Gout and Hyperuricemia

Ron Butendieck, M.D.
Mayo Clinic
April 9, 2016
Disclosures

• None
Outline

• Hyperuricemia

• Brief background on gout

• Making the diagnosis

• Treatment of acute gout

• Treatment during inter-critical period
Asymptomatic Hyperuricemia

- Prevalence of hyperuricemia
  - Men: 21.5% (SUA level >7.0 mg/dL)
  - Women: 19.1% (SUA >5.7 mg/dL)
    4.7% (SUA >7.0 mg/dL)

- Age and serum uric acid
  - Relatively stable in men after puberty
  - Rises 25% in woman as they age
    - Estrogen promotes renal uric acid excretion
    - Sharp rise in SUA after menopause

Anton FM. Metabolism, 1986
Asymptomatic Hyperuricemia

• Associated with hypertension, obesity, renal insufficiency, atherosclerosis, and insulin resistance

• Increase risk for renal stones

• Family history of gout common

• While only about 1/3 pts with hyperuricemia will develop disease, increased risk with higher level of SUA
  • In patients with uric acid > 9.0 mg/dl, gout develops in 5 years in about 20%
Hyperuricemia

- Primary

- Secondary
  - Overproduction of uric acid (10%)
  - Underexcretion of uric acid (90%)
Secondary Hyperuricemia: Underexcretion

- Intrinsic renal disease
- Chronic renal insufficiency
- Volume depletion
- Familial juvenile hyperuricemic nephropathy
- Medullary cystic kidney disease
- Saturnine gout
- Drug-induced
Secondary Hyperuricemia: Underexcretion

- Drug-Induced
  - Thiazide and loop diuretics
  - Ethambutol
  - Low dose ASA
  - Cyclosporine/tacrolimus
  - Nicotinic acid
  - Pyrazinamide
  - Ethanol
  - Laxative abuse → alkalosis
Secondary Hyperuricemia: Overproduction

• Clinical disorders
  • Myeloproliferative disorder
  • Lympho/plasma cell proliferative disorder
  • Disseminated carcinoma/sarcoma
  • Sickle cell anemia
  • Psoriasis
  • Obesity
  • Down Syndrome
  • Glycogen storage diseases
Secondary Hyperuricemia: Overproduction

- Enzyme abnormalities in uric acid pathway
  - Lesch-Nyhan Syndrome
    Complete Deficiency of HGPRT-ase
  - 5-Phosphoribosyl-1-Pyrophosphate (PRPP) Synthetase Overactivity
  - Disordered ATP metabolism
Gout: Background

• Deposition of monosodium urate (MSU)
• Most common form of inflammatory arthritis
• Classically in a middle aged man
• Podagra in about 50% 1st attacks
• Prevalence
  • Men 5.9%, women 2%
• Incidence and prevalence on the rise

Smith E. Ann Rheum Dis, 2014
Acquired Gout and Sources of Uric Acid

• Purine source: 1/3 dietary, 2/3 cell turnover

• Diet: Not all purines contribute equally
  • Uric acid rises more from consumption of meat than vegetables with equivalent purine content
  • Purine-free diet lower SUA by 1.8 mg/dl

• Diet important, but often not sufficient
  • Recommend healthy diet with lower seafood intake

Gout: Making the Diagnosis

- 2015 ACR/EULAR Classification Criteria
- Sensitivity 92%; Specificity 89%

- Tried to address the following challenges:
  - Majority of gout managed in acute care or primary care setting where fluid analysis rarely performed
  - Prior criteria focused on acute attacks only
  - New imaging available to aid in diagnosis

Gout: Making the Diagnosis

• Step 1: Entry criterion
  • At least 1 episode of swelling, pain, or tenderness in a peripheral joint or bursa

• Step 2: Sufficient criterion
  • Presence of MSU crystals in a symptomatic joint or bursa or tophus

• Step 3: Criteria
  • If ≥ 8 points, fulfills criteria for gout
Gout: Making the Diagnosis

- Pattern of joint/bursa involvement during symptomatic episode(s)
- Characteristics of symptomatic episode(s)
- Time course of symptomatic episode(s)
- Clinical evidence of tophus
- Serum urate level, off-treatment
- Synovial fluid analysis
- Imaging evidence of urate deposition
- Imaging evidence of gout-related joint damage
Pattern of joint/bursa involvement during symptomatic episode(s)

• Ankle or midfoot → +1 point
• Podagra → + 2 points
Characteristics of symptomatic episode(s)

- Erythema overlying affected joint
- Can’t bear touch or pressure to affected joint
- Great difficulty with walking or inability to use affected joint

- 1 point each
Time Course of Symptomatic Episode

- Presence (ever) of ≥ 2
  - Time to maximal pain < 24 hours
  - Resolution of symptoms ≤ 14 days
  - Complete resolution (to baseline level) between symptomatic episodes

- One typical episode → +1 point
- Recurrent typical episodes → +2 points
Clinical evidence of tophus

- Draining or chalk-like subcutaneous nodule under transparent skin, often with overlying vascularity, located in typical locations: joints, ears, olecranon bursae, finger pads, tendons (e.g., Achilles)

- If present $\rightarrow + 4$ points
Laboratory

• Serum urate:
  • < 4 mg/dl → - 4 points
  • 6–8 mg/dl → +2 points
  • 8–10 mg/dl → +3 points
  • > 10 mg/dl → +4 points

• Synovial fluid analysis of a symptomatic (ever) joint or bursa
  • If negative, subtract 2 points
Imaging

• Imaging evidence of urate deposition
  • Ultrasound: “double contour sign”
  • DECT

• If present (either modality) → +4 points

• Imaging evidence for gout-related joint damage
  • Conventional radiography of the hands and/or feet demonstrates at least 1 erosion

• If present → +4 points
Double contour sign
Gout: Triggers for Attack

- Trauma
- Major medical illness/infection
- Fasting (acidosis)
- Dehydration
- Alcohol
- Surgery
- Dietary indiscretions
Gout: Treatment of acute attacks

Seminars in Arthritis and Rheumatism

Treatment of acute gout: A systematic review
Puja P. Khanna, MD, MPH¹,²,*,¹, Heather S. Gladue, DO³, Manjit K. Singh, MD⁴, John D. FitzGerald, MD, PhD⁵,², Sangmee Bae, MD⁶, Shraddha Prakash, MD⁶, Marian Kaldas, MD⁶, Maneesh Gogia, MD⁶, Veronica Berrocal, PhD³, Whitney Townsend, MLIS²,¹, Robert Terkeltaub, MD⁷,³, Dinesh Khanna, MD, MS¹,⁴

30 randomized control studies evaluated
Gout: Treatment of acute attacks

- NSAIDS
  - Indomethacin vs other NSAIDS, COX-2, corticosteroids, ACTH, IL-1 inhibitor, Chinese herbs
  - Naproxen vs etodolac or prednisolone
  - Celecoxinb vs indomethacin

- Corticosteroids
  - Oral vs NSAIDS
  - IM triamcinolone vs NSAIDS, IL-1 inhibitor, ACTH
Gout: Treatment of acute attacks

• ACTH vs Indomethacin
  • Faster resolution of pain ($p < 0.0001$)
  • ACTH with fewer side effects (GI, HA)

• ACTH vs Triamcinolone 60 mg IM
  • Similar efficacy
  • Fewer rebound attacks with triamcinolone

Gout: Treatment of acute attacks

- Colchicine
  - Multicenter, double-blind, placebo-controlled, parallel-group study of 184 pts
    - Low dose: 1.2 mg → 0.6 mg 1 hr later
    - High dose: 1.2 mg → 0.6 mg hourly x 6 hrs
    - Placebo

- Comparable efficacy high vs low
- More diarrhea with high dose (77% vs 23%)

Gout: Treatment of acute attacks

- IL-1 inhibition with canakinumab

- β-Relieved and β-Relieved II
  - 12-week randomized, multicentre, active-controlled, double-blind, parallel-group core studies with double-blind 12-week extensions
    - Superiority in both efficacy and prevention of new flares vs triamcinolone 40 mg IM
    - Noted more AE: infections, neutropenia, thrombocytopenia with canakinumab

Gout: Treatment of acute attacks

- 8-week single-dose, single blind, double-dummy, dose-ranging, active-controlled study
  - Refractory gout or contraindications to NSAIDS/colchicine

- Canakinumab 10, 25, 50, 90, 150 mg vs triamcinolone 40 mg IM

- All doses of canakinumab statistically superior to triamcinolone
  - VAS pain score
  - Time to pain reduction
  - Ability to prevent subsequent flare

MSU Crystal Triggered Gout Flare

1. MSU crystals trigger pro-IL-1β gene
2. Release of IL-1β
3. IL-1β diffuses toward neutrophils in peripheral tissues
4. Neutrophils migrate into joint
5. Neutrophils release inflammatory substances, amplification of inflammation
Gout: Treatment of acute attacks


The eye of the storm (s)
Indications for Pharmacologic Urate-Lowering Therapy

- Tophus or tophi
- Frequent attacks of gouty arthritis (≥2/yr)
- CKD stage 2 or worse
- Past urolithiasis

Acute Gouty Attack Prophylaxis

- Colchicine up to 1.2 mg daily*
- NSAIDS (naproxen 250 mg BID)
- Low-dose prednisone

- Beware of intolerances or contraindications
  - High risk CV disease
  - CKD
  - Diabetes

Acute Gouty Attack Prophylaxis

• For how long???

• At least 6 months

  OR

• 3 mo after achieving target SUA level (no tophi)
• 6 mo after achieving target SUA level (tophi)

Serum Uric Acid Level Target

• No tophi: <6.0 mg/dl
• Tophi: <5.0 mg/dl

• Lower = increased speed of tophi resolution
• Check every 2-5 weeks with medication titration
  • Also helps with ensuring compliance

Urate-Lowering Therapy: Allopurinol

• Xanthine oxidase inhibitor
  • Start dose 100 mg daily
  • Start 50 mg daily in pts with CKD stage ≥ 4
  • Titrate to SUA target
  • Can go above 300 mg in CKD with close monitoring (pruritis, rash, transaminitis)
• Pre-screening for HLA-B5801 in select pts
  • Han Chinese and Thai (hypersensitivity)

Urate-Lowering Therapy: Febuxostat

- Xanthine oxidase inhibitor
  - If intolerant or fails allopurinol
  - Start dose 40 mg daily.
  - Maximum dose in US is 80 mg daily.
  - No required dose adjustment for CKD
  - Titrate to SUA target
  - Cost concern

Mechanism of Action: Xanthine Oxidase Inhibitors

[Diagram showing the mechanism of action of xanthine oxidase inhibitors, with arrows indicating the conversion of purine nucleotides to uric acid through Allopurinol and Febuxostat.]
Urate-Lowering Therapy: Pegloticase

- Uricase
- Refractory gout or heavy burden of tophi
- 2 large placebo-controlled RCT studies
  - Achieved SUA target
  - Tophi resolution
- Expensive
- Safety concerns

Sundy JS, et al. *JAMA*, 2011
Mechanism of Action: Pegloticase
Urate-Lowering Therapy: Lesinurad

- URATE-1 inhibitor
- Newly FDA approved
- For use in combination with XOI
Uricosuric Agents

- Probenecid (unless CrCl <50)
- Fenofibrate
- Losartan
- Cannot use as 1st line agent if h/o urolithiasis
Mechanism of Action: Uricosurics
Mechanism of Action: Uricosurics
Take Home Points

• Many causes for hyperuricemia including medications, renal disease, high cell turnover, enzyme-defects, etc
• Risk of gout increases as SUA level rises
• Multiple triggers for gout attacks
• Colchicine as preferred agent for acute gout attacks and gout attack prophylaxis
• Multiple effective agents for SUA lowering with goal of at least SUA < 6.0mg/dl
Questions?