

# **Therapy of Gout and Hyperuricemia**

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# Introduction

**Gout describes a heterogeneous clinical spectrum of diseases including:**

- 1. Elevated serum urate concentration (hyperuricemia).**
- 2. Recurrent attacks of acute arthritis associated with:**
  - a. monosodium urate (MSU) crystals in synovial fluid leukocytes.**
  - b. deposits of monosodium urate crystals (tophi) in tissues in and around joints.**
  - c. interstitial renal disease.**
  - d. uric acid nephrolithiasis.**

# Introduction

- The underlying metabolic disorder of gout is **hyperuricemia**, defined as serum that is supersaturated with monosodium urate.
- At 37°C, serum urate concentrations around 7 mg/dL begin to exceed the limit of solubility for monosodium urate.
- **Elevated serum urate level is the single most important risk factor for the development of gout.**

# Introduction

- **Hyperuricemia does NOT always lead to gout, and many patients with hyperuricemia remain asymptomatic.**
- **Another major contributor to the increased prevalence of gout is obesity.**
- **Dietary and life-style factors linked to obesity (consumption of alcohol, sugary beverages, and red meat; along with a sedentary life-style) may be associated with gout.**

# Introduction

- **Uric acid is produced from purines ← increased breakdown of tissue nucleic acids:**
  - 1. Starvation.**
  - 2. Chronic hemolytic anemias.**
  - 3. Toxemia of pregnancy.**
  - 4. Obesity.**
  - 5. Acute alcoholism.**
  - 6. Psoriasis.**

# Introduction

- 7. Myeloproliferative and lymphoproliferative disorders.**
- 8. Polycythemia vera.**
- 9. Cytotoxic drugs use can result in overproduction of uric acid secondary to lysis and breakdown of cells.**

# Introduction

## Acute Gouty Arthritis:

- Acute inflammatory mono-arthritis.
- The first metatarsophalangeal joint is often involved.
- Any joint of the lower extremity, wrist or fingers can be affected.
- Gout may include: nephrolithiasis, gouty nephropathy, and aggregated deposits of sodium urate (tophi) in cartilage, tendons, synovial membranes, etc.

# Introduction

- **Acute attacks of gout can be precipitated by a rapid change in serum uric acid levels, either rapid increase or rapid decrease.**
- **When serum uric acid level is rapidly decreased by uric acid lowering agent, dissolution of tophi takes place which will increase serum uric acid levels.**



# Introduction

- ~ 90% of filtered uric acid is reabsorbed in the proximal tubule, by both passive and active transport mechanisms.
- Proximal tubular sodium reabsorption and uric acid reabsorption are linked, so that conditions that enhance sodium reabsorption (dehydration) lead to increased uric acid reabsorption. (Co-transport)
- Uric acid is also secreted in the tubules by an active transport process.

# Drug-Induced Hyperuricemia

**Drugs capable of inducing hyperuricemia and gout:**

- 1. Diuretics.**
- 2. Nicotinic acid.**
- 3. Ethanol.**
- 4. Pyrazinamide.**
- 5. Levodopa.**
- 6. Ethambutol.**

# Drug-Induced Hyperuricemia

7. Cytotoxic drugs.

8. Cyclosporine.

**9. Salicylates:**

a) At  $< 2\text{g/day}$ , salicylates block the active secreting system of uric acid leading to uric acid retention.

b) At  $> 2.5\text{g/day}$ , salicylates are uricosuric by blocking active uric acid reabsorption.

• Insulin resistance may be associated with gout, by enhancing renal urate reabsorption.

# Therapy of Gout and Hyperuricemia

The goals of treatment of gout:

1. To terminate the acute attack.
  2. To prevent recurrence of attacks.
  3. To prevent complications associated with chronic deposition of urate crystals in tissues.
- These goals can be accomplished through a combination of pharmacologic and nonpharmacologic methods, including focused patient education.

# Acute Gouty Arthritis

## Therapy:

- For most patients, acute attacks of gouty arthritis may be treated successfully with:
  1. Nonsteroidal anti-inflammatory drugs (NSAIDs).
  2. Corticosteroids.
  3. Colchicine.
- All are considered first-line monotherapy for the treatment of acute gout.

# Acute Gouty Arthritis

- Treatment should be started within 24 hours of the onset of an attack, and continued until complete resolution.
- Combination drug therapy is indicated in:
  1. More severe cases.
  2. Multiple joints involvement.
  3. High intensity pain.

# Acute Gouty Arthritis

## NSAIDs:

- NSAIDs are a mainstay of therapy for acute attacks of gouty arthritis - excellent efficacy and minimal toxicity with short-term use.
- Following resolution of the attack, NSAID therapy may be tapered, especially in patients with hepatic or renal insufficiency. (to prevent rebound)
- Resolution of an acute attack takes 5-8 days after initiating therapy.

# Acute Gouty Arthritis

## Adverse effects:

1. GI: gastritis, **bleeding**, perforation.
  2. Kidney: renal papillary necrosis, reduced creatinine clearance (**renal dysfunction**).
  3. Cardiovascular system: **sodium and water retention, increased blood pressure**.
  4. CNS: impaired cognitive function, headache, dizziness.
- etc



# Acute Gouty Arthritis

- Should be use with caution in patients with a history of peptic ulcer disease, congestive heart failure, uncontrolled hypertension, renal insufficiency, coronary artery disease, or who are concurrently receiving anticoagulants or antiplatelet drugs.
- Some of the choices include but are NOT limited to **indomethacin, naproxen, and sulindac**.
- Selective cyclooxygenase-2 (COX-2) inhibitors are better tolerated in patients with GI problems, but **have higher cardiovascular risk**. (**Celecoxib, etoricoxib and lumiracoxib** are options).

# Acute Gouty Arthritis

## Corticosteroids:

- Corticosteroids are equivalent to NSAIDs in the treatment of acute gout flares.
- They can be used either systemically or by intra-articular injection, depending on the number of joints involved.
- Should be tapered gradually to avoid rebound.
- Prednisone, prednisolone, and methylprednisolone are some options for systemic use, and triamcinolone acetonide for intra-articular injections.

# Acute Gouty Arthritis

## Adverse effects:

- Are generally dose- and duration-dependent.
- Short-term use for treatment of acute attacks is generally well tolerated.
- Increase blood sugar.
- Monitor patients with a history of GI problems, bleeding disorders, cardiovascular disease, and psychiatric disorders.
- Long-term corticosteroid use should be avoided because of the risk for osteoporosis, hypothalamic–pituitary-adrenal axis suppression, and cataracts.
- etc...

# Acute Gouty Arthritis

## Colchicine:

- Colchicine is an antimitotic drug that is highly effective at relieving acute attacks of gout.
- When started within the first 24 hours of an acute attack, it produces a response within hours of administration.
- **Should be started within 36 hours of attack.**
- **Delayed initiation of colchicine is associated with substantial reduction of response.**

# Acute Gouty Arthritis

## Adverse effects:

- Dose-dependent GI adverse effects: nausea, vomiting, and diarrhea.
- Neutropenia and axonal neuromyopathy, worsened in patients taking statins, or in those with renal insufficiency.
- Concurrent administration with P-glycoprotein or cytochrome P450 3A4 inhibitors (clarithromycin or cyclosporine), increases colchicine concentration.
- Use with caution in patients with renal and hepatic dysfunction.

# Hyperuricemia in Gout

## Nonpharmacologic Therapy:

- Recurrent gout attacks can be prevented by maintaining low uric acid levels.
- Patient education is a critical first step in the management of hyperuricemia.

## Lifestyle/Dietary modification:

1. Weight loss and exercise may enhance renal excretion of urate.

# Hyperuricemia in Gout

2. **Restriction of alcohol intake because alcohol reduces renal urate excretion.**
  - **Long-term alcohol intake increases production of purines** as a by-product of the conversion of acetate to acetyl coenzyme-A in the metabolism of alcohol.
3. **Encourage the consumption of vegetables and low-fat dairy products, which lower urates.**

# Hyperuricemia in Gout

4. Reduce consumption of **high-fructose diet**, and **purine-rich foods** (organ meats and some seafood), which cause uric acid elevation.
5. Avoid (**if possible**) **drugs** that may elevate uric acid levels:
  - a. Thiazide and loop diuretics.
  - b. Calcineurin inhibitors.
  - c. Niacin.
  - d. Low-dose aspirin.



# Hyperuricemia in Gout

- **Thiazide diuretics and Low-dose aspirin are useful in treating hypertension and cardio-protection, respectively.**

# Hyperuricemia in Gout

## Pharmacologic Therapy:

- After the first attack of acute gouty arthritis, consider **prophylactic use of uric acid-lowering drugs**.
- (Antiinflammatory drugs prevent attacks only).

## Other indications for lowering uric acid include:

- 1) the presence of tophi.
- 2) chronic kidney disease (stage 2 or worse).
- 3) history of urolithiasis.
- 4) Cancer chemotherapy.

# Hyperuricemia in Gout

- Uric acid-lowering therapy **should be long-term.**
- Reduction of serum uric acid concentrations can be accomplished pharmacologically by:
  - a. **decreasing the synthesis** of uric acid (**xanthine oxidase inhibitors**)
  - b. **increasing the renal excretion** of uric acid (**uricosuric agents**).

# Hyperuricemia in Gout

- **Xanthine oxidase inhibitors** are **first-line therapy**.
- **Probenecid**, a potent uricosuric, is **an alternative** in patients with a contraindication or intolerance to xanthine oxidase inhibitors.

# Hyperuricemia in Gout

## Xanthine Oxidase Inhibitors:

- Impair the conversion of hypoxanthine to xanthine and xanthine to uric acid.
- Effective in over-producers of uric acid, as well as in those with low excretion.

## **Allopurinol:**

- It is an effective uric acid-lowering agent, but long-term adherence is low.

# Hyperuricemia in Gout

## Adverse effects:

- **Mild-moderate adverse effects: skin rash, leukopenia, GI disturbances, headache, and urticaria.**
- **More severe adverse reactions including severe rash (toxic epidermal necrolysis, erythema multiforme, or exfoliative dermatitis), hepatitis, interstitial nephritis, and eosinophilia. These adverse effects are associated with a 20-25% mortality.**

# Hyperuricemia in Gout

## Febuxostat:

- Similar to allopurinol, but newer drug.

## Adverse effects:

- Nausea, arthralgias, and minor hepatic transaminases elevation.
- An **advantage** of febuxostat is that **it does not require dose adjustment** in patients with moderate hepatic and renal impairment.

# Hyperuricemia in Gout

## Uricosuric Drugs:

- They increase the renal excretion of uric acid by inhibiting its proximal tubular reabsorption.
- The drug used most widely is probenecid.
- Uricosuric drugs **cause marked uricosuria and may cause uric acid stone formation.**
- The maintenance of **adequate urine flow** and **alkalinization of the urine** may **reduce uric acid nephrolithiasis**.



# Hyperuricemia in Gout

- Other major adverse effects include GI irritation and precipitation of acute gouty arthritis.
- Salicylates at low dose ranges may interfere with their mechanism and result in treatment failure.
- Probenecid can inhibit the tubular secretion of other organic acids and increase plasma concentrations of penicillins, cephalosporins, sulfonamides, and indomethacin.

# Hyperuricemia in Gout

Uricosuric drugs are contraindicated in patients:

1. allergic to them.
2. with impaired renal function (a creatinine clearance less than 50 mL/min).
3. who are **overproducers of uric acid**. (for such patients, a xanthine oxidase inhibitor should be used).

# Hyperuricemia in Gout

## Lesinurad:

- It is a **selective uric acid reabsorption inhibitor (SURI)**.
- It inhibits urate transporter 1 (URAT1), a transporter found in the proximal renal tubules, resulting in uric acid excretion.

## Adverse effects:

1. Increased serum creatinine, elevated lipase, increased creatine kinase, and urticaria.

# Hyperuricemia in Gout

## 2. Acute renal failure.

- **It should not be used in patients with creatinine clearance less than 45 mL/min.**
- **May be used in a combination with a xanthine oxidase inhibitor for treatment of hyperuricemia in patients who have not achieved target serum uric acid levels with xanthine oxidase inhibitor monotherapy.**

# Hyperuricemia in Gout

3. Headache, flu-like symptoms.
4. Gastroesophageal reflux disease ([GERD](#)).
5. Kidney stones.

# Hyperuricemia in Gout

## Pegloticase:

- It is a **pegylated recombinant uricase** that reduces serum uric acid by **converting uric acid to allantoin**, a water-soluble and easily excretable compound.
- It is effective in reducing serum uric acid and resolving tophi in patients with **severe gout** and hyperuricemia who failed or had a contraindication to allopurinol therapy.

# Hyperuricemia in Gout

- **Severe gout has at least one of the following criteria:**
  1. **three or more gout flares within the last 18 months.**
  2. **one or more tophi.**
  3. **joint damage due to gout.**
- **Given as bi-weekly IV infusions over no less than 2 hours, which may NOT be convenient.**

# Hyperuricemia in Gout

- **May be associated with infusion-related allergic reactions, and patients must be pre-treated with antihistamines and corticosteroids before therapy.**
- **Duration of therapy is unknown.**
- **Immunogenic and leads to development of pegloticase antibodies.**
- **An agent of last resort that should be reserved for patients with refractory hyperuricemia with gout.**



# Anti-Inflammatory Gout Prophylaxis during Urate-Lowering Therapy (ULT)

- Initiation of ULT can prompt an acute attack of gout due to remodeling of urate crystal deposits in joints as a result of rapid lowering of urate concentrations.
- Thus, prophylactic antiinflammatory therapy is recommended to prevent gout attacks.
- Low-dose oral colchicine and low-dose NSAIDs are first-line prophylactic therapies, with stronger evidence supporting use of colchicine.

# Anti-Inflammatory Gout Prophylaxis during Urate-Lowering Therapy (ULT)

- **Low-dose corticosteroid therapy is an alternative** in patients with intolerance, contraindication, or lack of response to first-line therapy.
- **Continue prophylaxis for at least 3 months after achieving target serum uric acid or 6 months total, whichever is longer.**
- **For patients with one or more tophi, prophylactic therapy should be continued for 6 months following achievement of serum urate target.**

# Urate Nephrolithiasis

- Treatment by life-style modification mentioned earlier.
- Hydration to maintain a urine volume of 2 to 3 L/day.
- Reduction of urinary uric acid excretion.
- Alkalinization of urine. Urine pH should be maintained at 6-6.5, by the administration of potassium bicarbonate or potassium citrate.  
(At a urine pH of 6.75, > 90% of the total urinary uric acid will be as more soluble urate salt).

# Urate Nephrolithiasis

- **Administration of alkali with sodium salts should be avoided for two reasons:**
  1. **The sodium-induced volume expansion will increase sodium excretion, which can lead to proximal Na reabsorption.**
- **Such a mechanism may be associated with secondary calcium reabsorption with sodium, leading to **hypercalcemia**. This can lead to **calcium oxalate stone formation**.**

# Urate Nephrolithiasis

2. **Older patients with uric acid kidney stones may also have hypertension, congestive heart failure, or renal insufficiency. Overload with alkalinizing sodium salts or unlimited fluid intake can worsen these conditions.**
- **Acetazolamide produces rapid and effective urinary alkalization.**

# Urate Nephrolithiasis

- The mainstay of drug therapy for recurrent uric acid nephrolithiasis is xanthine oxidase inhibitors.
- They are also recommended as prophylactic treatment for patients who will receive cytotoxic agents for the treatment of lymphoma or leukemia.