Gout: Pathophysiology, Causes, and Treatment

Gout is a form of inflammatory arthritis characterized by the deposition of monosodium urate (MSU) crystals in joints and soft tissues, resulting from prolonged hyperuricemia. It manifests as acute, episodic arthritis and can progress to chronic tophaceous gout if left unmanaged.

Epidemiology

- **Prevalence** : Affects approximately 1–2% of the population in developed countries.
- **Gender** : Predominantly affects men (85% of cases); incidence in women increases post-menopause.
- **Age** : Commonly presents in middle-aged to older adults.
- **Risk Factors** :
    - **Non-modifiable** : Genetic predisposition, age, male sex.
    - **Modifiable** : Obesity, hypertension, chronic kidney disease, metabolic syndrome, dietary habits, alcohol consumption, and certain medications (e.g., diuretics, low-dose aspirin) .

Pathophysiology

Uric Acid Metabolism

- **Purine Degradation** : Uric acid is the end product of purine metabolism (adenine and guanine).
- **Excretion** : Approximately two-thirds excreted by the kidneys; one-third via the gastrointestinal tract.
- **Hyperuricemia** : Results from:
    - **Overproduction** : Increased purine synthesis or increased cell turnover.
    - **Underexcretion** : Impaired renal elimination of uric acid.

Genetic Factors

- **PRPP Synthetase Overactivity** : Leads to increased purine synthesis and uric acid overproduction.
- **HGPRT Deficiency** :
    - **Partial Deficiency** : Kelley-Seegmiller syndrome; associated with gout and uric acid nephrolithiasis.
    - **Complete Deficiency** : Lesch-Nyhan syndrome; characterized by neurological deficits and self-mutilation behaviors .
- **Glucose-6-Phosphatase Deficiency** : Seen in glycogen storage disease type I; leads to increased ribose-5-phosphate and PRPP, enhancing purine synthesis.

Risk Factors and Triggers

Dietary Factors

- **High Purine Intake** : Consumption of red meat, seafood, and organ meats increases uric acid production.
- **Alcohol** : Particularly beer and spirits; alcohol metabolism increases uric acid production and decreases excretion .
- **Fructose-Rich Beverages** : High fructose intake (e.g., sugar-sweetened sodas) elevates serum uric acid levels .

Medications

- **Diuretics** : Thiazides and loop diuretics decrease renal uric acid excretion.
- **Low-Dose Aspirin** : Impairs uric acid excretion.
- **Pyrazinamide and Ethambutol** : Antitubercular drugs that reduce uric acid clearance.

Other Factors

- **Obesity** : Increases uric acid production and decreases excretion.
- **Renal Insufficiency** : Impairs uric acid elimination.
- **Lead Exposure** : Chronic exposure can lead to nephropathy and decreased uric acid excretion.

Clinical Presentation

Acute Gouty Arthritis

- **Onset** : Sudden, often nocturnal.
- **Symptoms** :
  - Severe joint pain, swelling, erythema, warmth.
  - Commonly affects the first metatarsophalangeal joint (podagra).
  - Other joints: ankles, knees, wrists, fingers.
- **Duration** : Untreated attacks typically resolve within 3–14 days.

Chronic Tophaceous Gout

- **Tophi Formation** : Deposits of MSU crystals in soft tissues; commonly found in fingers, ears, and olecranon bursae.
- **Joint Damage** : Chronic inflammation can lead to joint deformity and erosion.
- **Renal Involvement** : Uric acid nephrolithiasis and chronic kidney disease.

Diagnosis

Synovial Fluid Analysis

- **Gold Standard** : Identification of negatively birefringent, needle-shaped MSU crystals under polarized light microscopy.
- **Leukocyte Count** : Elevated (2,000–50,000 cells/mm^3), predominantly neutrophils.

Serum Uric Acid Levels

- **Note** : May be normal or low during acute attacks; not solely diagnostic.

Imaging

- **X-rays** : May show "punched-out" erosions with overhanging edges in chronic gout.
- **Ultrasound** : Double contour sign indicating urate crystal deposition.

Management

Acute Attack Treatment

- **Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)** : First-line therapy; e.g., indomethacin, naproxen.
- **Colchicine** : Effective if initiated within 36 hours of symptom onset; gastrointestinal side effects limit use.
- **Corticosteroids** : Oral or intra-articular; used when NSAIDs and colchicine are contraindicated.

Urate-Lowering Therapy (ULT)

- **Indications** :
  - Recurrent gout attacks.
  - Presence of tophi.
  - Chronic kidney disease stage ?2.
  - History of urolithiasis.

Xanthine Oxidase Inhibitors

- **Allopurinol** : First-line ULT; start at low dose and titrate to target serum uric acid <6 mg/dL.
- **Febuxostat** : Alternative for patients intolerant to allopurinol; caution in patients with cardiovascular disease.

Uricosuric Agents

- **Probenecid** : Increases renal uric acid excretion; contraindicated in patients with nephrolithiasis or renal impairment.
- **Benzbromarone** : Potent uricosuric; limited use due to hepatotoxicity concerns.

Recombinant Uricase

- **Pegloticase** : Converts uric acid to allantoin; used in refractory gout cases.
- **Rasburicase** : Primarily used to manage tumor lysis syndrome-induced hyperuricemia.

Lifestyle and Dietary Modifications

- **Diet** :
  - Limit intake of purine-rich foods, alcohol, and fructose-containing beverages.

    - Encourage consumption of low-fat dairy products and vegetables.
- **Hydration** : Maintain adequate fluid intake to promote uric acid excretion.
- **Weight Management** : Achieve and maintain a healthy body weight.
- **Medication Review** : Evaluate and adjust medications that may contribute to hyperuricemia.

High-Yield tips

- **Podagra** : First MTP joint involvement is classic for gout.
- **MSU Crystals** : Negatively birefringent, needle-shaped crystals confirm diagnosis.
- **Serum Uric Acid** : Not reliable during acute attacks; may be normal.
- **Allopurinol** : Do not initiate during an acute attack; continue if already prescribed.
- **Tophi** : Indicative of chronic gout; necessitate initiation or intensification of ULT.
- **Lifestyle** : Dietary modifications and weight loss are crucial in management.

Mnemonic: "GOUT"

- **G** : Great toe pain (podagra).
- **O** : One joint involvement initially.
- **U** : Urate crystals (MSU) negatively birefringent.
- **T** : Tophi in chronic cases.