Treating Acute and Chronic Gout in Primary Care
Clinical Case Challenge Series

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Disclosures

Speaker’s Bureau

Abbott, Amgen, Pfizer, UCB
Accreditation

This program has been reviewed and is approved for a maximum of 1 hour of AAPA Category 1 CME credit by the Physician Assistant Review Panel. Physician assistants should claim only those hours actually spent participating in the CME activity.

This program was planned in accordance with AAPA’s CME Standards for Live Programs and for Commercial Support of Live Programs.
Pre-test Question 1

What is the metabolic underpinning of gout?

A. Hyperuricemia defined as serum urate levels exceeding population norms.
B. Undetermined, gout is an idiopathic periodic joint inflammatory process.
C. Hyperuricemia defined as serum urate levels exceeding ≥ 6.8 mg/dL.
D. Excess alcohol consumption.
Pre-test Question 2

When making a presumptive diagnosis of gout in your patient what factors do you have to be vigilant about?

A. A presumptive diagnosis does not require particular attention to alternative scenarios or co-morbid conditions of gout.
B. A presumptive gout diagnosis includes serum uric acid levels > 6.8 mg/dL at the time of diagnosis.
C. Differential diagnoses includes: septic arthritis, pseudo-gout, fracture, rheumatoid arthritis, and cellulitis.
D. Evaluate for bone marrow edema or malignancies.
Pre-test Question 3

A new patient presents for an annual exam. He has a 10-year treatment history of gout. You notice pale yellow nodules on several finger joints which you think may be tophi. What has likely contributed to this finding?

A. Overproduction of uric acid only.
B. Co-morbidities limiting use of anti-inflammatory treatment only.
C. Longstanding undertreated hyperuricemia.
D. Lack of available diagnostic testing.
You are discussing a treatment plan with your new patient. He presents with a 5-year history of uncontrolled, painful flares of gout. He is ready to start more comprehensive therapy. His current serum uric acid (sUA) is 8.0mg/dL. When should this patient start urate-lowering therapy (ULT)?

A. This patient is not a candidate for ULT since he is not having an acute flare at this time.
B. Only in the presence of tophi or with bone erosions.
C. Immediately, regardless of an acute flare, to provide the best possible care.
D. 1-2 weeks after a gout flare has subsided during the intercritical period.
Pre-test Question 5

Your patient has started ULT, but has experienced two flares since initiation. How long should you recommend use of anti-inflammatory flare prevention therapy when starting ULT?

A. 2 weeks
B. 2 months
C. 6 -12 months
D. 24 months
Learning Objectives

1. Understand the physiology of urate handling in humans
2. Identify the clinical features and natural history of gout
3. Clarify the clinical process for making the diagnosis of gout, including the concept of ‘presumed gout’
4. Describe the options available to treat acute gout
5. Review indications for the use of urate-lowering therapies in recurrent gout, including the control of treatment-induced flares
6. Develop and implement treatment plans that impact the progression of gout by the principle of treat to target
7. Describe ‘difficult to control gout’ and common pitfalls in reaching therapeutic success
Physiology of Uric Acid in Humans

Sources and Distribution of Uric Acid in an Adult Man

Reprinted with permission from the American Society of Clinical Rheumatologists
Endogenous purine synthesis
Tissue nucleic acids
Dietary purines

Total Body Uric Acid Pool

Miscible urate pool
2000 mg

Insoluble urate pool
1 to >40 grams

Renal excretion
Intestinal uricolyis

Reprinted with permission from the American Society of Clinical Rheumatologists
Consequences of Expanded Urate Pools

Miscible urate pool

2000 mg

Insoluble urate pool

1 to >40 grams

- Asymptomatic hyperuricemia
- Hypertension, kidney & heart disease
- Renal Manifestations
- Gouty arthritis
- Urate tophi

Reprinted with permission from the American Society of Clinical Rheumatologists
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Scope of the Problem
Gout Affects Millions of People

- US Adult Population: 228 million
- Hyperuricemic Population: 42.8 million
- Gout Total Population: 8.3 million (2011)

Other rheumatic disorders
Acute Gout

- Most common form of inflammatory joint disease as of 2011 data

- Acute inflammation - typically rapid onset, mono-articular and very painful

- Crystallization occurs when the blood level of urate > physiologic limit of solubility: 6.8mg/dL

- Serum uric acid levels can be normal during flare
Precipitating Events for Acute Flare

In the presence of hyperuricemia any of the following can tip to flare:

• Trauma (increased activity such as dancing, prolonged walking)
• Progressive renal insufficiency
• Initiation of diuretics or other urico-retentive medications
• Dietary indiscretion (beer, red meat, shell fish)
• Dehydration
• Alcohol overuse; beer, grain alcohol, wine
• Systemic illness/surgery causing bed rest
What Makes the Crystals so Inflammatory?

- Urate crystals are in the joints even in the absence of a flare. Why do crystals sometimes cause flare?

- One explanation lies in the observation that clumps or microtophi of urate crystals are normally coated with serum proteins that physically inhibit the binding of the crystals to immune cell receptors.

- A gout attack may be triggered by either a release of uncoated crystals, for example, due to partial dissolution of a microtophus caused by changing serum urate levels or precipitation of crystals in a supersaturated microenvironment, for example, release of urate due to cellular damage/trauma.

- From either source, naked urate crystals are then believed to interact with intracellular and surface receptors of local immune system cells and set off signals to activate parts of the very pro-inflammatory innate immune system.
Stages of Gout

- Asymptomatic Hyperuricemia
- Acute Gout with Intercritical Periods
- Advanced Gout
Common Sites of Acute Flares

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

Gout can occur in bursae, tendons, and joints

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

Post-menopausal female onset

Typical male onset
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Getting to Gout

**Historical clues:**
- previous attack of acute monoarthritis
- maximum inflammation developed within a day
- impressive pain, often cannot bear weight

**Exam clues:**
- joint is red, hot, swollen. Patient resists touching
- first MTP (great toe) most commonly
- mid-foot or ankle not uncommon site
- tophus (proven or suspected) in long-standing disease

**Lab/imaging clues:**
- serum urate may be normal or slightly elevated in flare
- may have been elevated in the past
- ESR very elevated and WBC usually elevated
- soft tissue swelling on x-ray, erosive changes if advanced
- may co-exist with changes of OA
Diagnosing Gout

- Hyperuricemia is the metabolic underpinning
- sUA may be not be high during flare
- A classic history and an often impressive physical examination
- Synovial fluid crystal analysis is the gold standard for a definitive diagnosis
- Imaging may be necessary
- ++ response to colchicine unique to crystal-induced arthritis
Differential Diagnosis

1. **Septic Arthritis**
2. Cellulitis
3. Pseudogout or OA with inflammation
4. Post-traumatic soft tissue injury
5. Fracture
6. Other inflammatory arthritis (reactive, RA)
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Dual-pronged Approach to Gout Management is Necessary

Controlling Pain and Inflammation

- Acute Flare Pain
- Antiinflammatory Prophylaxis

Reducing Urate Burden

- NSAIDs
- Colchicine
- Glucocorticoids

Xanthine Oxidase Inhibitors
Uricosurics

Optimal Pharmacologic Gout Management

Edwards NL, Crystal-Induced Joint Disease in ACPMedicine Textbook, 2012
Acute Gouty Arthritis: Podagra and Ankle Inflammation
Typical Regimens for Acute Gout

- **NSAIDs**
  - Ibuprofen 1600mg x 1 then 800 Q8H x 10d
  - Indomethacin 100mg x 1 then 50 Q8H x 10d
  - Naproxen 1000mg BID x 1d then 500 BID x 10d

- **Colchicine**
  - 1.2 mg at once; 0.6mg one hour later then 0.6 BID x 7-10d.

- **Corticosteroids**
  - 30-60 mg prednisone QD and taper by 5-10 mg every other day
Acute Gout Treatment Summary

• The critical issue in the management of acute gout is how quickly therapy can be initiated after the attack has begun and not which agent is selected

• Select an agent that is most compatible with the patient’s underlying co-morbidities and present medications:
  
  ex: anticoagulation
  ex: diabetes
  ex: history of GI bleeding

• PEARL:
  During an acute gout attack if the patient is on ULT, DON’T STOP. If the patient is off ULT, DON’T START.
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Indications for Urate-lowering Therapy

Urate lowering therapy (ULT) is indicated in patients with any of the following:

1. Greater than one attack per year
2. Tophi
3. Urate kidney stones
4. X-ray changes of gout on plain film or ultrasound
5. Chronic late stage gouty arthritis
Allopurinol

• FDA approval in 1964; most commonly used form of ULT.

• Well tolerated in ~90% of users; AHS occurs in 0.1% of allopurinol starts.

• Most allopurinol prescriptions in this country are for 300 mg/d or less. At this dose, only 35% will reach target of sUA < 6.0 mg/dL.¹

• Like all forms of ULT, allopurinol may increase the frequency of flares after initiation if anti-inflammatory prophylaxis is not co-administered.
Flare Prophylaxis When Starting Urate-lowering Therapy

- Start low-dose colchicine or NSAIDs 2 weeks prior to initiating ULT
- Begin allopurinol at 100 mg/d (CKD class I-III) or 50 mg/d (CKD class IV)
- Recheck sUA level every 2-4 weeks and increase allopurinol dose by 50-100 mg until sUA < 6.0 mg/dL up to a maximum dose of 800 mg/d
- Allopurinol therapy should be uninterrupted and life-long
- Anti-inflammatory prophylaxis can be stopped, if no flares in past 6 months

1. Allopurinol approved by FDA to 800mg in a split dose
Febuxostat - A Newer Urate-lowering Therapy

- Selective xanthine oxidase inhibitor
- Structurally dissimilar to allopurinol
- Metabolized by the liver with no dose adjustment for CKD
- Simple dosing schedule: 40 mg/d as initial dose, then increase to 80 mg/d after 2 weeks if sUA not at target

CONFIRMS Trial Efficacy in Renally-Impaired Subjects

Proportion of Subjects With Mild-to-Moderate Renal Impairment With sUA <6 mg/dL at Final Visit

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febuxostat 40 mg</td>
<td>50%</td>
</tr>
<tr>
<td>Febuxostat 80 mg</td>
<td>72%</td>
</tr>
<tr>
<td>Allopurinol 300/200</td>
<td>42%</td>
</tr>
</tbody>
</table>

* p < 0.05
** p < 0.01
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Case 1
Acute Gout

- Mr. T is a 41 year-old Cambodian man.
- Came to his PC’s office with his 3rd episode this year of swelling and redness in his big toe and ankle. This episode has lasted over five days.
- Has responded in the past to indomethacin 50mg bid and cephalexin in combination.
Case 1
Acute Gout

X-ray shows a degenerative heel spur and soft tissue swelling over the medial ankle

Lateral view
Acute Gout
Case 1

• HPI:
  ➢ His first attack lasted one day. Second attack 3 days. This attack has lasted > 5 days.
  ➢ Unsure how many beers he drank the day before this attack but quite a few
  ➢ sUA during the second attack when he was seen at the ER was 7.9 mg/dL (ULN 8.5 mg/dL)
Acute Gout
Case 1

• Past medical history:
  ➢ GI bleed treated in the ER. Patient does not know specific dates or why but knows it occurred ‘last year’
  ➢ Non-smoker, drinks beer ‘on occasion’
  ➢ No family history of gout or DM, HTN, or lipid disorder.

• Current medications:
  OTC prn NSAID for foot pain
Acute Gout
Case 1

Physical Exam:
- mild distress on walking
- BP 144/90
- T 98.9°F
- Slight erythema of right ankle and foot
- Mild warmth
- Chronic skin changes of stasis in both legs
- No tophi or joint deformities
Acute Gout
Plan

- This patient was well into his flare. Therapy is most effective given earlier.

- Mr. T. was given an IM injection of triamcinolone 40mg

- Colchicine 0.6 bid started as well because urate-lowering therapy was indicated.

- Follow-up set for 2-3 weeks, while remaining on the colchicine. Lifestyle issues

- BP will have to be monitored
Case 2
Chronic Tophaceous Gout

- Mr. J is a 60-year-old white man c/o episodic attacks of acute arthritis in one foot or ankle
- These began 9 years ago and continue in spite of ‘treatment’
- MSU crystals identified on joint aspiration in an ER two years ago
- Acute attacks treated with NSAIDs
- Last three years taking colchicine 0.6mg qod and allopurinol 300 mg qd
Case 2
Chronic Tophaceous Gout

• Medical History:
  - Hypertension
  - Non-insulin dependent diabetes mellitus
  - Coronary artery disease

• Present Meds:
  - amlodipine 10mg qd
  - furosemide 20 mg qd
  - colchicine 0.6 mg every other day
  - allopurinol 300mg qd
# Case 2
## Chronic Tophaceous Gout

<table>
<thead>
<tr>
<th>Lab Studies</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hct</td>
<td>34%</td>
</tr>
<tr>
<td>Hgb</td>
<td>11.6 g/dL</td>
</tr>
<tr>
<td>Platelet</td>
<td>504,000/cu mm</td>
</tr>
<tr>
<td>ESR</td>
<td>42 mm/hr</td>
</tr>
<tr>
<td>BUN</td>
<td>35 mg/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.5 mg/dL</td>
</tr>
<tr>
<td>Potassium</td>
<td>5.1 mEq/L</td>
</tr>
<tr>
<td>Uric acid</td>
<td>8.5 mg/dL</td>
</tr>
<tr>
<td>CRP</td>
<td>3.8 mg/dL</td>
</tr>
<tr>
<td>eGFR</td>
<td>45 mL/min</td>
</tr>
</tbody>
</table>
Case 2
Chronic Tophaceous Gout

• Physical Exam:
  - BP 128/72 mm Hg
  - Ankles and feet are swollen
  - Tophi on outer helix of left ear and right olecranon bursa
A Plan for This Case of Chronic Tophaceous Gout?

A. Add probenecid 500 mg bid
B. Change allopurinol to febuxostat 40mg
C. Increase allopurinol to 400mg daily
D. Refer for pegloticase therapy
Pegloticase
an Infusible Biologic Therapy for Tophi
Dissolution and Treatment of Refractory Gout

Baseline

Week 15

Sundy and Hershfield, unpublished data
Gout in Women
Case 3

• Ms. W is a 80-year-old white female with a 3 month history of recurrent episodes of severe pain, swelling, and warmth in a wrist, an elbow, and one knee, each of which lasted 3-5 days. She has had one episode per month.
Gout in Women
Case 3

• She self-treated the first two episodes with ice, rest and ibuprofen she had on hand.

• The ER treated her 3rd episode with a wrist splint, prednisolone and ketorolac IM. She was referred back to her PCP for follow-up. In the ER her ESR was 60mm, CBC WNL, Cr 1.4, glucose 250mg and uric acid 8.0. Her swollen wrist was not aspirated
Gout in Women
Case 3

• Medications:
  ➢ HCTZ 50mg qd increased from 12.5 to 50mg over the last three months for BP
  ➢ ASA 81mg qd for years
  ➢ Simvastatin 40mg for one year
  ➢ Acetaminophen prn for knee osteoarthritis
  ➢ Calcium and Vitamin D qd
Gout in Women
Case 3

- Past medical history included hypertension, hyperlipidemia and osteoarthritis
- She had become less active and obese over the last three decades since menopause
Gout in Women
Case 3

• Physical exam:
  - Obese female not in distress
    - BMI 33
    - BP 140/88
    - no tophi, no joint deformities
    - no active joint inflammation
    - crepitus bilat knees

• Labs
  - sUA 10.3 mg/dL
  - creatinine 1.4 eGFR 47
Question
Case 3

Which of the following is the best treatment to manage this patient’s presumed gout?

A. Counsel on association of metabolic syndrome and gout
B. Discuss the need to begin ULT and the concept of treating to target goal of an sUA of <6mg/dL
C. Start allopurinol at 100mg/qd
D. Providing flare prophylaxis and flare treatment medications
E. All of the above
Role of Diet and Lifestyle

Diet and alcohol questions from patients are common.

• Recent research makes it simple:
  - beer, red meat, shell fish and high fructose corn syrup raise uric acid the most
  - low fat dairy products lower sUA
  - All forms of excess alcohol promote hyperuricemia and trigger flares
Eat Less, Shoot for Moderation

- Hyperuricemia and gout are highly correlated with body weight in both men and women.
- Obesity is a common factor linking hyperuricemia, hypertension, hyperlipidemia and atherosclerosis.
- Core dietary recommendations are that of portion control and a Mediterranean style diet.
You Can Suggest

1. Drinking coffee reduces the risk of gout for men and women¹
2. Switch to diet soda¹
3. Go with good dairy¹
4. Drinking more water means fewer gout flares¹

Barriers to Success

- Patients often are confused as to which medicine is to be taken for which condition.
- Prescribers fail to provide adequate ULT and do not shoot for a set target of a sUA of <6mgs/dL.
- Flare backs while initiating ULT are usual and need prophylaxis to moderate.
- Flares are not treated early enough. Patients do not have rescue meds on hand.
Partnership Required

• Patents need to understand their disease, which medicine to take for which condition, and buy into long-term therapy with lifestyle changes.

• Providers need to explain the disease, its causes, its treatments, provide educational resources, and cover all the medication bases.
Post-test Question 1

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B. 2 months
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Patient Resources

- Arthritis Foundation- www.arthritis.org
- Gout Education- www.gouteducation.org
- American College of Rheumatology- www.rheumatology.org
General References

- Recommendations for the Diagnosis and Management of Gout and Hyperuricemia, *Postgraduate Medicine* November 2011 supplement 1
- The Image Bank of the American College of Rheumatology
- The American Society of Clinical Rheumatologists http://www.ascr.us
- U.S. Food and Drug Administration Center for Drug Evaluation and Research Web site (febuxostat chemical cpd)
- The personal slide collection of N.L. Edwards MD
Thank you

Questions?

• On behalf of Savient Pharmaceuticals and the AAPA we thank you!