is recommended** if patients have two or more attacks per year, even if serum uric acid is normal or only minimally elevated.
- **Other indications include** presence of tophi, kidney disease, or history of uric acid urolithiasis.
- Urate-lowering therapy can be started during an acute attack **if anti-inflammatory prophylaxis has been initiated.**

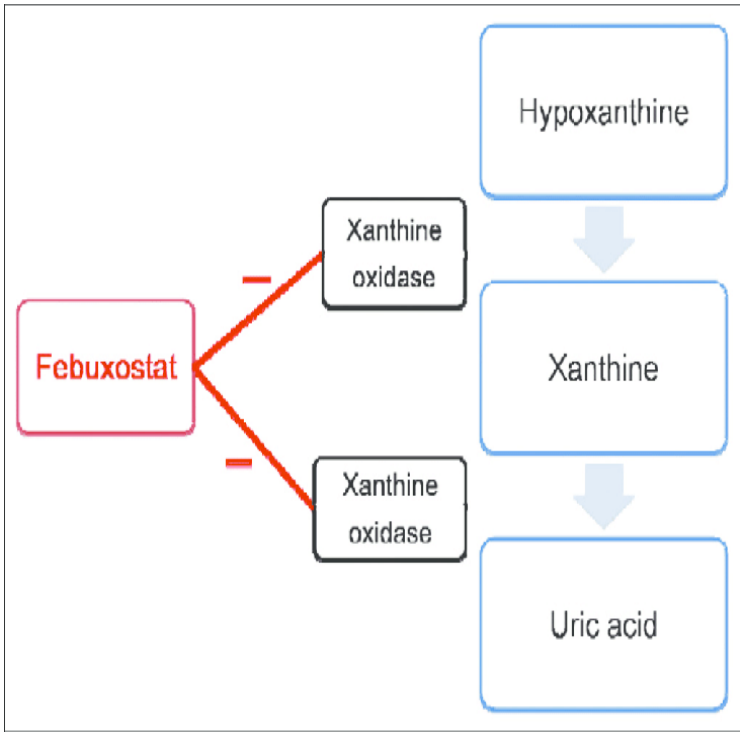
- **Xanthine oxidase inhibitors are recommended first-line therapy**, with uricosurics reserved for patients with a contraindication or intolerance to xanthine oxidase inhibitors.
- In refractory cases, **combination therapy with a xanthine oxidase inhibitor plus a drug with uricosuric properties** (lesinurad,probenecid, losartan, or fenofibrate) is suggested.
- **Pegloticase** may be used in **severe cases** in which the patient cannot tolerate or is not responding to other therapies.
- The ACR guideline goal of urate-lowering therapy is to achieve and maintain serum uric **acid <6 mg/dL and preferably <5 mg/dL if gout is severe or signs and symptoms of gout persist**. Urate lowering should be prescribed for long-term use

Pharmacologic Therapy

- **1- Xanthine oxidase inhibitors**
- **2- uricosuric properties** (probenecid, losartan, or fenofibrate)
- **3- Pegloticase**

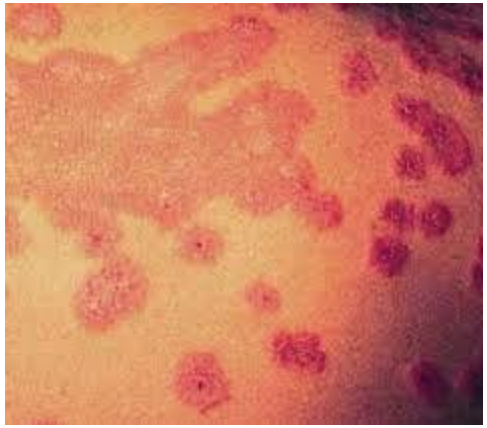
Xanthine oxidase inhibitors

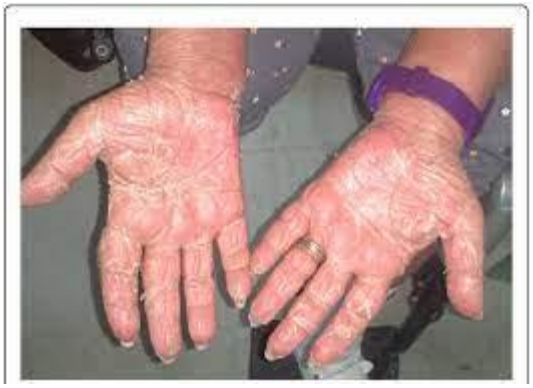
- 1- **allopurinol**
- 2- **Febuxostat**

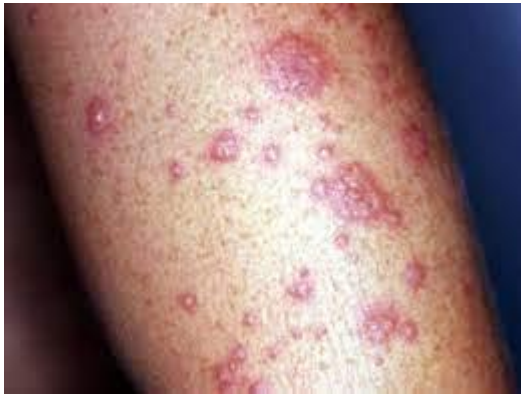


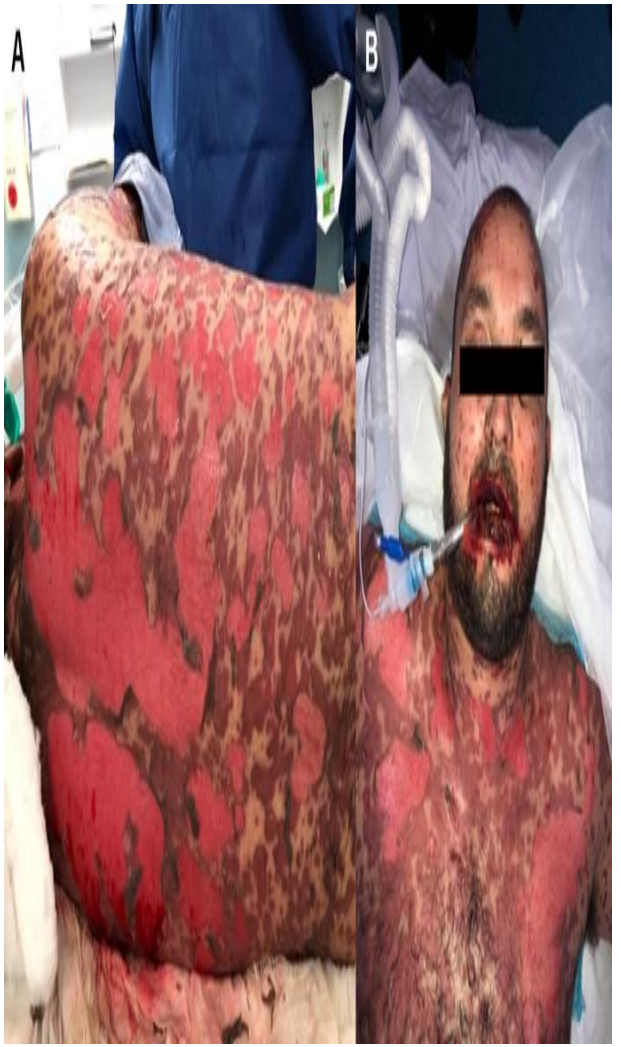
allopurinol

- **they are the most widely prescribed agents for long-term prevention of recurrent gout attacks**.
- Allopurinol dose should be titrated gradually every 2–5 weeks up to a maximum of 800 mg/day until the serum urate target is achieved.
- **side effect**
- skin rash, leukopenia, GI problems, headache, and urticaria.
- A **more severe adverse reaction known as allopurinol hypersensitivity syndrome**, which includes severe rash (toxic epidermal necrolysis, erythema multiforme, or exfoliative dermatitis), **hepatitis**, **interstitial nephritis**, and **eosinophilia,** occurs rarely but is associated with **a 20%–25% mortality rate.**





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Febuxostat

- **Febuxostat** Adverse events include nausea, arthralgias, and minor hepatic transaminase elevations.
- Recent evidence demonstrated an **increase in all-cause and cardiovascular mortality compared to allopurinol**, resulting in addition of a warning in the FDA-approved labeling.
- Because of these safety concerns, lack of evidence of superior efficacy compared to equivalent-dosed allopurinol, and increased cost, **febuxostat is considered a second-line option.**
- Due to rapid mobilization of urate deposits during initiation, **give concomitant therapy with colchicine or an NSAID for at least the first 8 weeks of therapy to prevent acute gout flares.**

B-Uricosurics

- Uricosuric drugs increase renal clearance of uric acid by inhibiting renal tubular reabsorption of uric acid.
- Patients with a **history of urolithiasis should not receive uricosurics**.
- Start uricosuric therapy at a low dose to avoid marked uricosuria and possible stone formation.
- **Maintaining adequate urine flow and urine alkalinization** during the first several days of therapy may also decrease likelihood of uric acid stone formation.
- **Major side effects** include GI irritation, rash and hypersensitivity, precipitation of acute gouty arthritis, and urolithiasis.

- **inhibits URAT1, a protein that is responsible for reabsorption of uric acid in the kidneys**.
- **Lesinurad** is approved as combination therapy with a xanthine oxidase inhibitor for treatment of hyperuricemia associated with gout in patients who **have not achieved target serum uric acid concentrations with xanthine oxidase inhibitor monotherapy**.
- **Lesinurad adverse effects include** urticaria and elevated levels of serum creatinine, lipase, and creatine kinase. It carries a black box warning about **increased risk of acute renal failure** when used in the absence of xanthine oxidase inhibitor therapy.

C-Pegloticase

- Pegloticase is a pegylated recombinant uricase that reduces serum uric acid by converting uric acid to allantoin, which is water soluble.
- Pegloticase is indicated for antihyperuricemic therapy in **adults refractory to conventional therapy.**
- Because of potential **infusion-related allergic reactions**, patients must be pretreated with antihistamines and corticosteroids.
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- Pegloticase is substantially **more expensive than first-line urate-lowering therapies**. The **ideal duration of pegloticase therapy is unknown**. Development of **pegloticase antibodies** resulting in loss of efficacy may limit the duration of effective therapy.
- **Because of its limitations**, reserve pegloticase for patients with refractory gout who are unable to take or have failed all other urate-lowering therapies.

D-Miscellaneous Urate-Lowering Agents

- **Fenofibrate** is thought to increase clearance of hypoxanthine and xanthine, leading to a sustained reduction in serum urate concentrations of 20%–30%.
- **Atorvastatin** and **rosuvastatin** have also been associated with serum uric acid lowering, although the effect is less than with fenofibrate. The mechanism is unclear but is thought to be due to decreased renal reabsorption of uric acid.
- **Losartan** inhibits renal tubular reabsorption of uric acid and increases urinary excretion, properties that are not shared with other angiotensin II receptor blockers. It also alkalinizes the urine, which helps reduce the risk for stone formation.
- **Amlodipine**, **nifedipine**, and **diltiazem** (calcium channel blockers) have been associated with a lower risk of gout, which has been attributed to increased renal elimination of uric acid.

Anti-Inflammatory Prophylaxis During Initiation of Urate-Lowering Therapy

- **Initiation of urate-lowering therapy can precipitate an acute gout attack due to remodeling of urate crystal deposits in joints after rapid lowering of urate concentrations**.
- **Prophylactic anti-inflammatory therapy is often used to prevent such gout attacks**. The ACR guidelines recommend **low-dose oral colchicine** or **low-dose NSAIDs** as first-line prophylactic therapies, with **stronger evidence supporting use of colchicine**.

- For patients on long-term NSAID prophylaxis, a proton pump inhibitor or other acid-suppressing therapy is indicated to protect from NSAID-induced gastric problems.
- **Low-dose corticosteroid therapy** (eg, prednisone ≤10 mg/day) **is an alternative** for patients with intolerance, contraindication, or lack of response to first-line therapy. The potential severe adverse effects of prolonged corticosteroid therapy preclude their use as first-line therapy.
- Continue prophylaxis **for at least 6 months or 3 months after achieving target serum uric acid, whichever is longer**. For patients with **one or more tophi**, continue prophylactic therapy for **6 months after achieving the serum urate target**.

Evaluation of therapeutic outcomes

- **Check the serum uric acid level**
- For patients receiving **urate-lowering therapy**, **obtain baseline assessment of kidney function, hepatic enzymes, complete blood count, and electrolytes**
- During titration of urate-lowering therapy, monitor serum uric acid every 2–5 weeks