Gout 2012
An Integrated Approach to Managing Gout

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Disclosures:

- Speaker bureau and advisory panels for Roche-Genentech
- Speaker bureau for Abbott Pharmaceuticals
- Honorarium: Pumpkin spiced latte-the rest will be figured out later
Discussion Points

• Myths and Realities regarding gout
• Interaction between gout, hyperuricemia and CVD
• Recognizing the necessity for a multidisciplinary approach to treatment of gout
• Review of newer urate lowering therapies
Authoritative Bodies

- European League Against Rheumatism
- Japan Society for Gout and Nucleic Acid Metabolism
- British Society for Rheumatism
- American College of Rheumatology
Recommendations

- Level A grading supported by more than 1 randomized clinical trial, or 1 or more meta-analyses
- Level B grading derived from a single randomized trial, or nonrandomized studies
- Level C grading consensus opinion of experts, case studies, or standard of care
Wikipedia

- An inflammatory arthritis induced by monosodium urate crystal deposits in tissues and joints
- Metabolic disorder characterized by chronic hyperuricemia - serum uric acid of 6.8 mg/dl - (the limit of urate solubility at physiologic pH and temperature)
The Gout, by James Gilray (1799)
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. ..... With its intensity the chills and shivers increase. After a time this comes to a full height, accommodating itself to the bones and ligaments.... Now it is a violent stretching and tearing of the ligaments- now it is a gnawing pain and now a pressure and tightening. So exquisite and lively.... that it cannot bear the weight of bedclothes nor the jar of a person walking in the room.
Gout Facts

- Asymptomatic hyperuricemia is common but under recognized (not on CMP)
- Risk of developing gout associated with the extent and chronicity of hyperuricemia. Increases significantly with uric acid levels >9.0 mg dL
- Only a minority actually develop gout
- Tophi not completely understood
  - undervascularized tissue milieu leads to cool temperatures of joints.
  - Low grade inflammation in and around tophi
Myth:  

*Gout is a new age disease*
Reality:

- First description - Egyptians in 2640 BC
- Podagra recognized by Hippocrates in the fifth century BC - referred to it as 'the unwalkable disease'.
- Gout is derived from the Latin word gutta (or 'drop')
Myth:

*Gout is a disease of indulgence*
This good Applec gives  
Cures the vapours who  
Will it Cure the Cured Pain I have got in my toe.

PALATABLE: PHYSIC.
Reality:

- Estimated 6 million Americans have gout
- Last 20 years gout has doubled in the USA
- Large increase in gout prevalence in those individuals over age 65
- Striking increase in those aged over 75

_Unlikely this is secondary to indulgence_

Wallace, K. L. et al J. Rheumatology 31, 2004
Why the increase in the elderly?

- Declining mortality from cardiovascular disease
- Frequent comorbidities that promote hyperuricemia such as CKD, CHF, and hypertension
- Prescriptions of diuretics-loop and thiazides

Bieber J.D. et al. Arthritis Rheum. 50  2004
Secondary Causes of Hyperuricemia

- Leukemia/lymphomas
- Psoriasis
- Tissue necrosis
- Seizures
- Renal insufficiency
- Dehydration
- Lead nephropathy
- Hypothyroidism
- Hyperparathyroidism
- Diuretics
- Ethambutol
- Pyrazinamide
- Aspirin
- Cyclosporine
- Niacin
Myth:

*Gout is common among men but rare among women*
Reality: Only true premenopausal

- Increases substantially after menopause and rises with age
- *In kidney (URAT1)* - Responsible for reabsorption of uric acid from proximal tubule
- *Estrogen direct effect on expression*

*Enomoto et al. Nature. 2002;417*
Gout and women

- NHANES: prevalence of gout among women aged 60-69 was 3.5%
- This increases to 5.6% for those 80 yrs and older
Women and Gout

• Even if true age-specific prevalence of gout was 50% lower, almost exceeds that of rheumatoid arthritis among women (3.3% in NHANES III).

• Take home: premenopausal - unlikely to be gout. Consider even without acute flares in postmenopausal with chronic joint pain.


Kramer HM. et al. Br J Nutr. 82 1999
Myth:

Gout occurs more often among African Americans than Caucasians
Meharry Cohort Study

- 353 Black/571 White
- Risk for gout *(self reported)* 70% higher among Black men
- Excess risk disappeared after adjustment for hypertension

*(adjusted relative risk -1.30 (95% CI .77-2.19))*

Hochberg et. al. Arthr Rheum 1995;38
Myth:

The Uric acid is normal - It cannot be gout
Reality:

- 339 patients (two studies) comparing treatment of etoricoxib or indomethacin for acute gout
- 14% uric acid less than 6.0 mg/dl at baseline
- 32% < than 8.0 mg/dL during acute attack

Schiessinger et al. J Rheum 2009 Jun;36(6)
Myth:

It’s just Arthritis
Reality: Managed Care Perspectives

- Gout accounted for 2.2 million ambulatory visits annually
- 1.2% (11,064) of 922,000 hospitalizations for a diagnosis of arthritis
- Mean annual cost of employee with gout $6870 versus $3705 without gout
- Patients with gout miss 3-5 days/year

Sacks et al Arthritis Care and Research 2010:62
Epidemiological Studies - Hyperuricemia

- Cerebrovascular disease
- Preeclampsia
- Metabolic syndrome
- Stroke

- Hypertension
- Vascular dementia
- Coronary artery disease
- Renal disease

This relationship with cardiovascular disease is especially high in those at risk for CVD and in women.

Does Gout cause or increase the risk of cardiovascular disease?
- Choi and Curhan (2007): Those with gout have a higher risk of death from all causes.

At least three other studies have confirmed similar findings between gout and shortened longevity primarily through risk of coronary artery disease.

Choi and Curhan. Circulation. 2007b;116

Krishnan et al. Arch Intern Med. 2008;168
Survival in a cohort of pts with cardiac disease/risk factors and Uric Acid Level

Ioachimescu. Arthritis Rheum 2008;58

3,098 patients

All cause mortality
Things to consider

- Teens with essential hypertension - elevated uric acid levels
- Teens with secondary hypertension - normal levels
- Experimental elevation of uric acid in rats causes kidney disease - glomerulosclerosis, arteriolar disease (no crystals)
- Elevated uric acid is an independent predictor of the development of microalbuminuria and renal dysfunction in those with normal renal function
Two studies

5 teens with hypertension treated with allopurinol - blood pressure lowered

30 teens with hyperuricemia and hypertension treated allopurinol. Double blind, placebo controlled crossover

***Significant reduction in blood pressure***

Those with UA levels lowered to less than 5mg/dL - BP normalized in 86% (19/22)

Allopurinol in chronic kidney disease

- 113 pts randomized-GFR<60
- Allopurinol 100mg/day (57) - 23 months

Decreased C reactive protein and slowed down progression of renal disease

Myth:

Hyperinsulinemia is the cause for elevation of uric acid in the metabolic syndrome
Reality: Metabolic Syndrome

- Historically increase in uric acid attributed to hyperinsulinemia (reduce renal excretion)
- Can precede hyperinsulinemia as well as diabetes and obesity
- 5.9% with normal BMI and a uric acid level of less than 6.0 mg/dL had the metabolic syndrome
- 59% of subjects with a normal BMI and a uric acid level of >10 mg/dL had evidence of the metabolic syndrome

Whincup et al Heart 1997;78

HK Choi and Ford ES. Am J Med 2007;120
Role of Uric Acid in Metabolic Syndrome

- Animal models showing that decreasing uric acid levels can prevent or reverse features of the metabolic syndrome

- Two theories
  - Endothelial dysfunction of nitrous oxide release
  - Oxidative changes uric acid induces in adipocytes

Myth:

Patients with diabetes have lower serum levels of uric acid compared to those with glucose intolerance
William Osler 1893: “Sugar should be reduced to a minimum. The sweeter foods should not be taken.”
Reality:

- High fructose corn syrup introduced in 1967
- Use has increased 0 to 29 kg/yr/person in US since 1967
- Sugar sweetened soft drinks represent the largest single food source of calories in the US; 43,000/person/lifetime

- Fructose and hyperuricemia
  - Fructose increases degradation of purine nucleotides
  - Fructose increases purine synthesis

- Fructose sweetened soft drinks increases the risk of gout

Hyon K Choi and Gary Curhan BMJ 2008;336;309-312
The Role of Wt Loss in Lowering Serum Uric Acid

55 y/o male With a Hx of Gout off all ETOH & on low purine diet. Studies done 18 months apart.

<table>
<thead>
<tr>
<th>Variable</th>
<th>1st Study</th>
<th>2nd Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>99 kg</td>
<td>81 kg</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>170/110</td>
<td>140/80</td>
</tr>
<tr>
<td>Serum Urate</td>
<td>7.0 mg/dl</td>
<td>5.3 mg/dl</td>
</tr>
<tr>
<td>Urate Clearance</td>
<td>5.3 ml/min</td>
<td>8.0 ml/min</td>
</tr>
<tr>
<td>Urate Production</td>
<td>885 mg/day</td>
<td>696 mg/day</td>
</tr>
</tbody>
</table>

# Results: multivariate relative risk of gout by intake of fructose containing beverages

<table>
<thead>
<tr>
<th>Intake Drink</th>
<th>&lt; 1/mo</th>
<th>1/mo to 1/wk</th>
<th>2-4/wk</th>
<th>5-6/wk</th>
<th>1/day</th>
<th>&gt;2/day</th>
<th>P level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweetened Soft Drinks</td>
<td>1.0</td>
<td>1.0</td>
<td>0.99</td>
<td>1.29</td>
<td>1.45</td>
<td>1.85</td>
<td>0.002</td>
</tr>
<tr>
<td>Diet Soft Drinks</td>
<td>1.0</td>
<td>1.18</td>
<td>1.15</td>
<td>1.09</td>
<td>1.07</td>
<td>1.12</td>
<td>0.99</td>
</tr>
<tr>
<td>Fruit Juices</td>
<td>1.0</td>
<td>1.34</td>
<td>1.57</td>
<td>1.55</td>
<td>1.74</td>
<td>1.81</td>
<td>0.01</td>
</tr>
<tr>
<td>Apple or Orange</td>
<td>1.0</td>
<td>1.24</td>
<td>1.22</td>
<td>1.43</td>
<td>1.64</td>
<td></td>
<td>0.006</td>
</tr>
</tbody>
</table>
Myth:

Purine rich foods of vegetable origin lead to gout
Reality:

- Prospective study over 12 years
- 47,150 male participant with no base line gout
- No increased risk with consumption of purine rich vegetables (*peas, beans, spinach, etc.*) or with overall protein intake
- Protect effect from dairy
- Meat and seafood increase

Choi HK. Et al. N Engl J Med 2004b;350
Cause and Effect

• Western diets- high intakes of meat, seafood, fructose and beer linked with development of gout in middle aged men

• High intakes of low fat dairy products, coffee and ascorbate linked with reduced rates in the same population

Myth:

All alcoholic beverages equally lead to gout
Reality:

Health Professionals follow-up study

- Risk for gout increased for 50% for every 12 oz serving
- Liquor increased risk of new gout by 15% for each drink
- Moderate levels of wine did not increase risk gout in this study

NHANES III Study

Association between consumption and serum uric acid

- Beer: an increase of .46mg/dl for each additional serving
- Liquor 0.29 mg/dL for each additional serving
- No independent association for wine consumption

Choi and Curhan. Arthritis Rheum. 2004
Doctors suggest 2 glasses of wine a day has health benefits.
Asymptomatic Hyperuricemia

- No one knows what to do
- Old thinking “do not treat”
- This is being revisited
What is the best drug for treating acute gout?
2012

- Colchicine
- NSAID's
- Corticosteroids
- ACTH
ACR Task Force Recommendations

- Treat within 24 hours of an acute attack
- Do not stop ULT

Instruct patient on how to initiate treatment upon signs and symptoms of an acute gout to eliminate the need to consult their health care provider
### ACR Task Force Grading System

#### Severity of Acute Gouty Arthritis Attack

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild</strong></td>
<td>≤ 4</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>5-6</td>
</tr>
<tr>
<td><strong>Severe</strong></td>
<td>≥ 7</td>
</tr>
</tbody>
</table>

#### Duration of the gouty arthritis attack since onset

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early</strong></td>
<td>&lt; 12 Hours after attack onset</td>
</tr>
<tr>
<td><strong>Well-Established</strong></td>
<td>12 to 36 Hours after attack onset</td>
</tr>
<tr>
<td><strong>Late</strong></td>
<td>&gt; 36 Hours after attack onset</td>
</tr>
</tbody>
</table>
Treatment

- Less than 6 on VAS and 1-2 joints - treat with NSAID, Corticosteroids or Colchicine (A)

- Severe attack or involving large joints - combination therapy (C)
ACR Recommendations

- No specific recommendation for which NSAID or topical/IM
- Decision is also based upon renal/hepatic/GI disease
- ACR task force suggested that celecoxib for acute gout in selected patients with contraindications or intolerance to NSAIDs (evidence B)
- Keep in mind that the risk/benefit ratio is not yet clear
- Dose 800 mg followed by 400 mg then 400 bid for 7 days
Colchicine 2012

Myths:
A. Specific for gout
B. Safe
C. Inexpensive
Answer

B. (Maybe)

Colcrys >$5.00 a tablet

Used in FMF, Pseudogout, Periodic fever syndromes, vasculitis
• First described 1500 as treatment for rheumatism

• Approved 2009 for Familial Mediterranean Fever, Prophylaxis for Gout and Treatment of Acute Gout

• Inhibit mitosis and neutrophil motility and activity
ACR Recommendations

- Acute gout if began within 36 hours of symptom onset (*Level C*)
- Dosage 1.2 mg followed by .6 mg one hour later then .6mg bid
- Prophylaxis .6 mg bid for 6 months (*Level A*) or 3 months with no tophi and target level reached (*Level B*)
Warnings

Inhibitors of P450 3A4 or P-Glycoprotein meds

Significant complications include:
- Neuromyopathy
- Blood dyscrasias

Concomitant administration with statins and cyclosporine - watch carefully

Renal disease: Cr Clearance 30-50 cc/min No Adjustment but remember that is in healthy volunteers
Update 2012

When to begin Uric Acid lowering Therapy *(ULT)*
ACR Recommendation

- Tophi on exam or imaging (A)
- 2 or more attacks per year (A)
- CKD stage 2 or worse (C)
- Previous history of nephrolithiasis (C)

The recommended target is a uric acid of 6 mg/dl noting that one may need to go below 5 for control.
Myth:

*Genetic Prescreening is essential for allopurinol*
Reality

• Check HLA-B *5801 in those at risk
  • Koreans with stage 3 or worse ckd *(Allele frequency 12%)*
  • Han Chinese or Thai extraction *(Allele frequency 6-8%)*
Myth:

If Uric acid is not controlled with 300 mg of allopurinol one should switch to another drug.
Reality

50% of patients will not be controlled with a dosage of 300mg daily - need to go higher

Taking with food better tolerated

May need adjustments of other meds - such as coumadin, theophylline, azathioprine

- Allopurinol hypersensitivity syndrome in 0.1% - be aware as this can be fatal

- Target is still 6mg /dl
### 1984 Hande guidelines for renal dosing of allopurinol


<table>
<thead>
<tr>
<th>Creatinine Clearance</th>
<th>Allopurinol Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 ml/min</td>
<td>100 mg/3 days</td>
</tr>
<tr>
<td>10 ml/min</td>
<td>100 mg/2 days</td>
</tr>
<tr>
<td>20 ml/min</td>
<td>100 mg/day</td>
</tr>
<tr>
<td>40 ml/min</td>
<td>150 mg/day</td>
</tr>
<tr>
<td>60 ml/min</td>
<td>200 mg/day</td>
</tr>
<tr>
<td>80 ml/min</td>
<td>250 mg/day</td>
</tr>
<tr>
<td>&gt;100 ml/min</td>
<td>300 mg/day</td>
</tr>
</tbody>
</table>

- Severe hypersensitivity reactions are not dose dependent; may not correlate with oxypurinol levels. Puig. J. Rheumatol 16:842-844, 1989
- Following Hande guidelines led to suboptimal control of hyperuricemia & did not prevent hypersensitivity. Dalbeth. J Rheumatol 2006;33: 1646-1650
- Gardner’s guideline: Go low go slow but use enough allopurinol to reduce UA to 5-6 mg/dl
Allopurinol - How it Works

Allopurinol
1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

Oxipurinol
1H-pyrazolo[3,4-d]pyrimidine, 4,6 (5H,7H)-dione

Hypoxanthine
purin-6(1H)-one

Xanthine
3,7-dihydro-1H-purine-2,6-dione

Uric Acid
7,9-dihydro-1H-purine-2,6,8(3H)-trione
Febuxostat

- Inhibits molybdenum pterin- center which is the active site of xanthine oxidase
- Studies show more reduction in uric acid than allopurinol 300 mg daily.
- Advantages: renal insufficiency and where allopurinol intolerances exist
- Still interferes with metabolism of drugs such as mercaptopurine
Xanthine Oxidase Inhibitors

- Febuxostat (Uloric) - AWP = $6.43/tab
- Allopurinol (Zyloprim) - AWP = $0.22-0.66/tab
<table>
<thead>
<tr>
<th></th>
<th>Excretion</th>
<th>Mechanism</th>
<th>Interactions</th>
<th>Other risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol</td>
<td>Renal</td>
<td>Purine analogue of Xanthine</td>
<td>Coumadin, Azathioprine</td>
<td></td>
</tr>
<tr>
<td>Febuxostat</td>
<td>Renal, Hepatic</td>
<td>Non purine inhibitor of XO</td>
<td>Azathioprine</td>
<td>Cardiac, liver</td>
</tr>
</tbody>
</table>
2012 ACR Recommendations

- Begin with allopurinol 100mg daily
- Increase every two weeks till uric acid under 6mg/dl
- May need to increase to 800mg
- Can use cautiously in renal insufficiency
- If fail switch to Uloric 40 mg for two weeks then increase to 80 mg

Begin Low Go Slow
Myth:

*Probenecid is a first line ULT*
ACR Recommendations-Probenecid

- Alternative first line ULT in patients who cannot tolerate or contraindicated to at least one XOI (evidence B)

- Do not use if Cr Clearance < 50ml/l (evidence C)

- Use of other uricosurics, Losartan and Fenobibrate, may be helpful in a comprehensive uric acid lowering treatment plan (evidence B)

- Consider urine alkalinization (potassium citrate) with monitoring of urine pH, as a management strategy for urolithiasis (evidence C)
Krystexxa 2012
Pegloticase: Mechanism of Action

Cell Breakdown

Diet

Purines

Hypoxanthine

Xanthine

Xanthine Oxidase Inhibitors

Tophaceous Deposits

Pegloticase

++ Uricosuric Agents

Uric Acid

Urinary Excretion

Allantoin

Urinary Excretion

Efficacy and Tolerability of Peloticase for the Treatment of Chronic Gout in Patients Refractory to Conventional Treatment

Two Randomized Controlled Trials

Methods

- Two replicated double blinded, placebo, 6 month trials
- 56 centers in North America
  - Infusion 8mg Pegloticase Q 2weeks
  - Infusion 8 mg Pegloticase Q 4 weeks
  - Infusion  Placebo
Plasma Uric Acid levels during Biweekly Pegloticase Treatment
Standardized serial digital photographs of tophus size reduction over time of biweekly pegloticase treatment
Myth:

Krystexxa should not be used in renal insufficiency
Objectives of post-hoc analyses

- Determine effect of CKD on response to pegloticase treatment
- Determine effect of pegloticase on renal function in patients with CKD
- Determine whether renal function is differentially affected based on treatment response
- Examine side effects by renal function status

Yood RA, Ann Rheum Dis 2012;71(Suppl3):87
CKD Patients in the Phase 3 Trials

CKD stage as defined by the National Kidney Foundation based on estimated glomerular filtration rate (mL/min/1.73m²) using the MDRD 4-variable equation

Yood RA. Ann Rheum Dis 2012 71(SUPP)
Stage 3 or 4 CKD (open label extension study)

Yood RA, Ann Rheum Dis 2012;71(Suppl3):87
Krystexxa conclusions

• Response to pegloticase is independent of CKD stage
• Pegloticase treatment does not impact eGFR in CKD patients
• Change in eGFR over time is not different by responder status
• No differences in safety profile by renal function status

Yood RA, Ann Rheum Dis 2012;71(Suppl3):87
Update: New treatments

- TNF inhibitors - risk of infection, poor efficacy in gout expensive,
- Interleukin 1Beta blockade may be helpful for inducing long term remissions and as a replacement for corticosteroids
If MSU is the sole activator of IL-1β.... then

Why do fewer than 10% with deposits of MSU crystal in joints develop gout?

Why when those with hyperuricemia lose weight they flare?

Why do acute flare occur in the middle of the night?

Why does certain foods and alcohol precipitate attacks?
MSU crystals require a cofactor to prime cell - the most likely cofactor is FFA.

Bind to toll like receptors.

Thus, rise in FFA level, after “overnutrition”, trigger the synthesis, processing and release of IL-1Beta.

Only in pre-primed cells with MSU.

• Theory IL-1 B blockade - reduces acute gout flares when initiating chronic treatment

• Anakinra (Kineret), Rilonacept(Arcalyst)

• Canakinumab (Ilaris)

• May lead to improved adherence
• IL-1 antagonists anakinra
  • Anecdotes only, daily SQ

• Canakinumab
  • Slightly better than triamcinolone 40mg
  • Significantly more side effects, even after one dose

Neogi. Arth rheum 2010 :10

Rilonacept- IL-1 trap-12 Wk Study

- 41 pts Rilonacept sq weekly
- 42 pts Placebo
- All began on allopurinol and titrated to uric acid. 6.0mg/dL

6 flares in Rilonacept group/33 with placebo P=.001

Ralph Schumacher Jr., H. Arth Rheum 2012:64
Conclusions

- A multidisciplinary collaboration between primary care and specialists (rheumatologists, cardiologists, nephrologists, and endocrinologists) essential for recognition and treatment of gout

- Treat early, treat to target

- Beware of cardiovascular risk factors-check uric acid levels in those at risk

- Education for your patient
Gout 2012
An Integrated Approach to Managing Gout

Keith Reich, DO, FACOI, FACR
Assistant Professor of Medicine,
Rheumatology Fellowship Director
Midwestern University