OBJECTIVES

• To be familiar with the clinical presentation and pathophysiology of gouty arthritis
• Be able to incorporate current guidelines when treating gout
• Be aware of other adverse health consequences of hyperuricemia
• Be aware of current developments in the treatment of gout

GOUT INCIDENCE AND PREVALENCE

• The prevalence of gout in the United States doubled between the 1960s and 1990s
• Both the incidence and prevalence of gout appear to be increasing worldwide, with 6.1 million adults with gout in the US
• According to NHANES 2007-2008 data, the prevalence in the US of diagnosed gout was 3.9%
• The same survey revealed the prevalence of hyperuricemia to be 21.4%

MONOSODIUM URATE CRYSTAL DEPOSITION DISEASE

• Uric acid is a final metabolite of purine metabolism
• Gout is a state of saturation of extracellular fluid urate
• Most individuals with hyperuricemia do NOT develop gout
• Serum uric acid (sUA) level is normal or low in the setting of a gout attack in 12-43 percent of patients

GOUTY INFLAMMATION

• Uric acid precipitates in the form of monosodium urate (MSU) crystals in joints, tendons, and other tissues
• Gouty inflammation appears to be mediated primarily by the pro-inflammatory cytokine, interleukin (IL)-1
• Phagocytosis of MSU crystals trigger the innate immune system, leading to IL-1β production
• The inflammatory cascade is a complex response involving cytokines, chemokines, release of lysosomal enzymes and superoxide anions from neutrophils
FIVE CLINICAL MANIFESTATIONS OF GOUT

- Recurrent attacks of acute inflammatory arthritis
- Accumulation of urate crystals as tophaceous deposits
- Chronic arthropathy
- Uric acid nephrolithiasis
- Chronic nephropathy

THREE CLASSIC STAGES OF GOUT ARTHROPATHY

- Acute gouty arthritis
- Intercritical gout
- Chronic recurrent and tophaceous gout

Note that with correct diagnosis, appropriate treatment with, and adherence to an antihyperuricemic regimen, a near “cure” can be achieved and the last stage avoided.

EARLY ACUTE GOUTY ARTHRITIS

- Severe pain
- Marked swelling
- Pronounced erythema
- Reaches maximum severity within hours
- Complete resolution within days, even without treatment
- 50% of first gout attacks present as podagra

DIFFERENTIAL DIAGNOSES

- Cellulitis
- Septic arthritis
- Reactive arthritis
- Pseudogout (may coexist with gout)

DIAGNOSIS

- Aspirate from inflamed joint/bursa revealing the characteristic needle-shaped, negatively birefringent crystal using compensated polarized light microscopy
- Ideally, crystals are noted to be intracellular
- Perform microscopy within 30 minutes of aspiration or refrigerate immediately for send out
- Acute gout and septic arthritis can coexist, so send aspirate for Gram stain as well as culture and sensitivity

RISK FACTORS/ASSOCIATIONS

- Hyperuricemia
- Males < 60 yrs, females > 80 yrs
  - Estrogen is uricosuric
  - Typically polyarticular gout in the elderly female
- HTN
  - 1/3 of those with gout have HTN
- Obesity
- Higher ETOH consumption, particularly beer and liquor
  - Higher quantities lead to both overproduction and underexcretion

PREDISPOSING FACTORS

- Organ transplantation
- Medications
  - Diuretics (especially HCTZ)
  - Cyclosporine
  - Low dose aspirin (< 325mg)
  - Niacin
  - Levodopa
- Renal insufficiency
- Metabolic syndrome and diabetes mellitus

FLARE TRIGGERS

- Recent or intermittent diuretic use
- ETOH binge drinking
- Rapid weight loss
- Hospitalization
- Surgery
- Initiation of urate-lowering therapy (ULT)

TREATMENT OPTIONS FOR ACUTE GOUT

- American College of Rheumatology (ACR) issued Guidelines for Management of Gout in 2012
- Covers therapy and prophylaxis of acute gouty arthritis
- Also pharmacologic and nonpharmacologic management of hyperuricemia
- For mono- or pauciarticular attack with mild-to-moderate pain, monotherapy is recommended

NSAIDs

- Historical first-line therapy is NSAIDs
  - Most effective within 24 hrs of onset
  - NSAIDs with FDA indication for gout
    - Naproxen
    - Indomethacin
    - Sulindac
  - Recommend use at full dose until attack resolves
  - Consider earlier taper if comorbidities warrant

COLCHICINE

- Historically, given as one tablet (0.6 mg) q 1-2 hrs until relief occurred, OR total of 6 mg was reached, OR GI symptoms occurred
- Newer FDA recommended regimen
  - 2 tablets (1.2 mg) po at first dose, then one tablet (0.6 mg) taken one hr later
  - Revealed similar efficacy to higher dose regimen in the AGREE trial, with toxicity similar to placebo
- Give only if within 36 hrs of attack onset
**COLCHICINE IN RENAL IMPAIRMENT**

- ACR did not weigh in on dosing adjustments
- No dose adjustment required for CrCl 30-80 ml/min in the acute setting
- In severe renal impairment, may use but limit use to once every 2 wks
- In dialysis patients, dose for acute flare is 0.6 mg (one tablet) and should not be repeated more than once every 2 wks

**PROPHYLAXIS DOSING**

- May initiate prophylaxis dosing of 0.6 mg once or twice daily 12 hrs after last flare dose given
- In severe renal impairment, prophylaxis dosing is 0.3 mg daily
- In dialysis patients, dose 0.3 mg twice weekly
- Avoidance or dose reduction recommended in those on moderate-high potency cytochrome P450 3A4 and P-glycoprotein inhibitors, such as clarithromycin, erythromycin, cyclosporine

**CORTICOSTEROIDS**

- Intraarticular steroids an option with flare in 1 or 2 joints (assuming not a septic joint)
- Oral corticosteroids for those with polyarticular disease
- Prednisone or prednisolone of at least 0.5 mg/kg per day for 5-10 days
- Alternately full dose for 2-5 days, then tapering off over 7-10 days
- Single dose of 60 mg triamcinolone IM followed by oral steroid also an option

**COMBINATION TREATMENT OPTIONS**

- For flare with severe pain in setting of polyarthritis involvement, ACR recommends combining therapies
- Recommended combinations include
  - Colchicine and NSAIDs
  - Colchicine and oral corticosteroids
  - Intraarticular steroids and any other modality
- Avoid NSAIDs and oral corticosteroids in combination
  - Concern about synergistic gastrointestinal toxicity

**HOSPITALIZED NPO PATIENTS**

- Hospitalized medical/surgical patients at increased risk of acute gout flare
- For 1-2 involved joints, use intraarticular steroids
- For polyarticular disease with no contraindications, ACR recommends IV or IM methylprednisolone
  - 0.5-2.0 mg/kg methylprednisolone initially
  - SQ ACTH at an initial dose of 25–40 IU with repeat doses as clinically indicated

**INDICATIONS FOR PHARMACOLOGIC URATE LOWERING THERAPY (ULT)**

- Tophus or tophi on exam or imaging
- Frequent attacks of gouty arthritis (>2/yr)
- CKD stage 2 or worse
- Past urolithiasis
**PROPHYLAXIS WITH ULT**

- ACR guidelines recommend initiating anti-inflammatory prophylaxis when ULT is initiated
- Oral colchicine is first-line option
- Another first-line option, though with lower evidence grade, is low-dose NSAIDs
  - Naproxen 250 mg po bid suggested
  - Consider concomitant use of proton pump inhibitor for peptic ulcer suppression
- For intolerance, contraindication, or refractoriness to colchicine and NSAIDs low-dose prednisone is recommended at ≤10 mg/day

**RECOMMENDED DURATION OF PROPHYLAXIS**

- ACR recommends for the greater of
  - 6 months' duration or
  - 3 months after achieving the target serum urate level for the patient without tophi detected on physical examination or
  - 6 months after achieving the target serum urate level where tophi have resolved
- Reassess the risk/benefit ratio frequently if using prednisone for prophylaxis

**ALLOPURINOL**

- Xanthine oxidase inhibitor (XOI)
- Has no role in treatment of an acute gout attack, but don’t discontinue it in this setting
- Useful regardless of mechanism of hyperuricemia
- The key is to achieve sUA level <6mg/dL
- Start at no more than 100 mg/day
- Start at 50 mg/day in stage 4 or worse CKD
- Increase dose every 2-5 wks until reaching target
- Average daily dose is 300 mg but maximal is 800 mg

**FAILURE TO TREAT TO TARGET**

- At 300 mg daily, only 53% of pts reached target in one study of 49 pts
- Longitudinal studies reveal only 30-60% are prescribed allopurinol beyond one yr
- Historically, we’ve used lower doses in renal patients and often failed to reach target
- A 2011 study escalated doses in renal patients to target sUA levels with no serious adverse events
- In setting of tophaceous gout, may need to lower sUA below 5 mg/dL

**ALLOPURINOL SEVERE CUTANEOUS REACTIONS (SCAR)**

- Includes Stevens-Johnson, toxic epidermal necrolysis
- Rare but mortality as high as 26%
- Patients at high risk of allopurinol hypersensitivity include Koreans with ≥ stage 3 CKD and those of Han Chinese or Thai descent
- Genotyping revealed HLA-B*5801 in 100% of patients with allopurinol-SCAR in study from Taiwan
- ACR Guidelines recommends consideration of genotyping in these populations
- Prevalence in Caucasian population is 2%, compared with 6-12% in the populations cited above

**ALLOPURINOL HYPERSENSITIVITY SYNDROME**

- Includes Stevens-Johnson, toxic epidermal necrolysis
- Rare but mortality as high as 26%
- Patients at high risk of allopurinol hypersensitivity include Koreans with ≥ stage 3 CKD and those of Han Chinese or Thai descent
- Genotyping revealed HLA-B*5801 in 100% of patients with allopurinol-SCAR in study from Taiwan
- ACR Guidelines recommends consideration of genotyping in these populations
- Prevalence in Caucasian population is 2%, compared with 6-12% in the populations cited above
FEBUXOSTAT (Trade name ULORIC)

- Newer XOI approved by the FDA in 2009
- ACR recommends as first-line therapy alternative to allopurinol, with no preference
- Has equal or greater efficacy than allopurinol in lowering sUA levels and preventing flares
- No dose adjustment in mild-to-moderate renal or hepatic insufficiency
- More costly than allopurinol

URICOSURIC ULT

- Inhibit the active reabsorption of urate at the proximal renal tubule by inhibiting URAT1
- Only Probenecid is available in the US
- ACR recommends as alternative in those intolerant of or with contraindication to either XOI, but not if CrCl <50 ml/min
- Associated with 9-11% risk of urolithiasis so is contraindicated in those with history of urolithiasis
- Recommend initial measurement and monitoring of urine uric acid levels
- Probenecid is contraindicated in uric acid overproducers

PROBENECID DOSING

- Start 250 mg po bid for one week then increase to 500 mg bid
- Initial measurement and monitoring of urine UA levels is recommended
- If gouty arthritis is not controlled or if 24-hr UA excretion is <700 mg, may increase by 500 mg increments every 4 wks up to 2000 mg daily
- Patient should maintain increased fluid intake to mitigate risk of urolithiasis
- Also consider urine alkalinization with potassium citrate

ON THE NEAR HORIZON

- FDA approved a new uricosuric in December 2015
- Lesinurad is a selective inhibitor of the renal urate transporter, URAT 1
- Must be taken with a XOI
- May be available later in 2016

OFF-LABEL URICOSURICS

- Losartan
  - Inhibits urate reabsorption in the proximal renal tubule
  - Unique among the ARBs
  - Reduces sUA by 20-25%
- Fenofibrate
  - 23% reduction in sUA in one study
- ACR recommends each as useful in refractory disease in combination with a XOI

PEGLIOTICASE (Trade name KRYSTEXXA)

- A recombinant, pegylated formulation of a modified porcine urate oxidase (uricase)
- Approved by the FDA in 2010
- Administered intravenously
- Indicated only in refractory gout
- Has Black Box Warning due to anaphylaxis and infusion reactions during and after infusions
- Incidence of anaphylaxis is 4.8-6.5%
- Contraindicated in G6PD deficiency
ON THE HORIZON

• Interleukin-1 (IL-1) inhibition
• MSU crystals induce release of proinflammatory cytokines such as IL-1 from WBCs
• A trial using anakinra on 10 pts who failed other therapy showed promising results, without adverse effects
• Currently off-label use
• An investigational IL-1 blocker has shown greater and faster benefit than IM triamcinolone

REFERENCES


REFERENCES

• Richette P, Bardin T. Gout. The Lancet 2010; 375:318–328
• Stamp, LK, O’Donnell JL, Zhang M, 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. Arth Rheum 2011; 63:412-421