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.**
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

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 administeration with P-glycoprotein or cytochrome P450 3A4 inhibitors (clarithromycin or cyclosporine), increases colchicine concentration.**
- **Use with caution inpatients 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 alkalinization 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).
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 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.**
- **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 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.**