Update on the Management of Gout

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“People wish their enemies dead, but I do not; I say give them the gout, give them the stone!”

Mary Worley Montagu

Henry VIII was famous for his Gout
Gout, Uric Acid, and Hyperuricemia

Definitions

• **Gout** is the disease state resulting from deposition of monosodium urate crystals in tissues

• **Uric acid (urate)** is the end product of purine degradation in humans

• **Hyperuricemia** is a serum urate concentration in excess of urate solubility (400 µmol/L or 6.8 mg/dL)
  – Results from overproduction and/or underexcretion of uric acid
  – Is a common serum abnormality but does not result in gout without crystal deposition
Natural History of Hyperuricemia and Gout

Asymptomatic Hyperuricemia

Acute Flares

Intercritical Segments

Advanced Gout

Painless Intercritical Segments

Painful Intercritical Segments

Flares last longer

Flares occur more often

Intercritical segments decrease

Persistent pain and stiffness

Acute Gout

• Sudden onset
• Exquisite pain and tenderness
• Self limiting
Common Sites of Acute Flares

Gout can occur in bursae, tendons, and joints.

- Olecranon Bursa
- Elbow
- Wrist
- Fingers
- Knee
- Ankle
- Subtalar
- Midfoot

1st MTP (eventually affected in ~90% of individuals with gout)
Acute Gout

Olecranon Bursitis

Podagra
Precipitation of Acute Flares

- Acute flares occur commonly with precipitating factors
  - Local trauma
  - Binges of alcohol, overeating, or fasting
  - Concurrent acute medical or surgical illness
  - Marked rise or fall in serum uric acid
  - Seasonal factors
Advanced Gout

• Polyarticular involvement may develop
  – History of intermittent attacks; additive and ascending

• **Serum urate can be normal during the flare**¹
  – During the acute flares, a normal serum urate was found in 49% of patients

Advanced Gout Arthritis Aspect

• As uncontrolled hyperuricemia continues
  – Total tissue urate stores increase
  – Deposition in joints may progress to chronic arthritis

• Chronic arthritis
  – Involved joints persistently uncomfortable, stiff, and swollen
    | Pain intensity often less than acute flares
    | May mimic rheumatoid or psoriatic arthritis
  – Acute flares may still occur
  – Radiographic changes are common
Advanced Gout
Arthritis Aspects and Radiographic Changes

• The characteristic gouty erosion is both destructive and hypertrophic, leading to “overhanging edges”

• The joint space is often preserved until very late in the disease process
Advanced Gout
Joint Damage

T1 weighted coronal

Fat suppressed proton density coronal

Tophi
Advanced Gout
Common Sites of Tophi

Subcutaneous gouty tophi occur frequently at sites of friction or trauma.

Connective tissues such as renal pyramids, heart valves, and sclerae also can be involved.

Undefined factors dictate tophus development and growth.

- Helix of the ear
- Olecranon bursa
- Extensor surface of the forearm
- Wrists
- Finger pads
- Knee
- Achilles tendon
Gout: Extra-articular Tophi
American College of Rheumatology Preliminary Criteria for the Clinical Diagnosis of Gout

Six or more criteria are needed to make a diagnosis:

- More than one attack of acute arthritis
- Maximum inflammation developed within one day
- Attack of monoarthritis
- Redness over joints
- Painful or swollen first metatarsophalangeal joint
- Unilateral attack on first metatarsophalangeal joint
- Unilateral attack on tarsal joint
- Tophus (proved or suspected)
- Hyperuricaemia
- Asymmetric swelling within a joint on radiograph
- Subcortical cysts without erosions on radiograph
- Joint fluid culture negative for organisms during attack
Gout Prevalence (GPRD 1999)

## Global Variations in Gout Epidemiology

<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>Population</th>
<th>Year(s)</th>
<th>Prevalence</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>Lawrence, et al</td>
<td>U.S.</td>
<td>&gt; 18 yrs</td>
<td>1992</td>
<td>86</td>
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<tr>
<td>Harris, et al</td>
<td>U.K.</td>
<td>All ages</td>
<td>1993</td>
<td>95</td>
<td>---</td>
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<td>Mikuls, et al</td>
<td>U.K.</td>
<td>All ages</td>
<td>1999</td>
<td>139</td>
<td>13.1</td>
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<tr>
<td>Klemp, et al</td>
<td>New Zealand</td>
<td>&gt; 15 yrs</td>
<td>1997</td>
<td>472</td>
<td>---</td>
</tr>
</tbody>
</table>
Monosodium Urate Crystal Formation From Hyperuricemia

• High levels of urate present throughout extracellular fluids during hyperuricemic state
  – including joint spaces and soft tissues

• Crystals precipitate in joints and soft tissues
STEPS IN THE PATHOGENESIS OF GOUT

- Genetic
- Drugs
- Diet
- Alcohol
- Metabolic
- Proliferative

- Underexcretion
- Over-production

- Hyperuricemia
  - Supersaturation
    - Seed nucleus
    - Crystal inhibitors

- Crystal promoters
- Urate concentration

- Proinflammatory (e.g. IgG)

- Crystal formation
  - Microcrystal shedding
    - Anti-inflammatory (e.g. apoE)

- Resident synovial cells

- IL-1, TNFα, NO, chemokines

- Adhesion molecules

- Neutrophils
  - Chemokines

- Acute inflammatory mediators
  - TGFβ, IL-10, Apo B, E

- Resolution
  - Recurrences
    - Chronic
INFLAMMATORY MEDIATORS INDUCED BY URATE CRYSTALS

- IgG coating
- Urate crystals
- Apo-E, B coating

**Stimulates**
- Macrophage, fibroblast, neutrophil, mast cell
  - Chemokines (CXCL8)
  - Lysosomal enzymes
  - PGE$_2$
  - LTB$_4$
  - IL-1
  - IL-6
  - TNF$\alpha$
  - Reactive N and O metabolites

**Inhibits**
Risk Factors for the Development of Gout

- Serum urate
- Family history
- Age
- Male gender
- Postmenopausal women
- Drugs
  - Diuretics
  - Low-dose aspirin
- Post-transplant patients
  - Cyclosporine
- High alcohol intake\(^1\)
  - Highest risk with beer consumption (purine-rich)
- High body mass index
- Diet high in meat and seafood\(^2\)

Relation between serum urate concentration and annual incidence of gout

The Hyperuricemia Cascade

Urate

Overproduction → Hyperuricemia ← Underexcretion

• Primary hyperuricemia
  – Idiopathic
  – Accelerated purine nucleotide synthesis (eg, HGPRT deficiency, PRPP synthetase activity $\uparrow$)

• Secondary hyperuricemia
  – Excessive dietary purine intake
  – Increased purine nucleotide turnover (eg, myelo- and lymphoproliferative diseases, psoriasis)
  – Accelerated ATP degradation (eg, ethanol abuse)

• Impaired Excretion
• Primary or idiopathic renal hyperuricemia
• Secondary hyperuricemia
  – Diminished renal function
  – Inhibition of tubular urate secretion (eg. competitive anions)
  – Enhanced tubular urate reabsorption (eg. dehydration, diuretics, insulin resistance (metabolic syndrome))
  – Mechanisms unclear
    • Hypertension, hyperparathyroidism, certain drugs, lead nephropathy
Purine Degradation to Uric Acid

- **Xanthine oxidase** catalyzes the final conversions to uric acid
Renal Elimination of Uric Acid
Operationally Defined 4 Component Model of Renal Uric Acid Handling

Hyperuricaemia

**Hyperuricaemia**

### Overproduction
- **Primary hyperuricemia**
  - Idiopathic
  - Accelerated purine nucleotide synthesis (e.g., HGPRT deficiency, PRPP synthetase overactivity, i.e., FAMILIAL)
- **Secondary hyperuricemia**
  - Excessive dietary purine intake
  - Increased purine nucleotide turnover (e.g., myelo- and lymphoproliferative diseases, psoriasis)
  - Accelerated ATP degradation (e.g., glycogen storage diseases, hypoxia and tissue underperfusion, ethanol abuse)

### Impaired Excretion
- **Primary or idiopathic renal hyperuricemia**
- **Secondary hyperuricemia**
  - Diminished renal function
  - Inhibition of tubular urate secretion
    - Competitive anions
  - Enhanced tubular urate reabsorption
    - Dehydration, diuretics, insulin resistance (metabolic syndrome)
  - Mechanisms unclear
    - Hypertension, hyperparathyroidism, certain drugs, lead nephropathy
The Hyperuricemia Cascade

- Overproduction
- Underexcretion

Urate

Dietary purines → Tissue nucleic acids → Endogenous purine synthesis → Urate

Hyperuricemia

- Silent tissue deposition
- Gout
- Renal manifestations
- Associated cardiovascular events and mortality
Risk Factors for the Development of Gout

Genetic Risk Factors

- 20% familial occurrence
- PRPP synthetase hyperactivity
- HGPRT deficiency
- Renal urate transporter in the kidney

- Consider hereditary disorder if gout presents 15 - 30 years
Risk Factors for the Development of Gout

Sex and Age

• Men
  – Have higher serum urate levels
  – In younger patients, gout overwhelmingly in men

• Women
  – Increased risk after menopause
    │ Decreased estrogen may diminish the renal excretion of uric acid
  – Of gout patients older than 60, half are women
  – Prevalence increasing along with increasing longevity

Arromdee E et al. J Rheumatol 2002;29:2403
Rott et al. JAMA 2003;289:2857
# Risk Factors for the Development of Gout

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>Leads to ↑ uric acid reabsorption</td>
</tr>
<tr>
<td>Low Dose Aspirin</td>
<td>Over 6% ↑ in mean serum urate and 23% ↓ in uric acid clearance</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Gout observed at higher incidence</td>
</tr>
<tr>
<td>Ethambutol</td>
<td></td>
</tr>
<tr>
<td>Niacin</td>
<td></td>
</tr>
</tbody>
</table>
Risk Factors for the Development of Gout

Transplant Patients

- Often attributable to cyclosporine
- Atypical presentations
  - Significantly elevated serum urate levels
  - Accelerated clinical course
    | Manifests after 1.5 years of asymptomatic gout
    | Over 40% with tophi or polyarticular involvement
  - Manifested in upper extremity and axial joints

## Risk Factors for the Development of Gout

### Diet

<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>High meat consumption</td>
<td>↑ risk of gout</td>
</tr>
<tr>
<td>High seafood consumption</td>
<td>↑ risk of gout</td>
</tr>
<tr>
<td>High dairy consumption</td>
<td>↓ risk of gout</td>
</tr>
<tr>
<td>High consumption of purine-rich vegetables</td>
<td>no association</td>
</tr>
<tr>
<td>or total protein</td>
<td></td>
</tr>
</tbody>
</table>

*Choi H et al* *NEJM*. 2004;350:1093
Total alcohol intake and relative risk of first attack of gout

Choi H et al  Lancet. 2004;363:1277
Effect of obesity on incidence of first attack of gout

Body Mass Index

Effect of obesity on incidence of first attack of gout

Body mass index

Choi H et al NEJM. 2004;350:1093
Renal Disorders Linked to Hyperuricemia

• Urate (or Gouty) Nephropathy
  – Sustained hyperuricemia causes interstitial urate crystal deposition
  – Inflammation, fibrosis, and renal insufficiency follow
  – Moderate hyperuricemia
    • Little harmful effect on renal function
    • Coexistent HTN, chronic lead exposure, ischemic heart disease, preexistent renal insufficiency play important roles in the pathogenesis of “urate” nephropathy

• Nephrolithiasis
  – Insoluble precipitate is produced when the concentration of uric acid exceeds solubility
Other Comorbidities Associated with Hyperuricemia

- Obesity\textsuperscript{1,2}
- Metabolic syndrome\textsuperscript{3}
- Diabetes mellitus\textsuperscript{4}
- Heart failure\textsuperscript{5}
- Hyperlipidemia\textsuperscript{1}
- Hypertension\textsuperscript{6,7}

Diagnosing Gout

• Serum urate
  – May be normal at the time of attack
  – May be elevated with joint symptoms from other causes

• History and physical
  – Presence of typical clinical manifestations of gout

• Synovial fluid analysis – the gold standard
  – MSU crystals visible with compensated polarized light

• Differential diagnosis important
  – CPPD (pseudogout), rheumatoid arthritis, osteoarthritis, septic arthritis, psoriatic arthritis, cellulitis
Acute monarthritis

Differential diagnosis

Usually mono-articular
- Gout
- Pseudogout
- Calcific periarthritis
- Septic arthritis
- Traumatic arthritis
- Haemarthrosis
- Foreign-body reaction

Usually polyarticular and more persistent episodes
- Reactive arthritis
- Gonococcal arthritis
- Rheumatoid arthritis
- Psoriatic arthritis
- Other spondyloarthritides
- Neoplasia-associated
- Erythema nodosum
- SLE
Clinical Assessment

• History and examination
  – Clues to alternative diagnosis and identify risk factors for gout

• Investigations
  – Full blood count
  – ESR (and CRP if available)
  – Renal Function
  – Urate
  – Joint aspiration
    • Visual inspection of synovial fluid
  – Synovial fluid analysis
    • Microscopy, culture and sensitivity
    • Polarising microscopy for crystals
  – Xray
    • Chondrocalcinosis
    • Do not expect radiological changes in acute gout unless longstanding history
Synovial Fluid Analysis
Compensated Polarized Light Theory

• Gold standard in diagnosis
• Urate crystals identified by
  – Strong negative birefringence
  – Needle and rod shapes
Crystals in Synovial Fluid by Polarising Microscopy

CPPD crystals are weakly positively birefringent, rhomboid, rods, squares or irregular.
Differential Diagnosis
Septic Arthritis

• Septic arthritis¹
  – Fever
    | However, 29% of gout patients and 38% of pseudogout patients have a fever >38°C ²
  – Elevated WBC
  – Positive gram stains and cultures
    | Often, but not always, positive
  – Co-occurrence with gout
    | Infection can occasionally be superimposed on a gouty joint

CPPD: Chondrocalcinosis

POSITION OF EROSIONS

JUXTA-ARTICULAR

GOUT
Chronic Polyarthritis

Differential diagnosis

Inflammatory arthritis
• Rheumatoid arthritis
• Psoriatic arthritis
• Reactive arthritis
• Ankylosing spondylitis
• Enteropathic arthritis
• Polyarticular gout
• Pyrophosphate arthropathy

Connective tissue diseases
• Systemic lupus erythematosus
• Scleroderma
• Behçet’s disease
• Polyarteritis nodosa
• Undifferentiated connective tissue disease

Non-inflammatory joint conditions
• Generalized nodal osteoarthritis
• Soft tissue rheumatism / hypermobility / fibromyalgia
Gout: Chronic Arthritis Resembles RA
Gout
Nodal Osteoarthritis
Pitfalls in Gout Diagnosis

• Can be polyarticular and chronic, especially in the elderly

• Serum urate levels can be normal, especially during the attack

• Other diseases may also respond to colchicine

• Women may also have gout

• Atypical joint involvement can occur, such as Heberden’s nodes
## Five Aphorisms of Hippocrates on Gout

<table>
<thead>
<tr>
<th>Aphorism</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>VI-28</td>
<td>Eunuchs do not take the gout, nor become bald</td>
</tr>
<tr>
<td>VI-29</td>
<td>A woman does not take the gout, unless her menses be stopped</td>
</tr>
<tr>
<td>VI-30</td>
<td>A youth does not get gout before sexual intercourse</td>
</tr>
<tr>
<td>VI-40</td>
<td>In gouty affections, inflammation subsides within 40 days</td>
</tr>
<tr>
<td>XI-55</td>
<td>Gouty affections become active in spring and in autumn</td>
</tr>
</tbody>
</table>
The Treatment Goals for Gout

I. Terminate the acute flare as rapidly as possible (Acute gout)

II. Protect against further attacks (Prophylaxis)
   – Reduce the chance of crystal-induced inflammation

III. Treat the hyperuricemia and prevent disease progression (Chronic Gout)
   - Provides long-term correction of the metabolic problem
   – Lower the serum urate sufficiently to deplete the total body urate pool
I. Termination of the Acute Flare
I. Termination of the Acute Flare

• Resolution of acute flare by controlling crystal-induced inflammation and pain
  – Not a cure for gout
    | Only resolves the symptoms
    | After resolution, urate crystals remain in the joint
  – Treatment options
    | NSAIDs, oral colchicine, corticosteroids

• Key issues are
  – Rapid initiation of therapy
  – Appropriate duration of therapy
Treatment of Acute Gout

NSAIDs

• NSAIDs
  – Indomethacin historically used for Acute Gout
  – Other NSAIDs effective – etoricoxib, diclofenac, naproxen etc
  – Begin full dose with food, taper rapidly with response
  – Initiate immediately, at first sign of an attack
  – AVOID low dose salicylate preparations

• Toxicities
  – Monitor closely in population at high risk of NSAID adverse GI effects and consider PPI
Treatment of Acute Gout
Colchicine

- **Indications/Effectiveness**
  - Works best if used within first 24 hours

- **Dose**
  - Initially 1mg, then 500µg every 4 hours until pain relieved or vomiting or diarrhea
  - NOT to exceed 6mg per course
  - Prevention of gout during initiation of allopurinol: 0.5 mg 2-3 times daily
  - Intravenous colchicine used with great caution

- **Toxicities**
  - Diarrhea, nausea, vomiting
  - Rare – neutropenia, neuromyopathy
Colchicine Neuropathy/Myopathy

- Usually presents with proximal weakness and ↑ CK
- EMG of proximal muscles - myopathy with abnormal spontaneous activity
- Vacuolar myopathy- marked by accumulation of lysosomes and autophagic vacuoles unrelated to necrosis or to the mild denervation in distal muscles
- Usually resolves within 3-4 weeks after drug discontinued
- Accompanying axonal polyneuropathy mild and resolves slowly

Treatment of Acute Gout
Glucocorticoids

• Useful when NSAIDs and colchicine contraindicated
  – Oral prednisone: 40-60 mg or more for 2-3 days, then decrease by 10mg/day every 3 days
  – Intra-articular injection of affected joints often treatment of choice
  – ACTH effective
  – Primary treatment with corticosteroids can be associated with rebound arthritis flares
  – AVOID longterm use
II. Protection Against Further Flares
II. Protection Against Further Flares

• Purpose
  – To maintain the intercritical segments of gout

• Prophylactic options
  – Low-dose, oral colchicine
  – NSAIDs
  – AND
  • Encourage lifestyle modifications
  • Review medications (diuretics, low dose aspirin)

• Initiate agents prior to starting urate-lowering therapy
Lifestyle Modifications for Gout

• Weight reduction and lipid control
• Decrease alcohol consumption
• Avoid excessive intake of purine-rich meat and fish?
  – Anchovies, herring, sardines, mussels, clams, organ meats, beer
  – Will only reduce urate levels by 1 mg/dL
# Agents Used for Protection Against Further Flares

<table>
<thead>
<tr>
<th></th>
<th>Use</th>
<th>Dosing</th>
<th>Complications of Chronic Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Colchicine</strong></td>
<td>Will not lower uric acid (no prevention of gout destruction)</td>
<td>0.5-1.5 mg/D adjusted to avoid GI complications Dose adjust for CrCl &lt;50 mL/min</td>
<td>Rare – neutropenia, neuromyopathy</td>
</tr>
<tr>
<td><strong>NSAIDs</strong></td>
<td>Useful if patients have other musculoskeletal complaints Will not lower uric acid (no prevention of gout destruction)</td>
<td>Lowest effective dose</td>
<td>NSAID gastropathy (worsens with low-dose aspirin) Renal dysfunction, fluid retention, hypertension, CHF</td>
</tr>
</tbody>
</table>
III. Treating Hyperuricemia and Preventing Disease Progression
III. Treating Hyperuricemia and Preventing Disease Progression

• Goals
  – Lower urate <6 mg/dL to allow depletion of serum urate pool and deposited crystals
  – Achieve appropriate urate levels without drug toxicity

• Therapy should be lifelong
  – Intermittent therapy or withdrawal of agents leads to recurrence of acute attacks, tophi, etc

• Approved urate-lowering agents for gout include
  – Uricosuric agents
  – Xanthine oxidase inhibitor
Treatment of Chronic Gout

Overview

- Consider if recurrent attacks or gouty complications
- Do not initiate until acute attack fully resolved (but absolute risk unknown)
- Use prophylactic NSAIDs or colchicine when initiating treatment for 3 - 6 months
- Serum uric acid level used as a gauge of effectiveness (goal < 6.0)
Protecting Against Acute Flares

Suggestions

• Initiate urate-lowering therapy with a prophylactic agent

• Continue prophylactic NSAIDs or colchicine until
  – The patient is attack free
    AND
  – Visible tophi are gone
    AND
  – The patient maintains an sUA <6.0 mg/dL for ~6 months

• Usually at least 6 months co-therapy needed

• Even after prophylaxis, patients are still susceptible to flares - educate the patient about potential recurrence
Importance of Continuous Lowering of Serum Urate to <6.0 mg/dL

Achieving mean urate <6.0 mg/dL demonstrated

<table>
<thead>
<tr>
<th>Effect</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>No recurrence of or fewer acute flares*</td>
<td>✓ Shoji et al (<em>Arthritis Care Res.</em> 2004;51:321-325.)</td>
</tr>
<tr>
<td></td>
<td>✓ Li-Yu et al (<em>J Rheum.</em> 2001;28:577-580.)</td>
</tr>
<tr>
<td>No recurrence of tophaceous deposits*</td>
<td></td>
</tr>
</tbody>
</table>

*Time periods assessed vary.
• 86% (71/81) of patients who had serum urate <6.0 mg/dL did not experience an acute flare during the study period

Lowering Serum Urate Decreases Tophi Size

The lower the serum urate, the faster the velocity of tophi reduction

63 patients followed for a mean of 5 years

Urate-Lowering Agents
Uricosurics

• Uricosuric agents
  – Probenecid
  – Benzbromarone (ex-US)
  – Sulfinpyrazone (ex-US)
– Mild uricosurics
  • Losartan
  • Fenofibrate

URAT-1, an anion exchanger, is essential for tubular resorption of urate

The potential actions of uricosuric drugs

Uricosuric Agents

• **Uricosuric agents**
  – Probenecid
  – Sulfinpyrazone
  – Benzbromarone
  – Losartan (mild uricosuric)
  – Fenofibrate (mild uricosuric)

• **Advantage**
  – Uricosurics reverse the most common physiologic abnormality in gout
Treatment of Chronic Gout

Probenecid

• Indications/Effectiveness
  – More symptomatic toxicities than allopurinol and less convenience
  – For underexcreters (~ 90%)
  – Must have GFR >50 mg/min, drink 2L water/day, no hx of renal stones, avoid ASA

• Dose
  – Start 0.5 gms/day, advance to 1 gram bid

• Toxicities
  – GI upset
  – Rash
  – Nephroureterolithiasis
Treatment of Chronic Gout
Other Urate-Lowering Drugs

• Sulfinpyrazone: 50 mg BID to 100-200 mg TID
• Benzbromarone: available in Europe
  – SE: skin rash, GI, precipitate an acute gout attack, renal stones
  – Can interfere with excretion of other weak organic acids (PCN, ampicillin)
• Losartan: inhibits tubular renal absorption of urate (urate diuresis)
Uricosuric Agents

• Limitations
  – Efficacy dependent on renal function
    – Ineffective if CrCL <50 mL/min
  – Risk of uric acid crystallization in the urine and formation of stones
  – Precipitation of an acute flare
    – Lowering the serum urate mobilizes the deposited crystals
  – Drug-drug interactions
    – Ampicillin, Salicylates, Penicillin, Indomethacin, Nafcillin, Heparin, Cephradine, Dapsone, Cephaloridine, Rifampicin
Uricosuric Agents

• Appropriate candidate characteristics
  – Compliant
    – Willing to drink at least 2 liters of fluid daily to maintain good urine flow
    – Willing to take multiple daily doses
  – Satisfactory renal function
    – CrCl >50 mL/min
  – No history of nephrolithiasis or excessive urine acidity
  – Lack of polypharmacy
  – Underexcretors of uric acid (24 hour urine)
Allopurinol and oxypurinol block the conversion of hypoxanthine to xanthine to uric acid.

Allopurinol and metabolite oxypurinol are purine analogs and both substrates and inhibitors of xanthine oxidase.
Treatment of Chronic Gout
Allopurinol

• Xanthine oxidase inhibitor
• Efficacious for both underexcretors and overproducers
• Indications for use:
  – Asymptomatic hyperuricaemia > 0.6 mmol/L
  – Recurrent acute gout (≥ 3 per annum)
  – Tophaceous gout
  – Bone or cartilage destruction
  – Uric acid nephropathy
  – Nephrolithiasis
• Precipitation of an acute attack
  – Need to cover with NSAID or colchicine
Limitations of Allopurinol

- “Standard” doses may not achieve target serum urate
- Need for dose adjustment according to renal function
- Precipitation of an acute attack
  - Lowering serum urate mobilizes deposited crystals
- Adverse effects
  - Mild hypersensitivity reactions (pruritus, dermatitis) in 2% (can be desensitised)
  - GI intolerance (diarrhea, nausea)
  - Bone marrow suppression (uncommon)
  - Severe hypersensitivity syndrome infrequent but life threatening (20% mortality)
Effect of Allopurinol
Urate-Lowering Therapy and Acute Flare Prevention

• Urate-lowering therapy increases incidence of acute flares
  – May be caused by potent reduction in urate levels

• Prevention of acute flares
  – Co-treatment with prophylactic agents partially prevents flares
  – Achieving and maintaining sUA <6.0 mg/dL over time decreases flares requiring treatment
  – Best results with dual therapy for 6 months

Colchicine Prophylaxis Proven Useful When Initiating Urate-Lowering Therapy

- Colchicine prophylaxis during allopurinol initiation reduced
  - Frequency and severity of flares
  - Likelihood of recurrent flares
- Best results with dual therapy for 6 months

Limitations of Allopurinol: Nonselective Enzyme Inhibition

Purine and Pyrimidine Metabolism Pathways (orange indicates enzyme inhibition)

Aspartate + Carbamoyl Phosphate (De novo pyrimidine synthesis)
Orotic acid (OA) + PRPP
OMP + PRPP → Orotidine
UMP → Uridine
UTP → Uracil

PRPP (De novo purine synthesis)
GMP → IMP → AMP
IMP → Adenosine
Inosine → HGPRT
Guanosine → GMP
Guanine Deaminase

OmpDC
OMP → UMP
UMP → Uridine
UTP → Uracil

XOD
Hypoxanthine → Xanthine → Uric acid

PNP
Guanosine → Guanine
Guanine → PNP

This may contribute to some of allopurinol’s limitations

Treatment of Gout
Special Considerations

• Transplant Gout
  – NSAIDs often contra-indicated
  – Cyclosporin associated with ↑ serum urate
  – Renal impairment limits colchicicine use
  – Allopurinol increases azathioprine levels, resulting in ↓ WBC count
  – No interaction between mycophenolate mofetil and allopurinol
  – Systemic or intra-articular corticosteroids are frequently helpful
Future Treatment of Hyperuricemia

• Identification of new urate-lowering agents needed to:
  – Effectively lower serum urate
  – Expand treatable populations such as those experiencing
    | Allopurinol intolerance
    | Renal failure
    | Drug interactions
  – Improve patient adherence
Uricase Enzymes

- Uricase enzymes further catabolize uric acid to a more soluble, readily excretable form

- Agents available
  - Include rasburicase and aspergillus uricase (ex-US)
  - PEGylated recombinant uricases in phase II clinical trials
    - Polyethylene glycol (PEG) modification reduces antigenicity and prolongs half-life

Febuxostat

- A nonpurine, selective inhibitor of xanthine oxidase for the treatment of hyperuricemia in patients with gout
- Potent inhibition with significant urate reduction
- Ability to administer in renal insufficiency and mild or moderate hepatic insufficiency with no dosage adjustments
Febuxostat: a nonpurine selective inhibitor of xanthine oxidase
Becker et al NEJM 2005; 353: 2450-61

- patients with gout and with serum urate concentrations > 480 µmol/L
- febuxostat (80 mg or 120 mg) or allopurinol (300 mg) once daily for 52 weeks
- 760 received the study drug.

### Proportion of Subjects with sUA <6.0 mg/dL (ITT Subjects)

<table>
<thead>
<tr>
<th></th>
<th>Febuxostat 80 mg</th>
<th>Febuxostat 120 mg</th>
<th>Allopurinol 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Last 3 sUA &lt;6.0 mg/dL</td>
<td>53% (136/255)*</td>
<td>62% (154/250)*</td>
<td>21% (53/251)</td>
</tr>
<tr>
<td>Wk 52 sUA &lt;6.0 mg/dL</td>
<td>81% (129/159)*</td>
<td>82% (119/145)*</td>
<td>39% (70/178)</td>
</tr>
</tbody>
</table>

*p<0.05 for each febuxostat group vs. allopurinol group
Management of Gout

Clinical situations
- Asymptomatic hyperuricaemia
- Acute attack
- Recurrent attacks
- Tophaceous gout
- Concurrent diseases and therapy
  - Renal failure
  - Cardiac failure
  - Hypertension
  - Gastric ulceration
- Drug sensitivities
  - NSAIDs
  - Allopurinol
## Therapeutic Dilemmas

<table>
<thead>
<tr>
<th></th>
<th>Acute attack</th>
<th>Renal failure</th>
<th>Cardiac failure</th>
<th>Warfarin interaction</th>
<th>Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol</td>
<td>no</td>
<td>≤100 mg/day</td>
<td></td>
<td>no interaction</td>
<td>hypersensitivity</td>
</tr>
<tr>
<td>Colchicine</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>Diarrhoea, vomiting</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>yes</td>
<td>caution</td>
<td>avoid</td>
<td>avoid</td>
<td>GI, CVS</td>
</tr>
<tr>
<td>Uricosurics</td>
<td>no</td>
<td>caution</td>
<td></td>
<td>potentiate</td>
<td>Avoid with GU/DU</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Pharmacoepidemiology of Gout Quality Issues In Prescribing

- Prescribed allopurinol exceeded recommended dose in 50% of pts.\(^1,^2\)
- Excessive allopurinol dose or lack of approved indication in 22%\(^3\)
- Over half with allopurinol hypersensitivity were treating asymptomatic hyperuricemia\(^4\)
- Serious colchicine errors still resulting in morbidity and mortality (MEDMARX)\(^5\)

1. In acute attacks the rapid development of severe pain, swelling, and tenderness that reaches its maximum within just 6–12 hours, especially with overlying erythema, is highly suggestive of crystal inflammation though not specific for gout.

2. For typical presentations of gout (such as recurrent podagra with hyperuricaemia) a clinical diagnosis alone is reasonably accurate but not definitive without crystal confirmation.

3. Demonstration of MSU crystals in synovial fluid or tophus aspirates permits a definitive diagnosis of gout.

4. A routine search for MSU crystals is recommended in all synovial fluid samples obtained from undiagnosed inflamed joints.

5. Identification of MSU crystals from asymptomatic joints may allow definite diagnosis in intercritical periods.
6. Gout and sepsis may coexist, so when septic arthritis is suspected Gram stain and culture of synovial fluid should still be performed even if MSU crystals are identified.

7. While being the most important risk factor for gout, serum uric acid levels do not confirm or exclude gout as many people with hyperuricaemia do not develop gout, and during acute attacks serum levels may be normal.

8. Renal uric acid excretion should be determined in selected gout patients, especially those with a family history of young onset gout, onset of gout under age 25, or with renal calculi.

9. Although radiographs may be useful for differential diagnosis and may show typical features in chronic gout, they are not useful in confirming the diagnosis of early or acute gout.

10. Risk factors for gout and associated co-morbidity should be assessed, including features of the metabolic syndrome (obesity, hyperglycaemia, hyperlipidaemia, hypertension).
1. Optimal treatment of gout requires both non-pharmacological and pharmacological modalities and should be tailored according to:
   (a) specific risk factors (levels of serum urate, previous attacks, radiographic signs)
   (b) clinical phase (acute/recurrent gout, intercritical gout, and chronic tophaceous gout)
   (c) general risk factors (age, sex, obesity, alcohol consumption, urate raising drugs, drug interactions, and comorbidity)

2. Patient education and appropriate lifestyle advice regarding weight loss if obese, diet, and reduced alcohol (especially beer) are core aspects of management

3. Associated comorbidity and risk factors such as hyperlipidaemia, hypertension, hyperglycaemia, obesity, and smoking should be addressed as an important part of the management of gout
4. Oral colchicine and/or NSAID are first line agents for systemic treatment of acute attacks; in the absence of contraindications, an NSAID is a convenient and well accepted option.

5. High doses of colchicines lead to side effects, and low doses (for example, 0.5 mg three times daily) may be sufficient for some patients with acute gout.

6. Intra-articular aspiration and injection of long acting steroid is an effective and safe treatment for an acute attack.
7. Urate lowering therapy is indicated in patients with recurrent acute attacks, arthropathy, tophi, or radiographic changes of gout.

8. Therapeutic goal of urate lowering therapy is to promote crystal dissolution and prevent crystal formation; achieved by maintaining serum uric acid below saturation point for monosodium urate ((360 mmol/l)

9. Allopurinol is an appropriate long term urate lowering drug; it should be started at a low dose (eg 100 mg daily) and increased by 100 mg every 2–4 weeks if required; dose must be adjusted in patients with renal impairment; if allopurinol toxicity occurs, options include other xanthine oxidase inhibitors, a uricosuric agent, or allopurinol desensitisation (only in cases of mild rash).
10. Uricosuric agents (eg probenecid, sulphinpyrazone) can be used as an alternative to allopurinol in patients with normal renal function but are relatively contraindicated in patients with urolithiasis; benzbromarone can be used in patients with mild to moderate renal insufficiency on a named patient basis but carries a small risk of hepatotoxicity.

11. Prophylaxis against acute attacks during the first months of urate lowering therapy can be achieved by colchicine (0.5–1 mg daily) and/or an NSAID (with gastro-protection if indicated).

12. When gout associates with diuretic therapy, stop diuretic if possible; for hypertension and hyperlipidaemia consider losartan and fenofibrate, respectively (both have modest uricosuric effects).
“People wish their enemies dead, but I do not; I say give them the gout, give them the stone!”

Mary Worley Montagu
Crystal Arthropathies

- Gout
- Pseudogout
- Calcium pyrophosphate arthropathy
- Apatite associated destructive arthritis
Calcium Pyrophosphate Dihydrate Crystals and the Joint

Nomenclature

• Chondrocalcinosis
  – Calcification of articular fibro- or hyaline cartilage

• Pyrophosphate arthropathy
  – Structural abnormality of cartilage and bone
    (cartilage loss, osteophyte, cysts) associated with
    intra-articular CPPD deposition

• Pseudogout
  – Clinical syndrome of acute synovitis associated
    with intra-articular CPPD deposition
Chondrocalcinosis

- Female > male
- Increases with age
  - Uncommon under 50 years
  - 10 – 15% in 65 – 75 years
  - 30 – 60% in >80 years
  - Population-based survey (Framingham)
    - Overall prevalence 8%
    - 3% in those < 70 years
    - 27% in those >85 years
- Reported in most countries and racial groups
- Familial predisposition
- Predisposing metabolic conditions rare – haemochromatosis, HPT, hypophosphatasia, hypomagnesaemia ...
Acute Pseudogout

- Any joint
  - Knee >> wrist > shoulder > ankle > elbow
  - 1st metatarsal can be affected
  - Concurrent attacks in more than one joint <10%

- Most occur spontaneously, but commonest provoking factor is stress response to intercurrent illness or surgery

- Develops rapidly, maximal in 6 – 24 hours
- Marked inflammation
- Fever common
- Elderly patients may be unwell and confused
- Self-limiting, resolving usually within 1 – 3 weeks
Chronic Pyrophosphate Arthropathy

- Common
- Mainly affects elderly females
- Predominantly large and medium sized joints
- Chronic pain, morning and inactivity stiffness, limitation of movement and activities
- Affected joints have signs of OA with varying amount of synovitis
- Differentiated from OA by
  - Pattern of joints involved
  - Often marked inflammation
  - Superimposition of acute attacks
- ? Marker for progression of OA
Chronic Pyrophosphate Arthropathy

- Calcification
- Structural changes of joint
  - Cartilage loss, sclerosis, cysts, osteophytes (OA)
  - Joint distribution and involvement within articulations atypical for OA (e.g., glenohumeral, patellofemoral compartment)
  - Often prominent, exuberant osteophyte and cyst formation (particularly knee and wrist)
  - Many cases similar to “uncomplicated” OA - ? distinct entity
  - Destructive arthropathy occasionally seen – can resemble Charcot joint (neuropathic)
Basic Calcium Phosphate (Hydroxyapatite) Crystal Deposition Disease

- Deposition of Hydroxyapatite and other related Basic Calcium Phosphate Crystals in and around joints are associated with various clinical manifestations
  - asymptomatic periarticular deposits
  - acute calcific periarthritis
  - acute intra-articular hydroxyapatite arthritis
  - apatite-associated destructive arthropathy (Milwaukee shoulder)