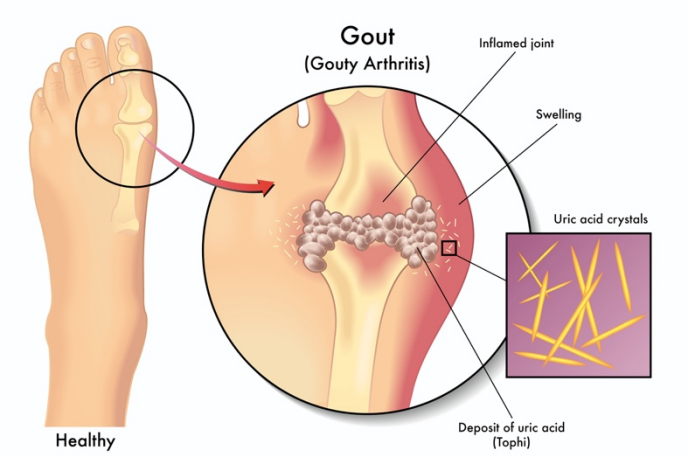
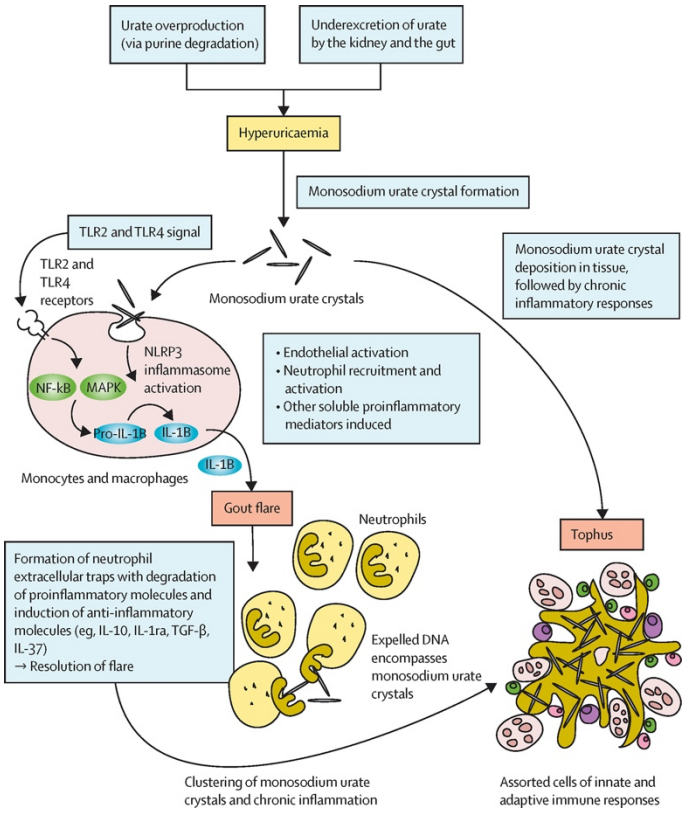
Treatment of Gouty Arthritis

Pathophysiology

- Gout is a disease that most commonly manifests as recurrent episodes of acute joint pain and inflammation secondary to the deposition of MSU (monosodium urate crystals) in the synovial fluid and lining.
- The acute inflammation of gout is believed to be initiated by ingestion of uncoated urate crystals by monocytes and synoviocytes.
- MSU deposition in the urinary tract can cause urolithiasis (kidney stones) and urinary obstruction
  - Uric acid kidney stones are present in 5-10% of patients with gout.
  - The risk of stone formation reaches 50% in patients with a serum urate levels > 13 mg/dL.
- Tophi are hard nodules of MSU crystals that have deposited in soft tissues and most commonly found in the toes, fingers, and elbows.
- Although gout is often associated with hyperuricemia (serum urate level ≥ 6.8 mg/dL), elevated serum uric acid is not a prerequisite for gout --> gout is considered a clinical diagnosis and hyperuricemia is a biochemical diagnosis.
- Uric acid is an end product of purine metabolism and serves no biologic function.
- Uric acid is primarily excreted renally (up to 30% can be eliminated through the GI tract).
- Increased SUA (serum uric acid) concentrations arise from an increase in production or a decrease in renal excretion of UA (uric acid), or a combination of the two.
- Overproduction of UA can also be the result of excessive intake of dietary purines from meat, seafood, dried peas and beans, certain vegetables (e.g., mushrooms, spinach, asparagus), beer and other alcoholic beverages.
  - Alcohol ingestion promotes hypouricemia by increasing urate production and decreasing the renal excretion of uric acid.
  - Fructose consumption (especially soft drinks) has also been linked with increased UA levels.
- A defect in the renal clearance of UA is the main cause of hyperuricemia and gout in 90% of patients.
  - UA is filtered in the renal glomerulus and is almost completely (98-100%) reabsorbed in the proximal tubule, then UA is secreted distal end of proximal tubule.
  - In normal patients, homeostasis between reabsorption and secretion of urate is maintained; however, many factors (e.g., renal impairment, certain drugs, alcohol excess, metabolic syndrome) can cause this balance to fail, resulting in excess serum concentration of UA and tissue deposition
- About 90% of patients with gout are men > 30 years-old; in women, the onset is postmenopausal.





Treatment of Acute Gout

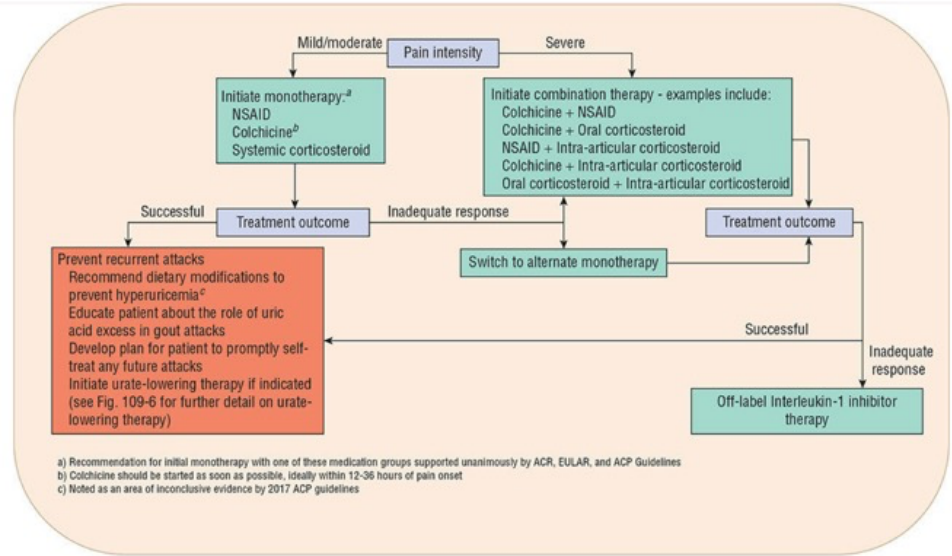
- The primary goal in treatment of an acute attack of gout is to relieve pain and inflammation within 24 hours of symptom onset to rapidly improve patient symptoms.
- The immediate goal of therapy should not be aimed at decreasing the SUA concentration with urate-lowering therapy (ULT), since a decrease in the SUA concentration might mobilize urate stores and precipitate another acute gout attack.
  - If a patient is already receiving ULT (e.g., allopurinol, febuxostat), it is not necessary to discontinue therapy during an acute attack.
- Acute gouty arthritis can be effectively treated in most cases by using monotherapy with NSAIDs, colchicine, or corticosteroids.
- Treatment should be based on patient preference, previous response or experience with an agent, and patient-specific factors (e.g., comorbidities, current medications, renal or hepatic impairment).
- Combination therapy is recommended in severe cases, especially gout involving multiple joints.
- Treatment of acute gout should be continued until patient is asymptomatic (usually 7-10 days).
- Once resolution of a gout flare, the patient is said to have entered a symptom-free period or interval between flares.

Nonpharmacologic Therapy

- Local ice application to the affected joint is the most effective nonpharmacologic approach for reducing pain, compared to other complementary therapies.
  - Ice application to an affected joint for 30 mins QID for 1 week enhances pain reduction of a gout attack, especially when used in conjunction with NSAIDs, corticosteroids, and colchicine.
- Reduction of alcohol consumption, especially beer, is helpful because of its high purine content.
  - ACR and EULAR (European Alliance of Associations for Rheumatology) recommend no more than 2 servings of alcohol per day for males and 1 serving per day for women.
- Minor diet modification may be helpful as non-pharmacological options, such as avoiding purine-rich meats (e.g., organ meats, beef, lamb, pork) and high fructose containing beverages/foods.

Pharmacologic Therapy

- Acute gouty arthritis can be effectively treated in most cases by using monotherapy with NSAIDs, colchicine, or corticosteroids.
- The ACR, EULAR guidelines recognize NSAIDs, colchicine, and corticosteroids as 1st line treatments for acute gout.
- Treatment should begin as soon as possible after the onset of a gout attack.
- In more severe cases, gout affecting multiple joints, or causing higher intensity pain, combination therapy or off label use of IL-1 inhibitor (e.g., anakinra) therapy may be used.



NSAIDs

- NSAIDs are a mainstay of therapy for acute attacks of gouty arthritis because of their excellent efficacy and minimal toxicity with short-term use.
- Indomethacin (Indocin) has been historically favored as the NSAID of choice for acute gout flares due its potency, but there is little evidence to support one NSAID as being more efficacious than another.
- Indomethacin (Indocin), naproxen (Naprosyn), and sulindac (Clinoril) have US FDA-approved labeling for treatment of gout, but all NSAIDs are considered equally efficacious.
- The choice of NSAID should be determined based on patient-specific factors.
    - GI bleeding/ulcers and inhibition of platelet aggregation are two of the most common serious adverse effects of non-selective NSAIDs, especially in patients taking anticoagulants (e.g., warfarin, DOACs).
    - Selective COX-2 inhibitors (celecoxib) and preferential COX-2 inhibitors (meloxicam) reduce the risk of GI bleeding, especially in patients taking anticoagulants because they do not inhibit platelets at normal doses; however, they demonstrate increased cardiovascular risk, and exacerbate HTN/heart failure by causing Na/H_2O retention.
    - NSAIDs also inhibit renal prostaglandin (PGI) --> potentiate AKI in patient with impaired kidney function.
- NSAID therapy should be initiated within 24 hours of gout attack for greater efficacy.
    - Resolution of an acute attack for most patients generally occurs within 5-8 days after initiating NSAID therapy.
    - Following resolution of the gout attack, tapering of NSAID therapy should be considered, especially in patients with comorbidities, such as impaired kidney function where prolonged therapy would be undesirable.
- Naproxen (Naprosyn) 500 mg PO BID or indomethacin (Indocin) 25-50 mg PO Q8H are potent and effective NSAID options for acute gout and should be continued until symptoms resolve (5-7 days).

Colchicine

- Colchicine inhibits microtubule polymerization as an antimitotic agent--> decreases the action of inflammatory mediators (cytokines, chemokines).
- Note: Colchicine should be given within 36 hours of a gout attack, since its efficacy is significantly reduced when delayed.
- Dose: 1.2 mg loading dose to start, followed by 0.6 mg in 1 hour on day 1; then, 0.6 mg PO BID until symptom resolution.
    - Patients already taking chronic colchicine therapy for prophylaxis may take 1.2 mg loading dose, followed by 0.6 mg 1 hour later; then resume the usual 0.6 mg PO daily or BID maintenance therapy.
- Colchicine should be used cautiously in patients with CrCl < 30 ml/min and with hepatic impairment.
- Colchicine has a number of significant drug-drug interaction that inhibit microsomal hepatic enzymes (cytochrome P-450 / P-glycoprotein) and increase serum levels of digoxin, statins, non-dihydropyridine calcium channel blockers (e.g., diltiazem), erythromycin, antifungals.
- SEs: nausea, vomiting, diarrhea

Corticosteroids

- Recent evidence has demonstrated corticosteroids to be as effective as NSAIDs for reducing pain and inflammation from acute gout, with no differences in adverse event when used short-term.
    - Corticosteroids are useful for elderly patients or those with renal disease who cannot tolerate NSAIDs.

Corticosteroids (cont.)

- Corticosteroids can be used either systemically or by intra-articular injection.
  - If an acute gout episode involves only 1 or 2 large joints, intra-articular corticosteroid may be administered after joint aspiration of synovial fluid to rule out an infectious process, such as septic arthritis.
  - Triamcinolone, 10-40 mg (depending on the size of the joint), administered intraarticular is considered a very effective treatment option.
  - If a gout attack is polyarticular, systemic corticosteroid therapy may be used with either IV methylprednisolone (Solu-Medrol) 40 mg/day or oral prednisone 40-60 mg/day.
    - A gradual corticosteroid taper over 7-10 days is recommended to prevent a rebound attack after steroid withdrawal.
  - Intramuscular corticosteroid with methylprednisolone (10-40 mg IM daily) is also recommended for patients who are unable to take oral medications.
- SEs: long-term side effects of corticosteroids (e.g., osteoporosis, myopathy, peptic ulcer diseases, CNS effects, HTN, immunosuppression) are not likely to occur with short-term therapy; however, hyperglycemia and fluid retention can occur with short-term use.

Analgesics

- When an occasional patient requires more pain control, a dose or two of non-opioid or opioid analgesic may be a reasonable adjunctive therapy to blunt the pain of acute gouty arthritis while awaiting the benefits of NSAIDs, colchicine, or corticosteroid.

Interleukin-1 Inhibitors

- IL-1 inhibitors, e.g., anakinra, has not been approved by the FDA for the treatment of acute gout, but the ACR guidelines recommend reserving IL-1 inhibitors for situations where traditional medications are contraindicated or ineffective.

Drug	Adverse Drug Reaction	Monitoring Parameter	Comments
NSAIDs	Impaired kidney function (acute and chronic [Chapter 61], gastritis (worse with concurrent aspirin), fluid retention, blood pressure elevation	Therapeutic Resolution of pain Avoidance of gout attacks when used for prophylaxis Toxic Blood pressure Kidney function Edema Dark stools	Avoid for patients with peptic ulcer disease, active bleeding Use caution in congestive heart failure, dehydration, impaired kidney function Consider coadministration with a proton-pump inhibitor when used long term for patients at risk for GI bleeding
Systemic corticosteroids	GI upset, increased appetite, nervousness/restlessness, transient glucose intolerance, fluid retention, blood pressure elevation	Therapeutic Resolution of pain Avoidance of gout attacks when used for prophylaxis Toxic Glucose levels in patients with diabetes	Limit duration of therapy in patients with diabetes
Intra-articular corticosteroids	Injection pain, rebound arthritis	Therapeutic Resolution of pain Toxic Signs of rebound arthritis (pain relief followed by reemergence of pain)	Avoid if joint sepsis cannot be ruled out
Colchicine	Dose-dependent GI adverse effects (diarrhea, nausea, vomiting), rare myelosuppression, and reversible neuromyopathy	Therapeutic Resolution of pain Avoidance of gout attacks when used for prophylaxis Toxic GI symptoms Complete blood count	
Interleukin-1 inhibitors	Injection site reaction, neutropenia, immune hypersensitivity reaction, infectious disease, malignancy	Therapeutic Resolution of pain Avoidance of gout attacks when used for prophylaxis Toxic Neutrophil count (prior to initiation, monthly for the first 3 months of therapy then after 6, 9, and 12 months of therapy) Temperature (periodically to detect infection)	Safety for use in acute gout and gout prophylaxis during initiation of urate-lowering therapy has not yet been established; not FDA approved for use in gout

Case Study

S.D. is a 72 year-old woman who was brought to the ED complaining of shortness of breath (SOB) and dizziness. On arrival, she is noted to have new-onset atrial fibrillation with a HR of 130 bpm and 2+ peripheral edema bilaterally to her knees, secondary to exacerbation of CHF caused by her rapid ventricular rate (RVR). In addition to administering diltiazem to control her HR, S.D. is given furosemide (Lasix) 40 mg IV every 12 hours for 3 doses. The following day she complains of severe pain in her left great toe, and it is noted on examination to be erythematous and swollen. V.D.'s CrCl is 40 ml/min, her SUA is 7.5 mg/dL, and her BP is 160/96. What therapeutic option would be appropriate for S.D.?

Case Study: Considerations

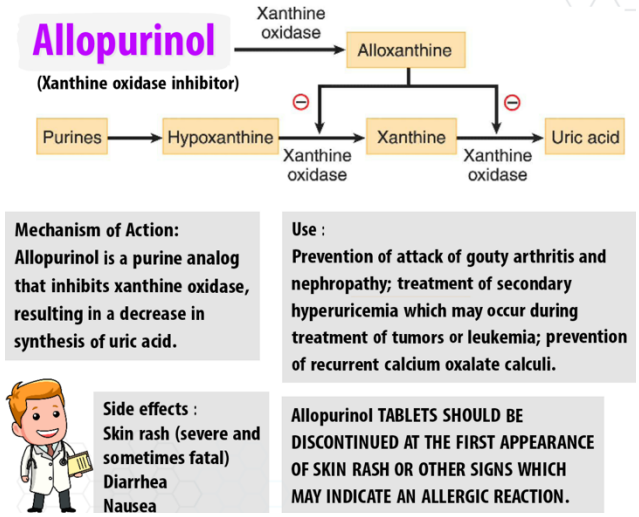
- Note V.D.'s advanced age, acute exacerbation of heart failure, and renal dysfunction.
- Note that V.D. is taking diltiazem (non-dihydropyridine calcium channel blocker) for atrial fibrillation.
- V.D.'s pain is monoarticular.
- Recommendation: _____
  _____

Hyperuricemia

- ULT (Urate-Lowering Therapy) should be initiated only when patients with gout have recurrent acute attacks (at least 2 attacks per year), urate tophi, uric acid stones, or chronic kidney disease (Stage 2 and above) with prior gout attack and current hyperuricemia.
- A patient's complete medication list should be reviewed to rule out drug-induced hyperuricemia before adding a medication to decrease SUA levels, since the only treatment needed may be to discontinue the offending agent.
  - Drugs knows to increase SUA include: thiazide and loop diuretics, niacin, calcineurin inhibitors (e.g., cyclosporin, tacrolimus), and aspirin.
- The SUA concentration in a patient who has clinical gout should be decreased to 6 mg/dL or less; however, the ACR guidelines recommend a goal of less than 5 mg/dL in patients with clinical gout.
- the guidelines recommend waiting 1-2 weeks after an acute attack to begin ULT due to risk of a recurrent attack.

Allopurinol (Zyloprim)

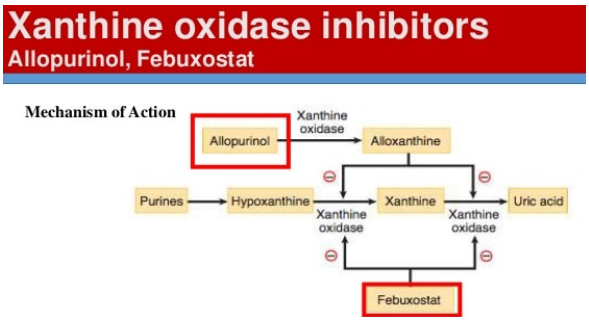
- Allopurinol inhibits the production of UA by inhibiting xanthine oxidase (XO) --> decreases SUA levels.
- Clinical practice guidelines recommend allopurinol as a 1st line agent for gout prevention.
- The ability of allopurinol to lower SUA level is dose related,
  - Allopurinol dose of 300 mg/day is typical maintenance dose.
  - Higher doses up to 800-900 mg/day may be needed for those with more severe disease.
  - The recommended initial dose of allopurinol is 50-100 mg once daily and then increase in 50-100 mg/day increments every 2-5 weeks until SUA levels is at the desired goal of less than 6 mg/dL or until patient intolerance.
  - Starting at the low dose and titrating slowly can reduce the risk of hypersensitivity reactions and improve tolerance in renal impairment.



Allopurinol (cont.)

- SEs: Allopurinol has been associated with a rare life-threatening hypersensitivity syndrome (2%) that may include rash, fever, elevated liver function tests, and renal failure.
  - If allopurinol hypersensitivity occurs, the drug should be stopped immediately because this can lead to skin necrosis, dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and even death.
  - These adverse effects are more common in patients with concomitant diuretic use and pre-existing renal insufficiency; therefore, dose adjustment in patients with renal impairment is essential.

Febuxostat (Uloric)



- Febuxostat is more selective than allopurinol for xanthine oxidase (XO) and does not inhibit other enzymes involved in purine and pyridine metabolism.
- Evidence suggests that febuxostat is more effective than allopurinol 300 mg in achieving SUA of less than 6 mg/dL.
- SEs: adverse effects have been shown to be minor and similar to allopurinol and febuxostat with increases in liver function tests, nausea, diarrhea, arthralgias, and rash (i.e., hypersensitivity reaction, similar to allopurinol).
  - Febuxostat is more widely used and has been associated with thromboembolic cardiovascular events, according to the FDA.
- Febuxostat starting dose is 40 mg PO daily, with a recommended dose increase to 80 mg once daily if SUA levels is not less than 6 mg/dL by 2 weeks of therapy.
- Febuxostat does not require dosage adjustments for CrCl > 30 ml/min.
- The ACR guidelines do not recommend one agent over another (allopurinol vs febuxostat) for 1st-line treatment.
- The clinician should keep in mind the significantly higher out-of-pocket cost for febuxostat ($160/month) and consider patient affordability.
- Most clinicians recommend that febuxostat be used only in patients who are intolerant or have contraindications to allopurinol therapy, or for patients who cannot achieve adequate SUA levels on allopurinol therapy.

Uricosuric Agent: Probenecid

- MOA: uricosuric drugs lower serum uric acid levels by blocking the tubular reabsorption of filtered urate --> increases uric acid excretion by the kidneys.
- Probenecid is a 2nd-line agent for patients who cannot achieve a serum uric acid level of ≤ 6.0 mg/dL with allopurinol or febuxostat alone.
- Probenecid is also indicated as a 2nd-line agent for patients who are unable to take at least one XO inhibitor due to tolerability, contraindications, or significant drug interactions.
- Uricosuric agents should not be administered to patients with impaired renal function (CrCl < 50 ml/min) or urolithiasis (uric acid stones).
- The usual initial dose of probenecid is 250 mg PO BID for the 1st week, then probenecid can be increased to 500 mg PO BID, if necessary (max dose: 2-3 gm/day).
  - Uricosuric therapy should begin with lower doses since the excretion of large amounts of uric acid increases the risk of urate stone formation in the kidney.
  - High fluid intake to maintain urine flow of at least 2 L/day also minimizes renal stone formation.

Uricosuric Agent: Probenecid (cont.)

- SEs: headache, GI upset, urolithiasis (11%)
- Probenecid inhibits secretion of penicillin into the renal tubule, and therapy prolongs the serum half-life of penicillin --> increases penicillin serum concentrations.
- Probenecid can also compete with salicylates for renal tubular transport, but low-dose ASA for antiplatelet, cardio-protection is unlikely to interfere with probenecid therapy>

Summary: Pharmacologic Management of Gouty Arthritis

Drug	Adverse Drug Reaction	Monitoring Parameter	Comments
NSAIDs	Impaired kidney function (acute and chronic [Chapter 61], gastritis (worse with concurrent aspirin), fluid retention, blood pressure elevation	Therapeutic Resolution of pain Avoidance of gout attacks when used for prophylaxis Toxic Blood pressure Kidney function Edema Dark stools	Avoid for patients with peptic ulcer disease, active bleeding Use caution in congestive heart failure, dehydration, impaired kidney function Consider coadministration with a proton-pump inhibitor when used long term for patients at risk for GI bleeding
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Intra-articular corticosteroids	Injection pain, rebound arthritis	Therapeutic Resolution of pain Toxic Signs of rebound arthritis (pain relief followed by reemergence of pain)	Avoid if joint sepsis cannot be ruled out
Corticotropin	Increased appetite, nervousness/restlessness, transient glucose intolerance, fluid retention, blood pressure elevation	Therapeutic Resolution of pain	Requires intact pituitary–adrenal axis Less effective for patients receiving long-term oral corticosteroid therapy
Colchicine	Dose-dependent GI adverse effects (diarrhea, nausea, vomiting), rare myelosuppression, and reversible neuromyopathy	Therapeutic Resolution of pain Avoidance of gout attacks when used for prophylaxis Toxic GI symptoms Complete blood count	
Interleukin-1 inhibitors	Injection site reaction, neutropenia, immune hypersensitivity reaction, infectious disease, malignancy	Therapeutic Resolution of pain Avoidance of gout attacks when used for prophylaxis Toxic Neutrophil count (prior to initiation, monthly for the first 3 months of therapy then after 6, 9, and 12 months of therapy) Temperature (periodically to detect infection)	Safety for use in acute gout and gout prophylaxis during initiation of urate-lowering therapy has not yet been established; not FDA approved for use in gout
Allopurinol	Rash, potential for fatal hypersensitivity syndrome	Therapeutic Serum urate level Reduced frequency of gout attacks Toxic Rash Kidney function	Can be used in both urate overproduction and urate underexcretion
Febuxostat	Liver enzyme elevation, nausea, arthralgias, rash, cardiovascular risk	Therapeutic Serum urate level Reduced frequency of gout attacks Toxic Liver function tests Kidney function	Can be used in both urate overproduction and urate underexcretion
Probenecid	Urolithiasis	Therapeutic Serum urate level Reduced frequency of gout attacks Toxic Kidney function	Useful in urate underexcretion Avoid for patients with history of urolithiasis