

# **Therapy of Gout and Hyperuricemia**

# Therapy of Gout and Hyperuricemia

- **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.**

# Therapy of Gout and Hyperuricemia

- 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 levels are the single most important risk factor for the development of gout.

# Therapy of Gout and Hyperuricemia

- **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.

# Therapy of Gout and Hyperuricemia

Uric acid is produced from purines :

- a. dietary purines.
  - b. conversion of tissue nucleic acid into purine nucleotides.
  - c. *de novo* synthesis of purine bases.
- Purines produce nucleic acid or uric acid.
  - Several enzyme systems regulate purine metabolism.
  - Abnormalities in these systems can result in overproduction of uric acid.

# Therapy of Gout and Hyperuricemia

- **Uric acid may be overproduced with increased breakdown of tissue nucleic acids, and excessive rates of cell turnover as observed with:**
  - 1. Starvation.**
  - 2. Chronic hemolytic anemias.**
  - 3. Toxemia of pregnancy.**
  - 4. Obesity.**
  - 5. Acute alcoholism.**
  - 6. Psoriasis.**

# Therapy of Gout and Hyperuricemia

- 7. Myeloproliferative and lymphoproliferative disorders.**
- 8. Polycythemia vera.**
- 9. Some types of anemias.**
- 10. Others.**
  - Cytotoxic drugs use can result in overproduction of uric acid secondary to lysis and breakdown of cellular matter.**

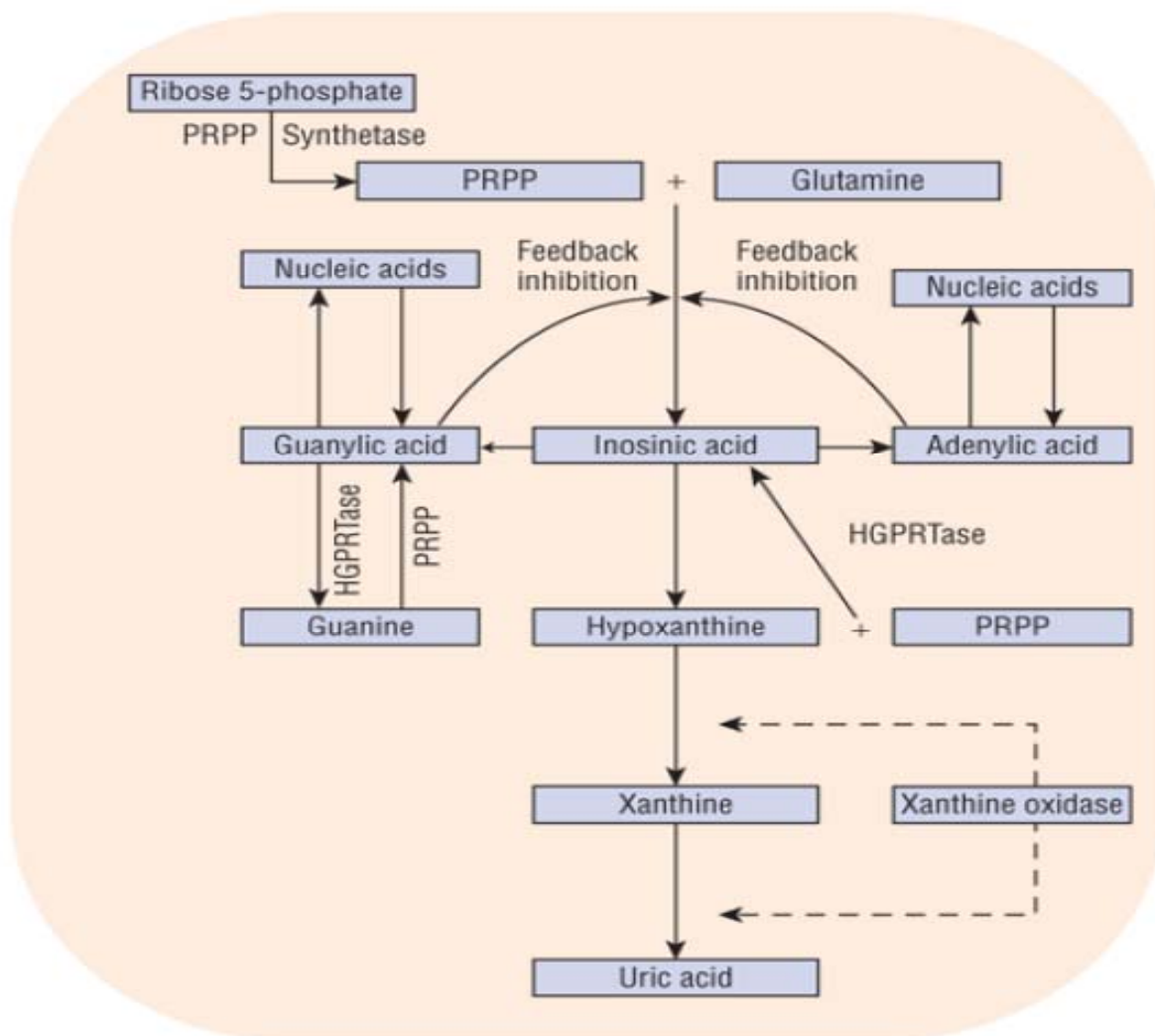
# Therapy of Gout and Hyperuricemia

Two enzyme abnormalities result in over-production of uric acid:

1. An increase in the activity of phosphoribosyl pyrophosphate (PRPP) synthase, which increases concentration of PRPP, a determinant of uric acid production.
2. A deficiency in the HGPRT leads to increased metabolism of guanine and hypoxanthine to uric acid, and to more PRPP.



# Therapy of Gout and Hyperuricemia



Purine metabolism.  
 HGPRT, hypoxanthine-guanine phosphoribosyltransferase.  
 PRPP, phosphoribosyl pyrophosphate.)

# Therapy of Gout and Hyperuricemia

## Acute Gouty Arthritis:

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

# Therapy of Gout and Hyperuricemia

- ~ 90% of filtered uric acid is reabsorbed in the proximal tubule, by both active and passive 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.
- Uric acid is also secreted in the tubules by an active transport process.

# Therapy of Gout and Hyperuricemia

## Drugs capable of inducing hyperuricemia and gout:

1. Diuretics.
  2. Nicotinic acid.
  3. Salicylates ( < 2g/day)
  4. Ethanol.
  5. Pyrazinamide.
  6. Levodopa.
  7. Ethambutol.
  8. Cytotoxic drugs.
  9. Cyclosporine.
- 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 recurrent attacks of gouty arthritis.
  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

## Nonpharmacologic Therapy:

- There are limited effective nonpharmacologic therapies for an acute gout attack.
- Local ice application results in pain reduction in patients receiving therapy.
- **Pharmacologic Therapy:**
- For most patients, acute attacks of gouty arthritis may be treated successfully with:

# Acute Gouty Arthritis

1. Nonsteroidal anti-inflammatory drugs (NSAIDs).
  2. Corticosteroids.
  3. Colchicine.
- All are considered first-line monotherapy for the treatment of acute gout.
  - Treatment should be started within 24 hours of the onset of an attack, and continued until complete resolution.

# Acute Gouty Arthritis

**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.
- 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

- 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 high cardiovascular risk**.
- **Celecoxib, etoricoxib and lumiracoxib** are options.<sup>19</sup>

# 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.
- 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 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 cause **lactic acidosis**, which 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 urate-lowering drugs. (? Antiinflammatory drugs prevent attacks).
- **Other indications include** the presence of tophi, chronic kidney disease (stage 2 or worse), and a history of urolithiasis.

# Hyperuricemia in Gout

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

# Hyperuricemia in Gout

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

## Xanthine Oxidase Inhibitors:

- Impair the conversion of hypoxanthine to xanthine and xanthine to uric acid.

# Hyperuricemia in Gout

- Effective in both under-excreters and over-producers of uric acid.
- **Allopurinol** and **febuxostat** are the agents of choice.

## Allopurinol:

- It is an effective urate-lowering agent.

## Adverse effects:

- long-term adherence is low.

# Hyperuricemia in Gout

- **Mild 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. and are associated with a 20% to 25% mortality.**



# Hyperuricemia in Gout

## Febuxostat:

- Similar to allopurinol.

## Adverse effects:

- Nausea, arthralgias, and minor liver transaminase elevations.
- 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 post-secretory renal proximal tubular reabsorption of uric acid.
- The drug used most widely is probenecid.
- Uricosuric drugs **cause marked uricosuria** and **may cause stone formation** (urolithiasis).
- The maintenance of **adequate urine flow** and **alkalinization of the urine** may **reduce uric acid stone formation**.

# Hyperuricemia in Gout

- Other major adverse effects include GI irritation, rash and hypersensitivity, and **precipitation of acute gouty arthritis.**
- **Salicylates 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 works by inhibiting urate transporter 1 (URAT1), a transporter found in the proximal renal tubule, resulting in uric acid excretion.

## Adverse effects:

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

# Hyperuricemia in Gout

2. Because of increasing renal uric acid secretion, it has been associated with 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 substance.
- 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 is that which meets 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 is inconvenient.

# Hyperuricemia in Gout

- May be associated with infusion-related allergic reactions, and patients must be 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 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.
- **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, more than 90 percent of the total urinary uric acid will be the 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, can lead to proximal Na reabsorption.**
- **Such a mechanism may be associated 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.