RhAPP

RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

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VIRTUAL CONFERENCE

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RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

Crystal Arthropathies

Robert Laugherty, JD, MBA, PA-C
Scenic City Rheumatology
Chattanooga, TN

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Faculty Disclosures

Robert Laugherty, PA-C

Consultant: Pfizer, Novartis, UCB

Speakers Bureau: Amgen, Eli Lilly, Novartis, Abbvie

Crystal Arthropathies

Gout

Calcium Pyrophosphate Deposition Disease (CCPD or Pseudogout)

Basic Calcium Phosphate Associated Syndromes

Calcium Oxalate Arthritis

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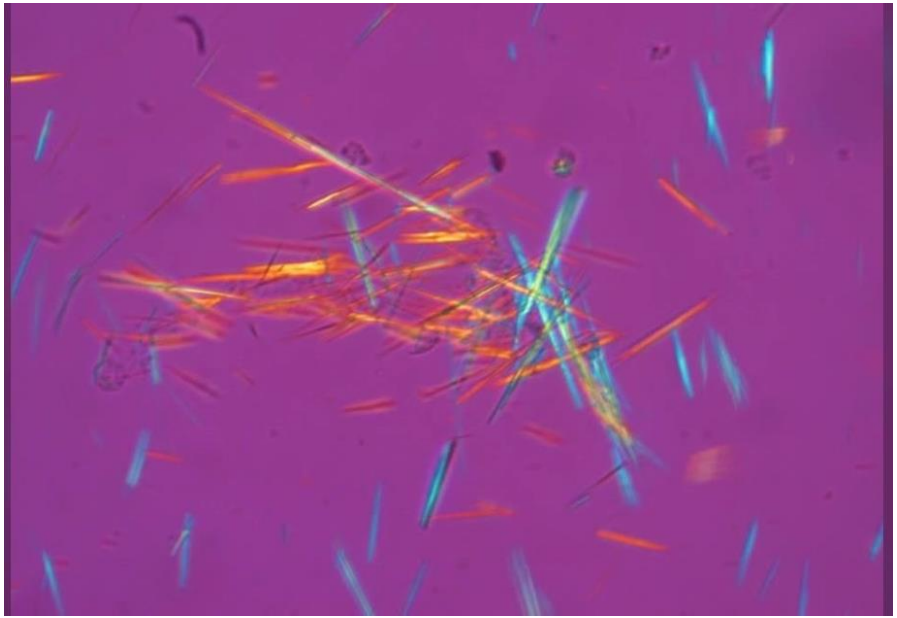
Gout

Monosodium Urate Crystal Deposition Disease

Gout

- Most common form of inflammatory arthritis
- Estimated 8.3 million Americans: 4% of US population
- By contrast only 1.3 million of Americans Dx with RA

Gout



- Needle-shaped crystals strongly negatively birefringent under polarized light
- 90% of cases are men 30-50 years of age
- Blacks > Whites (NHANES 2007-2008)
- Rare in premenopausal women due to the uricosuric effect of estrogen, but increases in postmenopausal women as this effect wanes

Common Features of Gout

- Rapid onset of intense joint pain
- Lingering discomfort
- Inflammation and redness
- Limited range of motion
- Common areas include 1st MTP, ankle/Achilles tendon, elbows
- Chronic cases may present with tophi (collections of uric acid crystals deposited in soft tissues)

Common Comorbid Conditions

- Hypertension
- Cardiovascular disease
- Chronic kidney disease
- Metabolic syndrome

American College of Rheumatology Diagnostic Criteria for Gout

- Presence of urate crystals in joint fluid
- Or
- Presence of tophus proven to contain urate crystals by chemical means or polarized light microscopy
- Or
- Presence of six or more of the following clinical, lab, or radiological findings
  - Asymmetric swelling within a joint on radiograph
  - Culture of joint fluid negative for microorganism during attack of joint inflammation
  - Development of maximal joint/tendon inflammation within one day
  - Hyperuricemia
  - Joint redness
  - More than one attack of acute arthritis
  - Pain or redness in the first metatarsophalangeal joint
  - Subcortical cyst without erosions on radiography
  - Suspected tophus
  - Unilateral attack involving first metatarsophalangeal joint
  - Unilateral attack involving tarsal joint

Pathophysiology

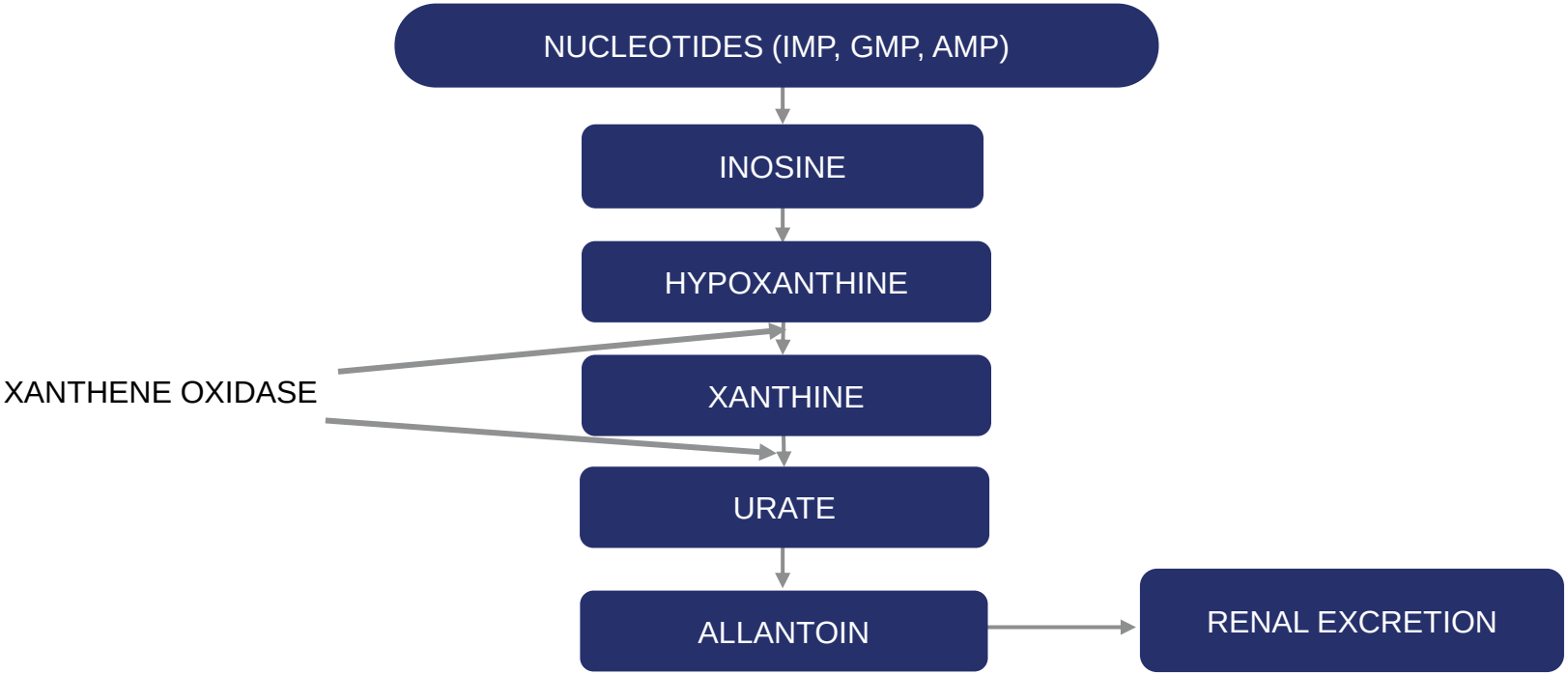
- At its most basic, it is a disease of abnormal purine synthesis and/or excretion causing a supersaturation of bodily fluids with uric acid
- Chronic serum uric acid levels of 6.8mg/dL lead to this super saturation
- Factors causing renal under excretion of uric acid (90% of cases)
  - Decreased urinary excretion due to renal insufficiency, drugs like diuretics, dehydration, hyperparathyroidism
  - Increased urinary reabsorption (alcohol, genetic defects)
- Factors causing overproduction or increases of uric acid (10% of cases)
  - Dietary intake (beef, pork, shellfish, alcohol)
  - Excess endogenous production (malignancies, hemolytic anemia, tumor lysis syndrome)
  - Rare genetic mutations:
    - PRPS: Phosphoribosyl pyrophosphate synthetase super activity
    - HGPT: Hypoxanthene-Guanine phosphoribosyl transferase deficiency (Lesch-Nyhan Syndrome)
- Combined overproduction and under excretion
  - Alcohol
  - G6PD Deficiency
  - Fructose 1 Phosphatase aldolase deficiency

Drugs Leading to Underexcretion of Uric Acid

- Thiazide Diuretics
- Aspirin
- Cyclosporine
- Tacrolimus
- Ethambutol
- Pyrazinamide
- L dopa

Foods and Beverages to Curtail or Avoid

- Avoid: Liver, kidney, anchovies, sardines, herring, mussels, codfish, scallops, trout, haddock, veal, venison, turkey, BACON, alcoholic beverages
- Curtail: Asparagus, beef, chicken, crab, duck, cured ham, kidney beans, lentils, lima beans, lobster, mushrooms, oysters, pork, shrimp, spinach


NUCLEOTIDES (IMP, GMP, AMP)
INOSINE
HYPOXANTHINE
XANTHENE OXIDASE
XANTHINE
URATE
ALLANTOIN
RENAL EXCRETION

Stages of Gout

- STAGE 0: Normouricemia
- STAGE 1: Hyperuricemia
- STAGE 2: First Attack of Articular Disease
- STAGE 3: Inter-Critical Gout (period between acute attacks)
- STAGE 4: Chronic Tophaceous Gout

Stage 2

- First attack of acute articular disease
- Erythema
- Tenderness
- Swelling
- Sudden onset
- Severe pain

Stage 3

- Inter critical period without joint pain or notable features or changes

Stage 4

- Chronic tophaceous gout.
- Occurs an average of approximately 11-12 years after the initial Stage 2 episode
- Common areas include elbow, 1st MTP, and fingers


R


A
B
C

Treatment Options

- Lifestyle: Diet, Exercise, Hydration
- Control of comorbid conditions such as HTN, DM, Metabolic Syndrome
- Drugs:
  - NSAIDs (not ASA)
  - Colchicine
  - Steroids (PO and intra-articular)

ACUTE ATTACK

  - Allopurinol (Zyloprim)
  - Febuxostat (Uloric)
  - Probenecid
  - Pegloticase (Krystexxa)

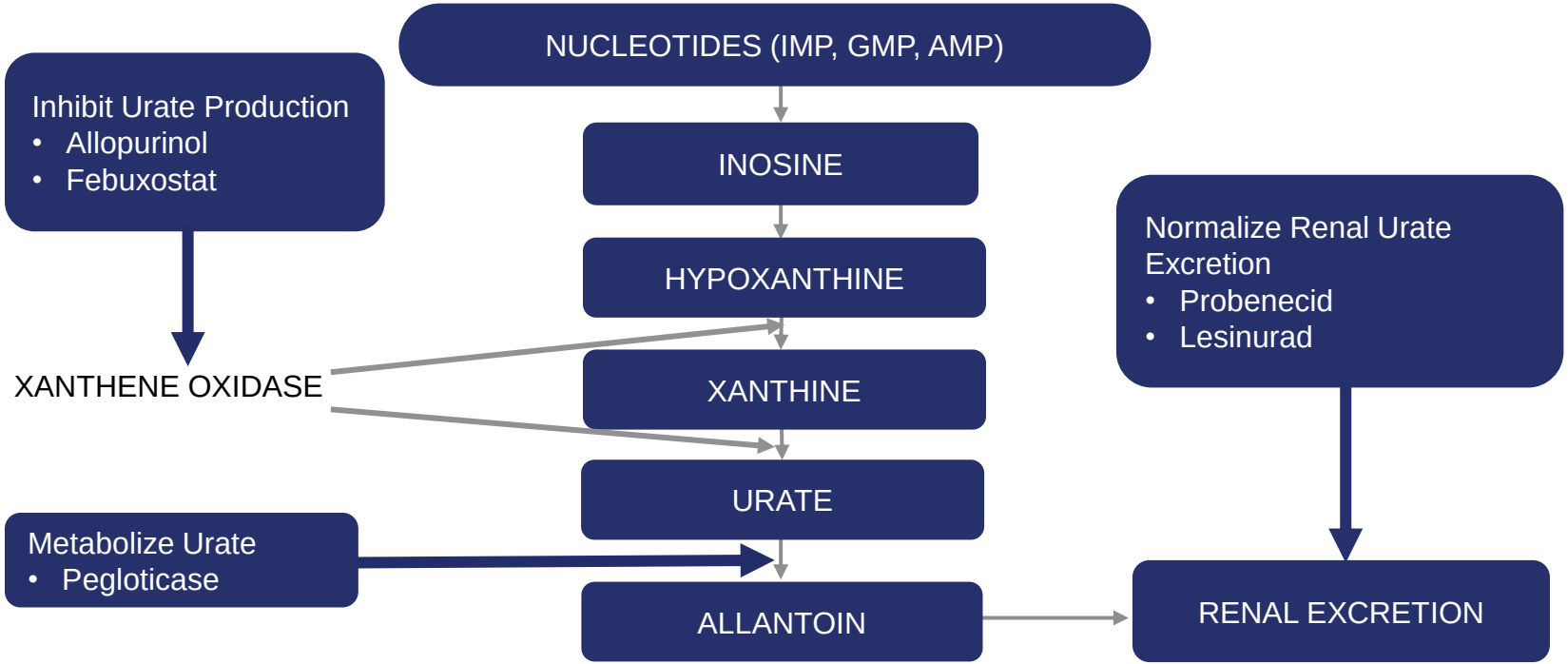
PROPHYLAXIS

NSAIDs, Steroids, Colchicine

- NSAIDs
  - Most commonly used are Indomethacin, Ibuprofen and Naproxen
  - NSAIDs are versatile and effective for rapid onset pain relief sometimes in less than 12-24 hours
  - Be aware of renal, hepatic and gastrointestinal toxicity and may use a cox-2 inhibitor if desired
  - Remember to avoid Aspirin as it reduces/prevents uric acid excretion
- Colchicine
  - Colchicine appears to inhibit proinflammatory mechanisms, and increase levels of anti-inflammatory mediators
  - At the onset of attack take 1.2 mg po followed by 0.6mg one hour later. Continue 0.6 mg BID until attack is aborted
  - Can also be use at 0.6mg QD in combination with uric acid lower drug for prophylaxis
  - Side effects include nausea, diarrhea and vomiting
  - Long term use in patient with renal insufficiency can be associated with risk of neuromuscular toxicity

NSAIDs, Steroids, Colchicine, cont.

- Steroids may be used when NSAIDs or Colchicine fail or are not tolerated
- Intra-articular Injections
  - Preferred for monoarticular presentations
  - Methylprednisolone 20-80mg or Triamcinolone 10-40mg injected intraarticularly using sterile technique
- Systemic
  - Prednisone may be used at doses from 20-40mg daily for 5-7 days then tapered over the next 7-10 days


NUCLEOTIDES (IMP, GMP, AMP)
Inhibit Urate Production
• Allopurinol
• Febuxostat
INOSINE
HYPOXANTHINE
XANTHENE OXIDASE
XANTHINE
URATE
Metabolize Urate
• Pegloticase
ALLANTOIN
Normalize Renal Urate Excretion
• Probenecid
• Lesinurad
RENAL EXCRETION

Urate Lowering Therapy

- These drugs interfere with xanthene oxidase activity to reduce uric acid production
- Target is to lower uric acid levels to <6mg/dL
- REMEMBER THAT GOUT FLARES MAY BE MORE FREQUENT DURING URIC ACID REDUCTION PHASE
- Allopurinol (Zyloprim)
  - Initial dose is 100mg po qd and may increased by 100mg/day every week until the goal of <6.0mg/dL is met
  - Most common dose is 300mg/day. Maximum dose is 800mg/day
  - Monitor renal function regularly
  - Avoid use with Azathioprine and 6-Mercaptopurine as concomitant use can cause bone marrow suppression
- Febuxostat (Uloric)
  - Initial dose is 40mg daily, may be increased to 80mg daily after the first 2 weeks until goal of <6.0mg/dL is met
  - Primarily hepatically cleared so may be used in patents with Cr Clearance >30mL/min) but monitor labs regularly
  - FDA issued warning in 2017 about increased risk of heart related deaths so choose patient accordingly

Uricosuric Therapy

- Generally used when other long-term therapies are contraindicated, not tolerated or cannot achieve uric acid goal of <6.0mg/dL
  - May be used in conjunction with xanthine oxidase inhibitors
  - Probenecid is the only uricosuric drug available in the US.Zurampic (lesinurad) was removed from the US by its manufacturer Ironwood Pharmaceuticals for business reasons and not for any safety, efficacy or quality issues
- PROBENECID
  - Competitively inhibits the reabsorption of uric acid at the proximal convoluted tubule thus increasing its excretion and reducing serum uric acid levels
  - Starting dose is 250mg/day and may be increased to a maximum of 500mg BID
  - Multitude of drug interactions including Methotrexate, Baricitinib, Mycophenolate, Pegloticase, Tylenol, Ativan, Loop Diuretics, Cephalosporins, Penicillins
  - Avoid use in patients with Hx of renal stones and consider agents to acidify urine (K-citrate, Na-bicarb) to reduce stone risk

Krystexxa (Pegloticase)

- Third-Line medication for the treatment of chronic, treatment-refractory gout
- PEGylated uric acid specific enzyme
- Given IV 8mg every 2 weeks after discontinuation of all other uric acid lower therapies
- No specific guidelines on duration of treatment, but common to continue until the disappearance of all tophi. No controlled trial data are available on the safety and efficacy of re-treatment with Krystexxa after discontinuation for longer than 4 weeks. Immunogenicity potential with Krystexxa means patients restarting treatment may be at increased risk of anaphylaxis and infusion reactions
- Patient must receive antihistamines and corticosteroids prior to each infusion to reduce risk of anaphylaxis and infusion reactions

Krystexxa (Pegloticase), cont.

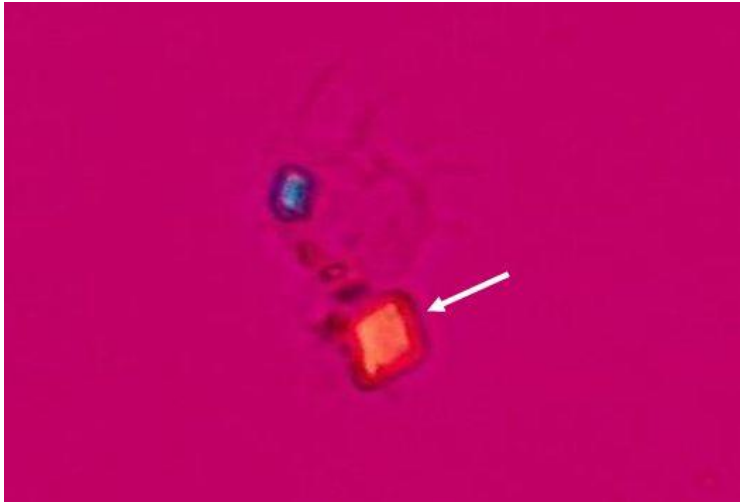
- Contraindicated in those with Glucose-6-phosphate dehydrogenase (G6PD) deficiency. Screen high risk patients before starting therapy (e.g. African or Mediterranean ancestry)
- Warning and Precautions include anaphylaxis, infusion reactions, gout flares, congestive heart failure
- May increase risk of gout flares due to rapid reduction of serum uric acid levels, and consideration to starting prophylactic therapy with NSAIDs or Colchicine before starting Krystexxa. Manage any flares as you would normally, based on patient Hx and response
- Monitor uric acid before each infusion and discontinue if uric acid is >6.0mg/dL on 2 subsequent labs draws (suggests immunogenicity) to reduce risk of anaphylaxis in those who have lost clinical efficacy

Pseudogout

- Calcium pyrophosphate dihydrate deposition disease (CPPD)
- Calcium pyrophosphate dihydrate crystals can deposit in articular cartilage, synovium, tendon and ligamentous structures
- More prevalent the older the patient and slightly
- Onset usually resembles a gout attack, hence the name pseudogout
  - Severe pain, warmth and swelling in one or more joints
  - Can last from days to weeks
  - Most affected joints are knees, hands, wrists and hips

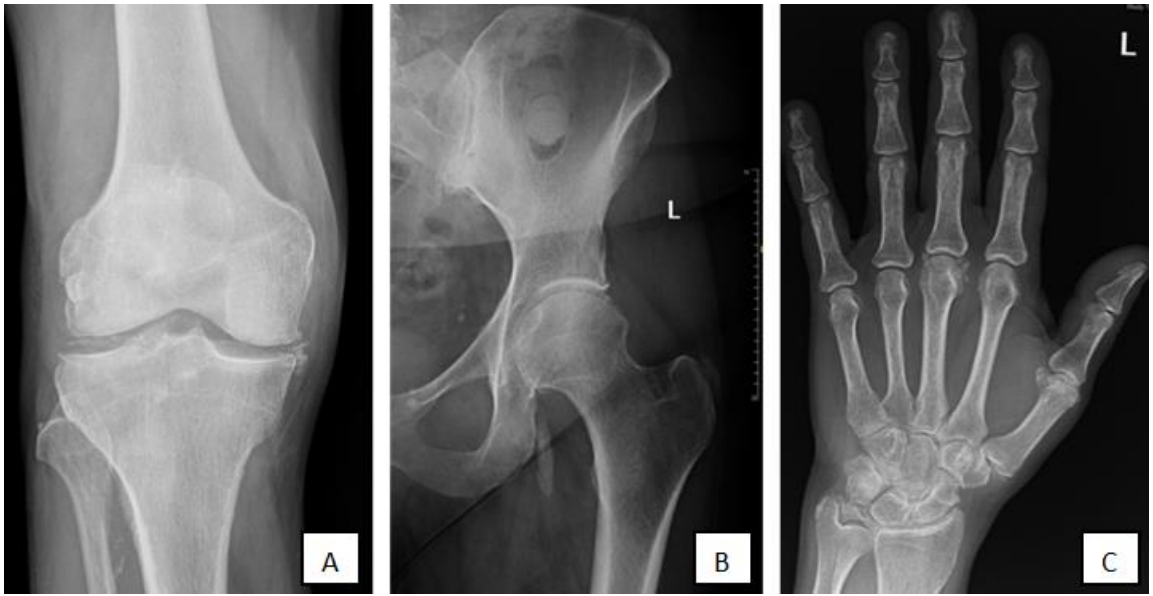
Pseudogout, cont.

- Crystals are rhomboid with weak bifrengence on polarized light microscopy
- Affects 4-7% of the adult US population
- More common in older patients and slightly more prevalent in women over men 1.4:1



Pseudogout, cont.

- Hallmark radiographic finding is chondrocalcinosis.



Pseudogout, cont.

- Conditions associated with CPPD disease
  - Hemochromatosis
  - Hypoparathyroidism
  - Hypomagnesemia
  - Hypothyroidism
  - Amyloidosis
  - Wilson’s Disease
  - Gout
- Treatment for acute attack is largely the same as for gout: NSAIDs, Steroids, Colchicine
- Chronic treatment in the absence of pain is not recommended
- For chronic recurrent disease there is emerging evidence the methotrexate and hydroxychloroquine may be effective

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Thank You!

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