The Primary Care Management of Patients with Gout
Learning Objectives

After attending this program, the family physician should be able to:

• Identify the risk factors and comorbidities that contribute to and exacerbate acute gout attacks.
• List the criteria for establishing a diagnosis of gout.
• Distinguish between treatments for acute attacks and chronic gout.
• Describe which patients with chronic gout should be treated with urate-lowering medication and with which class of agents.
• Establish goals for achieving, sustaining, and monitoring clinically meaningful urate lowering and means for optimizing patient adherence to long-term urate-lowering treatment.
Case Study- KR

• 63 yo white male
• Being seen in follow up for type 2 diabetes
• During the visit, his wife states that KR has been experiencing another episode of difficulty walking
• Upon questioning, KR reports experiencing right ankle/heel pain over past few days
• Last time this happened, it took a week or so for the pain to resolve
Background on Gout

- Heterogeneous disorder that results in the deposition of uric acid salts and crystals in and around joints and soft tissues or crystallization of uric acid in the urinary tract
- Hyperuricemia is the major risk factor
  - Serum urate level persistently > 6.8 mg/dL
  - Uric acid overproduction vs underexcretion: 10% vs 90%
- Most common microcrystalline arthropathy
- Peak incidence occurs in the fifth decade, but can occur at any age
- 5X more common in males than pre-menopausal females, but similar after menopause
Background on Gout (cont.)

• Chronic disease that is often silent in early stages
• Becomes punctuated by acute, extremely painful attacks →
  – Poor quality of life
  – Disability
  – ↑ Healthcare utilization
• Untreated/Insufficiently treated →
  – ↑ Attacks
  – Urate crystal formation
  – Joint damage
  – Urinary tract stones
  – Interstitial urate nephropathy
  – Cardiovascular disease
Diminished Quality of Life

**Physical**

*P*=0.007 gout vs normals (overall)

**Mental**

*P*<0.001 gout vs normals (overall)

Stages of Gout

- Asymptomatic hyperuricemia
  - Very common; majority never develop symptoms
- Acute intermittent gout (gouty arthritis)
  - Episodes of acute attacks
  - Symptoms may be confined to a single joint or may be systemic
- Intercritical gout
  - Symptom-free period between attacks
  - May have hyperuricemia and MSU crystals in synovial fluid
- Chronic tophaceous gout
  - Due to established disease
  - Deposition of urate, inflammatory cells and foreign body giant cells in tissues, including tendons or ligaments
  - Usually develops after 10 or more years of acute intermittent gout

MSU=Monosodium urate
Hyperuricemia as a Risk Factor for Gout

Annual Incidence Rate for a First Episode of Gouty Arthritis

N=2046 healthy men initially with asymptomatic hyperuricemia

Selected Risk Factors and Comorbidities Associated with Gout*

- Male gender
- Chronic renal failure
- Hypertension, Obesity
- Coronary heart disease, Diuretics
- Seafood, Red meat
- Alcohol (esp. beer), Diabetes mellitus

*Adjusted by age, gender, other risk factors and comorbidities

# Diagnosis of Gout

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painful joint, swelling, abrupt onset, remission in 2 wks</td>
<td>0.98</td>
<td>0.23</td>
</tr>
<tr>
<td>Erythema</td>
<td>0.92</td>
<td>0.62</td>
</tr>
<tr>
<td>Podagra</td>
<td>0.96</td>
<td>0.97</td>
</tr>
<tr>
<td>Definite tophus</td>
<td>0.30</td>
<td>0.99</td>
</tr>
<tr>
<td>Possible tophus</td>
<td>0.20</td>
<td>1.00</td>
</tr>
<tr>
<td>Urate crystals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Acute gout</td>
<td>0.84</td>
<td>1.00</td>
</tr>
<tr>
<td>- Intercritical gout</td>
<td>0.70</td>
<td>0.95</td>
</tr>
<tr>
<td>Serum uric acid (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- &gt; 6</td>
<td>0.67</td>
<td>0.78</td>
</tr>
<tr>
<td>- Male &gt;7, Female &gt;6</td>
<td>0.57</td>
<td>0.92</td>
</tr>
<tr>
<td>- Hyperuricemia (&gt;mean+2SD)</td>
<td>0.92</td>
<td>0.91</td>
</tr>
<tr>
<td>Radiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Asymmetrical swelling</td>
<td>0.42</td>
<td>0.90</td>
</tr>
<tr>
<td>- Subcortical cysts, no erosion</td>
<td>0.12</td>
<td>0.98</td>
</tr>
</tbody>
</table>

A presumptive diagnosis of gout can be made based on the combination of all of the following except:

1. Presence of hyperuricemia
2. Pain/Swelling/Tenderness of big toe or other joint
3. History and physical examination
4. X-ray of involved joint
Diagnosis of Gout (cont.)

• Gold standard: MSU crystals in synovial fluid or tophus
• Presumptive diagnosis can be made based on
  - Follow-up within a few days is essential
• Multiple attacks of monoarticular inflammatory arthritis of lower extremity joint(s) that resolves completely within several weeks is strongly suggestive of gout

Diagnosis of Gout (cont.)

Urate crystals in synovial fluid

Joint X-rays
Clinical Presentation of Acute Gout Attack

- Often begins during the night
- Usually no fever, rash, or other signs of systemic illness
- Joint is red, hot, swollen, intensely tender to touch/movement
- Men - monoarticular and distal initially
- Women
  - Often polyarticular
  - Hands before feet (postmenopausal)
Diagnosis of Gout (cont.)

- **Uric acid**
  - Limited value (alone) since most patients with hyperuricemia never develop gout
  - Level may be normal during acute attack
- **Complete blood count**
  - Mild leukocytosis in acute attack but may be > 25,000/mm³
- **Erythrocyte sedimentation rate**
  - Mild elevation or may be 2-3x normal
- **24-h urine uric acid**
  - Only useful in patients being considered for uricosuric therapy or if cause of marked hyperuricemia needs investigation
Differential Diagnosis

• Trauma
  – Stress or silent traumatic fracture

• Infections
  – Septic arthritis, gonococcal arthritis, cellulitis, septic joint

• Inflammatory
  – Rheumatic arthritis, Reiter’s syndrome, psoriatic arthritis

• Metabolic
  – Pseudogout

• Miscellaneous
  – Osteoarthritis

Case Study - KR (cont.)

• History
  – Has experienced 3-4 episodes of acute pain in right heel over past 2-2½ years, now also involving right ankle. No other joints involved. Pain now moderate in intensity (6/10) with some relief with acetaminophen (3/10). Peaks in a day or two and resolves over 7-10 days
  – Eats red meat 4-5x/wk; drinks a glass of red wine each night before dinner
  – Medications: metformin 2g/d, glimepiride 4 mg/d, ASA 81 mg/d, naproxen sodium 220 mg BID prn joint pain
Case Study - KR (cont.)

• Physical exam
  – Vitals normal
  – Right ankle/heel hot and red; 1+ swelling; pain 6/10
  – Small subcutaneous nodule on interior aspect of right ankle
  – No sign of skin/joint infection

• Laboratory
  – sUA 8.2 mg/dL
  – WBC 11,600/mm³
  – SCr 1.3 mg/dL
  – ESR 22 mm/h

• X-ray
  – Not ordered

ESR=erythrocyte sedimentation rate; SCr=serum creatinine; sUA=serum uric acid; WBC=white blood cell count
What Now?

• Based on a presumptive diagnosis of gouty arthritis
  – What are your goals of therapy?
  – Would you make any changes to his current medications?
  – What dietary changes would you recommend?
  – How would you manage the acute attack?
  – Would you initiate urate-lowering therapy?
During an acute gout attack

1. The serum urate level should be checked.
2. An X-ray of the affected joint should be obtained.
3. Anti-inflammatory therapy should be initiated.
4. Consumption of low-fat dairy products and vegetable proteins should be avoided.
Goals of Therapy

• Acute attack
  – Reduce inflammation $\rightarrow \downarrow$ symptoms & $\uparrow$ function
  – Lowering sUA level is NOT a goal

• Preventive/Urate-lowering
  – Lowering sUA $< 6.0$ mg/dL is the primary goal
  – Reverse urate crystal deposition
  – Prevent recurrent attacks
  – $\downarrow$ Risk of joint/tissue damage, cardiovascular complications

Serum Urate Level Often Normal During Acute Gout Attack

# Non-Pharmacologic Measures

<table>
<thead>
<tr>
<th>Medications</th>
<th>Foods/Beverages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Avoid</strong></td>
<td></td>
</tr>
<tr>
<td>Thiazide diuretics&lt;sup&gt;1-3&lt;/sup&gt;</td>
<td>Purine-rich foods such as red meat or seafood&lt;sup&gt;1,2,5&lt;/sup&gt;</td>
</tr>
<tr>
<td>Loop diuretics&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Beverages sweetened with sugar or high-fructose corn syrup&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Aspirin (≥ 600 mg/d)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Beer&lt;sup&gt;1,2,7&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cyclosporine&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Distilled alcohol&lt;sup&gt;1,2,7&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ethambutol&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Yeast extract&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Niacin&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Use (if indicated)</strong></td>
<td></td>
</tr>
<tr>
<td>Fenofibrate&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Low-fat dairy products&lt;sup&gt;1,5&lt;/sup&gt;</td>
</tr>
<tr>
<td>Losartan&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Soy beans, vegetable proteins, cherries&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Increase**

**Fluids, ice, rest, elevation also may be helpful**<sup>2,3</sup>

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Treatment- Acute Attack

- Anti-inflammatory are mainstay of therapy

**Comparable efficacy**

- NSAIDs
- Colchicine
- Corticosteroids

Patient-specific factors and drug adverse event profiles have an important role in treatment selection

Treatment- Acute Attack
Similar Efficacy of Naproxen and Prednisolone

Reduction in Pain Score: 0-90 hours

Treatment- Acute Attack

NSAIDs

- Efficacy comparable among NSAIDs$^{1,2}$
- Use in high dose for 1-2 weeks$^{3}$
- Avoid or use with gastroprotective agent in patients with peptic ulcer disease or gastritis$^{3}$
- ↑ Risk of serious cardiovascular thrombotic events$^{4}$
- Many drug interactions

After 24 hours, low-dose colchicine provides greater pain reduction and is better tolerated than high-dose colchicine.

1. True
2. False

Low-dose: colchicine 1.2 mg x1 then 0.6 mg in 1 hour
High-dose: colchicine 1.2 mg x1 then 0.6 mg q1h x6
Treatment- Acute Attack
Colchicine

- Effective, used for centuries with a standard ‘dose-to-toxicity’ regimen

<table>
<thead>
<tr>
<th>Colchicine 1 mg then 0.5 mg q2h until reduced pain or toxicity</th>
<th>Number Needed to Treat</th>
<th>Number Needed to Harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compared to placebo</td>
<td>Pain</td>
<td>Clinical Symptoms</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

Treatment- Acute Attack

Colchicine (cont.)

• Infrequent major toxicity with high levels
  – Bone marrow suppression (neutropenia), myopathy, neuropathy\(^1\)-\(^4\)

• Avoid in
  – Severe, end-stage kidney or liver disease
  – Patients taking macrolide, cyclosporine, statin (not fluvastatin), calcium channel blocker, dapsone, ketoconazole, quinidine, terfenadine\(^5\)

Treatment - Acute Attack

Colchicine: Efficacy

Low-dose vs ‘standard’ high-dose colchicine

Low dose: 1.2 mg x1, then 0.6 mg in 1 hour
High dose: 1.2 mg x1, then 0.6 mg q1h x6

Patients (%) who improved in each category of percent improvement for the pain score 24 hours after the initial dose

Primary end-point

\[ P = 0.034 \text{ high-dose vs placebo} \]
\[ P = 0.005 \text{ low-dose vs placebo} \]


Lo  

Low-dose colchicine: 1.2 mg x1, then 0.6 mg in 1 hour
High-dose colchicine: 1.2 mg x1, then 0.6 mg q1h x6

Low-dose colchicine: 1.2 mg x1, then 0.6 mg in 1 hour
High-dose colchicine: 1.2 mg x1, then 0.6 mg q1h x6

Low-dose Colchicine

• Rapid control of gout attack when used early
• Synergistic with other agents
• Cost-effective compared to NSAIDs

Treatment- Acute Attack
Corticosteroids

• Rapidly effective (especially intra-articular)\textsuperscript{1,2}

• Useful in patients
  – Who achieve an inadequate response to, are intolerant of, or have a contraindication to NSAIDs and colchicine\textsuperscript{1,2}
  – With severe oligoarticular/polyarticular attacks or attacks in sites not amenable to aspiration\textsuperscript{2}

• Caution in patients with infection, diabetes, HTN, heart failure; avoid in septic arthritis\textsuperscript{1,2}

• Multiple routes of administration

Case Study- KR (cont.)

• For acute attack
  – Colchicine 1.2 mg x1 at first sign of gout flare, then 0.6 mg in 1 hour
  – Consider colchicine 0.6 mg QD or BID for prophylaxis of gout flares

• Dietitian referral

• Care plan
## Care Plan: Acute Attack

<table>
<thead>
<tr>
<th>Acute Attack</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Goals</strong></td>
</tr>
<tr>
<td>- To recognize and manage acute attack</td>
</tr>
<tr>
<td>- To treat pain as quickly as possible</td>
</tr>
<tr>
<td><strong>Educational points</strong></td>
</tr>
<tr>
<td>- Promote patient self-management for very early recognition and treatment of acute attack symptoms</td>
</tr>
<tr>
<td>- Provide an action plan and a means to record attack number, duration, and intensity as well as medication for treating acute attacks at home</td>
</tr>
<tr>
<td>- Provide guidance on when to call the clinic during acute attack and what to do if acute treatment is not effective</td>
</tr>
<tr>
<td>- Provide guidance on the most likely adverse drug reactions</td>
</tr>
</tbody>
</table>

Urate-Lowering Therapy

• Goals:
  – To prevent further acute attacks
  – To prevent complications (e.g., kidney or cardiovascular disease) by promoting dissolution of MSU crystals in joints and tissues

• Target sUA: 5.0* - 6.0 mg/dL

• Treating asymptomatic hyperuricemia of any level of serum urate to prevent gout or the co-morbid disease associated with gout is controversial but generally not recommended

*Using a specific uricase assay

Indications for Urate-Lowering Therapy in Symptomatic Gout

- Frequent or disabling acute gout flares
- Tophaceous gout (soft tissue or bony)
- Gout with renal function impairment
- Gout with urolithiasis
- Radiographic changes of gout
- Uric acid overproduction and urinary overexcretion (>1000 mg daily)
- Radiation or chemotherapy for lymphoma or leukemia

Becker MA. Personal communication; March 12, 2010.
Indications for Urate-Lowering Therapy in Symptomatic Gout (cont.)

- In uncomplicated patients who have experienced a single acute attack, there is no consensus about starting ULT$^{1,2}$

  - Initiate after 1\textsuperscript{st} attack since MSU load is relatively small
  - Patient preference
  - Potential risks of not treating
  - Potential benefits, risks, costs of treatment

  Initiate after attacks become frequent or troublesome since estimated recurrence rates are$^{3}$
  - 60% within 1 year
  - 78% within 2 years
  - 84% within 3 years
  - > 90% within 10 years

ULT=urate-lowering therapy

Initiating Urate-Lowering Therapy

• Wait at least 1-2 weeks after acute attack has resolved\(^1,2\)

• Patient education regarding non-pharmacologic measures

• Since acute attacks are more likely during weeks/months following initiation of ULT → consider prophylactic
  – Colchicine 0.6 mg QD/BID\(^3\) for 6 wks to 6 mos\(^1\)
  – If colchicine is not effective/tolerated → NSAID (with gastroprotection prn) for 4-6 weeks\(^1,2\)

Options for Urate-Lowering Therapy

- **Uricostatic agents (Xanthine oxidase inhibitors)**
  - Allopurinol, febuxostat
- **Uricosuric agents**
  - Probenecid, sulfinpyrazone
  - Alternative to or in combination with uricostatic
- **Others**
  - Fenofibrate, losartan
Survival Benefit with Allopurinol

At baseline, patients had a sUA > 7.0 mg/dL

Database included 9924 persons with 23,903 person-years of follow-up

*Adjusted for baseline urate level, age, race, body-mass index, gender, comorbidities, healthcare utilization, cardiovascular and other medications, and baseline cholesterol, albumin, glomerular filtration rate.

**HR 0.77; 95% CI 0.65, 0.91

The urate-lowering efficacy of allopurinol plateaus at 300 mg/d.

1. True
2. False
Allopurinol Efficacy is Dose-Dependent

Patients (%) who achieved sUA ≤5.0 mg/dL

- Patients (n=36) with CrCl ≥ 50 mL/min received allopurinol 300 mg QD for 2 mos.
- If sUA > 5.0 mg/dL, allopurinol was increased to 300 mg BID.
- Two patients stopped allopurinol due to an adverse reaction.

Febuxostat vs Placebo: Efficacy

Patients (%) with sUA < 6.0 mg/dL at each study visit
(sUA ≥ 8.0 mg/dL on day -2 )

Note: Febuxostat currently approved as 40 mg or 80 mg once daily

Febuxostat vs Allopurinol: Efficacy

Patients (%) with sUA < 6.0 mg/dL at last 3 monthly visits

- All patients (N=756)
- Baseline sUA 8.0-<9.0 mg/dL
- Baseline sUA 9.0-<10.0 mg/dL
- Baseline sUA ≥ 10 mg/dL

P values vs allopurinol
*0.04; **0.001; †<0.001

52 weeks of treatment
- Allopurinol 300 mg
- Febuxostat 80 mg
- Febuxostat 120 mg

Note: Febuxostat currently approved as 40 mg or 80 mg once daily

Febuxostat vs Allopurinol: Safety & Tolerability

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Allopurinol 300 mg (n=253)</th>
<th>Febuxostat 80 mg (n=256)</th>
<th>Febuxostat 120 mg (n=251)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver function abnormality</td>
<td>4</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Headaches</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Arthralgia, joint stiffness/swelling</td>
<td>2</td>
<td>&lt;1</td>
<td>2</td>
</tr>
<tr>
<td>Back, chest wall, flank, or extremity pain and musculoskeletal stiffness</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Constipation, GERD</td>
<td>2</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Nausea &amp; vomiting</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness, dysgeusia</td>
<td>&lt;1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Asthenia, fatigue</td>
<td>&lt;1</td>
<td>2</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Note: Febuxostat currently approved as 40 mg or 80 mg once daily.

# Urate-Lowering Therapy

<table>
<thead>
<tr>
<th></th>
<th>Allopurinol</th>
<th>Febuxostat</th>
<th>Probenecid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>100-800 mg/d (&gt;300 mg/d as divided dose)</td>
<td>40-80 mg QD</td>
<td>250-1000 mg BID</td>
</tr>
<tr>
<td><strong>Drug interactions</strong></td>
<td>Avoid with substrates of xanthine oxidase; many others</td>
<td>Avoid with substrates of xanthine oxidase</td>
<td>Salicylate, methotrexate, many others</td>
</tr>
<tr>
<td><strong>Adverse reactions</strong></td>
<td>Maculopapular rash, pruritus, hypersensitivity reaction, nausea, diarrhea</td>
<td>Liver function abnormalities, nausea, arthralgia, rash</td>
<td>Flushing, dizziness, nausea, vomiting</td>
</tr>
<tr>
<td><strong>Cautions</strong></td>
<td>Acute gout attack upon initiation</td>
<td>Severe renal or hepatic impairment; monitor for MI, stroke</td>
<td>Peptic ulcer disease, urate overproducers, CrCl ≤ 30 mL/min, 2L fluid/d</td>
</tr>
</tbody>
</table>

Fenofibrate Added to Allopurinol

1=Baseline
2=3 months allopurinol 200 mg bid
3=2 months allopurinol 200 mg bid + fenofibrate 300 mg qd
N=14 hyperuricemic males with fasting triglyceride > 150 mg/dL

Losartan Added to Allopurinol

1=Baseline
2=3 months allopurinol 200 mg bid
3=2 months allopurinol 200 mg bid + losartan 50 mg qd
N=12 hyperuricemic males with systolic blood pressure > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg

Case Study- KR (cont.)

• Urate-lowering therapy
  – Allopurinol 100 mg QD x 1 week; then 200 mg QD x 1 week; then 300 mg QD
  – Increase dose if sUA ≥ 6.0 mg/dL in 1 month

• Serum uric acid level in 1 month

• Follow-up in 1 month

• Care plan
# Care Plan: Chronic Gout

<table>
<thead>
<tr>
<th><strong>Goals</strong></th>
<th><strong>Chronic Gout</strong></th>
</tr>
</thead>
</table>
| • To prevent future acute attacks  
• To slow and reverse joint and soft tissue damage | |

<table>
<thead>
<tr>
<th><strong>Educational points</strong></th>
<th><strong>Chronic Gout</strong></th>
</tr>
</thead>
</table>
| • Discuss the silent phases of the disease and the importance of monitoring sUA levels and continued adherence with ULT  
• Inform patients that initiation of ULT may increase the early risk for attack, and provide attack prophylaxis for at least 6 mos  
• Remind patients that acute attacks during treatment should be treated with anti-inflammatory medications but to continue ULT for long-term prevention  
• Provide guidance on lifestyle modifications to reduce sUA  
• Provide guidance on the most likely adverse drug reactions | |