Therapy of Gout and Hyperuricemia
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 associated with 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

• ~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.
Drug-Induced Hyperuricemia

Drugs capable of inducing hyperuricemia and gout:

1. Diuretics.
2. Nicotinic acid.
3. Salicylates (< 2g/day)
4. Ethanol.
5. Pyrazinamide.
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

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.
- 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 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 causes **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 only).

Other indications for lowering urate include:

1) the presence of tophi.
2) chronic kidney disease (stage 2 or worse).
3) 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 (uricosuric agents).
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-excretors and over-producers of uric acid.

• **Allopurinol** and **febuxostat** are the agents of choice.

**Allopurinol:**

• It is an effective urate-lowering agent, but long-term adherence is low.
Hyperuricemia in Gout

Adverse effects:

• 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 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 alkalization of the urine may reduce uric acid nephrolithiasis.
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).
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 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 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.
• Alkalization 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 alkalinization.
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.