Gout is the most common inflammatory joint disease in men aged > 40 years. It is a disease characterized by recurrent acute attacks of inflammation in one or more joints, typically affecting the large joints of the foot, especially the big toe. Gout affects 5 million adults in the United States. Gout is caused by the deposition of monosodium urate crystals in tissues and is characterized by elevated levels of uric acid in the blood.

How Prevalent Is Gout Compared to Other Common Conditions?

- Gout affects 5 million adults in the United States.
- Gout is the most common inflammatory joint disease in men aged > 40 years.

Uric Acid, Hyperuricemia, and Gout

- Uric acid (urate) is the end product of purine degradation in humans.
- Hyperuricemia is a serum urate concentration in excess of urate solubility (≥ 6.8 mg/dL).
- Results from underexcretion and/or overproduction of uric acid.
- Gout is the disease state resulting from deposition of MSU crystals in tissues.

Learning Objectives

- Recognize the general clinical presentations of gout, differentiating between acute attacks and chronic underlying disease.
- Advise patients about lifestyle interventions for the prevention and management of gout, focusing on the importance of weight loss and dietary modifications.
- Implement a patient education program for gout to improve knowledge about the disease state, the importance of adherence to medications, and patient commitment to treatment.
- Counsel patients about the appropriate medications to be used for acute and chronic gout, with a special focus on comorbidities, medication contraindications, and drug interactions and advise when a physician visit is necessary.
**Uric Acid: End Product of Purine Degradation in Humans**

- Solubility decreases
- Purines → Nucleosides → Purines

**Distribution of Serum Urate Values and Hyperuricemia**

- Development of MSU crystals associated with:
  - Decreased solubility of urate (temperature)
  - Trauma or tissue injury

- Serum urate levels in 1515 men and 1670 women aged 20-30 years in Taiwan: 1987-1992

**Medications Altering Urate Levels**

<table>
<thead>
<tr>
<th>Urate-Increasing Agent</th>
<th>Urate-Decreasing Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrazinamide</td>
<td>Uricosuric: Probenecid</td>
</tr>
<tr>
<td>Nicotinate</td>
<td>Losanat</td>
</tr>
<tr>
<td>Lactate, β-hydroxybutyrate, acetocetate</td>
<td>Salicylate (high dose)</td>
</tr>
<tr>
<td>Salicylate (low dose)</td>
<td>Fenofibrate</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Amlopidine</td>
</tr>
<tr>
<td>Diuretics</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td></td>
</tr>
<tr>
<td>β-blockers</td>
<td></td>
</tr>
<tr>
<td>Uricase</td>
<td></td>
</tr>
</tbody>
</table>

Other components may also affect uric acid clearance: 1-3
- excessive alcohol intake, niacin, levodopa, cytotoxic drugs, and vitamin B6

**The Hyperuricemia Cascade**

- Dietary purines
- Tissue nucleic acids
- Endogenous purine synthesis
- Urate
- Underexcretion 80%-90% of all gout patients
- Gout
- Renal manifestations
- Silent tissue deposition

**Risk Factors for the Development of Gout**

- Male gender
- Postmenopausal women
- Longevity/improved survival of comorbidities
- Diet:
  - High alcohol intake
  - Red meat
  - Red/organ meats and seafood
  - High-fructose corn syrup

**Some Comorbidities Associated With Hyperuricemia Warrant Consideration**

- Obesity
- Metabolic syndrome
- Diabetes mellitus
- Heart failure
- Hyperlipidemia
- Hypertension
- Renal disease
- Cardiovascular disease

No reliable predictor that gout will develop in a given hyperuricemic patient

Currently, asymptomatic hyperuricemia is not treated

*But, higher serum urate levels are more likely to lead to gout*
M70  Add Schumacher Cleve Clin J Med 2008 to verify this.
    MOng, 10/6/2008
Control of Metabolic Syndrome Components Essential to Reduce Cardiovascular Disease Risk in Patients With Hyperuricemia and Gout

- Higher prevalence of metabolic syndrome associated with gout across age groups.
- High prevalence of the metabolic syndrome in hyperuricemic patients.
- Patients with gout have an approximately 30% elevated cardiovascular disease (CVD) risk.

Hyperuricemia Increases Risk of Renal Manifestations

- Elevated serum urate with no clinical manifestations of gout
- Crystal deposition may be starting
- Acute inflammation in the joint caused by urate crystallization and crystal phagocytosis
- Intervals between acute flares
- Crystals persist in joints
- Long-term complications of uncontrolled hyperuricemia
- Chronic arthritis and tophi

Features of Acute Gouty Attacks

- Lower extremities most often involved
  - Most common initial site (~90%): first metatarsophalangeal joint (podagra)
  - 80% of first attacks are monoarticular
- Pain and inflammation
  - Dramatic inflammatory response
- Fever in some patients
- Can occur in bursae, tendons, and joints
  - Rarely affects shoulders, sternooclavicular joints, hips, spine, sacroiliac joints
- Untreated, an initial acute gout attack resolves completely within 3 to 14 days
  - Majority of patients experience second acute flare within 1 year of first gout flare.

Typical Clinical Features of Gout Differ With Age of Onset

<table>
<thead>
<tr>
<th>Feature</th>
<th>Typical Gout</th>
<th>Elderly Onset Gout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of Onset</td>
<td>Peak in mid-40s</td>
<td>Over 65</td>
</tr>
</tbody>
</table>
| Rheumatologic Symptoms | Acute monarthritic | Chronic polyarthritis
| Presentation | Lower extremity (podagra 90%) | Upper extremity affected |
| Associated Features | Hyperuricemia, Hypertension, Alcohol use, heavy drinking | Kidney stones, hypertension, albuminuria |

Hyperuricemia and Incidence of Hypertension Among Men Without Metabolic Syndrome

- Baseline hyperuricemia and risk of subsequent hypertension
- Hyperuricemia increases the risk of developing hypertension by approximately 80%

Clinical Stages of Gout

1. Asymptomatic Hyperuricemia
2. Acute Gouty Arthritis
3. Intercritical Periods
4. Advanced Gout

Typical Clinical Features of Gout

- Fever
- Associated Features
- Hyperlipidemia
- Hypertension
- Renal insufficiency
- Diuretic use, especially in women
- Alcohol use less common

Reference:
Diagnosing Gout: Why Aspirate the Joint?

Separate Septic Arthritis From Gout

• Does the patient have gout?
• Are current inflammatory symptoms due to gout?

**Inflammatory Joint Fluids**

- Septic arthritis
  - Crystal-induced monoarthritis (eg, gout, pseudogout)

Other potential causes:
- Rheumatoid arthritis
- Spondyloarthropathy
- Systemic lupus erythematosus
- Other inflammatory arthritides

**Synovial fluid analysis**

- Normal synovial fluid
  - Viscous, straw-colored substance (small amounts in joints, bursae, tendon sheaths)
  - 1-2 mL of fluid sufficient for studies


Differential Diagnosis:

**MSU (Gout) or CPPD ("Pseudogout") Crystals?**

- **MSU crystals:** strong negative birefringence;
  - Usually needle-shaped under compensated polarized light
- **Calcium pyrophosphate dihydrate (CPPD) crystals:**
  - Weak positive birefringence
  - Rhomboidal, rods, rhomboids, or irregular under compensated polarized light; frequently missed; consider septic arthritis

**Advanced Gout**

- **Risk factors include**
  - Long duration of hyperuricemia
  - High serum urate levels
  - Long periods of active, untreated gout

- **Subcutaneous gouty tophi** occur frequently at sites of friction or trauma
- **Be careful:** Chronic gout can mimic rheumatoid or psoriatic arthritis

**Serum Urate Level**

Not a definitive test; normal SUA levels common during acute attacks
- Laboratory SUA level of population-defined "normal" often equivalent to significant hyperuricemia

**Some Patients Refuse Tapping the Joint**

Alternative: presumptive clinical diagnosis
- History and physical examination for characteristic features
- Clinical diagnosis wrong in about 20% of the cases
- Sepsis may lead to joint destruction within 24-48 hours

**Factors involved in acute attacks also contribute to chronic inflammation:**

- Cytokines
- Chemokines
- Proteases
- Oxidants

**Histology:**

- Tophi on cartilage surface may contribute to chondrolysis, which can occur despite adequate treatment

**Possible Sites of Tophi**

- Olecranon bursae
- Extensor surface of the forearms
- Wrists
- Finger pads
- Knees
- Achilles tendons

**Long-term Consequences of Chronic MSU-induced Inflammation**

- Low-grade synovitis in involved joints can persist after acute attacks

- Chronic synovitis
- Bone erosion
- Cartilage erosion
- Tophi on cartilage surface

**History and Physical Examination**

- Acute versus chronic state, atypical joint involvement
- Elderly onset gout, (postmenopausal) women

**Serum Urate Level**

- Not a definitive test; normal SUA levels common during acute attacks
- Laboratory SUA level of population-defined "normal" often equivalent to significant hyperuricemia

**Some Patients Refuse Tapping the Joint**

- Alternative: presumptive clinical diagnosis
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**References:**

**Question to Ask the Patient**

Presumptive Diagnosis of Gout

- When did the symptoms start? Was the onset sudden?
- Was this the first time you experienced pain/swelling at this joint? If not, which other joints have been affected and how long ago has this been?
- Are you running a fever?
- Do you have relatives with similar complaints?
- Are you taking any medications, and which?
- Do you have any relatives with similar complaints?
- Are you taking any medications, and which?
- What have you been eating and/or drinking? Anything like red meat, shellfish, or beer?

**Gout and sepsis may coexist; if sepsis is suspected, Gram stain and culture of synovial fluid should be carried out even if MSU crystals are identified**

**Although the most important risk factor for gout, serum urate levels do not confirm or exclude gout**

**Renal uric acid excretion should be determined in selected gout patients (family history of young onset gout, onset of gout under age 25, or with renal calculi); hyperuricemia as a marker in acute gout**

**Radiographs may be useful for differential diagnosis and may show typical features in chronic gout; they are not useful in confirming a diagnosis of early or acute gout**

**Risk factors for gout and associated comorbidity should be assessed, including features of metabolic syndrome**

**Case Presentation**

Matthew, 66 Years Old

- Matthew comes to the pharmacist for an over-the-counter (OTC) pain reliever: He limps on the left foot using a cane
- Questioning the patient reveals:
  - Swelling/erythema of first metatarsophalangeal joint on left foot started last night; patient runs a light fever
  - Patient cannot bear any weight on the painful toe
  - No other symptoms/recent injury, but similar episode in elbow a few months ago

Matthew adheres to medication schedule:

- Hydrochlorothiazide 50 mg/day
- Glipizide 10 mg/day
- Enalapril 20 mg/day
- Aspirin 81 mg/day
- BMI 33 kg/m²

**Difficulties with dietary changes:
Consumption of red meat, alcohol, and caffeinated nondiet sodas**

**What Is the Evidence for Gout Diagnosis?**

Ten Recommendations From EULAR Modified to US Standards (Cont.)

**What Is the Evidence for Gout Diagnosis?**

Ten Recommendations From EULAR Modified to US Standards

1. In acute attacks, rapid development of severe pain, swelling, and tenderness, reaching peak within 6-12 hours is highly suggestive of crystal inflammation, though not specific for gout.
2. For typical gout presentations (eg, recurrent podagra), a clinical diagnosis of gout is reasonably accurate but not definitive unless crystal confirmed.
3. Demonstration of MSU crystals in synovial fluid or tophus aspirates permits a definitive gout diagnosis.
4. A routine search for MSU crystals is recommended in all synovial fluid aspirates from inflamed joints.
5. Identification of MSU crystals from asymptomatic joints may allow gout diagnosis between attacks.

**Clinical Picture and Radiographic Evidence**

Polyarticular, tophaceous gout in a patient originally treated for rheumatoid arthritis for 8 years.

**Considerations for the Treatment of Acute Gout**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Considerations and Cautions</th>
</tr>
</thead>
</table>
| Anti-inflammatory doses of NSAIDs* | - All NSAIDs equally effective<br> - Caution with: older patients, renal insufficiency, heart failure, peptic ulcer disease, liver disease, anticoagulant therapy<br> - Taper off after attack has resolved*<br> - Can be effective with early use*
| Colchicine (oral) | - Avoid in patients with severe renal or hepatic impairment<br> - Interacts with cyclosporine, statins, and macrolides<br> - Low-dose approach: similar efficacy without gastrointestinal concerns with higher dose**
| Corticosteroids (oral, intra-articular, intramuscular) | - Useful when renal and/or gastrointestinal contraindications to other therapies<br> - Avoid in patients with joint stiffness<br> - Caution with diabetes patients***

***Adapted from EULAR Evidence. 2007;3:801-840.
Anti-inflammatory Prophylaxis Prior to Urate-lowering Therapy

- Prophylactic agents\(^1\)-\(^3\)
  - NSAIDs, low-dose, oral colchicine
  - Useful for decreasing the frequency and severity of acute flares
  - Will not stop silent tissue deposition of crystals
- Initiate prophylaxis prior to starting urate-lowering therapy and continue for 6-12 months\(^1\)-\(^3\)
  - Crystals often persist during intercritical periods\(^2\)
  - Risk for continued flares, low-grade persistent inflammation, and progressive disease\(^1\)-\(^4\)

Patient dialogue and consistent follow-up

Urate-lowering Therapy to Prevent Disease Progression

- Urate-lowering therapy (ULT) often started at week 2-4 with continuous prophylaxis, but no evidence from studies\(^4\)
  - Incidence of flares and SUA levels decline over time with treatment
- Therapy should be lifelong\(^1\)
  - Do not discontinue if attack occurs during therapy initiation (flux in urate levels likely)\(^2\)
  - Uricosurics and xanthine oxidase inhibitors\(^1\)
    - Weigh potential drug interactions/adverse events

Patient dialogue and consistent follow-up

What Is the Evidence for Gout Management?

Twelve Recommendations From EULAR Modified to US Standards (1)

1. Utilize both nonpharmacologic and pharmacologic modalities, tailored to risk factors and clinical phase
2. Stress patient education and lifestyle changes (eg, weight loss and alcohol reduction)
3. Address comorbidities like hypertension, hyperglycemia, obesity, and smoking
4. Oral colchicine and/or NSAIDs are first-line agents for systemic treatment of acute attacks
5. Side effects with high doses of colchicine: low doses (eg, 0.5 mg TID) may be sufficient for some patients, with acute pain
6. Intra-articular aspiration and injection of long-acting steroid is effective and safe for an acute attack
7. Urate-lowering therapy: patients with recurrent acute attacks, antirheumatic, tophi, or radiographic changes

Adapted from Becker MA and Chohan S.

Twelve Recommendations From EULAR Modified to US Standards (2)

8. Therapeutic goal of urate-lowering therapy: promote crystal dissolution and prevent crystal formation by maintaining the SUA level below the saturation level for MSU (6.8 mg/dL), target for SUA level < 6.0 mg/dL
9. Allopurinol: appropriate long-term urate-lowering drug; start at a low dose (eg, 100 mg daily) and increase by 100 mg every 2-4 weeks, if required; adjust dose in patients with renal impairment; watch with allopurinol toxicity (other xanthine oxidase inhibitors, uricosuric agent, allopurinol desensitization (cases of mild rash)
10. Urate-lowering agents (gallbladder cholesterol dissolution with normal renal function); relatively contraindicated in patients with uric acid nephropathy
11. Prophylaxis against acute attacks during the first months of urate-lowering therapy; colchicine (0.5-1.2 mg daily) and/or an NSAID (with gastro-protection, if indicated)
12. Good associated with diuretic therapy; use diuretic, if possible, hypertension, and hyperlipidemia (especially in patients with tophi and nephropathy, respectively)

Both have modest uricosuric effects

Adapted from Becker MA and Chohan S.

Adjunctive Therapy for Gout and Associated Comorbidities

Dietary and Lifestyle Recommendations

- Control weight with daily exercise\(^1\)-\(^2\)
- Limit red meat consumption\(^2\)
- Replace fish consumption with omega-3 fatty acids\(^1\)
- Or supplements of docosahexaenoic acid and eicosapentaenoic acid
- Refrain from high-fructose-containing foods/drinks\(^3\)-\(^3\)
- Consume 1-2 servings of dairy or calcium supplement daily\(^2\)
- Consume nuts and vegetables daily\(^2\)
- Supplementation with vitamin C 500 mg/day\(^4\)-\(^4\)
- Some evidence for beneficial effect of coffee consumption\(^4\)

- Health benefits may extend beyond gout\(^1\)
  - Prevents atherosclerotic plaques in patients with existing disorders may not be sufficient\(^5\)
  - Limited impact on SUA level (1-2 mg/dL)
    - Less than 20% of patients make sustained lifestyle changes\(^6\)

Uricosurics correct renal urate underexcretion by inhibiting postsecretory SUA reabsorption\(^1\)

- Probenecid\(^1\)-\(^2\)
  - Mild uricosurics as adjunctive approach:
    - Lower effectiveness as renal function deteriorates\(^1\)-\(^4\)
  - Other agents with urate-lowering properties:
    - Allopurinol\(^1\)
    - Amiodarone\(^1\) (increased renal urate excretion)\(^6\)
    - Vitamin C (400-500 mg/day)\(^7\)

Steps During Treatment\(^6\)

Alkalinate urine
Increase fluid consumption
Multiple medication doses required

Emphasize Compliance

- Stop if tinnitus or rash occurs
- Avoid high-fructose–containing foods/drinks
- Control weight with daily exercise
- Refrain from high-fructose–containing foods/drinks
- Consume nuts and vegetables daily

Adapted from Becker MA and Chohan S.
Xanthine Oxidase Inhibitor

Allopurinol

- Effective in overproducers and underexcretors
- Maximal dose 800 mg/day

Limitations

- Drug interactions
  - Rare but life-threatening hypersensitivity reaction possible
- Dose adjustments required:
  - Concomitant azathioprine and 6-mercaptopurine
  - Renal function

Allopurinol Hypersensitivity Reaction

Extremely rare, occurs in < 1% of patients on allopurinol

Can present as mild erythema and progress to fatal reactions with continued therapy

Usually appears within first 5 weeks of treatment

Rechallenge with allopurinol should not be performed

Target Serum Urate Levels Are Often Not Achieved

Median SUA level with allopurinol treatment decreased from 8.7 to 7.1 mg/dL (P < 0.001)1,4

Patients on pharmacotherapy with nontarget levels were 59% (allopurinol: 75%) more likely to flare than those at target level

Majority of gout patients on varying doses of allopurinol therapy did not reach target SUA level of < 6.0 mg/dL1

Typical Prescribing Errors With Available Xanthine Oxidase Inhibitor

- Allopurinol is frequently prescribed inappropriately; more common with advancing age, male gender, and presence of polypharmacy

Potential Drug Interactions With Allopurinol

- Allopurinol dose increase
  - Prevent flare risk in all gout patients with gradual introduction2
  - Monitor titration in patients with CKD, emphasize target SUA level of ≤ 6 mg/dL2,3
- Inform patients of the risks and benefits trade off:
  - Potential allopurinol toxicity versus gout progression3

Potential Effect

- Increased 6-MP serum concentration with increased risk of bone marrow suppression; reduce AZA dose to one-quarter
- Increased risk of allopurinol hypersensitivity
- Increased risk of bone marrow suppression
- Increased renal elimination of oxypurinol; analgesics of probenecid metabolism
- Inhibited metabolism of phenytoin resulting in increased serum concentrations
- Increase in theophylline AUC, t1/2, and reduction in clearance
Febuxostat* with gout

New Xanthine Oxidase Inhibitor

- Potent inhibition with significant urate reduction
- No dose adjustments in renal and mild/moderate hepatic insufficiency
- Different molecule, no cross-reactions in allopurinol-intolerant patients observed
- No safety studies available
- Adverse events:
  - Gout flares, CV events, and elevated liver function tests
- Coadministration:
  - Concurrent use of azathioprine, enalapril, and theophylline

Febuxostat 80 mg efficacy superior to both febuxostat 40 mg and allopurinol 300 mg
- Febuxostat 80 mg efficacy superior to both febuxostat 40 mg and allopurinol 300 mg/200 mg in healthy adults

Patients achieving SUA levels < 6.0 mg/dL at final visit at 6 months


- Rapid and effective reduction in SUA levels and tophus burden
- Reduced tophus burden in 40% of patients in phase III clinical trials (pegloticase 8 mg IV every 2 or 4 weeks)
- Investigations needed
  - Short- and long-term effects
  - Role of immunogenicity
  - Cardiac risk
  - Hemolysis risk

Investigational Recombinant Pegylated Uricase Enzyme

Investigational Recombinant Pegylated Uricase Enzyme: Treatment Response in Patients With TFG GOUT1/GOUT2

Phase III Randomized, Double-blind Efficacy and Safety Trials

- Significant relationship between GFR improvement and SUA reduction
- 1.0 mL/min GFR improvement for each 1.0 mg/dL reduction in SUA (P = 0.02)

SUA Reduction May Benefit Estimated Long-term GFR in Hyperuricemic Patients

Mean changes in expected GFR after 5 years of treatment with febuxostat 40, 80, and 120 mg/day (baseline mean SUA: 8.7 mg/dL)*

No dose adjustments in renal and hepatic insufficiency
- Similar adverse event rates, including CV events, across study groups or by renal function
- Comparably efficacious in patients with moderate shunt

Patients with plasma urate < 6.0 mg/dL after 6 months of intravenous pegloticase

- Investigations: unpublished or preliminary data
- *P value was significant versus placebo (mean values from GOUT1 and GOUT2 depicted)
- **Body weight (BW) > 100 kg, or 2 times upper limit of normal (ULN) in bilirubin, or 2 times ULN of aspartate transaminase (AST) or alanine transaminase (ALT)
- **Body weight (BW) > 100 kg, or 2 times upper limit of normal (ULN) in bilirubin, or 2 times ULN of aspartate transaminase (AST) or alanine transaminase (ALT)
- **Body weight (BW) > 100 kg, or 2 times upper limit of normal (ULN) in bilirubin, or 2 times ULN of aspartate transaminase (AST) or alanine transaminase (ALT)
Immunoreactivity and Clinical Response to Intravenous Uricase Enzyme

Pooled Data From GOUT1 and GOUT2

- Main adverse events were gout flares and infusion reactions
  - Infusion reactions associated with anti-polyethylene glycol and high antipegloticase titers


Managing Inflammatory Manifestations of Gout

- Relative contraindications to symptomatic therapies frequent in refractory gout patients:
  - eg. NSAIDs or corticosteroids
- Potential benefit of biologic therapies:
  - Pain assessment, reduction of tender and swollen joint and c-reactive protein levels
- Use not established in large trials
- Small uncontrolled trials
  - Interleukin-1 inhibition (anakinra, rilonacept)
  - Tumor necrosis factor-α inhibition (etanercept, infliximab, and adalimumab)

Fiehn C and Zeier M. Rheumatol Int. 2006;26:274-276.

Case Discussion

Matthew, 66 Years Old

- An acute gout attack has been confirmed by MSU crystal analysis:
  - The patient returns to the pharmacist with new prescriptions

Previous medications:
- Hydrochlorothiazide 50 mg/day
- Glipizide 10 mg/day
- Enalapril 20 mg/day
- Aspirin 81 mg/day

Question to consider:
- Should this patient be started on urate-lowering therapy at this point?

Conclusions

- Hyperuricemia is defined as an SUA level > 6.8 mg/dL
- The target goal of uric acid treatment is < 6.0 mg/dL
- SUA levels can be normal, especially during the attack
- Lifestyle modifications may benefit overall treatment
- Proper timing, dosing, and adherence to pharmacotherapy important:
  - Anti-inflammatory treatment and when to initiate urate-lowering therapy
  - Counsel on potential adverse events with therapy
  - Ensure that contributory comorbidities are addressed
- New therapies are available and may benefit patients

Questions and Answers