DISEASE SUMMARY

GOUT

Risk Factors

Family history, male gender, hypertension, metabolic syndrome, obesity, CVD, purine-rich diet (alcohol, seafood, red meat), use of diuretics, renal failure, OA (damage to joint can predispose to gout), psoriasis (increased purine turnover), genetics (enzyme defects - HGPRT).

Epidemiology

The most common inflammatory arthritis which affects people from 30s-40s onwards. It is more common in men and rare in pre-menopausal women.

Pathogenesis

Stage 1. Asymptomatic hyperuricemia

Overproduction of uric acid or under excretion by the kidneys results in hyperuricemia.

Stage 2. Acute gouty arthritis

After 20-30 years of asymptomatic hyperuricemia, acute pain, swelling and tenderness develops often in the first metatarsophalangeal joint, known as podagra. High plasma uric acid levels causes more uric acid to move into synovial joints. The synovial fluid is more acidic due to the presence of hyaluronic acid and peripheral joints can be as cold as 20°C, favouring crystallisation.

Monosodium urate crystals activate complement and are phagocytosed by monocytes and activate the NALP3 inflammasome, which activates caspase 1 which cleaves and activates C5a, IL-1β and IL-8. IL-1β induces the expression of adhesion molecules and IL-8 triggers neutrophil recruitment and accumulation at the site of inflammation and their release of lysosomal enzymes, leukotrienes, prostaglandins and previously phagocytosed urate crystals into the joint upon lysis, which exerts further tissue damage.

Stage 3. Intercritical period

Acute attacks of gout may resolve with treatment or spontaneously. 10% of patients never experience another attack, but 90% experience recurring attacks.

Stage 4. Chronic tophaceous gout

Following years of repeated uric acid crystallisation, tophi develop which deposit in joints, ligaments, bursae and tendons. This triggers an inflammatory giant cell response, which causes the synovium to become hyperplastic, fibrotic and thickened by inflammatory cells, destroying the underlying cartilage. Without adequate treatment it can lead to secondary OA.

Signs & Symptoms

Acute inflammation sensitises nociceptors (via TNF-a, IL-1, IL-1b and prostaglandins etc) in the joint capsule causing excruciating pain. The first metatarsophalangeal joint is most commonly affected. Peripheral joints are colder favouring crystal formation and have a tendency for blood to pool at
night, causing pain to occur during this time. The big toe also has less venous drainage, so crystals are more likely to accumulate in this part of the body, triggering the resulting immune response.

The affected joint is stiff, due to the presence of MSU crystals, oedema and inflammatory cells. In chronic tophaceous gout, tophi can lead to secondary OA which causes the formation of osteophytes and cartilage damage that further limit the joint’s range of motion.

**Histological Features**

Pale, granular material due to the proteinaceous matrix in which there are needle-like spaces that are the outline of urate crystals present in the affected tissue.

Dense neutrophil infiltrates due to acute inflammation.

The synovium is congested and oedematous, with lymphocyte infiltrates and macrophages.

Visible deposits of urates in the synovium, surrounded by macrophages, lymphocytes and large foreign body giant cells.

The synovium is hyperplastic, fibrotic and thickened due to inflammation.

**Investigations**

- **Fluid aspiration**
  - Polarised light microscopy shows negative birefringent, needle-shaped MSU crystals
  - Gram staining can rule out risk of septic arthritis
- **Blood tests**
  - Serum urate may be normal or low following an acute attack because inflammation can reduce the level of urate (mechanism is unknown but it’s not because there’s less MSU in the plasma compared to the joint)
  - Can indicate hyperuricemia but this doesn’t always lead to gout
  - Raised inflammatory markers (ESR, CRP)
  - Serum urea & electrolytes can monitor for signs of renal impairment which may be the cause of reduced uric acid excretion
- **Radiography**
  - Rules out alternative disease i.e. OA, RA
  - Tophi can sometimes be seen on x-ray
  - MSU crystals appear as a halo of radio-opacity (fuzzy appearance)

**Management & Treatment**

No treatment is given in the asymptomatic stage in the absence of gout.

During an acute attack, NSAIDs are prescribed to reduce the inflammation, including ibuprofen and diclofenac as a more potent alternative that is more selective against COX-2. If the person is contraindicated to NSAIDs, colchicine can be prescribed instead.
Colchicine is also administered during the acute phase, to target the neutrophilic response and reduce the inflammation in the affected joint. Colchicine is toxic and can cause diarrhoea, so must be started at a low dose which is gradually built up.

Allopurinol is given as a life-long treatment to prevent further attacks of gout, by reducing uric acid synthesis. It must not be given during an acute attack as it can precipitate or worsen the symptoms due to its disturbance of uric acid homeostasis. It is initially co-administered with colchicine to prevent this from happening.

**Long Term Effects**

Chronic tophaceous gout and chronic arthritis and damage to the affected joint can lead to secondary OA.

With treatment, gout can be managed.

**Additional Points**

Patients with no additional conditions have primary gout, but a diagnosis of gout in someone with diabetes or renal failure etc. is known as secondary gout.

Although 10% of the population of the Western hemisphere have hyperuricemia, only 0.5% of these develop gout. Hyperuricemia does not always lead to gout.

Renal damage can occur as a result of uric acid nephropathy. Uric acid can precipitate in the acidic renal tubular fluid forming kidney stones and obstructing the tubules. This causes increased tubular pressure, increased intrarenal pressure and affects the tubular-glomerular feedback mechanism, causing an increase in renal vascular resistance and a fall in renal blood flow and GFR, eventually leading to acute renal failure. Tophi can also deposit in renal tubules, triggering inflammation and fibrosis and progressive kidney failure.

Gout is a form of inflammatory arthritis.