AAFP Chapter Lecture Series:
Management of Gout – Individualizing the Approach

Presented By

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AAFP Chapter Lecture Series: Management of Gout - Individualizing the Approach

Please select the most appropriate answer to each of the following questions by filling in the bubble next to the corresponding answer. Please be sure to fill in the bubble of your response completely.

### Pre-Assessment Questions:

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<tr>
<th>Question # 1</th>
<th>A</th>
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### Post-Assessment Questions:

*NOTE: The orders of the questions and answers have been scrambled and are not in the same order as the pre-assessment questions.*

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Please rate your agreement to the following statements. Please be sure to fill in the bubble of your response completely.

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<tr>
<th>Statement</th>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Neutral</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
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<tr>
<td>Overall, I would rate B. Wayne Blount, MD, MPH, FAAFP as excellent.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
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<td>The content presented in this session covered the stated learning objectives.</td>
<td>5</td>
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<td>The session was appropriately paced to sufficiently cover the amount of material presented.</td>
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<td>The content of this session was of an appropriate level.</td>
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<td>The content of this session was free from commercial bias.</td>
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<td>The course material content adequately supported the presentation.</td>
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Please provide any additional comments related to the faculty/session.

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
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Based on the session content, my next step will be to (check all that apply):

1. Pursue additional education/reading
1. Discuss content with colleagues to obtain a consensus about a practice change
1. Continue current practice
1. Implement a change in practice from what I have learned in this session

If you intend to make a practice-based change(s) in patient care, please describe the change(s):

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

Future topics of interest:

________________________________________________________________________
Why worry about gout?
- Prevalence increasing (3.9%)
- Most common inflammatory arthritis: 3.9% of adults
- May be signal for unrecognized comorbidities (Not to point of searching)

Urate, hyperuricemia, & gout
- Urate: end product of purine metabolism
  Hyperuricemia: serum urate > urate solubility
  (> 6.8 mg/dL)
- Gout: deposition of monosodium urate crystals in tissues

Two pathologic mechanisms cause hyperuricemia
1. Overproduction
2. Underexcretion
  - Which one is the predominant cause (in 90% of patients)?
  - Underexcretion

Hyperuricemia & gout
- Hyperuricemia caused by
  - Overproduction
  - Underexcretion
- No Gout w/o crystal deposition

The gout cascade

Gout: a chronic disease of 4 stages
- Asymptomatic hyperuricemia
- Acute flares of crystallization
- Intervals between flares
- Advanced gout & complications

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Asymptomatic hyperuricemia

- Most people with hyperuricemia never develop clinical gout.
- In those who do, the hyperuricemia can last 20 years before an initial attack.
- Onset before age 35 is often related to an inherited defect.

2nd Stage: acute flares

- 2nd stage of gout is heralded by the 1st acute attack
- 90% of 1st attacks are monoarticular; any joint is a possibility
- ___% are podagra
  50

Acute gouty flares

- Abrupt onset of severe joint inflammation, often nocturnal
  - Warmth, swelling, erythema, & pain; possibly fever
  - Untreated? Resolves in
    - 3-10 days

Sites of acute flares

- ___% of gout patients eventually have podagra: 1st MTP joint
  - 90

Sites

- Can occur in other joints, bursa, & tendons

3rd Stage: intervals sans flares

- Asymptomatic
- If untreated, may advance
- Intervals may shorten
- Crystals in asx joints
- Body urate stores increase
Flare intervals

Silent tissue deposition & hidden damage

4th Stage: advanced gout

- Chronic arthritis
- X-ray changes
- Tophi develop
- Acute flares continue

Advanced gout

- Chronic arthritis
- Polyarticular acute flares with upper extremities more involved
- Avg. time from initial attack to chronic gout is 11.6 yrs.

Tophi

Solid urate deposits in tissues

Tophi

Irregular & destructive

Tophi risk factors

- Long duration of hyperuricemia
- Higher serum urate
- Long periods of active, untreated gout
Radiologic signs (Difference vs. R.A.?)

- Calcified, overhanging edge is typical of gout

Diagnosing gout
- Hx & PE
- Synovial fluid analysis
- Not serum urate
- ? Clinical diagnosis?

Serum urate levels
- Not reliable
- May be normal with flares
- May be high with joint Sx from other causes

Gout risk factors
- Male
- Postmenopausal female
- Older
- Hypertension
- DM
- HLD
- Pharmaceuticals
- Diuretics
- ASA
- Niacin
- Cyclosporine
Gout risk factors
- Transplant
- Alcohol intake
  - Highest with beer
- High BMI (obesity)
- Diet high in meat & seafood
- High Fructose corn syrup sweetened drinks (not diet drinks)
- Dairy products may decrease risk

Other comorbidities to check for
- Lead toxicity
- Hx of urolithiasis
- CKD

Synovial fluid analysis (polarized light microscopy)
- The gold standard
- Crystals intracellular during attacks
- Needle & rod shapes
- Strong negative birefringence

Differential diagnosis
- Pseudogout
- Chondrocalcinosis
- CPPD
- Psoriatic arthritis
- Osteoarthritis
- Rheumatoid arthritis
- Septic arthritis
- Cellulitis

Gout vs. CPPD
- Similar acute attacks
- Different crystals under micro
  - Rhomboid (irregular in CPPD)
Gout vs. CPPD

RA vs. gout

Both have polyarticular, symmetric arthritis
Tophi can be mistaken for RA nodules

RA vs. gout

? Clinical Dx ?

Typical presentation
Use colchicine in a typical presentation
Familial Mediterranean fever (now also pericarditis)
Ultrasonography use is increasing
New rule for Dx: next slide

Rule for clinical Dx

Scoring:
- Male: 2 Pts
- Previous attack: 2 Pts
- Onset < 1 Day: ½ Pt
- Joint redness: 1 Pt
- 1st MTP involved: 2½ Pts
- HTN or another CV Dz: 1½ Pts
- Urate > 5.88 mg: 3½ Pts

Kienhorst L. Rheumatology, Sept 16, 2014

Treatment goals

- Rapidly end acute flares
  - Protect against future flares
  - Reduce chance of crystal inflammation
  - Prevent disease progression
- Lower serum urate to deplete total body urate pool
- Correct metabolic cause

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Ending acute flares

- Control inflammation, pain, & resolve the flare
- Not a cure
- Crystals remain in joints
- Choice of med not as critical as alacrity (within 24 hrs) & duration(?) EBM
  - At least 3 days; usually 5-7 days (or 1-2 days after Sx relief)

MED considerations

- NSAIDs:
  - Interaction with warfarin
  - Contraindicated in:
    - Renal disease
    - PUD
    - GI bleeders
  - ASA-induced RAD at full dose
  - ASA-treated CAD
  - CHF

- Colchicine:
  - Not as effective “late” in flare (>72 hrs)
  - Only 1 branded agent on US market now: $$
  - Now have generic
  - Contraindicated in dialysis pts
  - Cautious use in: renal or liver dysfunction; active infection, age > 70
    - Numerous Meds increase serum colchicine: Statins, digoxin, macrolides, azoles, CCBs, grapefruit
  - *Loading dose = 1.2 mg; then 0.6 mg 1 hr. later

MED considerations

- Corticosteroids:
  - Worse glycemic control
  - Oral, intraarticular (esp. in monoarticular flare), or parenteral
  - May need to use mod-high doses.
  - New Guidelines suggest 10 mg/day: I disagree
    - Needs to be higher: ≥ 20 mg
    - Useful in patients who have contraindications to NSAIDs & colchicine

General considerations

- Patients with repetitive flares can be instructed to start flare med at home w/o consulting physician.
- Can use ice.
- Choose monotherapy based on patient's preference, previous response and assoc. comorbidities.
- May need combination med Rx in a flare; esp. if < 20% relief in 24 hrs.
Treatment goals

- Rapidly end acute flares
  - Protect against future flares
  - Reduce chance of crystal inflammation
- Prevent disease progression
  - Lower serum urate to deplete total body urate pool
  - Correct metabolic cause

Protection vs. future flares

- Colchicine: 0.6-1.2 mg/day (0.3 if CRI)
- Low-dose NSAIDs (e.g., 25 mg of indomethacin or 250 mg of naproxen)
- Both decrease freq. & severity of flares
- Prevent flares with start of urate-lowering RX
  - Best with 6 mos of concomitant RX; ≥3 months w/o flare or > 3 mos after urate < 6.0 & no tophi
  
  EBM: B
  - Won’t stop destructive aspects of gout

Use of colchicine

- Only drug approved by FDA for preventing acute flares
  - Used as 0.6 mg Q day or BID for 6 months EBM: B; (3% flares vs. 40%)
  - A.E.s: Diarrhea, LFTs, HA

  *Start the prophylactic dose 12 hrs. after the 2nd dose for the acute flare

New evidence for preventing flares

- Cherry intake lowers risk for flares by 35%
- Cherry extract intake lowers risk for flares by 45%
- Allopurinol alone reduces risk by 53%
- Allopurinol & cherries together reduced it by 75%
- Anti-inflammatory and/or reduce urate reabsorption in kidneys
  
  Arthritis & Rheumatism, Sept 28, 2012

Urate-Lowering Therapy (ULT)

- Not to be started during an acute attack? New ACR guidelines say can start it right away if still on a flare med. Two good studies support this.
- Difference of opinion on whom to start ULT
  - Everyone with Gout?
  - Not in patients with only 1 attack & no complications (tophi, CRI, stones, or diuretic use)
  - Shared Decision*
  - Definitely all patients with 3 attacks or tophi or urolithiasis or CKD > stage 2

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Prevent disease progression

- **Lower urate to < 6.0 mg/dL:** This depletes total body urate pool & deposited crystals **EBM: A**
- Rx is lifelong & continuous
- MED choices:
  - Uricosuric agent
  - Xanthine oxidase inhibitor
  - Uricase

Prevent this

Conservative measures to lower urate

- Diet: Reduce purines
- Alcohol: Cut
- Obese?: Lose Weight
- Avoid meds that cause inc. urate: thiazides, loops, niacin
- The above 4 measures will lower urate by 10-15%
- Avg. starting level is 9.5 – 10
- Rarely get to < 6.0 with these measures, but they help.

Conservative measures to lower urate

- Stay hydrated
- Exercise regularly
- Avoid drinks with high fructose corn syrup
- Eat more veggies: lower urate

Uricosuric agents

- Probenecid: The only FDA approved one
- Avoid in pts with lithiasis or Ccl < 50 mL/min
- Losartan & fenofibrate for mild disease
- Vitamin C supplements
- Increased secretion of urate into urine (increases stones)
- Reverses most common physiologic abnormality in gout (90% pts are underexcretors)
- 1/3 patients discontinue it
- Increases levels of methotrexate & ketorolac

Xanthine oxidase inhibitor

- **Allopurinol, oxypurinol, or febuxostat:**
  - Block conversion of hypoxanthine to uric acid
  - Effective in overproducers
  - Also effective in underexcretors
  - Can work in patients with renal insufficiency

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**Which agent?**

<table>
<thead>
<tr>
<th></th>
<th>Allopurinol</th>
<th>Uricosuric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Issue in renal disease</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Potentially fatal hypersensitivity syndrome</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Risk of nephrolithiasis</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Multiple daily dosing</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

**Which agent**

- Base choice on previous considerations & whether pt is an overproducer or underexcretor:
  - Need to get a 24-hr. urine for urate excretion:
    - < 700 --- underexcretor (uricosuric)
    - > 700 --- overproducer (allopurinol)

**NO!!!**

**However ...**

- New evidence:
- Allopurinol is now the 1st choice for U.L.T.
- ACR
- WHY?

**Allopurinol**

- Allopurinol may lower all-cause mortality & C.V. events; EBM: C
- In CKD, allopurinol may slow progression of CKD; EBM: C
- Adjust dose in CKD
- Remember AEs; esp. allopourinol hypersensitivity syndrome. (0.1%) If rash, stop med, and come in. (CKD & diuretics!)
- Lowering sUA is dose-dependent:
  - Achieved goal sUA: 26% @ 300 mg/day vs. 78% @ 300 mg BID

**Using allopurinol “Treat to Goal”**

- *Start at 100 mg/day (higher starting dose can increase risk for AHS)*
- 50 mg/day in stage 4 CKD patients
- Gradually titrate up by 50-100 mg/day every 2 – 5 weeks
- Slower titration in CKD
- Treat to Goal (Lowest dose that gets < 6.0)
- Lowering urate too quickly can trigger a flare

- Goal is ...
- Serum urate ≤ 6 mg/dL

*Most patients will need > 300 mg/day of allopurinol to achieve this goal*
New recommendation

- To reduce allopurinol toxicity, consider HLA-B*5801 screening patients @ high risk:
  - Koreans > Stage 3 CKD &
  - All patients of Han Chinese & Thai descent

New recommendation

- To get to goal, can use combination of xanthine oxidase inhibitor & uricosuric

Febuxostat

- Xanthine oxidase inhibitor
- Does lower sUA
- May slow renal disease progression
- Dose: 40 mg or 80 mg Q day. Start low and increase as tolerated if needed
- AEs: LFTs
- Best candidate may be pt intolerant of allopurinol, not controlled with other ULT, or CRI; preferred over uricosurics in patients with lithiasis. Can use in patients with AHS.
- $$

Febuxostat

- You may have heard it is more effective than allopurinol:
  - Wait! The study was done with doses commonly used.
  - Febuxostat was used at effective doses.
  - Allopurinol was not used at effective doses.
  - Study also funded by maker of febuxostat.


Uricase

- Only 1 in U.S.: Pegloticase
- Given by I.V. infusion every 2 weeks
- Steroids & H1 blocker before RX
- Even with prophylaxis, flares will occur
- 25% patients have serious AE: inc. anaphylaxis
- Not in G6PD patients
- A urate debulking agent
- I would let my subspecialty consultants use this med for now in limited patients
- A 3rd line agent
- $$$

Future agents

- RX gaps
- Can’t always get urate < 6
- Allergies
- Drug interactions
- Allopurinol intolerance
- Worse renal disease
IL-1 inhibitors

- IL-1: an important mediator of the early inflammatory response to urate crystals
- Proof of concept established for both treatment and prophylaxis of flares
- In Development: stay tuned
- Better uricosurics: selective urate reabsorption inhibitor

CASE STUDIES

CASE J.F.

- 80 yo W F c/o acute overnight pain and swelling in R knee
- PE: 5’1” and 180 lbs.
  - R knee swollen, warm, and erythematous
- PMH: HTN x 5 yrs
- Meds: HCTZ (25 QD) & ASA
- SH: 20 PY smoker; 5 wine drinks/wk

What are J.F.’s risk factors for gout?

- HTN
- Smoker
- HCTZ
- ASA
- Wine consumption
- Obesity
- Age
- Postmenopausal

How would you Dx gout?

- Hx and PE compatible
- Check serum urate level
- Assess synovial fluid
- Trial of colchicine
- Check x-rays

IF you Dx gout, which Rx today? (Why?)

- Motrin
- Indomethacin
- Prednisone
- Allopurinol
- Probenecid
- Colchicine
Next step for J.F.?
- Modify risk factors
- Give refills to Rx next flare
- Start colchicine to prevent flares
- Check serum urate level
- Start allopurinol
- Start probenecid

Case M.B.
- 56 YO W M c/o hand stiffness & growths
- PE: 6'2'' and 205 lbs.
  Multiple tophi; chronic arthritis
- PMH: DM x 8 yrs.; gout x 4 yrs., but no flares x 3 yrs., & lost 20 lbs. on Atkins diet
- Meds: Glyburide; colchicine (0.6 mg TID)
- Labs: Creat. = 2.0; Urate = 11.4

In what stage of gout is M.B.?
- Doesn’t have gout
- ASX. hyperuricemia
- Interflare period
- Advanced gout

Would you change MD’s Rx?
- No – Not gout
- No – No flare x 3 yrs.
- Yes - Increase colchicine
- Yes – Add allopurinol
- Yes – Add probenecid

What other issues would you consider?
- Renal dysfunction
- Weight
- DM
- Glyburide
- Diet

Practice recommendations
- Use the correct criteria to diagnose gout
- Know and use in practice the 4 stages of gout
- Know the meds that work in each stage
- Allopurinol is 1st line for ULT
- Overlap flare prevention with ULT
- Watch for & advise of T.E.N.S.
- Set a goal of ≤ 6.0 for the serum urate level for gout patients

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Conclusions

- Gout is chronic with 4 stages
- Uncontrolled gout can lead to severe disease
- Separate Rx for flares & preventing advancement
- Many meds for flares
- Treating the disease requires lowering urate
- Get a 24-hr urine for urate excretion

Question & Answers

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