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Debunking 10 Popular Myths Regarding Gout

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Disclosures

• I have no financial relationships to disclose
• I will not discuss off-label or investigational use in my presentation
Primary Objective

• Improving quality and quantity of life of your patients with gout by debunking popular myths related to gout
• To identify and treat acute & chronic gout in an evidence-based way
Why is this important?

- > 3 million patients with gout in US; incidence increasing
- About 175000 ER visits in US in 2008
- ER costs >$160 million in 2008 in US.
- Associated with increased mortality & CV risk
- Treatable disease and attacks are preventable!

  » Garg et al. Arthritis Care Res. 2013 (National ER data)
  » Clarson L et al. Eur J Prev Cardiol 2015 (Systematic review and meta-analysis- gout and mortality; UK group)
Myth #1: Gout is a benign joint disease

- Increased CV risk especially in women with gout RR 1.39 (95% CI 1.2 to 1.6)

De Vera, Choi et al. Ann Rheum Dis 2010
(Canadian population-based study on elderly women with gout)
Increased risk of Coronary Heart disease mortality in gout

(Systematic review and meta-analysis- gout and mortality; UK group)
Hyperuricemia linked to development of HTN

Feig et al. Uric acid and cardiovascular risk. NEJM 2008 (Baylor)
Clinical Pearl #1

Myth #1: Gout is a benign joint disease

Clinical Pearl #1

Gout is associated with increased CV risk especially in women; also increased risk of CHD mortality. Hyperuricemia is linked to development of hypertension.
Myth #2: Autoimmune arthritis and gout cannot co-exist with each other

• Important to know because:
  - Co-existing gout in RA and PsA may be wrongly managed by intensifying immunomodulatory therapy
  - Gout can very closely mimic RA
Gout may co-exist with RA

Psoriatic arthritis increases risk of gout

<table>
<thead>
<tr>
<th></th>
<th>Cases of gout (primary outcome)</th>
<th>Person-years</th>
<th>Age-adjusted HR (95% CI)</th>
<th>Multivariate-adjusted HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPFS</td>
<td>No psoriasis</td>
<td>1329</td>
<td>634 372</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Psoriasis only</td>
<td>14</td>
<td>2743</td>
<td>2.44 (1.44 to 4.14)</td>
</tr>
<tr>
<td></td>
<td>Psoriasis with PsA</td>
<td>6</td>
<td>441</td>
<td>6.67 (2.97 to 15.0)</td>
</tr>
<tr>
<td>NHS</td>
<td>No psoriasis</td>
<td>812</td>
<td>813 880</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Psoriasis only</td>
<td>15</td>
<td>11 863</td>
<td>1.34 (0.80 to 2.23)</td>
</tr>
<tr>
<td></td>
<td>Psoriasis with PsA</td>
<td>5</td>
<td>1207</td>
<td>5.01 (2.08 to 12.1)</td>
</tr>
<tr>
<td>HPFS/NHS</td>
<td>No psoriasis</td>
<td>2141</td>
<td>1 448 252</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Psoriasis only</td>
<td>29</td>
<td>14 606</td>
<td>1.80 (1.00 to 3.25)</td>
</tr>
<tr>
<td></td>
<td>Psoriasis with PsA</td>
<td>11</td>
<td>1648</td>
<td>5.85 (3.22 to 10.6)</td>
</tr>
</tbody>
</table>

Clinical Pearl #2

• Myth #2: Autoimmune arthritis and gout cannot co-exist with each other

• Clinical Pearl #2: Psoriatic arthritis/Rheumatoid arthritis may co-exist with gout in the same patient.
Myth #3: Wine is not associated with gout attacks

- Ethanol may decrease urate excretion and increase urate production
- Beer higher risk because it also contains highly absorbable purine - guanosine

» Neogi et al. Am J Med 2014 (Boston University online study)
• Number of alcohol servings is a risk factor for acute gout attacks regardless of type of alcohol beverage
• Episodic intake of any type of alcohol increase risk of gout attacks.

Spline regression depicting the relation of total alcohol intake to the risk for recurrent gout attack.
Clinical Pearl #3

- Myth #3: Wine is not associated with gout attacks
- Clinical pearl #3: Episodic intake of any type of alcohol may increase risk of gout attacks.
Myth #4: Normal uric acid rules out gout

- Acute gout attack – uric acid trends down
- More accurate uric acid level if checked after the acute episode is over
Proportion (n) of patients with serum urate (SU) ≤ 6 mg/dl and SU ≤ 8 mg/dl during acute gout at baseline (combined treatments) by allopurinol use.

<table>
<thead>
<tr>
<th></th>
<th>SU ≤ 6 mg/dl</th>
<th>SU &gt; 6 mg/dl</th>
<th>SU ≤ 8 mg/dl</th>
<th>SU &gt; 8 mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Allopurinol yes (n = 55)</td>
<td>29.1</td>
<td>16</td>
<td>45.5</td>
<td>25</td>
</tr>
<tr>
<td>Allopurinol no (n = 284)</td>
<td>11.3</td>
<td>32</td>
<td>78.2</td>
<td>222</td>
</tr>
<tr>
<td>Total (n = 339)</td>
<td>14.2</td>
<td>48</td>
<td>72.9</td>
<td>247</td>
</tr>
</tbody>
</table>

Schlesinger et al. J Rheum 2009 (Data from Etoricoxib in gout RCT)

Upper limit of normal uric acid level in Fairview lab: 7.2 mg/dl
Clinical Pearl #4

Myth #4: Normal uric acid level rules out gout

Clinical Pearl #4:
Normal uric acid level does not rule out gout
Myth #5: Keep giving colchicine every hour until resolution of acute gout

- Low-dose colchicine (1.2mg stat followed by 0.6mg 1 hour later) yielded early gout flare efficacy comparable with that of high-dose colchicine (4.8 mg over 6 hrs), with a safety profile indistinguishable from that of placebo.
Figure 3. Distribution of percent improvement (intent-to-treat [ITT] population, n = 184). Shown is the percent of patients who improved in each category of percent improvement for the pain score 24 hours after the initial dose of study medication (ITT population).

Clinical Pearl #5

Myth #5: Keep giving colchicine every hour until resolution of acute gout

Clinical Pearl #5:

Low dose colchicine (1.2mg stat + 0.6mg 1 hour later) is as effective as high-dose colchicine for acute gout attack.
Myth #6: Do not start urate lowering therapy during acute attacks

- Because providers think urate lowering therapy may worsen the symptoms during acute attack and want to start it during next visit. (not evidence-based)
- Problem: Some patients don’t get started on urate lowering therapy even when indicated
Myth #6: Do not start urate lowering therapy during acute attacks

Taylor [Dartmouth Medical School] et al. Initiation of Allopurinol at First Medical Contact for Acute Attacks of Gout: A Randomized Clinical Trial. Am J Med 2012. [Small study about 25 patients each group]
Clinical Pearl #6

Myth: Do not start urate lowering therapy during acute attacks

Clinical Pearl #6:

It is okay to start urate lowering therapy during acute gout attack provided anti-inflammatory agent is also on board. (ACR 2012 Gout guidelines)
Myth #7: Allopurinol treats only the joints in gout

- Allopurinol use may be associated with decreased MI risk
- Allopurinol use may be associated with decreasing the risk of progression of CKD.


De Abajo et al. Allopurinol use and risk of non-fatal acute MI. Heart 2015. (Spanish. Population-based study)

Allopurinol associated with reduced mortality risk in gout

Allopurinol associated with 19% lower risk of mortality in patients with gout

Dubreuil et al...Choi. Allopurinol initiation and all-cause mortality in the general population. Ann Rheum Dis 2014 [Boston group; UK THIN database- population based]
Allopurinol may be associated with decreased MI risk

Also showed reduced rate of non-fatal MI associated with allopurinol dose >300mg/day

De Abajo et al. Allopurinol use and risk of non-fatal acute MI. Heart 2015. (Spanish. Population-based case control study)
Does Allopurinol slow the progression of CKD?

Forest plot showing the effect of uric acid-lowering therapy compared with placebo or no treatment on change in serum creatinine concentration (mg/dL) from baseline.

<table>
<thead>
<tr>
<th>Study name</th>
<th>Year</th>
<th>Difference in means</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-Value</th>
<th>Relative weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siu</td>
<td>2006</td>
<td>-0.7</td>
<td>-1.3</td>
<td>-0.0</td>
<td>0.04</td>
<td>26.35</td>
</tr>
<tr>
<td>Sarris</td>
<td>2007</td>
<td>-0.6</td>
<td>-1.2</td>
<td>-0.1</td>
<td>0.03</td>
<td>31.34</td>
</tr>
<tr>
<td>Momenni</td>
<td>2010</td>
<td>-0.1</td>
<td>-0.5</td>
<td>0.3</td>
<td>0.65</td>
<td>42.31</td>
</tr>
</tbody>
</table>

Summary Difference
Q = 3.0 ; F = 34 ; p = 0.22

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Forest plot showing the effect of uric acid-lowering therapy compared with placebo or no treatment on change in GFR (mL/min/1.73 m²) from baseline.

Clinical Pearl #7

Myth #7: Allopurinol treats only the joints in gout

Clinical Pearl #7:
Allopurinol is associated with reduced risk of mortality in gout and it may decrease MI risk.
Myth #8: Allopurinol is nephrotoxic

- Few articles in 1980s and 1990s
- Happens in high doses in rodents
- **Clinical Pearl #8**: There is no evidence that allopurinol is nephrotoxic in humans

Myth #9: Maximum allopurinol daily dose is 300mg

- Retrospective data from large southeastern US health plan database
- <5% of the patients were on >300mg daily dose of allopurinol
- Sub-optimally dosed from target uric acid level standpoint

Chaitanya A. et al. Gout Medication Treatment Patterns and Adherence to Standards of Care From a Managed Care Perspective. Mayo Clinic Proceedings 2006
Clinical Pearl #9

Myth #9: Maximum allopurinol daily dose is 300mg

Clinical Pearl #9

FDA approved daily dose for Allopurinol is up to 800 mg in normal renal function

British society of rheumatology: up to 900 mg daily
Myth #10: Allopurinol dose is creatinine-clearance based to prevent AHS

- FDA: Allopurinol dosing based on renal dysfunction:
- limit the maximum allopurinol dose to 200 mg/d (CrCl 10–20) and to 100 mg/d (CrCl < 10), without specifying a scale for dosing allopurinol in moderate CKD
The viral article regarding allopurinol dosing!

Severe Allopurinol Toxicity
Description and Guidelines for Prevention in Patients with Renal Insufficiency

KENNETH R. HANDE, M.D.
RICHARD M. NOONE, B.S.
WILLIAM J. STONE, M.D.
Nashville, Tennessee

A life-threatening toxicity syndrome consisting of an erythematous, desquamative skin rash, fever, hepatitis, eosinophilia, and worsening renal function in 78 patients receiving allopurinol is described. In a majority of cases, the development of this syndrome was associated with the use of standard (200 to 400 mg per day) doses of allopurinol in patients with renal insufficiency. In pharmacologic studies, it was demonstrated that the renal clearance of the major metabolite of allopurinol, oxipurinol, is directly proportional to the renal clearance of creatinine (oxipurinol clearance = 0.22 × cre-
• Based on previously reported 78 allopurinol hypersensitivity cases.
• Accumulation of oxipurinol in CKD was thought to be related to Allopurinol hypersensitivity (NOT PROVEN). Hence their guidelines based on CrCl.

Widely followed guideline on allopurinol dosing in CKD

These specific guidelines were designed for calibration to serum oxypurinol levels to prevent Allopurinol hypersensitivity reaction. NOT EVIDENCE-BASED.

NOT PROVEN THAT AHS RISK IS DOSE DEPENDENT IN CKD.

IS NOT EFFECTIVE IN TREATING GOUT
Dose adjustment of allopurinol according to creatinine clearance does not provide adequate control of hyperuricaemia in patients with gout. Dalbeth N., Stamp et al. J Rheumatol 2006 [New Zealand; retrospective data; n=250]

*Figure 2. SUA levels based on allopurinol dose guidelines. Percentage of patients achieving SUA ≤ 0.36 mmol/L. **p < 0.01.*
Allopurinol hypersensitivity syndrome

- Incidence < 1%
- About 25% fatality
- Usually occurs within 4 to 6 weeks after initiation of allopurinol

CKD increases risk of AHS. BUT IS THE RISK DOSE DEPENDENT?

• Mean daily dose of allopurinol in AHS group was 100mg.
• AHS did not occur more frequently in those taking higher than recommended doses, compared with those on renal-based dose.
• Stamp et al. Using allopurinol above the dose based on creatinine clearance is effective and safe in patients with chronic gout, including those with renal impairment. Arthritis Rheum 2011 [prospective study; 0 AHS in both ‘dose escalation’ vs Hande group n= about 40 each]

• Hung et al. Proc Natl Acad Sci USA. 2005 [case control study; 51 AHS SCAR cases; all were HLA B5801 positive; Han; majority were on allopurinol dose 100mg]

Myth #10: Allopurinol dose is creatinine-clearance based to prevent AHS.

Clinical Pearl #10
No evidence that up-titration of allopurinol dose increases risk of AHS in CKD patients.
ACR 2012 gout guidelines

“Allopurinol dose can be raised above 300 mg daily, even with renal impairment, as long as this is accompanied by adequate patient education and monitoring for drug toxicity (eg, pruritis, rash, elevated hepatic transaminases)”
Starting dose is a risk factor for allopurinol hypersensitivity syndrome: A proposed safe starting dose of allopurinol
Other risk factors for AHS

- HLA-B allele B*5801 was present in all 51 Han patients with allopurinol-induced SCAR. 90% of the people living in China and more than 97% of the people in Taiwan are Han.
- Use of thiazide may also be associated with AHS.
Clinical pearls

• #1 Gout is associated with increased CV risk especially in women; also increased risk of CHD mortality. Hyperuricemia is linked to development of hypertension.

• #2 Psoriatic arthritis/Rheumatoid arthritis may co-exist with gout in the same patient.
Clinical pearls

• #3 Episodic intake of any type of alcohol may increase risk of gout attacks.
• #4 Normal uric acid does not rule out gout
• #5 Low dose colchicicine (1.2mg stat followed by 0.6mg 1 hour later) is as effective as high-dose colchicicine for acute gout attack
Clinical Pearls

• #6 It is okay to start urate-lowering agent during acute gout attack provided anti-inflammatory agent is also on board.

• #7 Allopurinol is associated with reduced risk of mortality in gout and it may decrease MI risk.

• #8 No evidence that allopurinol is nephrotoxic.
Clinical pearls

• #9 Maximum allopurinol dose is up to 800mg daily

• #10 No evidence that up-titration of allopurinol dose increases risk of AHS in CKD patients. HLA B5801 gene and higher starting dose of allopurinol increase risk of AHS.
Thank you

TROUBLE IS I DRINK LOTS OF BEER TO TRY TO FORGET THE GOUT!