Updates on Management of Gout in Older Adults

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Case 1

An 80 year old man is seen in the geriatrics clinic for a 2-week history of painful swollen left index finger PIP joint. Over the past 2 years, he has had a few episodes of pain and swelling in his right knee and left foot, for which he received naproxen and once was treated with an antibiotic. PMH includes DMII, CAD, HL and HTN and is on glipizide, baby ASA, simvastatin, metoprolol and hydrochlorothiazide. BMI = 30

He drinks a couple of beers a day but does not smoke.

Labs:

- WBC 13/cu mm
- Hb 11.5 g/dL
- Platelets 110/cu mm
- AST 66 U/L
- ALT 70 U/L
- Creatinine 1.7 mg/dL
- ESR 76mm/hr

What are the most appropriate next steps?
Case 2

A 75yo African American presents with a 3-day history of a warm, swollen right knee. PMH includes gout, COPD, DM, esophageal cancer, HCV (cirrhosis, portal HTN, multifocal hepatocellular carcinoma) and polysubstance abuse (IV heroin, marijuana).

**Labs:**

- WBC: 10
- Hb: 10.5
- Plt 99
- Cr 1.2, urinalysis normal
- ESR 55
- AST 110
- ALT 120
- Total bilirubin 2.5
- Synovial fluid: 5600 RBCs; 18,000 WBCs (80%N, 15%L); MSU crystals

*Now what?*
Prevalence of gout in the US according to age

Gonzalez EB. *Clin Rheumatol* 2011
The changing epidemiology of gout

- Prevalence of gout and hyperuricemia increasing worldwide - the commonest inflammatory arthropathy affecting the elderly

- Potential reasons
  - Aging population
  - Metabolic syndrome/obesity and HTN
  - Renal insufficiency
  - Western diet, alcohol, medications

Barriers to managing gout in the elderly

• Atypical clinical presentation
• Co-morbid conditions such as CKD, CHF, CAD, liver disease, memory issues, peptic ulcer disease make it difficult or dangerous to use traditional gout medications
• Drug interactions
• Dietary advice difficult to follow in this age group
• Physician factors/Gout Quality Indicators: less than 50% gout patients on allopurinol achieved target uric acid level; less than 50% have uric acid level rechecked within 6 months after starting treatment
The 4 clinical phases of gout

• Asymptomatic hyperuricemia
• Acute/recurrent gout
• Intercritical gout
• Chronic tophaceous gout
Clinical features of Gout: ‘Young’ versus old

<table>
<thead>
<tr>
<th>Feature</th>
<th>Middle-aged</th>
<th>Late-onset</th>
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</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>40-50s</td>
<td>&gt;70</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>M＞W</td>
<td>M=W (after 80 yrs)</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td>Acute monarthritis</td>
<td>Oligo or Polyarticular</td>
</tr>
<tr>
<td></td>
<td>90% podagra</td>
<td>Upper extremities</td>
</tr>
<tr>
<td></td>
<td>Acute onset</td>
<td>Subacute onset</td>
</tr>
<tr>
<td><strong>Tophi</strong></td>
<td>After years of attacks</td>
<td>Early or without h/o</td>
</tr>
<tr>
<td></td>
<td>Elbows＞fingers</td>
<td>More often fingers</td>
</tr>
<tr>
<td><strong>Associated</strong></td>
<td>Obesity, hyperlipidemia,</td>
<td>Diuretic and ETOH use</td>
</tr>
<tr>
<td><strong>features</strong></td>
<td>HTN, ETOH use</td>
<td></td>
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Disease-Related and All-Cause Health Care Costs of Elderly Patients With Gout

• Integrated Healthcare Information Services (IHCIS) claims database (1999-2005), which includes 40 private health plans and 13 million beneficiaries

• 11,935 gout patients aged 65 years or older. Average age 71.4 years

• After statistical adjustment for comorbidities, the difference in total 12-month health care costs between gout patients and gout-free members was $3,038 (P < 0.001)

• Gout-related costs represent about 6% of total health care costs in elderly patients with gout

Wu et al. J Manag Care Pharm 2008
Gout and myocardial infarction

- Framingham study
  - Gout = 60% increased risk of MI
- MRFIT (Multiple Risk Factor Intervention Trial)
  - Gout = 26% increased risk of MI (taking into account FH, BMI, cholesterol, DM, HTN, ASA use)
  - Hyperuricemia = 11% increased risk of MI
- Framingham Offspring Study
  - Gout = 2-3 times higher incidence of clinical heart failure and echocardiographic measures of systolic dysfunction, and 58% greater risk of death

What’s new....

- 2 relatively new medications
- 2012 treatment guidelines from the American College of Rheumatology
Febuxostat (Uloric)  
*non-purine analogue inhibitor of xanthine oxidase*

- FDA approval Feb 2009 for chronic management of gout
- 80mg: twice as many patients reach uric acid level target compared to allopurinol. *However*—study compared fixed dose (300mg) of allopurinol
- UK National Institute of Health and Clinical Excellence: the benefits of febuxostat compared with allopurinol (using a fully titrated dosing schedule) in improving clinical outcomes (gout flare control, reduction in tophi size and number, and avoidance of joint and organ damage) in the longer term, had not been clearly demonstrated
- No dose adjustment in mild or moderate renal disease
- Patients intolerant to or if allopurinol is contraindicated
Pegloticase (Krystexxa)

Recombinant urate oxidase conjugated to polyethylene glycol

- FDA approval September 2010 for chronic gout refractory to conventional therapy
- Oxidation of urate to allantoin
- IV 8mg q2 wks: reduces plasma urate to < 1mg/dl within 24 hrs
- Selected issues
  - Cost ($2000-3000 per dose)
  - G6PD deficiency → methemoglobinemia and hemolytic anemia
  - Increase gout flare rate (first 3 months)
  - Antibodies to drug are common - associated with loss of response
  - Urate lowering therapies should be discontinued prior to the use of pegloticase and should not be initiated during a course of pegloticase therapy
  - Infusion reactions and anaphylaxis
  - Exacerbation of CHF possible
Interleukin-1β Blockade for gout

Canakinumab*  Rilonacept**  Anakinra

* FDA voted against approval June 2011  ** FDA voted against approval May 2012

"Many of the patients I see are not representative of the patients that were in the sponsor's study. Mine are older and often have other comorbidities and renal dysfunction, and are at high risk of infection" Dr. David Felson

2012 American College of Rheumatology Guidelines for Management of Gout

• **Part 1**: Systematic Nonpharmacologic and Pharmacologic Therapeutic Approaches to **Hyperuricemia**

• **Part 2**: Therapy and Antiinflammatory Prophylaxis of **Acute Gouty Arthritis**

*Arthritis Care & Research October 2012*
Comorbidity Checklist for Patients With Gout

- Obesity, dietary factors
- Excessive alcohol intake
- History of urolithiasis
- Chronic kidney disease (CKD)
- Potential genetic or acquired causes of uric acid overproduction (inborn error of purine metabolism, psoriasis, myeloproliferative or lymphoproliferative disease)
- Lead intoxication
Hyperuricemia

- Patient education/diet and lifestyle
- Consider secondary causes
- Eliminate non-essential medications that induce hyperuricemia
- Evaluate gout disease burden (palpable tophi, frequency/severity of attacks)
Drug-induced hyperuricemia

• Amiloride
• Bumetanide
• Chlorthalidone
• Cisplatin
• Cyclophosphamide
• Cyclosporin
• Ethambutol
• Furosemide
• Hydrochlorothiazide

• Isotretinoin
• Ketoconazole
• Levodopa
• Metolazone
• Pyrazinamide
• Salicylate (low dose)
• Theophylline
• Thiazide diuretics
• Vincristine

****Plus any renal toxic drugs****
Hyperuricemia

- Indication for drug treatment
  - Tophus by clinical exam or imaging study
  - Acute gouty arthritis ≥2/year
  - CDK stage 2 or worse if prior gout attack
  - Past urolithiasis
Hyperuricemia

• Treat to serum urate target
  – Minimum serum urate target is <6mg/dl
  – Serum urate lowering below 5mg/dl may be needed to improve gout signs and symptoms
  – First line agent: allopurinol or febuxostat
  – Alternate first line ULT: probenecid
Use of allopurinol in gout

- Starting dosage should be **no greater than 100 mg/day** for any patient, and start at 50mg/day in stage 4 or worse CKD
- Gradually titrate maintenance dose upward every 2–5 weeks in order to treat to chosen SUA target
- Dose can be raised above 300 mg daily, even with renal impairment, as long as it is accompanied by adequate patient education and monitoring for drug toxicity e.g. pruritis, rash, elevated hepatic transaminases
- Prior to initiation, consider HLA–B*5801 in selected patients, specifically in subpopulations at higher risk for severe allopurinol hypersensitivity reaction e.g., Koreans with stage 3 or worse CKD, and Han Chinese and Thai irrespective of renal function
HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol

- 51 patients with allopurinol-SCAR and 228 control individuals (135 allopurinol-tolerant subjects and 93 healthy subjects from the general population)
- HLA-B*5801 allele was present in all (100%) 51 patients with allopurinol-SCAR, but only in 20 (15%) of 135 tolerant patients [odds ratio 580.3 (95% confidence interval, 34.4-9780.9); corrected P value = 4.7 x 10(-24)] and in 19 (20%) of 93 of healthy subjects [393.51 (23.23-6665.26); corrected P value = 8.1 x 10(-18)]

Refractory gout

- Attempt upward dose titration of 1 XOI to respective maximum appropriate dose
- Febuxostat can be substituted for allopurinol or vice versa
- Effective therapeutic options include addition of a uricosuric agent (e.g., probenecid, fenofibrate, or losartan)
- Pegloticase is appropriate for patients with severe gout disease burden and refractoriness to, or intolerance of, conventional and appropriately dosed ULT
- LACK OF CONSENSUS: appropriate duration of pegloticase therapy relative to intended and achieved decrease in symptoms and signs of gout, including decrease in tophus size
Acute Gout

- An acute gouty arthritis attack should be treated with within 24 hours of onset.
- Established pharmacologic urate-lowering therapy should be continued during an acute attack of gout.
- NSAIDs, corticosteroids, or oral colchicine are appropriate first-line options, and combinations can be employed for severe or refractory attacks.
- Pharmacologic antiinflammatory prophylaxis is recommended for all gout patients when pharmacologic urate lowering is initiated, and should be continued if there is any clinical evidence of continuing gout disease activity and/or the serum urate target has not yet been achieved.
Acute Gout

- Oral colchicine is an appropriate first-line gout attack prophylaxis therapy, including with appropriate dose adjustment in chronic kidney disease and for drug interactions, unless there is a lack of tolerance or medical contraindication.

- Low-dose NSAID therapy is an appropriate choice for first-line gout attack prophylaxis, unless there is a lack of tolerance or medical contraindication.
Acute Gout

- **NSAIDs**
  - Full dose antiinflammatory doses
  - FDA approved: naproxen, indomethacin, sulindac
  - Celecoxib (800 mg once, followed by 400 mg on day 1, then 400 mg twice daily for a week) an option for patients with GI contraindications
Acute Gout

- **Colchicine**
  - Only where onset was no greater than 36 hrs
  - **Loading dose of 1.2 mg followed by 0.6 mg 1 hour later**
  - Can then be followed by gout attack prophylaxis dosing 0.6 mg once or twice daily (unless dose adjustment is required) 12 hours later, until the gout attack resolves
  - EULAR recommendations 0.5 mg 3 times daily
  - BSR recommended maximum dosage of 2 mg per day
  - Dosing reduction in severe CKD
  - Drug interaction e.g. clarithromycin, erythromycin, cyclosporine, and disulfiram
  - IV colchicine no long available
Acute Gout

- **Systemic and intraarticular corticosteroids and ACTH**
  - First consider the number of joints with active disease
  - 1-2 joints: oral corticosteroid, with option of IA steroid for large joints. Combination with oral steroid, NSAIDs or colchicine possible
  - Multiple joints: oral methylprednisolone dose pack
  - Alternate regimen: intramuscular single-dose (60 mg) triamcinolone acetonide, followed by oral prednisone or prednisolone
  - Role of ACTH unclear
Acute Gout

• **Initial combination therapy for acute gout**
  – Severe attack (pain ≥7/10), acute polyarthritis or more than 1 large joint
  – Appropriate to initially simultaneous use of full doses (or a full dose of 1 agent and prophylaxis dosing of the other) of 2 of the pharmacologic modalities e.g. colchicine and NSAIDs, oral corticosteroids and colchicine, or intraarticular steroids with any of the other modalities
Acute Gout

• Inadequate response
  – Either <20% improvement in pain score within 24 hours or <50% improvement in pain score >24 hours after initiating therapy
  – Consider alternate diagnosis
  – Switch to another monotherapy or adding a second agent
  – Option: IL-1 inhibitor (anakinra 100 mg subcutaneously daily for 3 consecutive days, or canakinumab 150 mg subcutaneously)
Acute Gout

- **Nothing by mouth (NPO) patient**
  - IA injection of corticosteroids for involvement of 1 or 2 joints
  - IV or IM methylprednisolone at an initial dose at 0.5–2.0 mg/kg
  - Subcutaneous synthetic ACTH at an initial dose of 25–40 IU
  - No consensus on the use of IM ketorolac or IM triamcinolone acetonide
  - IL-1 inhibition therapy has not been evaluated in this population
Acute Gout

- Critical drug therapy adverse event considerations
  - Moderate and severe CKD (NSAIDs, COX-2 inhibitors, colchicine)
  - Congestive heart failure (NSAIDs, COX-2 inhibitors)
  - Peptic ulcer disease (NSAIDs, COX-2 inhibitors, corticosteroids)
  - Anticoagulation or antiplatelet aggregation therapy (NSAIDs)
  - Diabetes mellitus (corticosteroids)
  - Ongoing infection or high risk of infection (corticosteroids)
  - Hepatic disease (NSAIDs, COX-2 inhibitors, colchicine)
Acute Gout

• Complementary therapies for acute gout attack
  – Appropriate: topical ice
  – Inappropriate: cherry juice or extract, salicylate-rich willow bark extract, ginger, flaxseed, charcoal, strawberries, black currant, burdock, sour cream, olive oil, horsetail, pears, or celery root
Acute Gout

• Gout attack prophylaxis
  – **First-line**: colchicine 0.6mg once or twice a day, with dosing further adjusted downward for moderate to severe renal function impairment and potential drug–drug interactions. Colchicine dose should be decreased by 50% below a creatinine clearance of 50 ml/minute
  – **First-line (lower evidence)**: low dose NSAIDs (e.g. naproxen 250mg BID), with PPI in PUD
  – **Alternate (low evidence)**: low-dosage prednisone or prednisolone (≤10 mg/day)
  – Continue if evidence of disease activity, new tophi, recent acute attack, serum urate target not achieved
  – Continue the prophylaxis for:
    • 3 months after achieving the target serum urate level for the patient without tophi detected on physical examination
    • 6 months after achieving the target serum urate level, where there has been resolution of tophi previously detected on physical examination