Clinical Overview of Gout

John J. Cush, MD
Baylor Research Institute, Dallas, TX
Gout

- 1st described 5th century BC – Hippocrates described gout as “the king of diseases and the disease of kings”
- Disorder of urate metabolism, with resultant hyperuriciemia and deposition of monosodium urate (MSU) crystals in joints and soft tissues.
Societal Burden

- Prevalence in US and UK ~1%, Dutch 3%
  - Men >> Women
- National Arthritis Data WorkGroup estimates
  - 3.1 million have self reported gout in last yr (6.1 million Ever)
- In 1981, 37 million lost work days in US*
- 2003 Kim et al estimates the annual cost of Acute Gout is $27,378,494 in the USA
  - Probable underestimate as women excluded & not all indirect and intangible costs included

Piscavet HSJ, Ann Rheum Dis 2003; 62: 644
Lawrence RC Arthritis Rheum. 2008 58:26
Roubenoff et al, JAMA 1981
Gout Epidemiology-

● Men: Peak onset is 40-50 yrs
  ▶ most common inflammatory arthritis in men

● Women: peak onset is post-menopausal
  ▶ Less than have 15% onset prior to menopause

● Prevalence influenced by hormonal, geographic, racial, genetic, dietary, background conditions:
  ▶ Males > Females. Estrogen is uricosuric
  ▶ Populations: Maori, Tokelauan migrants, Filipinos, Taiwan males, etc (genetics or dietary)
  ▶ Renal transplant (2-13%); HTN (↑RR ≥2.7)
  ▶ Seasonal: Gout more often in spring (possibly summer)
## Frequency of Gout Increasing?

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; Era Incidence rate</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; Era Incidence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHIS</td>
<td>Self-report (prevalence)</td>
<td>1969</td>
<td>1996</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5/1000</td>
<td>9.4/1000</td>
</tr>
<tr>
<td>Arromdee</td>
<td>Rochester MN</td>
<td>1977-78</td>
<td>1995-96</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45/100,000</td>
<td>62.3/100,000</td>
</tr>
<tr>
<td>Wallace Wortmann</td>
<td>USA Managed Care</td>
<td>1990</td>
<td>1999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.9/1000</td>
<td>5.2/1000</td>
</tr>
</tbody>
</table>

Increasing Prevalence of Gout

- Increased longevity
- Increased prevalence of Hypertension
- Increased use diuretics and low dose ASA
- Dietary trends
- Alcohol consumption
- Obesity epidemic
- Increased prevalence of Metabolic syndrome
- Increased organ transplantation, CsA use
- Increased survival in CAD and CHF

Terkeltaub R. Medscape 2005
## Prevalence of Gout

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Men 3.4 Million Population %</th>
<th>Women 1.7 Mill Population %</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>0.2</td>
<td>0.6</td>
</tr>
<tr>
<td>30-39</td>
<td>2.1</td>
<td>0.1</td>
</tr>
<tr>
<td>40-49</td>
<td>2.2</td>
<td>0.6</td>
</tr>
<tr>
<td>50-59</td>
<td>5.7</td>
<td>2.3</td>
</tr>
<tr>
<td>60-69</td>
<td>9.1</td>
<td>3.5</td>
</tr>
<tr>
<td>70-79</td>
<td>10.8</td>
<td>4.7</td>
</tr>
<tr>
<td>≥80</td>
<td>8.6</td>
<td>5.6</td>
</tr>
</tbody>
</table>

NHANES III 1988-94
Gout

**Associations:**
- Hypertension
- Obesity
- Diabetes
- Renal insufficiency
- Diuretics & CHF
- Alcohol consumption
- Lead exposure
- Family history
- Sweetened Soft drinks
- Males

**Precipitants:**
- Alcohol (beer, not wine)
- Hospitalization (fever, Poly)
- Surgery: joint replacement, carpal tunnel release
- Drugs: Diuretics, ASA, IV NTG, PZA, GCSF, CyA
- Total parenteral nutrition
- Septic arthritis, reactive arthritis, lupus, elderly
Serum Uric Acid & Incidence of Gout*

<table>
<thead>
<tr>
<th>Serum Urate mg/dl</th>
<th>Gout attack/yr/1000</th>
<th>5 year cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 7.0</td>
<td>0.8</td>
<td>5</td>
</tr>
<tr>
<td>7.0 – 7.9</td>
<td>0.9</td>
<td>6</td>
</tr>
<tr>
<td>8.0 – 8.9</td>
<td>4.1</td>
<td>9.8</td>
</tr>
<tr>
<td>&gt; 9.0</td>
<td>49 (4.9%)</td>
<td>220 (22%)</td>
</tr>
</tbody>
</table>


Hyperuricemia Associations

- Obesity
- Metabolic syndrome
- Diabetes mellitus
- Heart failure
- Hypertension
- Hyperlipidemia
- Renal Disease
  - CRI
  - ESRD

↑ Urate

Over Producer

Under Excreter

Hyper Uricemia

Asymptomatic

Gout ± Tophi

Nephrolithiasis Renal

Metabolic CVE HTN
Gout and Metabolic Syndrome

- ↑↑ Frequency of gout & metabolic syndrome
  - Common = Obesity epidemic
- BMI>35 assoc > 3-7X risk Gout
- Gout→60% ↑risk of CVD(men)
- No known assoc w/ insulin resistance & dyslipidemia
- ?Hyperuricemia: an independant risk factor for CVD? HTN? Renal Dz?
  - Causal or circumstantial relationships?

Diet and Gout

Survey of 47150 males over 12 yrs. (no prior hx Gout). Identified 730 new cases of gout

- Comparing highest /lowest quintiles:  
  - Meat intake  
    RR 1.41 (1.07-1.86)  
  - Seafood intake  
    RR 1.51 (1.17 – 1.95)  
  - Dairy products  
    0.56 (0.42-0.74)  
  - Not associated: Purine Vegetables & protein intake

Choy HK. NEJM 350:1093, 2004
Choy on Gout

- Alcohol
  - Dose related Risk of gout (>50g/d, RR=2.53).
    - Increased with Beer (1.49/12oz); Wine 1.04/4 oz ser
- Obesity: women's health study
  - BMI 30-34 → RR 4.69
  - BMI >35 → RR 7.25
  - HTN and diuretic use increased RR 4.1-4.8
- Sweetened (Fructose) Soft Drinks
  - > 2 Servings/day RR 1.85 (diet drinks not assoc.)

INFLAMMATORY MEDIATORS PRODUCED IN RESPONSE TO URATE CRYSTALS

IgG coating

Urate crystals

Apo-E coating

Stimulates

Responding cell
Neutrophil leukocyte, monocyte, fibroblast, synoviocyte, renal cell

Chemotactic factors
Lysosomal enzymes
PGE$_2$
LTB$_4$
IL-1
IL-6
Oxygen radicals
Collagenase

Inhibits
Phases of Gout

- **Asymptomatic hyperuricemia**: elevated uric acid without evidence of gout, nephrolithiasis.
  - higher levels increase risk
- **Acute**: intermittent/recurrent, LE, ascending, inflammatory mono/oligoarthritis, “Podagra”
- **Intercritical gout**: intervals between attacks
  - Tissue deposition continues
- **Tophaceous gout**: chronic, large volume accumulation of MSU crystals (tophi) tissues
- **Renal**: nephrolithiasis, gouty nephropathy, uric acid nephropathy
Acute (Classic) Gout

- Acute, severe pain, warmth, inflammation, Limited motion ➔ cant walk, cant put sheet on it.
- Podagra (50-90%): pain/swell warmth in 1st MTP
  - Other Joints: MTP, tarsus, ankle, knee
- Initially lower extremity monarthritis (80-90%)
- w/ repeated attacks ➔ arthropathy ascends
  - (initially a polyarthritis in elderly, women, myelo-proliferative disorders, Cyclosporine)
- Associated with fever, leukocytosis, high ESR or C-reactive protein levels.
- Chronology: untreated attacks last 7-14 days. Acute gout risk of repeat attack estimated to be 78% w/in 2 yrs
Natural Hx of Acute Attack

- 11 volunteers with acute podagra studied x 7d
  - 2 withdrew on day 4 for severe pain
  - 9 remaining showed improvement
    - Pain improved by day 5
    - Swelling improved by day 7
    - Tenderness improved in 7/9 by day 7 (2 persisted)
    - But only 3 noted resolution of pain during 7d study

- Implications for clinical trial endpoints?
  - Pain improvement/resolution by day 7
  - Resolution of symptoms, return to normal activity
Gouty Tophi

- Incidence has decreased over last few decades
- Seen in 25-50% of untreated patients (after 10-20yrs)
- Location: Olecranon, bursae, digits, helix of ear
- Damages bone, periarticular structures and soft tissues
- Palpable measure of total body urate load
Gout: Diagnostics

- Crystal identification is diagnostic
- Laboratory Findings
  - 40-49% will have normal uric acid levels
  - Common: Leukocytosis; ESR and CRP elevated
  - Usual indices of inflammation absent (↓ alb, Hgb)
- Radiographic findings
  - Soft tissue swelling
    - (Opacities = tophi)
  - Normal Joint space
  - Erosions: nonarticular, punched out, Sclerotic margins, overhanging edge

Uric Acid

- Random hyperuricemia ≠ gout (likely CRI, diuretic use)
- Acute attack: Urate levels may be normal, low or high
- 40-49% of acute gouty attacks are \textit{normouricemic}
  - Mechanism: increased excretion of uric acid
    - Increased Urate excretion mediated by IL-6, inflammation

- Negative association between Gout – RA
  - Few reports of both coexisting in literature
  - RF preferentially binds MSU coated with IgG and inhibited neutrophil chemiluminescence (RF may block interaction of crystal bound IgG and Fc recpt)
1977 ARA Criteria for Diagnosis of Gout

- Urate crystals*: Intraarticular or Tophus
  - Plus any 6 of following:
    - > 1 attack acute arthritis;
    - Maximal inflammation w/in 1day;
    - Erythema over joint;
    - Podagra;
    - Hx of podagra;
    - Unilateral tarsal involvement;
    - Tophus;
    - Hyperuricemia;
    - Asymmetric swelling on exam/ xray;
    - Subcortical cyst w/o erosion;
    - Joint fluid culture negative during attack

* Wallace et al 1977 (sensitivity 84.4%, specificity 100%)
Practical Diagnosis of Gout

Acute/recurrent inflammatory mono-/oligoarthritis

- With evidence of MSU crystal identification

OR

- One of the following:
  - History of prior intermittent like attacks
  - Evidence of hyperuricemia
  - X-ray evidence of antecedent gouty damage
Goals of Treatment

- Rapidly terminate the acute flare
- Protect against further flares
  - Reduce the chance of crystal-induced inflammation
- Treat the hyperuricemia to prevent disease progression
  - Serum urate < 6.0 to prevent attacks
Treatment Acute Gout

NSAIDs Contraindicated?
- Renal insufficiency
- Peptic ulcer disease
- Congestive heart failure
- NSAID intolerance

Are Corticosteroids Contraindicated?

NSAIDs Antiinflammatory doses

Corticosteroids

Oral or Intraarticular Steroid

Oral Colchicine

Intraarticular PO Steroid

# Joints Involved?
1

Treatment of Interval Gout

Number of Gouty Attacks per Year

<2

Can pt. Stop Alcohol, Diuretics, Lose Weight?

no

Hx of nephrolithiasis?

yes

Tophi present?

Serum urate > 11?

yes

Serum Creat > 2.0?

yes

Uric acid > 650mg/24h?

no

Allopurinol Therapy (colchicine during Initiation)

Observe Educate Rx Acute Attack

Gout – Sad and Sorry Truths

- Totally Treatable and Preventable
- Largely Dx & managed by PCPs and ER Physicians
  - Cant/wont do arthocentesis
- Very few managed by Rheumatologists
  - only those with severe, recalcitrant, chronic disease
  - Rheum referral more accurate dx, shorter Sx duration (3.1 day), shorter hospitalization (7.4 days), lower hospitalization costs ($5995 less)*
  - Krishnan showed 2/3 visits to PCP and 1.3% to Rheumatology
- Many MDs equate hyperuricemia = gout
- Most believe that colchicine is the drug of choice**
- Significant amount of inappropriate management

Survey of 484 US Rheumatologists

Most disappointing in the care of gout pts?

- Lack New Rx
- Noncompliance
- Rx by nonRheums
- Rx Toph.Gout

Survey completed 5/13/08
Gout: management

- **Acute Rx**: NSAIDs > steroids > colchicine (oral only)
- **Steroids**: PO, IM, intraarticular
- > 2-3 attacks/year → **Chronic Rx**: Urate lowering Rx
- **Chronic Rx**: allopurinol, probenecid, colchicine
- **Probenecid**: uricosuric, promotes excretion
  - Don’t use with CRI, nephrolithiasis or Tophaceous gout
- **Colchicine**: (diarrhea) decr. PMN motility
- **Allopurinol**: decrease formation - use w/ CRF, renal stones, Tophaceous gout, Uric acid > 11

* Adjust dose for renal insufficiency
Return to Main