Current Strategies for Gout and Other Types of Monoarticular Arthritis

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Disclosures

• None
Teaching Objectives

• Be able to distinguish septic arthritis from crystal induced arthritis
• Be familiar with management of acute & chronic gout
• Be familiar with diagnosis and management of calcium pyrophosphate disease

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 101.4. 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
Case 1

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Differential Diagnosis of monoarticular arthritis

- Septic Arthritis
  - Gram Positive cocci
  - Gram Negative Rods
  - Lyme disease
  - Tb/Fungal
- Crystal Arthritis
  - Gout
  - Pseudogout
- Spondyloarthritis (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 determine if an infection is present without waiting for the cultures?
Risk factors for septic arthritis

- Recent joint surgery (Likelihood ratio 6.9)
  - Recent arthroplasty (LR 3.1)
- Age >80 (LR 3.5)
- Local wound/skin infection (LR 2.8)
- Diabetes (LR 2.7)
- Rheumatoid arthritis (LR 2.5)
- Immunosuppression (esp. TNF inhibitors)
- HIV
- IV drug use

About 50% of patients will have a fever >101°

Margaretten ME, et al, JAMA 2007, PMID 17405973

Synovial Fluid Analysis is Somewhat Helpful to Identify Septic Arthritis

- 49 culture-positive synovial fluid aspirates
- 39% had WBC <50,000/mm³
- 55% had a negative Gram’s stain
  - 56% of those patients had a synovial WBC of <50000/mm³.
- WBC <10,000/mm³ has a very strong negative predictive value for septic arthritis
- WBC >100,000/mm³ has a strong positive predictive value
- Gram stain is 40-60% sensitive
- Cultures are 90% sensitive

An aside about septic arthritis

All of the following tests should be considered in a 30 year old woman with subacute development of a warm swollen knee with synovial fluid 50,000 WBCs/mm$^3$ EXCEPT:

a) Blood cultures
b) Lyme disease ELISA on serum
c) Synovial fluid LDH and glucose
d) Vaginal swab for gonococcus & chlamydia (by nucleic acid amplification testing)
e) PPD & synovial biopsy for AFB stain & mycobacterial culture
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Septic Arthritis

- Blood cultures are reported to be positive in 50–70% of pts
- Route of infection:
  - Hematogenous seeding
  - infected contiguous foci or neighboring soft-tissue sepsis
  - direct inoculation due to trauma
- Organisms
  - *Staph aureus* (~50%)
  - *Streptococcus* species (~20%)
  - Gram Negative Rods (20%)
- Septic joints should be drained (repeated aspiration or arthroscopically)

Subacute Arthritis of the Knee

Table 1  Final diagnoses in 296 consecutive outpatients presenting with isolated knee monoarthritis observed over a 6-year period

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No.</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoarthritis and knee degenerative disorders</td>
<td>164</td>
<td>55.4</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>49</td>
<td>16.5</td>
</tr>
<tr>
<td>Spondyloarthritides</td>
<td>34</td>
<td>11.5</td>
</tr>
<tr>
<td>Chondrocalcinosis</td>
<td>22</td>
<td>7.4</td>
</tr>
<tr>
<td>Gout</td>
<td>10</td>
<td>3.4</td>
</tr>
<tr>
<td>Septic arthritis</td>
<td>6</td>
<td>2.0</td>
</tr>
<tr>
<td>Non-small-cell lung cancer</td>
<td>5</td>
<td>1.7</td>
</tr>
<tr>
<td>Villonodular synovitis</td>
<td>4</td>
<td>1.3</td>
</tr>
<tr>
<td>Hemarthrosis</td>
<td>2</td>
<td>0.7</td>
</tr>
</tbody>
</table>

No Lyme Disease?... Italian Study

Cantini F et al, Ann Rheum Dis, 2007, PMID 17768172

Back to our question:
What can help us determine if an infection is present 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

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.
Case 3

A 53 year old man with HTN & nephrolithiasis comes to see you for recurrent foot pain. His first attack of joint pain 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 affecting joints in both feet. 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 BID, indomethacin 50mg TID)
b) Prednisone: 40-60 mg/d, tapered over 6-18 days
c) Intra-muscular corticosteroid injection. (Triamcinalone 60-80 mg IM; may need to repeat in a couple of days)
d) Intra-articular steroid injection (Triamcinalone 20-40 mg)
e) Colchicine 0.6 mg every 30 minutes until resolution or GI upset
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 q 30 min

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e) Colchicine 0.6 mg every 30 minutes 1.2 mg then 0.6 mg 1 hour later. Do not repeat for 2 weeks if Pt has CKD.
Efficacy of Oral Colchicine for Acute Gout


Diarrhea
26%, 0%
77%, 19%

“high-dose” colchicine (1.2 mg followed by 0.6 mg every hour for 6 hours [4.8 mg total])

“low-dose” colchicine (1.2 mg followed by 0.6 mg in 1 hour [1.8 mg total])

% improvement vs. % patients improved

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**

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

<table>
<thead>
<tr>
<th></th>
<th>Cases (n/Total)</th>
<th>Controls (n/Total)</th>
<th>OR* (95% C.I.)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No previous renal disease or gout/hyperuricaemia</td>
<td>6/43</td>
<td>33/143</td>
<td>0.57 (0.20, 1.6)</td>
<td>0.3</td>
</tr>
<tr>
<td>Previous renal disease, but no gout/hyperuricaemia</td>
<td>14/38</td>
<td>2/20</td>
<td>6.6 (0.8, 57.9)</td>
<td>0.089</td>
</tr>
<tr>
<td>Gout/hyperuricaemia, but no previous renal disease</td>
<td>8/17</td>
<td>4/21</td>
<td>7.1 (1.3, 39.7)</td>
<td>0.027</td>
</tr>
<tr>
<td>Previous renal disease and gout/hyperuricaemia</td>
<td>4/12</td>
<td>0/5</td>
<td>82.2 (4.1, 1661.1)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Henry D, et al, Br J Pharmacol 1997,

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


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**Mechanism of Inflammation in Gout**

![Mechanism of Inflammation in Gout](image)

Neogi T, NEJM 2011, PMID 21288096
IL-1 antagonism in 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

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 his diet to avoid all foods with high purine content
B. Stop the thiazide
C. Stop the ACE inhibitor
D. Treated 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:

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Non-Pharmacologic Treatment of Gout

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

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
- Loop diuretics
- Aspirin (< 1 gm/d)

Beverages associated with hyperuricemia
- Beer
- High fructose drinks

Johns Hopkins: Diet and Gout
http://www.johns-hopkinshealthlets.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)
c. History of erosions on x-rays characteristic of gout
d. Serum uric acid ≥8.0
e. Presence of CKD class II or greater
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**d. Serum uric acid ≥8.0**  
e. Presence of CKD class II or greater
Incidence of Gout among Men

<table>
<thead>
<tr>
<th>Serum Urate Level:</th>
<th>&lt;6</th>
<th>6-6.9</th>
<th>7-7.9</th>
<th>8-8.9</th>
<th>9-9.9</th>
<th>&gt;10</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year cumulative</td>
<td>0.5%</td>
<td>0.6%</td>
<td>2.0%</td>
<td>4.1%</td>
<td>9.8%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Recurrence of acute gout arthritis following initial attack:

- <1 year: 62%
- 1-2 years: 16%
- 2-5 years: 11%
- Never: 7%


Gutman AB, Gout, Beeson & McDermott (ed): Textbook of Medicine, 12th Ed., 1958

Chronic Management in patients with recurrent attacks of gout

Uric Acid Lowering Therapy to Prevent & Treat Tophi!
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 with reduction of NSAID use

Slows progression of existing renal disease

Pharmacologic Uric Acid Lowering Therapy

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

- Uricosurics (probenecid) are recommended for patients with normal kidney function & without urate nephrolithiasis who are “underexcretors” (24 hr urine collection: <700 mg/d of uric acid)
- The majority of patients with recurrent gout will have chronic kidney disease and should be treated with xanthine oxidase inhibitors (allopurinol, febuxostat).

2012 American College of Rheumatology guidelines for management of gout

Pharmacologic Uric Acid Lowering Therapy

Many patients are started on Allopurinol 300 mg/d and do not achieve Uric Acid <6.0

So what is the concern about allopurinol in patients with CKD?
Allopurinol warnings

- 2% develop a rash
  - Much higher in patients with HLA–B*5801. High frequencies seen in Han Chinese & Thai populations

- 0.1% develop hypersensitivity reaction (DRESS)
  - Cutaneous Rash 92%
  - Fever 87%
  - Renal Dysfunction 85%
  - Eosinophilia 73%
  - Hepatitis 68%
  - Leukocytosis 39%
  - Death 21%


Recommended maintenance dose of allopurinol based on the GFR

<table>
<thead>
<tr>
<th>GFR (ml/min)</th>
<th>Dose (mg/d)</th>
</tr>
</thead>
<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
Dose Adjustment of Allopurinol According to Creatinine Clearance Does Not Provide Adequate Control of Hyperuricemia in Patients with Gout

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
Why not just prescribe febuxostat?

Costs of urate-lowering therapies

<table>
<thead>
<tr>
<th></th>
<th>Allopurinol</th>
<th>Probenecid</th>
<th>Febuxostat</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-month</td>
<td>19</td>
<td>59</td>
<td>162</td>
</tr>
<tr>
<td>12-month</td>
<td>230</td>
<td>706</td>
<td>1944</td>
</tr>
</tbody>
</table>

Courtesy of Gabriela Schmajuk, UCSF

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


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

Case 4

An 82 year old man with a history of diabetes, CKD, and osteoarthritis is brought to see you for agitation. On exam his temp is 101.1°F and he is somewhat disoriented. The exam is only notable for warmth & swelling of the right knee. In addition to obtaining blood and urine tests & cultures, you aspirate the knee to evaluate for:

A. Septic Arthritis
B. Gout
C. Pseudogout (acute CPPD)
D. All of the above
82 y.o. man with fever, delerium and knee swelling. You aspirate the knee to evaluate for:

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B. Gout  
C. Pseudogout  
D. All of the above

How many of you have been in this situation and **always** performed the joint aspiration?
Tips for Knee Aspiration

watch NEJM video: DOI 10.1056/NEJMvcm051914

- If sending cultures,
  - Achieve sterile environment with betadine or hibiclens.
  - Use sterile gloves
- Anesthetize with 1% lidocaine (but can dissolve crystals)
- Use a 20-22G needle and 10 cc syringe

Don’t:
- Aspirate through cellulitis
- Aspirate after acute injury and fracture is a concern
- Aspirate a prosthetic joint
- (patient is anti-coagulated)

Acute CPPD is an excellent mimicker of septic arthritis

- Systemic Symptoms are common, especially in the elderly
  - 25% of patients present with fever 38-39°C
  - 10% of patients have mental status changes
- Preferentially affects larger joints (wrists, elbows, shoulders, hips, knees, ankles)
- CPPD can coexists with septic arthritis (just like gout)

Masuda I & K Ishikawa, Clin Orthop Relat Res, 1988, PMID 3349673
Papanicolas LE, et al, J Rheumatol 2012
Chondrocalcinosis
Calcium pyrophosphate (CPP) crystal mediated disease (CPPD)

Rosenthal AK & Ryan LM, Nat Rev Rheumatol 2011

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Calcium pyrophosphate (CPP) crystal mediated disease (CPPD)

<table>
<thead>
<tr>
<th>Clinical presentations associated with CPPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic CPPD</td>
</tr>
<tr>
<td>OA with CPPD</td>
</tr>
<tr>
<td>Acute CPP crystal arthritis</td>
</tr>
<tr>
<td>Chronic CPP crystal inflammatory arthritis</td>
</tr>
</tbody>
</table>

Abhishek A & Doherty M, Nat Rev Rheumatol 2011
Secondary causes of CPPD

- Hyperparathyroidism
- Hypophosphatasia
- Hypomagnesemia
  - Bartter syndrome (hypomagnesemia, hypokalemia, metabolic alkalosis)
  - Gitelman syndrome (hypomagnesemia, tubular hypokalemia, hypocalciuria)
- Hemochromatosis

Treatment of Pseudogout

- Joint Aspiration
- Corticosteroid Injection

- NSAIDS (naproxen 500mg BID, indocin 50mg TID, voltaren)
- Prednisone: 30-60mg qd, taper over 6-18 days
- Colchicine 0.6 mg qD - BID
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).
- Acute calcium pyrophosphate disease (CPPD) is a strong mimicker of septic arthritis in the elderly.

Thanks!
Additional Reading


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

- EULAR recommendations for calcium pyrophosphate deposition. Part I & II; Ann Rheum Dis, 2011