Gout in the Elderly: Updates on an Ancient Disease

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Objectives

- Discuss the impact of gout in the primary care of the elderly.
- Explore issues regarding the diagnostic approach and treatment of gout.
- Evaluate new gout therapies being examined in phase III trials.
Gout: Sydenham’s Description

“...the victim goes to bed and sleeps in good health. About 2 o’clock in the morning he is awakened by a severe pain in the great toe...this pain is like that of a dislocation, and yet the parts feel as if cold water were poured over them...it is a violent stretching and tearing of the ligaments... the night is passed in torture...”
The Vet’s Description

“I’ve been shot, beat up, stabbed and thrown out of a helicopter, but none of that compared to the gout.”

- Birmingham, AL VA
  March, 2001
Serum Urate, Hyperuricemia, and Gout

- **Serum urate (uric acid):** formed in process of purine metabolism / degradation
- **Hyperuricemia:** serum urate values in excess of 6.8 mg/dl
- **Gout:** inflammatory arthritis developing as a consequence of urate deposition in the joint
Acute Gout

ACR Clinical Slide Collection on the Rheumatic Diseases, 1998.
Gout
One Chronic Disease, Best Described by 4 Stages

Asymptomatic Hyperuricemia
Elevated serum urate with no clinical manifestations of gout

Acute Flares
Acute inflammation in the joint caused by urate crystallization

Intercritical Segments
The intervals between acute flares

Advanced Gout
Long-term gouty complications of uncontrolled hyperuricemia

Uncontrolled Hyperuricemia
Severe Joint Involvement From Gout

Photo courtesy of N. Lawrence Edwards, MD, University of Florida.
Advanced Gout: Clinically Apparent Tophi

1. Photos courtesy of Brian Mandell, MD, PhD, Cleveland Clinic.
2. Photo courtesy of N. Lawrence Edwards, MD, University of Florida.
Epidemiology: Incidence of Gout in U.S.

- Annual Incidence
  - 8 per 10,000 person-years in Framingham\(^1\)
  - 28 per 10,000 for male veterans\(^2\)

- Cumulative Incidence
  - 8.6% cumulative incidence in US white male doctors\(^3\)

- Increasing incidence?
  - Age and sex-adjusted incidence of gout in 3 decades increased 1.5-fold using ACR gout criteria in Rochester\(^4\)
  - Two-fold increase in *primary* gout

Prevalence of Gout

• Most common inflammatory joint disease in **men >40 years**

• Prevalence varies by study population
  
  – US National Health Interview Survey of 1996 on self-reported prevalence
    
    ♦ Prevalence estimated at 1.56 million men and 550,000 women\(^1\)
    
    ♦ 4.6% in men, 2% in women in highest risk group\(^2\)
    
    ♦ Increased from 0.5% of cases in 1969 to 1% of cases in 1996

Why is gout on the rise?

- Increased longevity
- Aging population
- Increased comorbidity
  - HTN, obesity, renal failure, transplants
  - Metabolic syndrome
- Low-dose ASA
- Thiazides
- CSA and others

- Fructose intake
- Decreased HRT (WHI results)
- Other
**Figure 1** Fructose-induced production of uric acid in the hepatocyte

Multivariate relative risk of incident gout in 46 393 men from health professionals follow-up study, according to fifths of free fructose intake in subgroups. Reference group for comparisons was men in lowest fifth of fructose intake and (top) with body mass index

RR = 1.85 (95% CI 1.08-3.16)

*For consumption of >= 2 soft drinks per day
Gout Prevalence, GPRD 1999

<table>
<thead>
<tr>
<th>Age group</th>
<th>Men</th>
<th>Women</th>
<th>Men and Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 55 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55-64 years</td>
<td>10</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>65-74 years</td>
<td>20</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>75-84 years</td>
<td>30</td>
<td>20</td>
<td>50</td>
</tr>
<tr>
<td>&gt; 85 years</td>
<td>40</td>
<td>30</td>
<td>70</td>
</tr>
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Hippocrates’ Aphorisms

- Eunuchs do not take the gout
- Woman does not take the gout unless her menses has ceased
- A young man does not become susceptible to gout until the time of indulging in copulation

460-357 B.C.
“…like sugar candy on a string…”
- Sir Alfred Barring Garrod

Fig. 10. Garrod's thread test.
Purine Degradation to Uric Acid

- **Xanthine oxidase** catalyzes the final conversions to uric acid

![Diagram showing the Purine Degradation process](image-url)
Distribution of Serum Urate Values

Urate crystallizes at a level of 6.8 mg/dL

Females (3011)
Males (2983)

Risk Factors for the Development of Gout: Serum uric acid (SUA)

Risk Factors for the Development of Gout: Sex and Age

• Men
  – Have higher serum urate levels
  – In younger patients, gout overwhelmingly in men (~9:1 in subjects under 40 yrs)

• 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

## Risk Factors for the Development of Gout: Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</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>
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</table>

Caspi D et al *Arth Rheum.* 2000;43:103
Risk Factors for the Development of Gout: Transplant Patients

• 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

• Common occurrences attributed to cyclosporine use

Purine-Rich Food Group and Gout: Health Professional Follow-up Study

Total Meat

Seafood

Purine-rich Vegetables

Multivariate Relative Risk

Q1 Q3 Q5
(0.6) (1.3) (2.3)

Q1 Q3 Q5
(0.1) (0.3) (0.7)

Q1 Q3 Q5
(0.2) (0.6) (1.4)

P for trend = 0.016

P for trend = 0.016

P for trend = 0.779

Choi H et al. NEJM 2004;350:1093
Dairy Intake and Gout - HPFS

Choi H et al *NEJM* 2004;350:1093
Alcoholic Beverages and Gout - HPFS

P for trend < 0.001  
P for trend = 0.01  
P for trend = 0.68

Multivariate Relative Risk

<table>
<thead>
<tr>
<th>Alcohol Types (serving/time)</th>
<th>&lt; 1/m</th>
<th>5-7/w</th>
<th>&gt;1/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liquor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wine</td>
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Risk Factors for the Development of Gout: Lead Intoxication (Clinical or Sub-clinical Plumbism)
Gout-Related Comorbidity: Nephrolithiasis (Uric Acid Stones)

- Develop in the presence of a low urinary pH hyperuricosuria
  - Decreased NH₄ excretion is a risk factor
  - Concentration of uric acid exceeds solubility, and insoluble precipitate produced

Comorbidities Associated With Hyperuricemia That Warrant Consideration

- Obesity\(^1,2\)
- Metabolic syndrome\(^3\)
- Diabetes mellitus\(^4\)
- Heart failure\(^5\)
- Hyperlipidemia\(^1\)
- Hypertension\(^6,7\)

Hyperuricemia induces glomerular hypertension and endothelial dysfunction in rats


A = Normal rats, C = OA, E = OA + allopurinol
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 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

MSU crystal

CPPD crystal
Urate crystallizes at a level of 6.8 mg/dL.

Pitfalls in Gout Diagnosis

• Can be polyarticular and chronic, especially in the elderly (20% polyarticular)
• Systemic symptoms can be observed
• Urate levels can be normal, especially during the acute flare
• A ‘normal value’ may not be normal
• Other diseases may also respond to colchicine
• Women get gout
• Atypical joint involvement occurs – e.g. Heberden’s nodes
Gout Treatment

Setons and Issues
Goals of Gout Therapy

1. Terminate the acute attack

2. Prevent recurrence while lowering serum urate

3. Prevent or reverse complications from the deposition of monosodium urate or uric acid crystals (kidney disease, joint destruction)

4. Address comorbidity

5. Do NO Harm (Gout’s generally not lethal until the doctor gets involved)
I. Termination of the Acute Flare = The Gout ‘Danger Zone’ for Elderly

- 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
  - Medication options
    - NSAIDs, colchicine, steroids/ACTH
    - Experimental: IL-1B inhibition

- The critical issues are
  - Rapid initiation of therapy
  - Appropriate duration of therapy
Termination of the Acute Flare: Considerations for Agent Selection

<table>
<thead>
<tr>
<th>Agent</th>
<th>Considerations</th>
</tr>
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<tbody>
<tr>
<td><strong>NSAIDs</strong></td>
<td>• Contraindicated in peptic ulcer disease, GI bleeds, history of aspirin or NSAID-induced asthma, renal dysfunction</td>
</tr>
<tr>
<td></td>
<td>• Interaction with warfarin (consider COX-2)</td>
</tr>
<tr>
<td><strong>Colchicine</strong></td>
<td>• Contraindicated in dialysis patients</td>
</tr>
<tr>
<td></td>
<td>• Use with caution with renal or hepatobiliary dysfunction, active infection, &gt;70 years of age</td>
</tr>
<tr>
<td></td>
<td>• Drug interactions with cyclosporine, statins, <strong>macrolides</strong></td>
</tr>
<tr>
<td></td>
<td>• Can cause local tissue necrosis</td>
</tr>
<tr>
<td></td>
<td>• <strong>Use of IV formulation controversial and should be used with extreme caution</strong></td>
</tr>
<tr>
<td><strong>Corticosteroids</strong> and <strong>ACTH</strong></td>
<td>• Worsening of glycemic control in diabetics</td>
</tr>
<tr>
<td></td>
<td>• May need to add other anti-inflammatories or use moderate-to-high doses</td>
</tr>
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</table>
Prophylaxis Against Flares

• **Purpose**
  - To maintain the intercritical segments of gout
  - Agents useful for decreasing the frequency and severity of acute flares *will not stop the destructive aspects of gout*

• **Prophylactic options**
  - Low-dose, oral colchicine (0.6 mg daily to b.i.d.)
  - NSAIDs (i.e. naprosyn in low dose, 375mg b.i.d)

• **Initiate agents prior to starting urate-lowering therapy**
  - Duration? Likely 6 months or longer!!
Treating Hyperuricemia and Preventing Disease Progression

• Goals
  – Lower urate <6 mg/dL to allow depletion of serum urate pool and deposited crystals (often lower than upper normal lab values)
  – 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 (Allopurinol)
Uricosuric Agents

• Uricosuric agents
  – Probenecid
  – Sulfinpyrazone (ex-US)
  – Benzbromarone (ex-US)
  – Losartan (mild uricosuric)
  – Fenofibrate (mild uricosuric)

• Advantage
  – Uricosurics reverse the most common physiologic abnormality in gout
Uricosuric Agents

- Limitations
  - Efficacy dependent on renal function
    - Ineffective if CrCL <50 mL/min
  - BID to TID dosing
  - Risk of uric acid crystallization in the urine and formation of stones
  - Precipitation of an acute flare
  - Drug-drug interactions

<table>
<thead>
<tr>
<th>Drugs potentially affected by probenecid therapy</th>
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</thead>
<tbody>
<tr>
<td>Ampicillin</td>
</tr>
<tr>
<td>Penicillin</td>
</tr>
<tr>
<td>Nafcillin</td>
</tr>
<tr>
<td>Cephradine</td>
</tr>
<tr>
<td>Cephalaridine</td>
</tr>
</tbody>
</table>

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.
Advantages of Allopurinol

• Effective for both overproducers and underexcretors

• Convenience of single daily dose
  – vs. Probenecid (b.i.d. to t.i.d. dosing)

• Can be efficacious in patients with renal insufficiency
Limitations of Allopurinol

• “Standard” doses may not achieve target serum urate
  – In one study, only 53% of allopurinol (300 mg qd) patients achieved target serum urate <6 mg/dL
    ♦ Higher doses were effective
• Need for dose adjustment according to renal function
  – Metabolites excreted by kidney
• Precipitation of an acute attack
  – Lowering serum urate mobilizes deposited crystals

Limitations of Allopurinol

• Potential for drug interactions

**Drugs potentially affected by allopurinol therapy**

<table>
<thead>
<tr>
<th>Ampicillin/amoxicillin</th>
<th>6-mercaptopurine*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine*</td>
<td>Probenecid</td>
</tr>
<tr>
<td>Chlorpropamide</td>
<td>Vidarabine</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Warfarin</td>
</tr>
<tr>
<td>Dilantin</td>
<td>ACE inhibitors (suspected)</td>
</tr>
</tbody>
</table>

*Requires careful dose reduction (combination can be hazardous)

1. Thiazide diuretics interfere with the excretion of allopurinol and may enhance toxicity²

Limitations of Allopurinol

- **Adverse effects**
  - Rash
  - GI intolerance (diarrhea, nausea)
  - Increase in transaminases
  - Bone marrow suppression (uncommon)
  - **Severe hypersensitivity syndrome**
    - Occurs early in treatment
    - Infrequent, but life threatening (20% mortality)
    - Multi-symptom involvement – fever, rash, decreased renal function, vasculitis, hepatocellular injury, leukocytosis, and eosinophilia
    - Immediate drug withdrawal and supportive therapy
Addressing Comorbidity

• Treat HTN (role of ARB?), hyperlipidemia
• Weight reduction
• Decrease alcohol consumption (wine??)
• Vitamin C (uricosuric effect)
• Avoid excessive intake of purine-rich foods?
  – Anchovies, herring, sardines, mussels, clams, organ meats, beer
  – Will only reduce urate levels by 1 mg/dL
New Gout Therapies in the Last 40 years
New Gout Therapies in the Last 40 years

- Febuxostat (Uloric)

- A non-purine, xanthine oxidase inhibitor

- Current data support
  - Potent inhibition with significant urate reduction
  - Ability to administer in renal insufficiency with no dosage adjustments\(^1\)
    - Mainly metabolized by oxidation and glucuronidation in the liver\(^2\)
  - Appears to be safe and tolerable agent
Fubuxostat (Uloric) in Gout

• Adverse Effects
  – Gout flares
  – LFTs
  – CVD events

• Primary outcome = SUA < 6.0, last 3 mos.
• Dose = 40mg to 80mg once daily
Future Treatment of Hyperuricemia: Uricase Enzymes

• Uricase enzymes further catabolize uric acid to a more soluble, readily excretable form
• Agents available:
  – Rasburicase
  – PEG-uricase (pegloticase), phase II/III trials
    • PEG reduces antigenicity and prolongs half-life


Diagnostic Pitfalls

72 year-old man with ‘refractory rheumatoid arthritis’

Labs: RF / anti-CCP antibody negative
Uric Acid 7.3 (normal 3.8 to 8.3)
Creatinine 1.7 mg/dl
Treatment for this patient?

- Acute flare?
- Prophylaxis?
- Urate lowering therapy?
A 78 year-old woman unable to work with physical therapy – post-op Day 3 following total joint replacement
A 63 year-old man with recurrent ‘paronychia’ requiring multiple rounds of antibiotic therapy
A 63 year-old man with recurrent ‘paronychia’ requiring multiple rounds of antibiotic therapy
“The best medicine I know for rheumatism is to thank the Lord it isn’t the gout”

- Josh Billings