Disclosures

• Speaker for Abbvie
• Advisory board for Crescendo Bioscience
Objectives

• History of gout
• Discuss clinical features of gout
• Review 2012 ACR guidelines of management
The King of Diseases
It’s a long story

• We have about 250 slides
• Plan to be done in time for breakfast tomorrow morning
It’s a long story

• Between 16 and 11 million years ago
  – Middle Miocene epoch
  – Dogs, bears, horses
• Columbia River basalt plateau forming
• Disappearance of uricase in hominids
  – Humans and some other primates lack all uricase genetic function
  – Gorillas and chimpanzees also affected

Antiquity

- Uric acid deposited in joints of Egyptian mummies dating back 4,000 years
- Hippocrates considered to be first person to describe it
- He believed that, “the best natural relief of this disease is an attack of dysentery.”
  - Use of Colchicum autumnitae (meadow saffron)
  - Originated on kingdom of Culchis on the Black Sea
Fall of the Roman Empire?

• Why was gout rampant?
• Average intake 1-5 L wine/day
• Lead present in cooking utensils
  – Grape juice boiled down to enhance color
• Lead inhibits tubular secretion of uric acid and impairs the enzyme guanine aminihydrolase resulting in guanine accumulation
• Recreated recipes produce 240-1,000 mg per liter
  – Several thousand times greater than consumption today
  – Skeletal remains support saturnine gout
History repeats itself

• Late 1600s British Parliament banned French wine
• Spanish and Portuguese wines favored
  – High in lead
• Gout rare in other N. European countries
• American satirist Ambrose Bierce in England in the 1870s noted, “gout was a physician’s name for the rheumatism of a rich patient.”
Advantage to losing uricase?

• Uric acid is a powerful antioxidant
• Yet hyperuricemia associated with
  – Worsening renal function
  – Heart disease
  – Metabolic syndrome
• Intelligence theory discredited
• Potential neuroprotective effect
  – Very low incidence of Parkinson’s, Alzheimer’s, ALS
• High uric acid can raise BP in low salt diet
  – A potential problem for frugivores
Clinical features

• Hyperuricemia
  – Values above 6.8 are supersaturated at 37° C
• Increases above 7 carry increased risk for gouty arthritis and renal stones
• Hyperuricemia is common
  – Directly associated with serum creatinine, BMI, age, sex, blood pressure, alcohol intake
  – May be the link between OSA and CVD
• Prevalence of gout ranges from 1-15%
  – Clear increase recently related to western diet and obesity epidemic

The Incidence of Gout Appears to Be Increasing

>2-fold increase in the rate of primary gout over 2 time periods assessed

Incidence rates x 100,000

Environmental Factors

• Alcohol consumption and diet
  – Beer, purine rich, associated with gout
  – Risk goes up from 12 g EtOH per day
  – Wine less risky, but still associated
  – Meat and seafood associated with gout

• Some foods may be protective
  – Oatmeal and purine rich vegetables NOT linked
  – Daily milk or every other day yogurt associated with lower uric acid levels
  – Cherries seem to reduce risk of gout activity
Incidence of Gout in US

• 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\(^3\)

Relationship between beer, liquor, wine, and serum urate in US

Differences adjusted for age; sex; total energy intake; BMI; use of diuretics, beta-blockers, allopurinol and uricosuric agents; hypertension and gout; serum creatinine level

Choi HK. *Arthritis Rheum (Arth Care Res)* 2004; 51: 1023
Alcohol beverages and gout

Alcohol intake and gout


**Alcohol Intake (g/d)**

- 0
- 0.1-4.9
- 5-9.9
- 10-14.9
- 15-29.9
- 30-49.9
- >50

**Multivariate Relative Risk**

- 0
- 1
- 2
- 3
- 4

P for trend < 0.001
Genetic factors

• Gout runs in families
  – 40% have family history of gout
  – Majority are underexcreters

• Rare forms of hyperuricemia are genetic (<1%)
  – Hypoxanthine phosphoribosyltransferase def
  – Phosphoribosyl-1-pyrophosphate synthetase
  – Familial hyperuricemia nephropathy
Fructose raises serum uric acid

- 1-4 mg/dL SUA rise after ingestion of large fructose-based meal
- High-fructose corn syrup ≥ 50% of all sweeteners
- 5 apples/day → 35% ↑ in serum uric acid

Classification

• Primary gout
  – 90% underexcretion
  – 10% overproduction
    • Cancer, psoriasis, sarcoidosis (thyroid, obesity)
  – Both – MI, CHF, sepsis

• Secondary gout
  – Reduced GFR
  – Diuretic therapy
  – Low dose aspirin
  – Ethanol
“The use of fermented liquors is the most powerful of all the predisposing causes of gout, nay so powerful that it may be a question whether gout would ever have been known to mankind had such beverages not be indulged in”

- Sir Aflred Garrod, 1876
Excretion

• GI excretion
  – 20% into the gut where microflora break it down

• Renal excretion
  – At ultrafiltration nearly 100% excreted
  – But up to 98% resorption in proximal tubule
    • URAT1 and OAT4
  – Followed by secretion step
From Crystal to Gout

- Not all hyperuricemia leads to gout
- Temperature related to crystal formation
- Trauma can precipitate gout attack
  - Like icebergs sloughing off surfaces
- Urate lowering drugs can start process
- Rare for a person to have gout without 1\textsuperscript{st} MTP involvement
Acute Gout Attack

• 1962 – established inflammatory nature of uric acid crystals
  – Complement activation via classical or alternative pathway
• Uric acid crystals can bind immunoglobulin
• Immune cells stimulated to recognize

JAMA180 (6):469-475
Inflammasome

- Monosodium urate crystals internalized by monocytes activate the NLRP3 inflammasome that leads to the processing and release of IL-1β

- IL-1β induces the expression of adhesion molecules and chemokines that are critical for the recruitment of PMNs into the site of acute inflammation
Resolution

- Attacks are self limited
- Macrophages clear uric acid crystals
- ACTH may be released
  - Stimulate glucocorticoid secretion
  - Melanocyte-stimulating hormone receptors
Chronic gout and tophi

- Reservoirs of uric acid
- Cartilage degradation
  - IL-1β, MMPs
- Articular erosions
  - IL-1β and TNF can stimulate RANK/RANK ligand
- Inhibits NO
  - Arterial vasoconstriction
  - Renin-angiotensin system stimulation
- Increased risk of renal failure, MI, insulin resistance, OA, ED
Clinical Features

• Three stages
  – Asymptomatic hyperuricemia (20 years)
  – Acute and intercritical gout (62% recur in 1st year)
  – Chronic gouty arthritis

• First gout attack
  – 40-60 years old for males
  – >60 years old for females

• Pattern
  – Typically monoarticular
  – Podagra
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<table>
<thead>
<tr>
<th>Differential Diagnosis</th>
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<tbody>
<tr>
<td><strong>Acute Gouty Arthritis</strong></td>
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<tr>
<td>Other crystals (CPPD, BCP)</td>
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<tr>
<td>Septic arthritis including gonorrhea</td>
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<tr>
<td>Trauma</td>
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<td>Cellulitis</td>
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<td>Lyme disease</td>
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<tr>
<td>Reactive arthritis</td>
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<td>Psoriatic arthritis</td>
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<td>Sarcoidosis</td>
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<td>Unusual presentation of other IA like RA</td>
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<tr>
<td><strong>Chronic Gouty Arthritis</strong></td>
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<tr>
<td>RA or other chronic IA</td>
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<tr>
<td>CPPD</td>
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<tr>
<td>(Inflammatory) osteoarthritis</td>
</tr>
<tr>
<td>Lyme disease</td>
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<tr>
<td>Indolent infections like mycobacterium</td>
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</tbody>
</table>
The presence of urate crystals in joint fluid or a tophus proved to contain urate crystals by chemical means or polarized light microscopy and at least 6/12 of these

1. More than 1 attack of acute arthritis
2. Maximal inflammation developed in 1 day
3. Attack of monoarticular arthritis
4. Joint redness observed
5. First MTP joint painful or swollen
6. Unilateral attack involving first MTP
7. Unilateral attack involving tarsal joint
8. Suspected tophus
9. Hyperuricemia
10. Asymmetric swelling within a joint
11. Subcortical cysts without erosions
12. Negative culture of joint fluid

Acute Gouty Arthritis

• NSAIDs - antiprostaglandin
  – Naproxen, indomethacin, sulindac FDA-approved
  – Monitor for high blood pressure, worsening heart disease, fluid retention, GI bleeding, elevated LFTs
  – Caution in CKD, elderly patients who are volume depleted and/or on concomitant diuretic therapy
  – Asthma patients can have fatal bronchospasm in aspirin-sensitive individuals
  – NSAIDs + ACE inhibitors may lead to deterioration in renal function
Acute Gouty Arthritis

• Colchicine - IL-1β
  – 0.6 mg Q1 hour until symptoms abate, N/V/D, 10 tabs
Acute Gouty Arthritis

- **Colchicine - IL-1β**
  - 0.6 mg Q1 hour until symptoms abate, N/V/D, 10 tabs
  - 1.2 mg followed by 0.6 mg one hour later only
  - First marketed in 1939, Colcrys in 2009
  - Metabolism excretion via P-gp and CYP 450
  - Most common adverse effects include blood dyscrasias, neuromuscular toxicity, rhabdomyolysis
  - Caution with prophylaxis in CKD

*Arthritis Rheum.* 62:1060, 2010
Acute Gouty Arthritis

• Corticosteroids
  – Intra-articular preferred if single joint or bursa
  – Oral/IM/IV in those intolerant of NSAIDs
  – High doses (20-60 mg per day) generally needed
  – Side effects include fluid retention, increased BP, mood swings, weight gain, cataracts, hyperglycemia, increased susceptibility to infections, and osteoporosis
  – Caution in recent MI due to risk of ventricular free wall rupture, active or latent peptic ulcers, diverticulitis, fresh intestinal anastomoses and ulcerative colitis controversial link to perforations
Acute Gouty Arthritis

• ACTH
  – Awesome
  – Contraindicated in patients with hypersensitivity to porcine proteins, systemic fungal infections, ocular herpes simplex, recent surgery, history of peptic ulcer
  – Cost and limited availability make it rarely used

• IL-1 inhibitors
  – Anakinra – off label, but it works
  – Most common reaction is injection pain (71%), but also neutropenia, increased infectious risk
  – Requires at least 3 month labs
  – Skin reactions COMMON
Urate Lowering Therapies

• When to start ULT open to interpretation
• In general an individual with 2 attacks per year
• Once started ULT is lifelong
• Serum uric acid goal is <6 mg/dL
• The lower the uric acid level the faster the reduction in tophaceous deposits
Urate Lowering Therapies

• Allopurinol
  – Start at 100 mg/day (50 mg/day for CrCl < 50 ml/min)
  – Titrate up to maximum of 800 mg/day
  – Relatively few drug-drug interactions
    • Warfarin, theophylline, azathioprine
  – Up to 20% report side effects
    • GI intolerance and rashes
    • TEN, cytopenias, vasculitis (death), hypersensitivity
    • Korean, Thai, Han Chinese check HLA-B*5801
Allopurinol hypersensitivity syndrome

- Occurs ~0.1 – 0.5% of patients taking allopurinol
- Mortality reported as high as 20%
- HLA B*5801
  - 1% Caucasians
  - 7% Asians
- A life-threatening toxicity syndrome consisting of:
  - Diffuse, erythematous, desquamative skin rash (often TEN)
  - Fever
  - Hepatitis
  - Eosinophilia
  - Worsening renal function

*J Dermatol.* 38: 246-54, 2011
*Proc Natl Acad Sci. USA* 2005; 102: 4134
Allopurinol guidelines

Stamp LK et al. *Arthritis Rheum* 2012; 64: 2529
Urate Lowering Therapies

• Febuxostat (Uloric)
  – Potent xanthine oxidase inhibitor
  – Might outperform allopurinol
  – Does not require renal adjustment
  – Possibly more cardiovascular events
  – Contraindicated with azathioprine
  – Caution with theophylline
Uricosuric Agents

• Probenacid
  – Caution with history of renal calculi
  – Caution with blood dyscrasias
  – Lower doses when used with methotrexate, naproxen, rifampin, and acetaminophen
  – Gastric intolerance sign for dose reduction

• Fenofibrate
  – 75% gout patients have hypertriglycerideridemia

• Losartan
Uricase

• Pegloticase (Krystexxa)
  – Pegylated mammalian (porcine-like) recombinant
  – 8 mg IV every 2 weeks
  – Uric acid level often drops to 1
  – Patients get fexofenadine, acetaminophen, and hydrocortisone 200 mg IV before each infusion
  – Gout flares, infusion reactions, and serious adverse events somewhat frequent CHF flares
  – Antibodies against pegloticase predict reactions (25%)
  – Contraindicated in G-6PD deficiency
  – Like debulking the urate load
Tophi resolution with pegloticase

- Complete resolution 40% of tophi
  - 73% patients had tophi
- 11 to 4 joints at 6 months

Data from four phase III clinical trials BLA submitted to the FDA in June 2009
Adherence to treatment

• Hopefully patients understand this
• The matches analogy
  – Urate crystals are compared with matches
  – When the match strikes it causes gout attack
  – NSAIDs or steroids to put out the fire
  – Although this resolves the attack the matches are still there
  – Colchicine is given to make the matches damp and harder to strike
  – Allopurinol, febuxostat, pegloticase actually remove the matches from your body
Summary

• Dietary modifications are not likely to work
• Multidrug regimens are effective
• Lifestyle changes are ideal of course
• ACR gout guidelines are open source
• Thanks to Ken Saag for slides
• Happy to help – 503-754-3676
and the *Tisick*,

the *Colic*,

PUNCH cures the *Gout*.