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# **Crystal Arthropathies**

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- Horizon – Speaker Program (Gout)
- Sanofi – Ad Board (PMR)

# Crystal Arthropathies

## Outline

1. Calcium Pyrophosphate Deposition Disease
  - Pseudogout
2. Hydroxyapatite Deposition Disease
3. Calcium Oxalate Deposition Disease
4. Monosodium Urate Deposition Disease
  - Gout
  - ACR 2020 guidelines



# **Calcium Pyrophosphate Deposition Disease**

# Calcium pyrophosphate deposition disease (CPPD)

- Calcium pyrophosphate crystals deposit into articular cartilage and cause inflammatory response
- Pseudogout – describes the attack
- Chondrocalcinosis – process and seen on imaging
- Most commonly seen in a knee

# Calcium pyrophosphate deposition disease (CPPD)

- 4-7% adults US and Europe
- Older population
  - average ~72yo
  - 50% over >84yo
  - Appear to be worse with age
    - Study by Rosenthal showed articular chondrocalcinosis increases with age.

# CPPD – Risk Factors

- Age
- Trauma, illness
- OA
- Loop diuretic association
- Metabolic disorders affecting
  - Hyperparathyroidism – affects Ca metabolism
  - Hypomagnesaemia – increases CPP solubility

# CPPD - Pathophysiology

- Not fully understood
- Crystals form in the pericellular matrix of cartilage and cause an inflammatory response
- Chondrocytes produce pyrophosphate from ATP
- Pyrophosphate binds to calcium to form crystals
- Inflammatory response causes tissue/cartilage degradation through multiple mechanisms

# Calcium pyrophosphate deposition disease (CPPD)

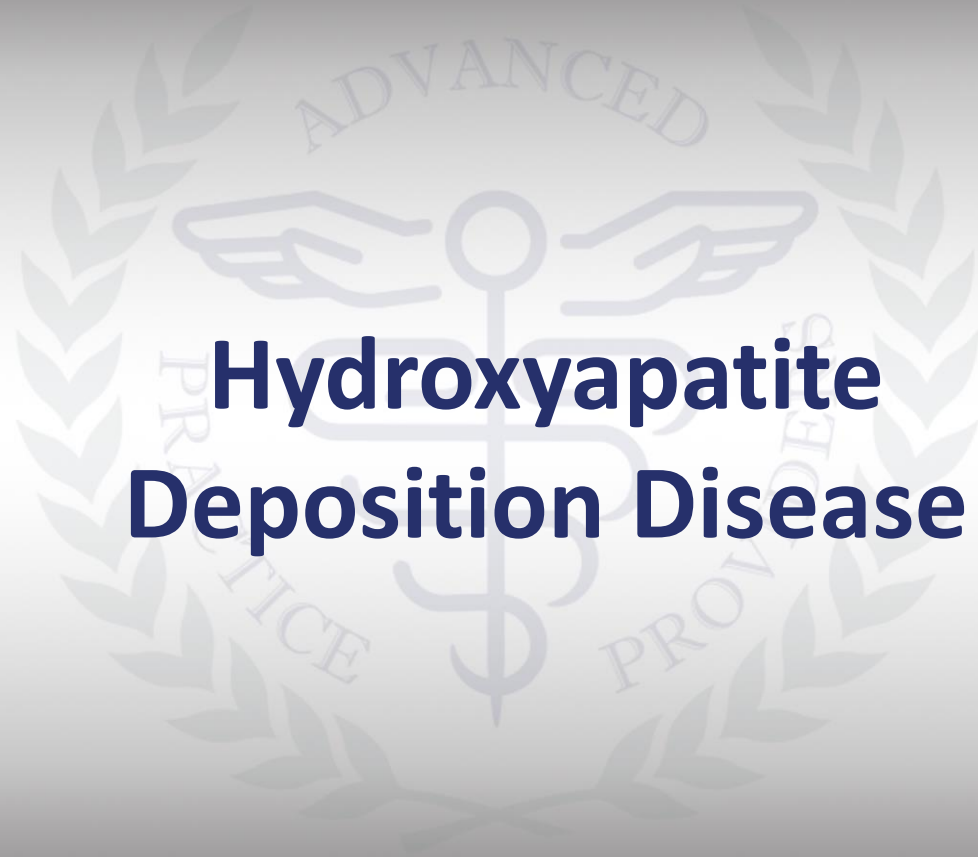
- Asymptomatic
  - Most common
- Acute - Knees (50%), hands, wrists, ankle
  - Triggers – trauma, surgery, severe illness, parathyroidectomy
- Chronic – resembles RA
  - AM stiffness, synovial thickening, edema, ↓ROM
  - Polyarticular, mostly peripheral joints

# Calcium pyrophosphate deposition disease (CPPD)

- Synovial fluid
  - Positively birefringent CPP crystals
  - WBC 15-30,000, neutrophils predominating
  - Can be present with MSU crystals
- Imaging
  - Plain films: calcification of fibrocartilage structures
  - US: depends on the location, can see Double Contour Sign (MSU)

# Calcium pyrophosphate deposition disease (CPPD)

- Diagnosis
  - Presence of CPPD crystals
  - Radiograph
- Treatment
  - NSAIDs, colchicine, corticosteroids
  - Resistance disease
    - IL-1 pathway – studies show effectiveness but expensive
    - MTX/HCQ – limited data



# **Hydroxyapatite Deposition Disease**

# Hydroxyapatite Deposition Disease

- Hydroxyapatite and calcium phosphate and are often used synonymously with the more accurate term basic calcium phosphate (BCP) crystals.
- BCP crystals form at sites of local tissue damage, shoulder most common.
- Can be asymptomatic, chronic, acute.
- Associated with OA, CTD, ESRD.

# Hydroxyapatite Deposition Disease

- BCP crystals associated with 2 syndromes:
  - **Calcific periarthritis:** tendon, bursae, soft tissues
  - **Intra-articular arthritis:** highly destructive OA, Milwaukee Shoulder Syndrome
- Hydroxyapatite pseudopodagra
  - acute calcific periarthritis around 1<sup>st</sup> MTP.
  - Presents like podagra but...
  - Mostly young women who over pronate, excessive walking/running causing repetitive trauma

# Hydroxyapatite Deposition Disease

- Treat with NSAIDs, corticosteroids.
- Shockwave to break up large densities, not well studied but reported effective and well tolerated.
- Colchicine - small study with 36 patients showed benefit



# **Calcium Oxalate Deposition Disease**

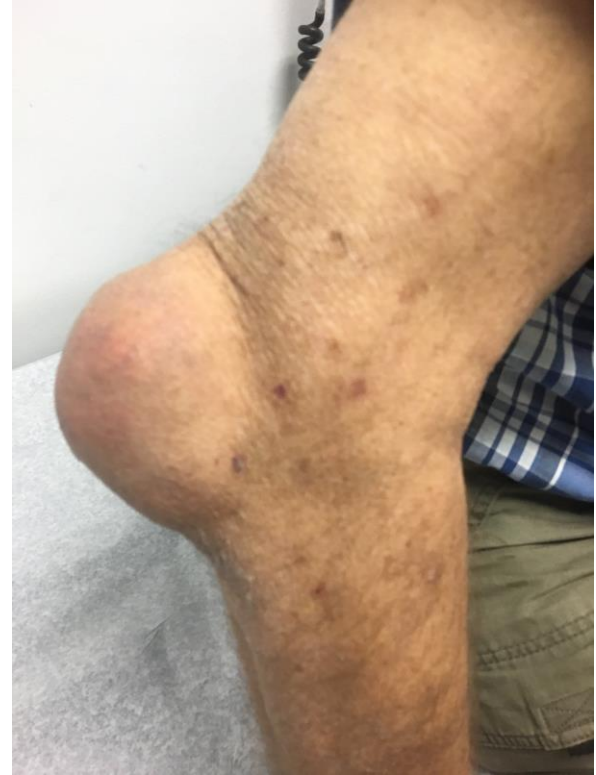
# Calcium Oxalate Deposition Disease

- Rare form of crystal arthropathy but most common kidney stone
  - Oxalate, produced from breakdown of ascorbic acid, binds to calcium
  - Oxalate crystal deposits are found mainly in kidneys, bone, skin, and vessels, and less often inside the joints.
- Associated with:
  - Hyperoxaluria (primary or secondary)
  - ERSD on Long-term dialysis.
- Limit Vitamin C and oxalate intake (tea, okra, spinach, sweet potato, nuts)



# **Monosodium Urate Deposition Disease**

# GOUT



# Since Antiquity

- First recognized by Egyptians 2640 BC
- Hippocrates “unwalkable disease” 5<sup>th</sup> century BC
- “Disease of Kings” and “King of Diseases”
- Goes beyond Kings - *Punch* magazine in 1964:
  - "In keeping with the spirit of more democratic times, gout is becoming less upper-class and is now open to all ... It is ridiculous that a man should be barred from enjoying gout because he went to the wrong school."

**Gout has been around since antiquity, but our treatment regimens don't have to be!**

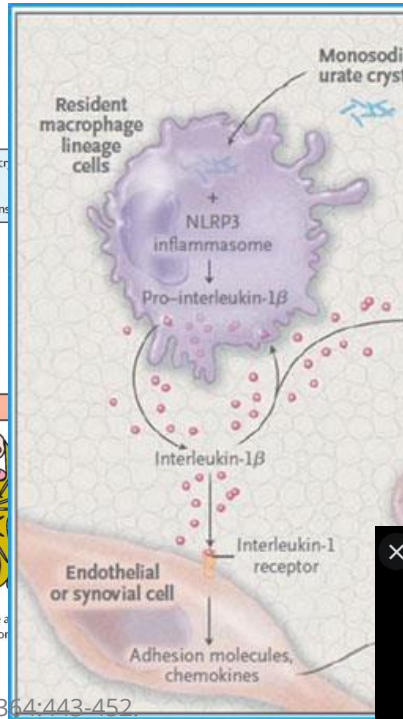
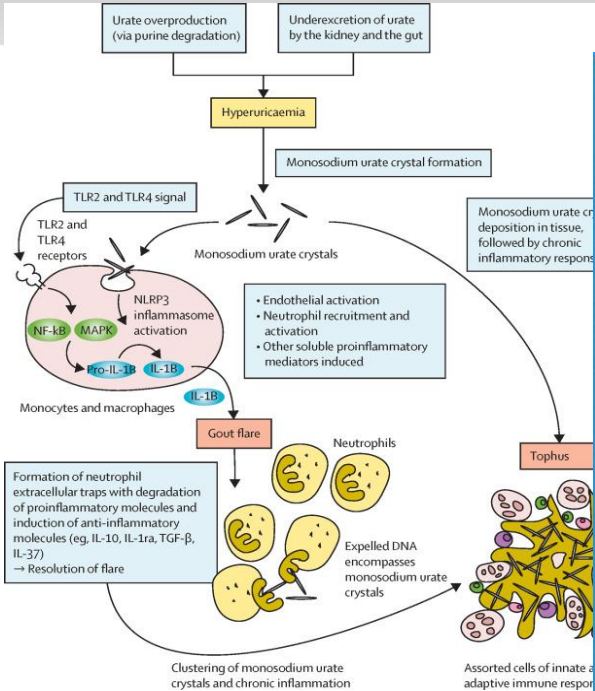
# Gout

- Monosodium urate crystal deposition disease
- Most common inflammatory arthritis
- 9.2M US adults have gout
  - 3.3M on urate lowering therapy (ULT).
  - In 20 years, no increase in ULT use.
  - Low adherence (worse of 7 chronic conditions)
  - Long term consequences.

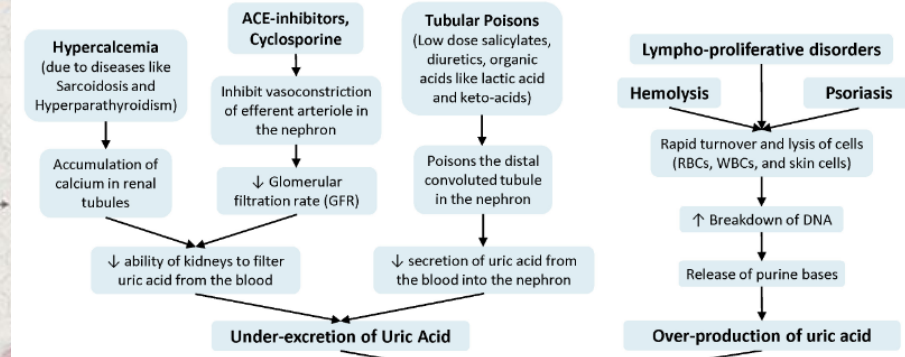
# Gout

- Risk Factors
  - Male>Female
  - Diet, alcohol, certain medications
- Comorbidities that can contribute to and affect management of gout
  - Metabolic Syndrome
  - HTN, DM, HLD, CVD
  - Kidney stones

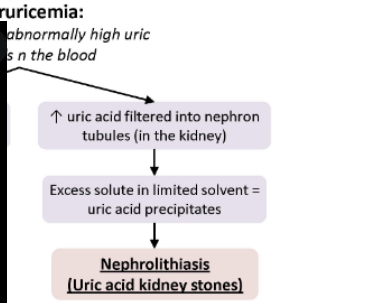
# Pathophysiology



## Hyperuricemia: Pathogenesis and complications



**Gout pathophysiology**  
 Khan Academy  
 1,280 x 720  
 5:54



Neogi T. Clinical practice. Gout. *N Engl J Med.* 2011;364:443-452  
<https://www.kidney.org/atoz/content/rare-diseases/refractory-gout-management>  
<https://calgaryguide.ucalgary.ca/hyperuricemia-pathogenesis-and-complications/>  
<https://www.youtube.com/watch?v=2r95ZVqAysQ>

# Gout

- Hyperuricemia is central to MSU crystal formation
- Urate is end product in purine metabolism
  - High purine diet, alcohol, fructose
  - Historical offenders
- More recently, renal transport is the main factor in urate concentrations.
  - *More than purine metabolism*
  - *Less about diet, more about the kidneys*

# Gout

- MSU deposition is systemic
- Imaging advances have demonstrated MSU crystals that may not be detected on exam
  - Dual Energy CT – can detect MSU crystals
- Case reports on MSU crystal deposition outside of the joints.
  - Heart, arteries, kidney, prostate, spine, eyes, skin

# Gout - DIAGNOSIS

- MSU crystals in joint fluid or tophaceous material
  - Negatively birefringent
- If not crystal proven, clinical diagnosis can be made
  - Acute inflammatory arthritis, podagra

## Probability of gout:

Low:  $\leq 4$  points,

Intermediate: 4 to 8 points


High:  $\geq 8$  points

- Male sex (2 points)
- Previous patient-reported arthritis flare (2 points)
- Onset within one day (0.5 points)
- Joint redness (1 point)
- First metatarsal phalangeal joint involvement (2.5 points)
- Hypertension or at least one cardiovascular disease (1.5 points)
- Serum urate level greater than 5.88 mg/dL (3.5 points)

# Gout - Imaging

- Plain films
  - Erosive findings: punched out or intraosseous lesions, sclerotic overhanging edges
  - Typically, late findings, years later
- MSK Ultrasound
  - Double contour sign
- DECT Scan
  - Can detect systemic urate deposition

## Clinical Utility of Dual-Energy CT for Evaluation of Tophaceous Gout

Madhura A. Desai , Jeffrey J. Peterson, Hillary Warren Garner, Mark J. Kransdorf



7a.



7b.

Acute tophaceous gout in a 46yo man with normal sUA

Desai MA. Published Online: September 06, 2011  
<https://doi.org/10.1148/rg.315115510>



a.



b.

8.3% change in MSU burden after 6 weeks of ULT  
sUA change 10.5 to 8.3 mg/dL

# Gout - TREATMENT

*Treatment is different based on the goal.*

<b>Acute</b>	<b>Prophylaxis</b>	<b>Chronic ULT</b>
NSAIDs	Low dose NSAIDs	XOI - Allopurinol - Febuxostat
Colchicine	Low dose Colchicine	Uricosuric - Probenecid
Glucocorticoids	Low dose Prednisone	Uricase - Pegloticase
IL-1	IL-1	

# Gout - TREATMENT

## ACR

- Treat-to-target
- $<6.0\text{mg/dL}$
- Crystals no longer form
- Existing crystals will dissolve
- 2 attacks  $\rightarrow$  start ULT

## EULAR

- Treat-to-target
- $<5.0\text{mg/dL}$  for severe
- Crystals no longer for 3m
- Existing crystals will dissolve
- 1 attack  $\rightarrow$  start ULT

# Medication considerations

- **NSAIDs** – GI, CKD, anticoagulants
- **Colchicine** – low dose, GFR <30mg/min, CYP3A4
- **Allopurinol** – check HLA-B5801 in certain populations, start 100mg, 50mg CKD, titrate, hypersensitivity syndrome, no AZA
- **Febuxostat** – CVD, a little more potent XOI, GFR <30mg/min 20-40mg, can affect LFTs, no AZA
- **Probenecid** – increased daily fluid intake ~2L, avoid kidney stones, less effective in CKD
- **Pegloticase** – infusion, check G6PD, monitor preinfusion sUA, MTX 4 weeks prior to infusion improves response














# 2020 ACR Guidelines

AMERICAN COLLEGE  
of RHEUMATOLOGY  
*Empowering Rheumatology Professionals*

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## ACR GUIDELINE FOR MANAGEMENT OF GOUT

### 2020 American College of Rheumatology Guideline for the Management of Gout

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# 2020 ACR Guidelines

## Indications for ULTs

Strongly Recommend	Conditionally Recommend	Conditionally Recommend Against	Strongly Recommend Against
<ul style="list-style-type: none"><li>- 1 or more subcutaneous tophi</li><li>- Radiographic damage (any modality) attributable to gout</li><li>- Frequent gout flares (&gt;2/year)</li></ul>	<ul style="list-style-type: none"><li>- 1 flare but have infrequent flares (&lt;2/year)</li><li>- First flare and CKD stage &gt;3, SU &gt;9 mg/dl, or urolithiasis</li></ul>	<ul style="list-style-type: none"><li>- First flare</li><li>- Asymptomatic hyperuricemia (SU &gt;6.8 mg/dl with no prior gout flares or subcutaneous tophi)</li></ul>	<ul style="list-style-type: none"><li>- <del>Pegloticase</del> as first-line therapy</li></ul>

# 2020 ACR Guidelines

## Patients on ULTs

<b>Strongly Recommend</b>	<b>Conditionally Recommend</b>	<b>Conditionally Recommend Against</b>
<ul style="list-style-type: none"><li>- Treat-to-target strategy with dose titration and serial SU values rather than fixed, standard-dose ULT</li><li>- Continuing ULT to achieve and maintain an SU target of &lt;6mg/dl over no target.</li></ul>	<ul style="list-style-type: none"><li>- Delivery of an augmented protocol of ULT dose management by nonphysician providers to optimize the treat-to-target strategy that includes patient education, shared decision-making, and treat-to-target protocol.</li><li>- Continuing ULT indefinitely over stopping ULT.</li></ul>	

# 2020 ACR Guidelines

## Allopurinol

Strongly Recommend	Conditionally Recommend	Conditionally Recommend Against
	<ul style="list-style-type: none"><li>- Testing HLA-B*5801 prior to in patients of Southeast Asian descent (e.g., Han Chinese, Korean, Thai) and African American patients, who have a higher prevalence of HLA-B*5801.</li><li>- Allopurinol desensitization for patients with a prior allergic response to allopurinol who cannot be treated with other oral ULT,</li></ul>	<ul style="list-style-type: none"><li>- HLA-B*5801 testing in all others</li></ul>

# 2020 ACR Guidelines

## Febuxostat

<b>Strongly Recommend</b>	<b>Conditionally Recommend</b>	<b>Conditionally Recommend Against</b>
	- History of CVD or a new CV event, we switching to an alternative ULT agent if available and consistent with other recommendations in this guideline.	

## Uricosurics

<b>Strongly Recommend</b>	<b>Conditionally Recommend</b>	<b>Conditionally Recommend Against</b>
		- Checking urinary uric acid over checking urinary uric acid. - alkalinizing urine agents

# 2020 ACR Guidelines

## When to consider switching to new ULT

Strongly Recommend	Conditionally Recommend	Strongly Recommend Against
<p>For patients with gout where XOI, uricosurics, and other interventions <b>have failed to achieve SU target and who have frequent gout flares or nonresolving subcutaneous tophi</b>, we strongly recommend switching to <u>pegloticase</u> over continuing current ULT.</p>	<p>At maximum-tolerated or FDA-indicated dose who are not at SU target and/or have continued frequent gout flares or <u>nonresolving subcutaneous tophi</u>, we conditionally recommend <b>switching the first XOI to an alternate XOI agent over adding a uricosuric agent.</b></p>	<p>For patients with gout for whom XOI, uricosurics, and other interventions have failed to achieve serum urate target and who <b>have infrequent gout flares (&lt;2 flares/year)</b> and no tophi, we strongly recommend against switching to <u>pegloticase</u> over continuing current ULT.</p>

# 2020 ACR Guidelines

## Gout Flare Management

Strongly Recommend	Conditionally Recommend	Conditionally Recommend Against
<ul style="list-style-type: none"><li>- Oral colchicine, NSAIDs, or glucocorticoids (oral, IA, or IM) as appropriate first-line therapy for gout flares over IL-1 inhibitors or ACTH (the choice of colchicine, NSAIDs, or glucocorticoids should be made based on patient factors and preferences).</li><li>- Low-dose colchicine over high-dose colchicine given its similar efficacy and fewer adverse effects.</li><li>- NPO patients: glucocorticoids (intramuscular, intravenous, or intraarticular) over IL-1 inhibitors or ACTH.</li></ul>	<ul style="list-style-type: none"><li>- When other <u>antiinflammatory</u> therapies are poorly tolerated or contraindicated, we conditionally recommend using IL-1 inhibition over no therapy (beyond supportive/analgesic treatment).</li><li>- Using topical ice as an adjuvant treatment over no adjuvant treatment.</li></ul>	

# 2020 ACR Guidelines

## Management of lifestyle factors

Strongly Recommend	Conditionally Recommend	Conditionally Recommend Against
	<ul style="list-style-type: none"><li>- Limiting alcohol intake.</li><li>- Limiting purine intake.</li><li>- Limiting high-fructose corn syrup.</li><li>- Weight loss for overweight/obese patients</li></ul>	<ul style="list-style-type: none"><li>- Vitamin C supplementation (insufficient data)</li></ul>

## Management of concurrent medications

Strongly Recommend	Conditionally Recommend	Conditionally Recommend Against
	<ul style="list-style-type: none"><li>- Switching hydrochlorothiazide to an alternate antihypertensive when feasible.</li><li>- Choosing losartan preferentially as an antihypertensive when feasible.</li></ul>	<ul style="list-style-type: none"><li>- Low-dose aspirin (in those who are taking this medication for appropriate indications).</li><li>- Adding or switching to fenofibrate.</li></ul>

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**Thank You!**