GOUT

Crystal-induced arthritis
- monosodium urate (MSU)
- calcium pyrophosphate dihydrate (CPPD)
- calcium hydroxyapatite (HA)
- and calcium oxalate (CaOx)

Monosodium urate (MSU) gout
A gout is a metabolic disease most often affecting middle-aged to elderly men and postmenopausal women. It is typically associated with an increased uric acid pool, hyperuricemia, episodic acute and chronic arthritis, and deposition of MSU crystals in connective tissue, tophi and kidneys.

Epidemiology
Occurs mostly in men. Women represent only 5-17% of all patients with gout. Premenopausal gout is rare and accounts for only about 17% of all women with gout; it is seen mostly in individuals with a strong family history of gout. Two forms:

Primary: Family prevalence: 40-60%

Secondary: Hyperuricemia occurs in > 5% of the adult population

Pathogenesis and pathology
I. Hyperuricemia
II. Urate deposition
III. Inflammation induced by urate crystals

I. Hyperuricemia
Occurs in >5% of the adult population. Uric acid is a breakdown product of purine

The purine metabolism
Phosphoribosyl-pyrophosphate (PRPP) synthetase - amidophospho-ribosyltransferase (amidoPRT) - adenylosuccinate lyase - adenylate (AMP) deaminase - 5’-nucleotidase - adenosine deaminase - purine nucleoside phosphorylase - hypoxanthine phosphoribosyltransferase (HPRT) - adenine phosphoribosyltransferase (APRT) - xanthine oxidase.

Classification of hyperuricemia
Urate overproduction
- Primary idiopathic
- HPRT hypoxantine-phosphoribosyl transferase) deficiency (Lesch-Nyhan syndrome)
- PRPP (phosphoribosyl pyrophosphate) synthetase overactivity
- Haemolytic processes
- Lymphoproliferative diseases
- Myeloproliferative diseases (esp. polycythemia vera, PCV)
- Psoriasis
• Paget’s disease
• Glycogenosis III, V, VII
• Rhabdomyolysis
• Exercise
• Obesity
• Purin-rich diet

**Decreased uric acid excretion**

• Primary idiopathic
• Renal insufficiency
• Polycystic kidney disease
• Diabetes insipidus
• Hypertension
• Acidosis (lactic, diabetic keto-, starvation ketosis)
• Berylliosis
• Sarcoidosis
• Lead intoxication (saturnine gout)
• Hyperparathyroidism
• Toxemia of pregnancy
• Bartter’s syndrome
• Down syndrome
• Drugs: salicylates (>2g/d), diuretics (esp. thiazide, furosemide, etacrinic acid), levodopa, ethambutol, pyrazinamide, nicotinic acid, cyclosporine

**Combined mechanism**

• Glucose-6-phosphatase deficiency
• Fructose-1-phosphate aldolase deficiency
• Alcohol
• Shock

**II. Uric acid deposition**

• Sites: articular cartilage, tendon sheaths, synovium, synovial fluid, subcutaneous tissues. Rarely in parenchymal organs.
• High affinity to proteoglycans → entrapment → deposition
• Lysosomal and other proteolytic enzymes → ↑metabolic rate of proteoglycans → ↓stabilization of urate → supersaturated urate crystallizes in tissues
• Deposited uric acid → local necrosis, subsequent fibrosis. Cartilage degeneration, bone destruction

**III. The pathomechanism of inflammation in gout**

Gout is an autoinflammatory disease: activation of the molecular pattern recognition molecules in leukocytes, leading to the development of inflammosomes. Urate crystals activate the Hageman factor (kinins), the phagocytosis (FcR), chemotaxis, leukocyte microtubules, lysosomal enzymes, and the complement system. These lead to the development of inflammation.
Acute gouty arthritis

**Podagra** (1st MTP joint) occurs during the first attack in 75%. *Sydenham 1683*: Occurs at night. Toe is painful, swollen, shining, red, sometimes violaceous, fever. If untreated, lasts for several days, but may persist longer. Early attacks resolve completely in 3-10 days. Other small joint of the feet and the ankles, knees, elbows, wrists are frequently involved. Finger joints and large joints are rarely affected. Monarthritis is typical, but polyarthritis is also seen (¼). In elderly patients, finger joints may be inflamed. Inflamed Heberden’s or Bouchard’s nodes may be a first manifestation of gouty arthritis. 60% recurrence rate in one year, especially if untreated.

**Precipitating factors of acute gouty arthritis**

Alcohol (esp. excessive wine intake), gluttony (dietary excess), overweight, hypertriglyceridemia, dramatic fluctuation in serum urate (fasting, allopurinol, thiazides), trauma, surgery

**Chronic gouty arthritis**

After many acute mono- or oligoarticular attacks, a proportion of gouty patients may present with a chronic nonsymmetric synovitis. Less commonly, chronic gouty arthritis will be the only manifestation and, more rarely, the disease will manifest as inflamed or noninflamed periarticular tophaceous deposits in the absence of chronic synovitis. Most women with gouty arthritis are postmenopausal and elderly, have arterial hypertension causing mild renal insufficiency, and are usually receiving diuretics. Also, most of these patients have underlying degenerative joint disease, and inflamed tophaceous deposits may be seen on Heberden's and Bouchard's nodes.

**Uric acid and renal disease**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Clinical setting</th>
<th>Features</th>
<th>Therapeutic issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uric acid nephrolithiasis</td>
<td>Hyperuricosuria</td>
<td>Uric acid nephrolithiasis</td>
<td>Allopurinol; alkalinize urine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Calcium nephrolithiasis</td>
<td>Allopurinol</td>
</tr>
<tr>
<td>Acute uric acid nephropathy</td>
<td>Cytotoxic chemotherapy for leukemia or lymphoma; occasionally spontaneous</td>
<td>Intratubular obstruction by uric acid crystals in acidic urine</td>
<td>Prevention with allopurinol, fluids, and alkalinization</td>
</tr>
<tr>
<td>Chronic gouty nephropathy</td>
<td>Gout or hyperuricemia in the setting of hypertension, preexisting renal disease, advanced age, vascular disease, inflammatory reaction, and chronic exposure to lead</td>
<td>Intrarenal tophi; sodium urate crystals in interstitium with accompanying destructive inflammatory reaction</td>
<td>Hemodialysis for renal failure</td>
</tr>
<tr>
<td>Familial hyperuricemic nephropathy</td>
<td>AD inheritance</td>
<td>Interstitial fibrosis, chronic inflammation; crystals are rare</td>
<td>No consensus regarding allopurinol</td>
</tr>
</tbody>
</table>

**Uric acid lithiasis**

Occurs in 20-25% of primary and 50% of secondary gout. Can precede the first gouty attack in more than ⅓ in primary gout.

**Laboratory diagnosis**

- ↑ESR, ↑WBC count during acute attack.
• Serum uric acid levels can be normal or low at the time of the acute attack, but are almost always elevated some time. Normal value: 100-360 μM/l.
• 24-h uric acid excretion predicts uric acid stones. >800 mg/24 h on a regular diet suggests overproduction of purine
• Urinalysis, BUN, serum creatinine, serum lipid levels
• **Synovial fluid characteristics:** Color: yellow-white, clarity: cloudy-opaque, viscosity: poor, WBC: 3,000-50,000/µl, >70% PMN, glucose normal or decreased, protein: > 3 g/l, complement: normal, **microscopic: birefringent needle-shaped MSU crystals** with negative elongation are largely intracellular.

**Radiological features**
Nothing during the first attack. Later: tophaceous lesions in joints, esp. in feet. Sharply defined, marginal erosion of subchondral bone, thin shell with overhanging edge. Occurs typically on the 1st MTP, but is not diagnostic.

**Diagnosis**
Confirmed by needle aspiration of acutely or chronically inflamed joints or tophaceous deposits. Prompt effectiveness of colchicine in the first 24-48 hours.

**Differential diagnosis**
Pseudogout, rheumatoid arthritis, osteoarthritis, sarcoidosis, psoriatic arthritis, infectious arthritis, palindromic rheumatism, cellulitis, acute bursitis, acute rheumatic fever, local trauma.

**Treatment**
**Treatment of acute gouty arthritis**
**NSAIDs:** indomethacin, 25-50 mg tid, ibuprofen, 800 mg tid, or diclofenac, 50 mg tid.

**Colchicine:** is effective in 75% and specific. 3-4x1 tablet (0.6 mg). Side effects: gastrointestinal toxicity, local tissue damage by extravasation.

**Glucocorticoids** (esp. in old patients) prednisone, 30 to 50 mg/d PO as the initial dose and tapered over 5 to 7 days, a single IV dose of methylprednisolone, 7 mg of betametasone, or 20 to 40 mg of intraarticular triamcinolone if one joint is affected.

Warm soaks, ice application, immobilization, hydration

**Treatment of chronic gout**
**Hypouricemic therapy**
Simple means: control of body weight (gradual weight loss if needed), low-purine, low-protein diet, increase in liquid ingestion, limitation of ethanol intake, and avoidance of diuretic use

**Uricosuric agents:** should not be initiated during acute attacks!

• **allopurinol:** 300-800 mg/day. Side effects: skin rash, progression to toxic epidermal necrolysis (TEN), vasculitis, bone marrow suppression, granulomatous hepatitis, renal failure
• **febuxostat:** 80-120 mg/d
• **probenecid:** from 2x200 mg up to 2 g/day
• **benzbromarone**
• **Recombinant urate oxidase uricase**: for short-term prophylaxis and treatment of chemotherapy-associated hyperuricemia

**Asymptomatic hyperuricemia**
Represented a cardiovascular risk so has to be treated.

**Intercritical gout**
No drug therapy needed when attacks are rare. If they become frequent and prolonged: colchicine. If not enough or radiographic changes take place: uric acid lowering drugs.

**Chronic tophaceous gout**
  • Surgical removal
  • Uric acid-lowering drugs: probenecid, sulfinpyrazone, allopurinol

**Uric acid stones**
  • Large daily fluid intake
  • Alkalization of urine by sodium citrate or bicarbonate, pH>6
  • Allopurinol

**Dental correlations**
  • Gout rarely affects the temporomandibular joint.
  • Bone destruction due to chronic renal failure