Resolving Controversies in Gout Management

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Teaching Objectives

• Understand management of acute gout
• Understand the management of chronic gout and the approaches to uric acid lowering therapy.

Disclosures

• None

Acute Gout Management
Acute Gout - Case 1
A 75 year old man with a history of diabetes, CKD, and gout is admitted with 1 day of acute swelling and pain in the right ankle. His temp is 99.4. The ankle is warm and swollen. The other joints seem unremarkable. Arthrocentesis in the ED demonstrates negatively birefringent crystals. Cell count 85,000 WBC – 91% PMNs.

What do you do next:
A. Hold allopurinol & wait for cultures
B. Inject corticosteroids into the joint
C. Prescribe a prednisone taper
D. Prescribe naproxen 500 mg BID
E. Prescribe IV antibiotics & wait for the results of the gram stain & Cx

75 y.o. man with DM, CKD with 1 day acutely swollen & warm ankle with low-grade fever. Synovial fluid shows negatively birefringent crystals & WBC 85,000.

What do you do next:
A. Hold allopurinol & wait for GS & Cx
B. Inject corticosteroid
C. Prednisone taper
D. Naproxen 500 mg BID
E. IV antibiotics and wait for GS & Cx

Differential Diagnosis of monoarticular arthritis
- Septic Arthritis
  – Gram Positive cocci
  – Gram Negative Rods
  – Lyme disease
  – Tb/Fungal
- Crystal Arthritis
  – Gout
  – Pseudogout
- Spondyloarthitis (e.g. Reactive Arthritis)
- Vasculitis
- Palindromic Rheumatism
- Trauma
- Exacerbation of Osteoarthritis

1-5% of patients with crystal arthritis will also have septic arthritis of the same joint Papanicolas et al, J Rheumatol 2012, Shah K, et al, J Emerg Med 2007
What can help us feel more confident this is a gout attack and not infection without waiting for the cultures?

Acute Gouty Arthritis

- Provocation: trauma, ethanol, exercise, new medication
- First Attack:
  - fourth to sixth decade of life
  - 90% Monoarticular
  - 50% Podagra
- Sites:
  - 1st MTP
  - Instep, mid-foot, ankle, knee
  - wrist, fingers, elbow

Septic Arthritis most commonly affects large joints

Septic Arthritis

The Value of a Careful Joint Exam

Tip:
In a patient with a history of many attacks of gout, attacks tend to be oligoarticular or polyarticular. This can be appreciated by doing a very careful joint examination.

Acute Gout - Case 2

A 53 year old man with HTN, nephrolithiasis, and a history of “crystal proven gout” comes to see you for acute foot pain.

His first attack of gout came in his 1st toe about 2 years ago with a sudden onset of intense pain that gradually improved over 2 weeks. Since then he has had 2 more attacks in both feet. Negatively birefringent crystals were seen in joint fluid aspirated from his ankle.

The most recent attack started 3 days ago in his 1st toe and instep. On examination there is marked swelling, erythema and tenderness over the 1st MTP bursa as well as the 1st metatarsal-tarsal joint.
Test Your Knowledge...

All of the following are reasonable treatments for acute gout EXCEPT:

a) NSAIDS (naproxen 500mg 2x/d, indomethacin 50mg 3x/d)
b) Prednisone 20-60 mg/d, tapered over 6-18 days
c) Intra-muscular corticosteroid injection. (Triamcinolone 60-80 mg IM; may need to repeat in a couple of days)
d) Intra-articular steroid injection (Triamcinolone 20-40 mg)
e) Colchicine 0.6 mg every hour for 6 doses

Test Your Knowledge...

All of the following are reasonable treatments for acute gout EXCEPT:

A. NSAIDS
B. Prednisone Taper
C. IM Triamcinolone
D. Intra-Articular Triamcinolone
E. Colchicine every hour

Update: Low dose Colchicine is effective for acute gout

Diarrhea

26%, 0%

77%, 19%

Any, Severe

Update: Low dose Colchicine is effective for acute gout

Efficacy of NSAIDs & Corticosteroids for Acute Gout

- NSAIDs (naproxen 500mg BID, indocin 50mg TID, diclofenac 50 mg BID)
- Prednisone: 60mg qd, taper over 6-18 days

also see Rainer TH, et al, Ann Intern Med 2016, PMID 26903390

Treatment of Acute Gout

NSAIDs are problematic in patients with CKD

Withdrawal of NSAIDs for 1 year (along with control of hyperuricemia) resulted in improved renal function in patients.


NSAIDs use was associated with increased risk of CKD in patients with hyperuricemia or gout (matched case-control study)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Case (n/Tot)</th>
<th>Control (n/Tot)</th>
<th>OR* (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No previous renal disease or hyperuricemia</td>
<td>6/63</td>
<td>33/163</td>
<td>0.57 (0.20, 1.6)</td>
<td>0.3</td>
</tr>
<tr>
<td>Previous renal disease, but no hyperuricemia</td>
<td>14/38</td>
<td>2/20</td>
<td>6.6 (0.8, 57.9)</td>
<td>0.099</td>
</tr>
<tr>
<td>Gout/Hyperuricemia, but no previous renal disease</td>
<td>8/17</td>
<td>2/21</td>
<td>7.1 (0.3, 38.7)</td>
<td>0.027</td>
</tr>
<tr>
<td>Previous renal disease and hyperuricemia</td>
<td>4/12</td>
<td>6/5</td>
<td>82.2 (4.1, 1661.1)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

NSAIDs are problematic in patients with CKD

Update: Targeting Inflammatory Pathways to treat acute gout

All patients received anakinra (IL-1 receptor antagonist)
Treated with 100 mg SQ injection daily for 3 days ($50-100/injection)
All 10 patients with acute gout responded rapidly to anakinra.
9/10 had complete resolution of gout symptoms in 3 days
No adverse effects were observed.
Similar Results reported by Chen K et al, Semin Arthritis Rheum 2010
ASGARD Study in process comparing anakinra vs. solumedrol in CKD

Burns CM, Wortmann RL, Lancet, 2011, PMID 20719377
Chronic Gout Management

Chronic Gout - Case 3

The same 53 year old man with HTN, nephrolithiasis and gout returns 9 months later complaining of another flare of joint pain in his feet (now 4 total in 3 years). His medications include ASA, HCTZ, lisinopril, and ibuprofen for the joint pain. He asks what can be done to prevent future attacks.

Choose the most correct answer:
A. Modify his diet to avoid foods with moderate-high purine content
B. Stop the thiazide
C. Stop the ACE inhibitor
D. Treat with probenecid
E. Treat with colchicine

53 y.o. man with HTN and nephrolithiasis with 4 gout attacks over 3 years asks what can be done to prevent future attacks. Choose most correct answer:

A. Avoid moderate-high purine foods
B. Stop thiazide
C. Stop ACE inhibitor
D. Treat with probenecid
E. Treat with colchicine

Case 3 (continued)

The same 53 year old man with HTN and nephrolithiasis returns 9 months later complaining of another flare of joint pain in his feet (now 4 total in 3 years). His medications include ASA, HCTZ, lisinopril, and ibuprofen for the joint pain. He asks what can be done to prevent future attacks.

Choose the most correct answer:

A. Modify diet to avoid foods with mod-high purine content
B. **Stop the thiazide**
C. Stop the ACE inhibitor
D. Treat with probenecid
E. Treat with colchicine
Uric Acid homeostasis

Treatment Approaches:
- Reduce Intake
- Reduce Production
- (Increase Metabolism)
- Increase Excretion


Non-Pharmacologic Uric Acid Lowering Therapy

Treatment Approaches:
- Reduce Intake
- Reduce Production
- (Increase Metabolism)
- Increase Excretion

Update: Not all high purine foods contribute to development of gout

Diet and Risk of Gout in Men

Men in the top quintile of intake compared with those in the lowest quintile (multivariate analysis)
Adapted from Choi HK, et al, New Engl J Med 2004, PMID 15014182

Treating Gout: Diet & Meds

Foods Moderately to Very High in Purines
- Hearts, sweetbreads, liver, Kidney, Herring, smelt, sardines, mussels, anchovies, Yeast
- Grouse, Turkey, Partridge, Goose, Pheasant, Mutton, Veal, Bacon
- Salmon, Trout, Haddock, Scallops

Medications that inhibit uric acid secretion
- Thiazide diuretics
- Aspirin (< 1 gm/d)

Beverages associated with hyperuricemia
- Beer
- High fructose drinks

Johns Hopkins: Diet and Gout
http://www.johnshopkinshealthalerts.com/reports/arthritis/460-1.html
Reasons to Start Uric Acid Lowering Therapy (ULT):

All of the following are indications for starting Uric Acid Lowering Therapy in patients with an established diagnosis of gouty arthritis EXCEPT:

a. Tophaceous Gout
b. Recurrent attacks of gout (≥2 attacks/year)
  - History of erosions on x-rays characteristic of gout
d. Serum urate ≥8.0
e. Presence of CKD class II or greater

Improved Outcomes in Gout Patients who achieve Uric Acid Reductions to Levels ≤6.0 mg/dl

- Reduced frequency of attacks

- Reduced tophus size

- Deplete crystal stores in synovial fluid

- Improved renal function in gout patients from less NSAID use

- Slows progression of existing renal disease

High serum urate level increases the risk of recurrent gout flares

Observational study of 267 patients with 1st episode of gout

Incidence of recurrent gouty attack >1 year after each patient’s first visit (%)

Average serum urate during the whole investigation period (mg/dL)

Uric Acid Reduction: The Controversy

"Evidence was insufficient to conclude whether the benefits of escalating urate-lowering therapy to reach a serum urate target ("treat to target") outweigh the harms associated with repeated monitoring and medication escalation."

ACP’s “5th recommendation”: “An alternative strategy [to "treat to target"] bases the intensity of urate-lowering treatment on the goal of avoiding recurrent gout attacks ("treat to avoid symptoms"), with no monitoring of urate levels.

Chronic Management in patients with recurrent attacks of gout

Uric Acid Lowering Therapy to Prevent & Treat Tophi!

Higher urate levels are associated with gout flares

229 gout patients treated for ≥ 5-yrs with ULT (with sUA < 6 mg/dL repeatedly)

**Personal Practice**

- Shared Decision-Making Model
- Long term ULT decisions
  - years, but not necessarily lifelong
  - Prophylaxis (or abortive Rx) during titration (3-6 months)
- Serum Urate Target (monitor sUA and adherence)
  - < 5 mg/dl for gout patients with aggressive disease
  - < 6 mg/dl for gout patients with active disease (flares or tophi)
  - < 7 mg/dl for gout patients that are in remission (on or off Rx)

**Pharmacologic Uric Acid Lowering Therapy**

Treatment Approaches:
- Reduce Intake
- Reduce Production
- (Increase Metabolism)
- Increase Excretion

**Uric Acid Lowering Therapy: Uricosurics**

- **Uricosurics**
  - **Probenecid**, 500-1000 mg 2x/d ($45/mo)
  - **Lesinurad**, 200 mg 1x/d ($371/mo)
    (Approved in combination with a xanthine oxidase inhibitor)
  - **Indication**:
    - Normal kidney function
    - Relatively low uric acid secretion ("underexcretors")
    - 24 hr urine collection: <700 mg/d of uric acid
  - **Contraindications**
    - Chronic Kidney Disease
    - Nephrolithiasis

*Modified from Burns CM, Wortmann RL, Lancet, 2011, PMID 20719377*

*The Medical Letter on Drugs and Therapeutics, 2017
Pharmacologic Uric Acid Lowering Therapy

Treatment Approaches:
• Reduce Intake
• Reduce Production
  • (Increase Metabolism)
  • Increase Excretion

Xanthine Oxidase Inhibitors:
Allopurinol - starting dose 100 mg/d (or less).
Gradually titrate up the dose every 2-5 weeks to chosen target.
Dose can be raised above 300 mg/d

Allopurinol warnings
• 2% develop a maculopapular eruption
• 0.1% develop hypersensitivity reaction (DRESS or SJS)

Rash onset:
• median 30 days after starting allopurinol
• 90% with 180 days

Update: Mitigating the Risk of Allopurinol Hypersensitivity

• HLA-B*5801 increases the risk of SJS/TEN up to 580 fold
• HLA-B*5801 has been found to vary by race/ethnicity and geographic region. In the US:
  – Caucasians & Hispanics <1%
  – African Americans 3.8%
  – Asians 7.4%
• Testing for HLA-B*5801 prior to allopurinol initiation in the US is cost-effective among African Americans and Asians, but not among Caucasians or Hispanics.

So what is the concern about allopurinol in patients with CKD?
Recommended maintenance dose of allopurinol based on the GFR

<table>
<thead>
<tr>
<th>GFR (ml/min)</th>
<th>Dose (mg/d)</th>
</tr>
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<tbody>
<tr>
<td>100</td>
<td>300</td>
</tr>
<tr>
<td>80</td>
<td>250</td>
</tr>
<tr>
<td>60</td>
<td>200</td>
</tr>
<tr>
<td>40</td>
<td>150</td>
</tr>
<tr>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>10</td>
<td>50</td>
</tr>
</tbody>
</table>

Adapted from Kelley, Textbook of Rheumatology, 1997

Renally-Dosed Allopurinol: Safety and Efficacy

Adherence to published allopurinol dosing guidelines led to suboptimal control of hyperuricemia and did not prevent hypersensitivity reactions. Dalbeth N et al. J Rheumatol, 2006

Severe hypersensitivity reactions are not dose dependent. Puig JG et al. J. Rheumatol, 1989


Starting allopurinol at a dose of 1.5 mg per unit of estimated GFR is associated with a reduced risk of allopurinol hypersensitivity. Stamp LK, et al, Arthritis Rheum 2012

What about febuxostat?

Update: Why not just prescribe febuxostat?

Costs of urate-lowering therapies

Use of febuxostat as 2nd line therapy after allopurinol is cost effective.

**Tip:** Treat with Colchicine when initiating uric acid reducing agent

- >60% of patients will have a gout flare after starting treatment with febuxostat or allopurinol. (Becker MA, et al, NEJM 2005)
- Colchicine 0.6mg/d prophylactic therapy helps prevent attacks
- Avoid continuing colchicine for more than 6 months
- Colchicine toxicity: (especially in renal insufficiency)
  - Myopathy
  - Neuropathy
  - Bone marrow suppression
  - GI upset

2012 American College of Rheumatology guidelines for management of gout

**“Treatment Failure Gout”**

- In the majority of patients with gout, there is inadequate control of hyperuricemia or gout symptoms
- Usually this is due to:
  - Inadequate management by the physician
  - Poor compliance by the patient with medical therapy

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**UK community-based RCT: Nurse-led care vs. general practitioner care of gout**

Methods: 517 participants with acute gout randomized to

- Nurse-led, trained about gout and its management according to recommended best practice (EULAR and BSR guidelines)
- Continuing GP care

<table>
<thead>
<tr>
<th></th>
<th>Nurse-led (n=255)</th>
<th>GP (n = 262)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62</td>
<td>64</td>
</tr>
<tr>
<td>Male (%)</td>
<td>90%</td>
<td>90%</td>
</tr>
<tr>
<td>Mean disease duration (yrs)</td>
<td>11.6</td>
<td>11.7</td>
</tr>
<tr>
<td>Attacks per year (prior year)</td>
<td>4.2</td>
<td>3.8</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>17.7</td>
<td>17.7</td>
</tr>
<tr>
<td>Mean sUA umol/L</td>
<td>462</td>
<td>459</td>
</tr>
<tr>
<td>GFR</td>
<td>75.5</td>
<td>75.2</td>
</tr>
<tr>
<td>ULT use</td>
<td>40%</td>
<td>30%</td>
</tr>
<tr>
<td>Withdrew during study</td>
<td>8.6%</td>
<td>20.6%</td>
</tr>
</tbody>
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**UK-RN study: ULT use**

- Mean Allopurinol dose (mg/day)
UK-RN study: Serum urate outcomes

UK-RN study: Clinical Outcomes

Summary

- In patients presenting with monoarticular arthritis, infection is the primary concern
- Recognize signs of acute gout
- Gout can cause severe arthritis but can easily be managed (although often it is not).
- Chronic Gout can be managed with diet, uricosurics and/or xanthine oxidase inhibitors
- Shared decision making with patients can help address the controversy of “treat to target” versus “treat to symptoms”

Thanks!
Additional Reading


- Does this adult patient have septic arthritis? Margaretten ME, et al, JAMA 2007, PMID 17405973