



Brigham and Women's Hospital

Founding Member, Mass General Brigham

Gout and CPPD Disease

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-
- Clinical focus: giant cell arteritis and CPPD disease
 - Research focus: CPPD disease

DISCLOSURES

Consulting: Amgen, Avalo, Alexion, Alesta, Fresenius Kabi, Novartis, Merck, Kyowa Kirin

Research grant: Alexion



LEARNING OBJECTIVES

1. Review gout prophylaxis and treatment
2. Discuss clinical associations with CPPD disease



Case 1: A hot, swollen joint

A 53-year-old man presents to urgent care with 1 day of extreme pain, redness, and swelling at the right 1st metatarsophalangeal joint. He reports 2 similar episodes in the past 5 years, each of which resolved with a week of NSAIDs. Current medications include hydrochlorothiazide and atorvastatin.

Which of the following would be LEAST useful for diagnosis in his current presentation?

- a) Joint aspiration and synovial fluid crystal analysis
- b) X-ray of the 1st metatarsophalangeal joint
- c) ESR and CRP
- d) Serum uric acid



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Which of the following would be LEAST useful for diagnosis in his current presentation?

- a) Joint aspiration and synovial fluid crystal analysis **crystals*
- b) X-ray of the 1st metatarsophalangeal joint **erosions*
- c) ESR and CRP **not specific*
- d) Serum uric acid **helpful if high, but can be paradoxically low during flares*



Gout diagnosis: best practices

- Acute monoarthritis differential diagnosis
 - Gout
 - Pseudogout
 - Septic joint
 - Trauma or hemarthrosis
 - Initial onset of rheumatoid, psoriatic, etc
- Send synovial fluid aspirate for the 3 Cs
 - Crystals
 - Cell count
 - Culture and gram stain
- 1st MTP joint can be difficult to aspirate (and very painful!)



Gout diagnosis: best practices

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Gout clinical prediction using clinical features + serum uric acid

	Points
Serum urate >5.9 mg/dL	3.5
1 st metatarsophalangeal	2.5
Male	2
Prior self-reported flare	2
Hypertension or CVD	1.5
Joint redness	1
Acute onset within 24h	0.5

Probability of gout by total points

≤4	low
>4 to <8	intermediate
≥8	high



Imaging studies can help diagnose gout



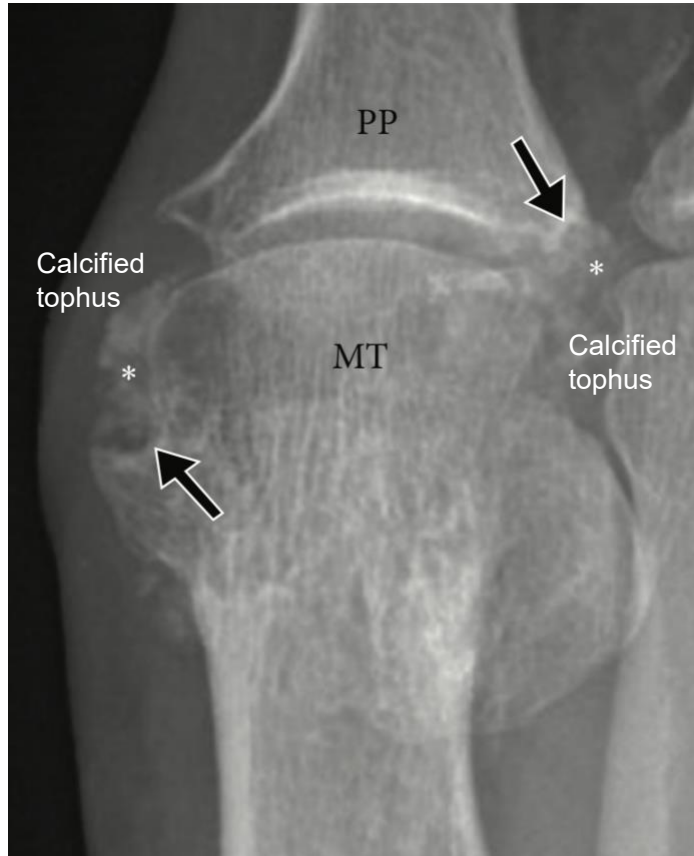
X-ray in gout

Gouty erosion

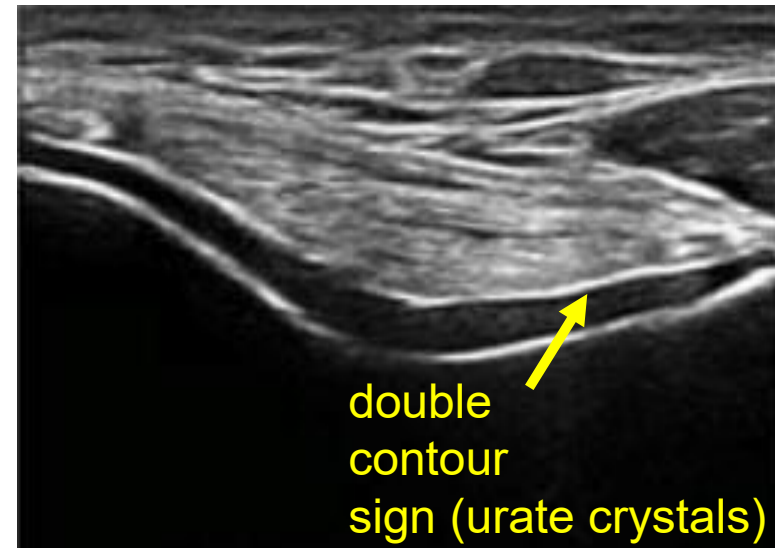
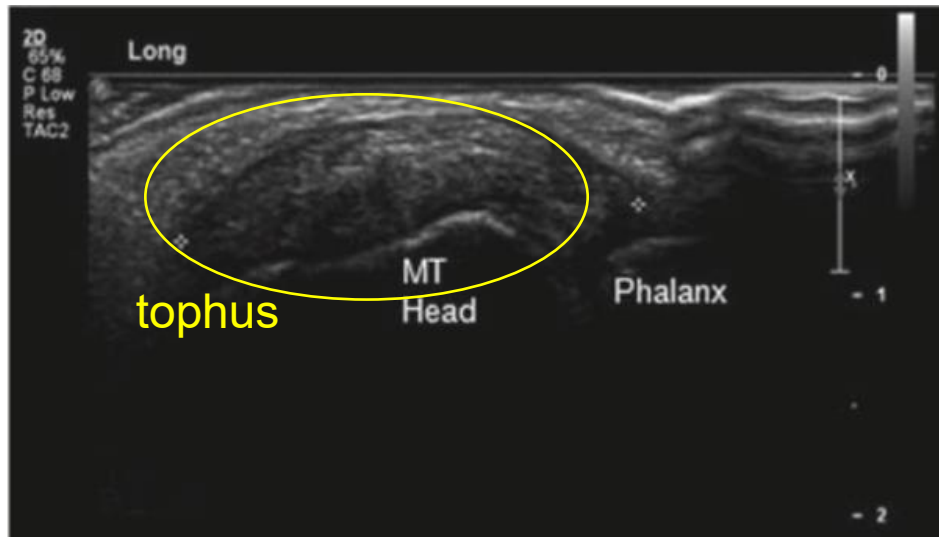


X-ray in gout

Gouty erosion
Tophus

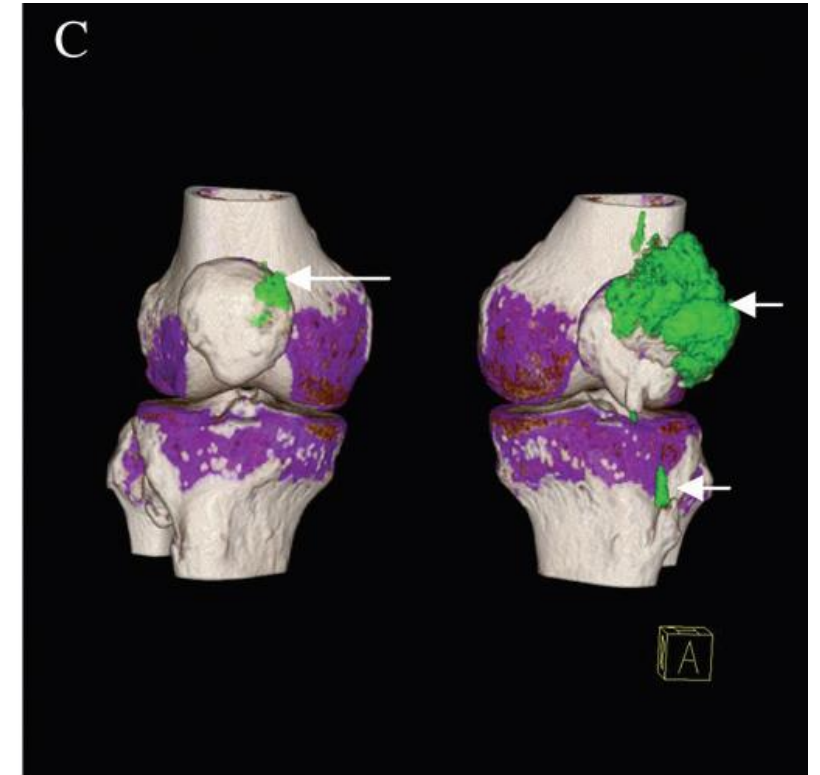
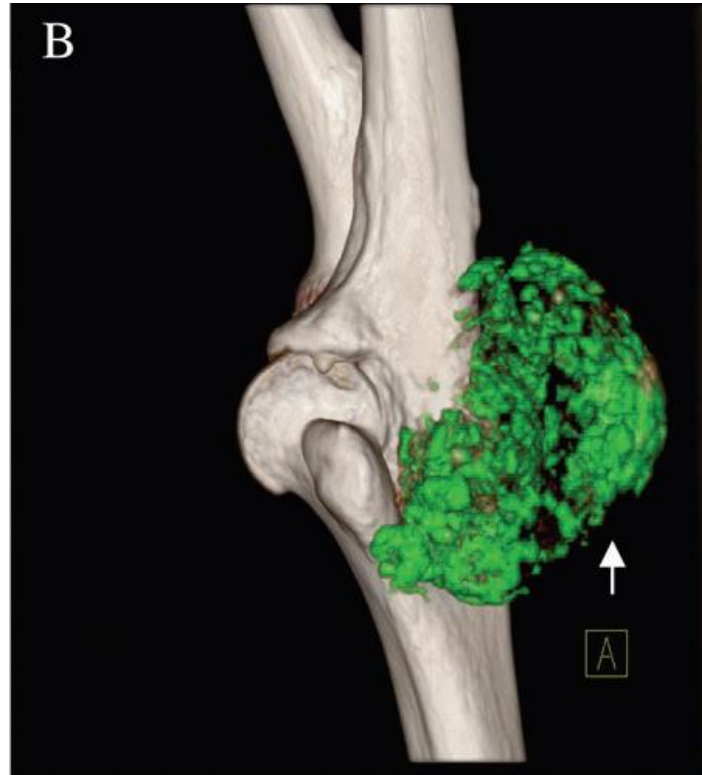
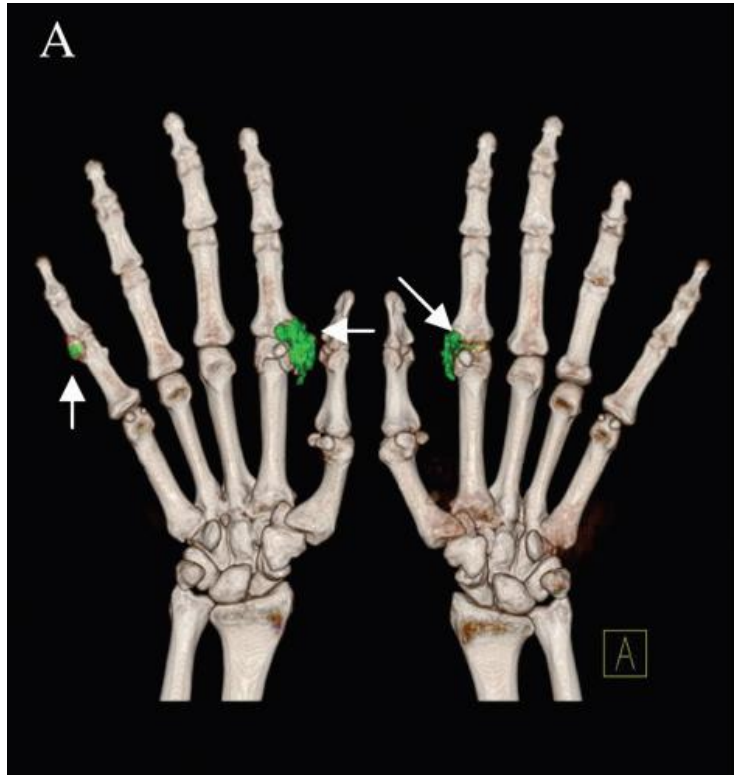


Ultrasound in gout



Sensitivity ~90%
Specificity ~90%

Dual-energy CT in gout



Sensitivity

~50% in new-onset gout (<6 weeks)
~80% on longstanding gout

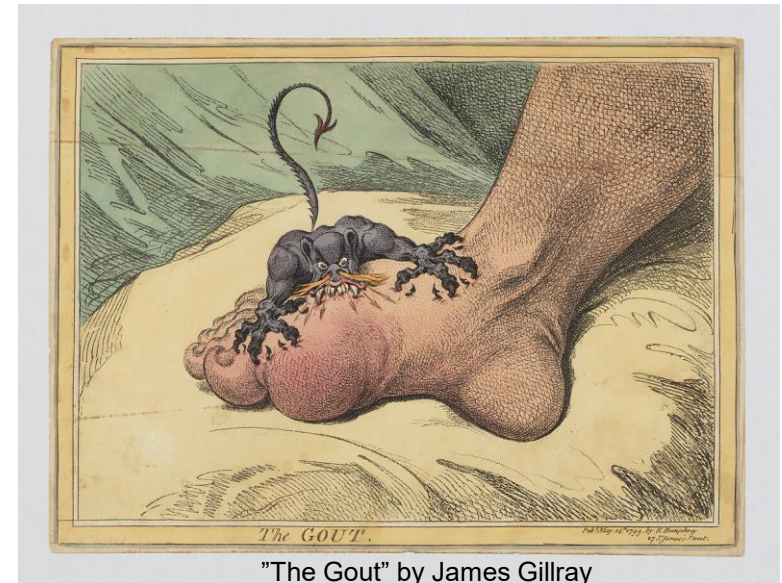
Specificity

~90%



Why do gout flares happen?

- Often no known trigger
- For some patients, triggers include
 - Fluid shifts (surgery, diuretics)
 - Stopping allopurinol!
 - High-purine diet: alcohol, red meat, shellfish
- Joint involvement
 - Lower extremity joints (podagra = “foot trap”)
 - Upper extremity joints
 - Spine



"The Gout" by James Gillray

<https://www.metmuseum.org/art/collection/search/853065>



Gout affects patients beyond the joints

Patient and society

- Quality of life
- Healthcare utilization
- Side effects from flare treatment

Multimorbidity

- Metabolic syndrome and diabetes
- Cardiovascular disease
- Chronic kidney disease

Gout flares are temporally associated with:

Cardiovascular events (myocardial infarction, stroke)














- 2x greater odds if gout flare in past 2 months

Venous thromboembolism

- 2x higher incidence if gout flare in past 1 month



2020 American College of Rheumatology Guideline for the Management of Gout

John D. FitzGerald,¹  Nicola Dalbeth,²  Ted Mikuls,³  Romina Brignardello-Petersen,⁴ Gordon Guyatt,⁴ Aryeh M. Abeles,⁵  Allan C. Gelber,⁶  Leslie R. Harrold,⁷ Dinesh Khanna,⁸  Charles King,⁹ Gerald Levy,¹⁰ Caryn Libbey,¹¹ David Mount,¹² Michael H. Pillinger,⁵  Ann Rosenthal,¹³ Jasvinder A. Singh,¹⁴  James Edward Sims,¹⁵ Benjamin J. Smith,¹⁶  Neil S. Wenger,¹⁷ Sangmee Sharon Bae,¹⁷  Abhijeet Danve,¹⁸ Puja P. Khanna,¹⁹ Seoyoung C. Kim,²⁰  Aleksander Lenert,²¹ Samuel Poon,²² Anila Qasim,⁴ Shiv T. Sehra,²³ Tarun Sudhir Kumar Sharma,²⁴ Michael Toprover,⁵ Marat Turgunbaev,²⁵ Linan Zeng,⁴ Mary Ann Zhang,²⁰  Amy S. Turner,²⁵ and Tuhina Neogi¹¹ 

American College of Rheumatology gout flare treatment recommendations



First-line

- **NSAID** (if no contraindication)
- **Glucocorticoid** (oral, IA, IV, IM)
 - Prednisone 20-40mg daily for 3 days, then decrease by 10mg every 3 days
- **Colchicine with loading dose**
 - CrCl ≥ 30 mL/min: 1.2mg x1, then 0.6mg 1 hour later, then 0.6mg once or twice daily
 - CrCl < 30 mL/min: same load over 1 hour, then 0.6mg every other day
 - Hemodialysis: 0.6mg x1 (or avoid)

Second-line: IL-1 inhibitors

- Anakinra
- Canakinumab

Don't stop allopurinol during a flare!



Ice in addition to medication

Case 1, continued

The patient is happy that you suggested several options to treat his current gout flare. He asks about medicine to prevent gout flares. This is his 2nd episode of podagra this year, and his only other episode was 4 years ago. His serum urate is 7.9 mg/dL and CrCl is >60 mL/min.

Which of the following do you recommend for him today? (choose all that apply)

- a) Switch from hydrochlorothiazide to losartan
- b) Start colchicine 0.6mg daily
- c) Start allopurinol 100mg daily
- d) Start febuxostat 40mg daily



Case 1, continued

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- a) Switch from hydrochlorothiazide to losartan
- b) Start colchicine 0.6mg daily **pharmacy may flag atorvastatin*
- c) Start allopurinol 100mg daily
- d) Start febuxostat 40mg daily



Who should receive urate-lowering therapy (ULT)?

American College of Rheumatology 2020 guidelines

STRONGLY RECOMMEND



Frequent flares (2 or more/year)
Tophus
Erosions

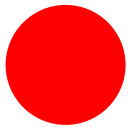
Start ULT during a gout flare
(rather than waiting until the flare
resolves)

CONDITIONALLY RECOMMEND



Infrequent flares
First-ever flare plus CKD stage 3 or worse, kidney stone, or serum urate >9 mg/dL

RECOMMEND AGAINST

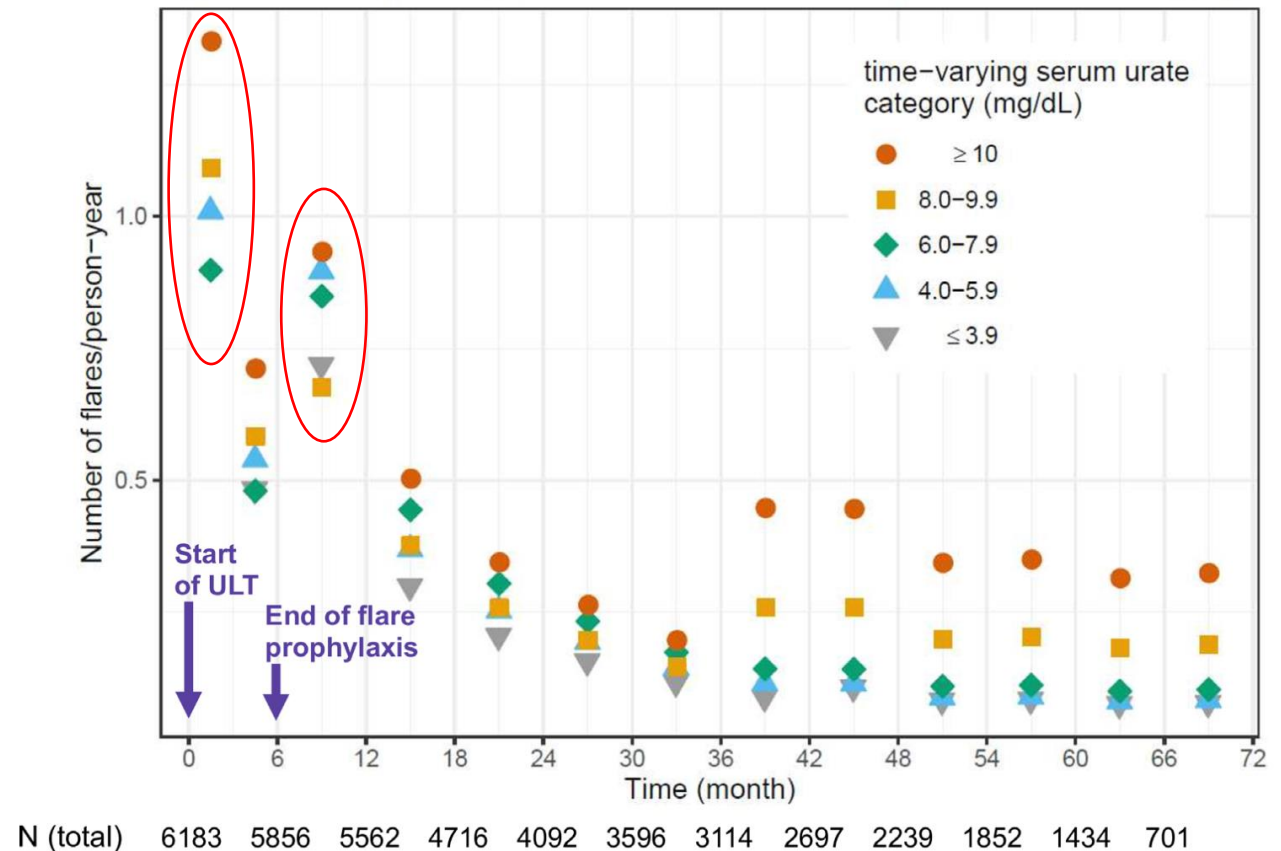


Hyperuricemia without joint symptoms or tophi



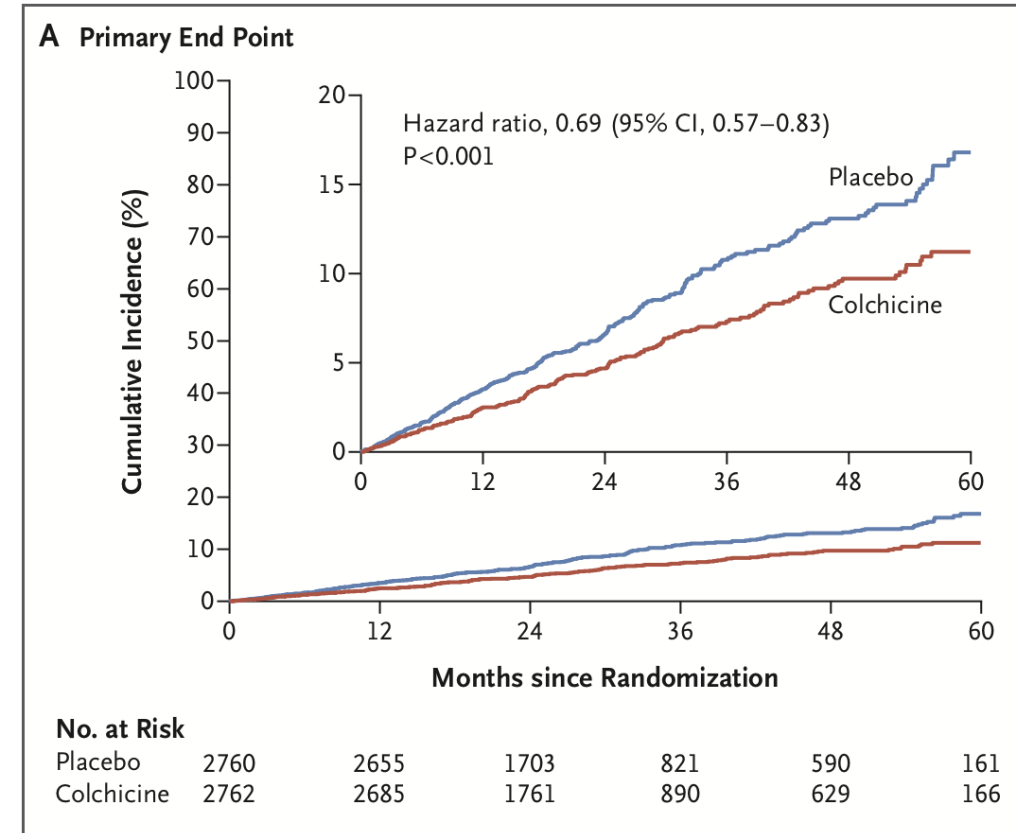
Gout flare prophylaxis is important when starting ULT

1. The first few months after starting ULT are *high risk* for gout flare
2. Start prophylaxis before (or with) ULT
 - **Colchicine is most common**
 - CrCl ≥ 30 : 0.6mg once daily
 - CrCl < 30 : 0.6mg every other day
 - Hemodialysis: 0.3mg twice a week (FDA package insert) or avoid
 - NSAID or low-dose prednisone
3. Continue prophylaxis for at least 3-6 months after serum urate is < 6 mg/dL
4. Gout flare risk increases after stopping prophylaxis



Colchicine updates

- FDA approved for secondary CV prevention (0.5mg daily)
- An extra benefit to using colchicine for flare prophylaxis!
- Strong CYP3A4 inhibitors (clarithromycin, HAART) and P-glycoprotein inhibitors (cyclosporin, ranolazine) dramatically increase colchicine concentration
 - Avoid
- Pharmacy may flag interaction with statins
 - 2 large RCTs with >10,000 patients with CV disease
 - >90% statin use
 - Neutropenia, myotoxicity, serious GI events: rates similar in colchicine & placebo groups



Picking and starting urate-lowering therapy

STRONGLY RECOMMEND

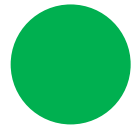


Xanthine oxidase inhibitors are 1st line ULT

- Allopurinol is 1st choice for most; safe in CKD!
- Febuxostat is 2nd line

Picking and starting urate-lowering therapy

STRONGLY RECOMMEND

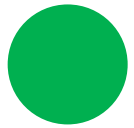


Xanthine oxidase inhibitors are 1st line ULT

- Allopurinol is 1st choice for most; safe in CKD!
- Febuxostat is 2nd line
- CARES trial compared CV safety of allopurinol vs. febuxostat in gout
~50% drop-out rate
Higher CV mortality in febuxostat arm → black box warning
- FAST trial also compared CV safety of allopurinol vs. febuxostat in gout
Similar CV event rate in both groups

Picking and starting urate-lowering therapy

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CONDITIONALLY RECOMMEND



- HLA-B*5801 haplotype
 - Allopurinol binds HLA-B58*01 allele → risk of allopurinol hypersensitivity syndrome
 - Test in patients of Southeast Asian descent and African American patients
 - Avoid allopurinol if present (can use febuxostat)



Other urate-lowering therapy options (not 1st line)

URAT1 inhibitors: prevent renal re-uptake of uric acid

- Probenecid
- Others in the pipeline (dotinurad approved in Japan)
- Avoid if prior uric acid kidney stone

Pegloticase: uricase infusion

- Indication: maximum-dose XOI & uricosurics have not reached SU target and having ongoing frequent gout flares or ongoing tophi
- Missed doses can result in anaphylaxis if later resumed
- Methotrexate improves pegloticase response, reduces infusion reaction rate, and reduces anti-drug antibody formation (FDA-approved combination with pegloticase)



Dosing ULT & treating-to-target serum urate

STRONGLY RECOMMEND

● Up-titrate ULT to achieve target serum urate <6 mg/dL

Allopurinol: maximum dose can be >900 mg!

- Normal renal function:
 - 100mg daily to start
 - Check serum urate after 1 month
 - Increase by 100mg every month until serum urate <6 mg/dL
- CKD stage ≥ 3
 - 50mg daily to start (to reduce risk of allopurinol hypersens. syndrome)
 - Increase by 50mg every month until serum urate <6 mg/dL
 - Do not stop at 300mg daily!



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Febuxostat: maximum dose 80mg

- 20mg or 40mg daily to start
- Labs as above
- Increase by 20mg every month until serum urate <6 mg/dL



SGLT2 inhibitors are associated with lower risk for incident gout and fewer gout flares

- Gout incidence rate in patients with type 2 diabetes
 - 11-36% lower among SGLT2i initiators vs. GLP1-RA or DPP-4i initiators
- SGLT2i in patients with type 2 diabetes & gout
 - 20% lower gout flare rate
 - 30% lower risk of mortalitycompared to those initiating GLP1-RA or DPP-4i
- SGLT2i promote uricosuria & reduce serum urate levels
 - mean reduction 0.6 mg/dL (meta-analysis of 62 trials)



Lifestyle factors and gout

CONDITIONALLY



Limit alcohol

Limit purine intake

Limit high-fructose corn syrup

Weight loss

Dietary changes can reduce serum urate by ~ 0.5 to 1 mg/dL

Cherry extract / cherries: insufficient data to make a recommendation





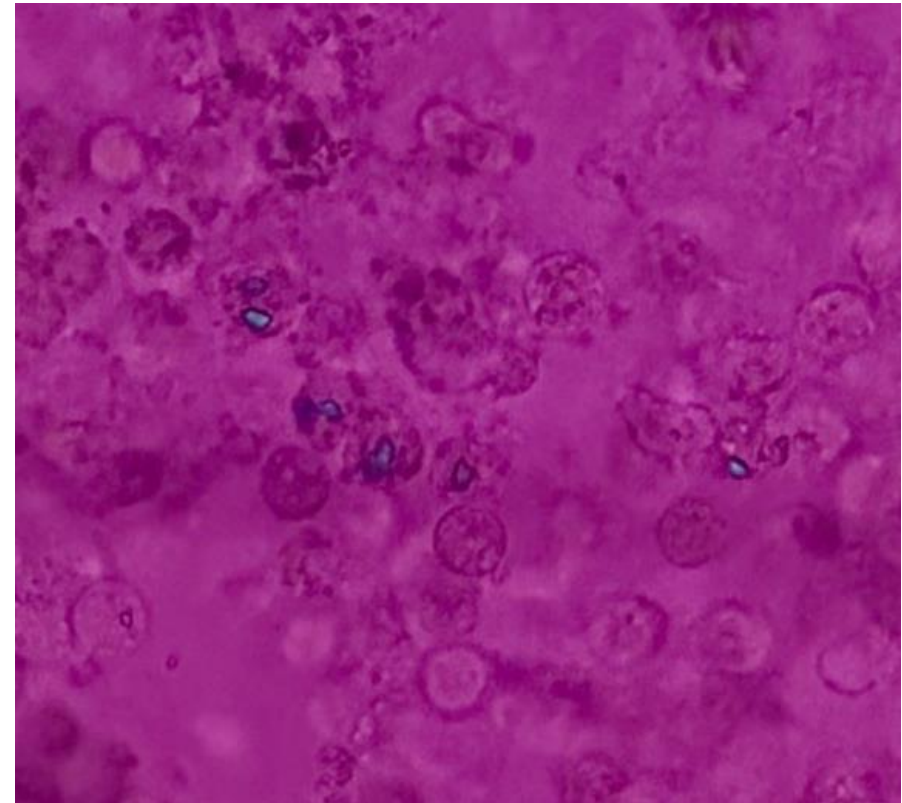
Calcium pyrophosphate deposition (CPPD) disease

Pseudogout.....Chondrocalcinosis.....CPPD....
What's the difference?

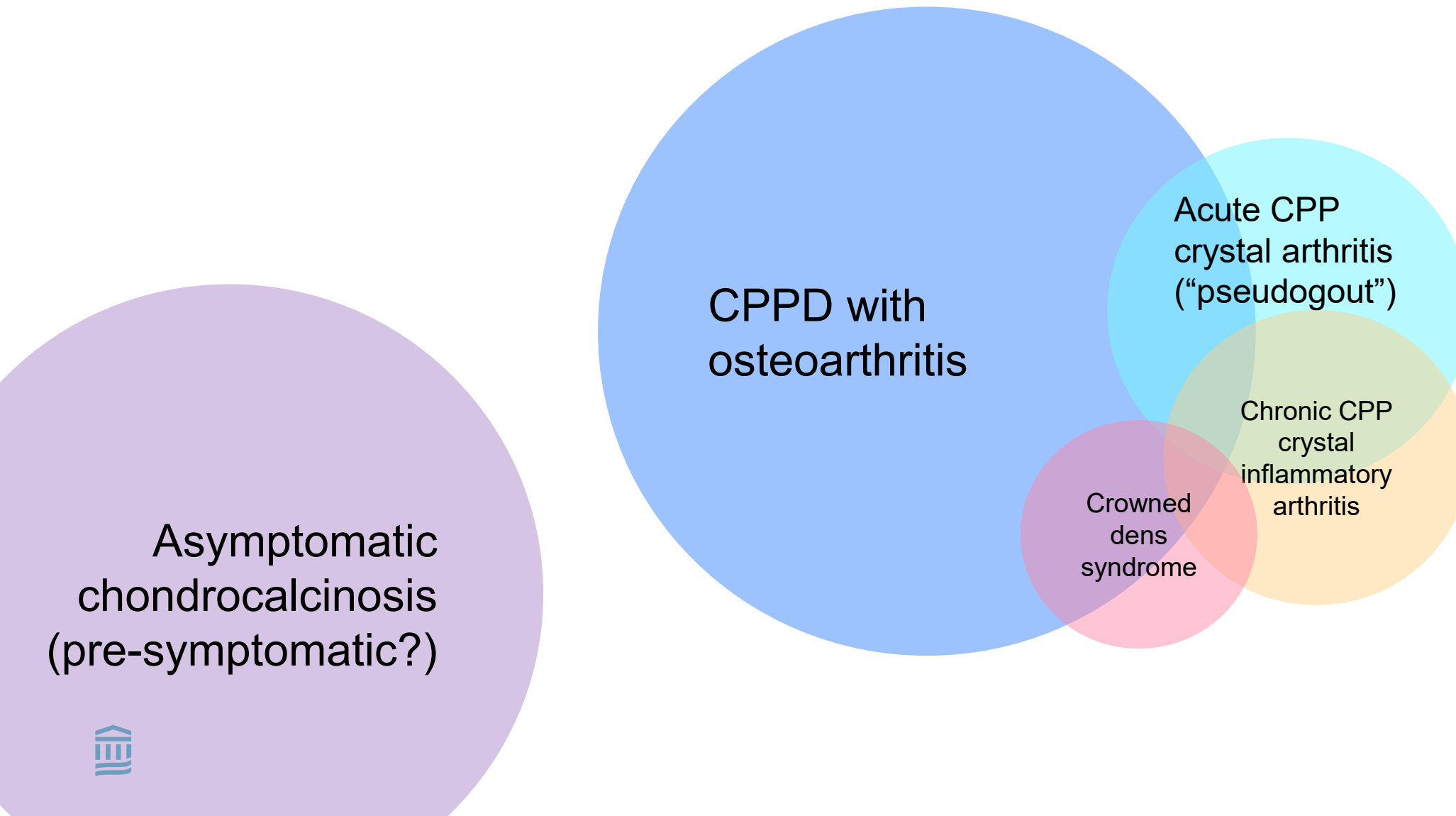


Calcium pyrophosphate deposition (CPPD) disease represents a common crystalline arthritis

- Symptomatic arthritis caused by calcium pyrophosphate (CPP) crystals
- Knee and wrist most commonly affected
- No targeted therapies



CPPD disease has multiple clinical manifestations



Who gets CPPD disease?

- Non-modifiable
 - Older age (>60 years) – **the** major risk factor!
 - Joint trauma or joint surgery
 - Osteoarthritis
 - Hyperparathyroidism
 - Hemochromatosis
 - Hypophosphatasia
 - Hypomagnesemia (if genetic)
 - **ANKH mutation** in rare familial cases: increases inorganic pyrophosphate levels
 - **ENPP1 polymorphisms**: recently identified in genome-wide association studies
- Modifiable
 - Bisphosphonates, diuretics, PPIs (all possible, not conclusive)
- CPPD and gout can co-exist (about 5%)



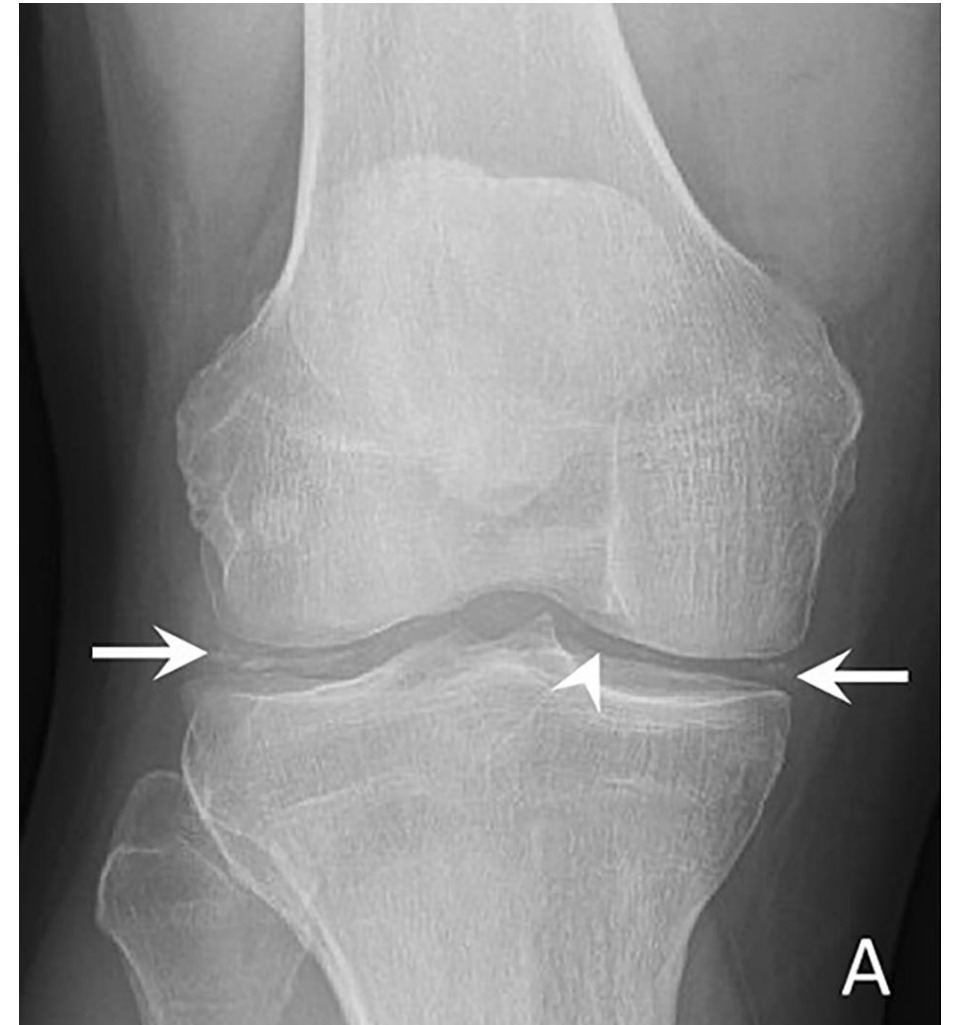
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Bartels CM, et al. *J Clin Rheumatol* 2015
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Takei R, et al. *Ann Rheum Dis* 2025
Tedeschi SK, et al. *Arthritis Care Res* 2021
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Hamilton E. *Arthritis Rheum* 1970

Imaging studies to identify CPPD

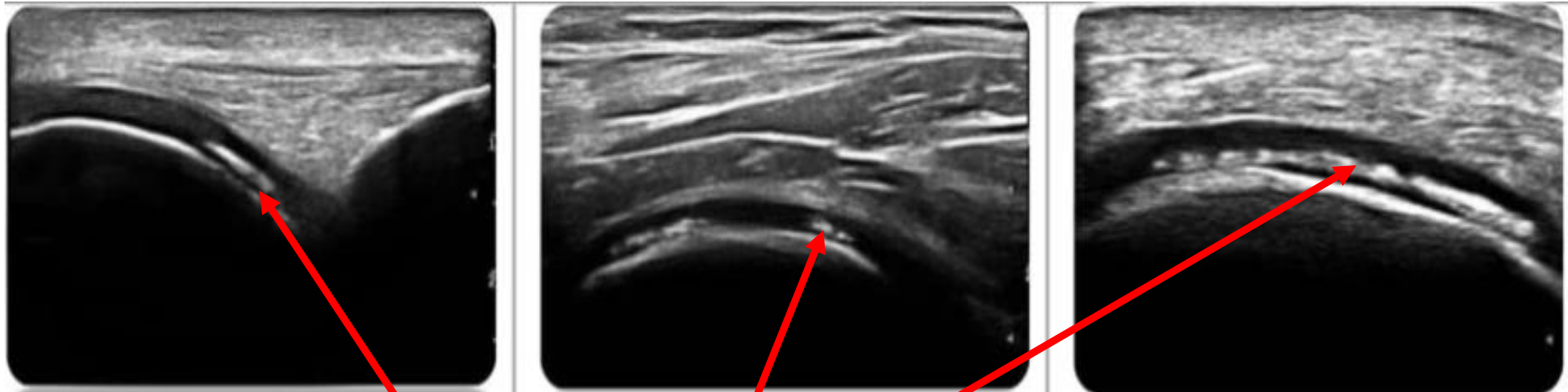


Conventional radiography (x-ray)

- **Chondrocalcinosis** in hyaline cartilage or fibrocartilage
- High specificity (>90%)
- Moderate sensitivity (~50%)

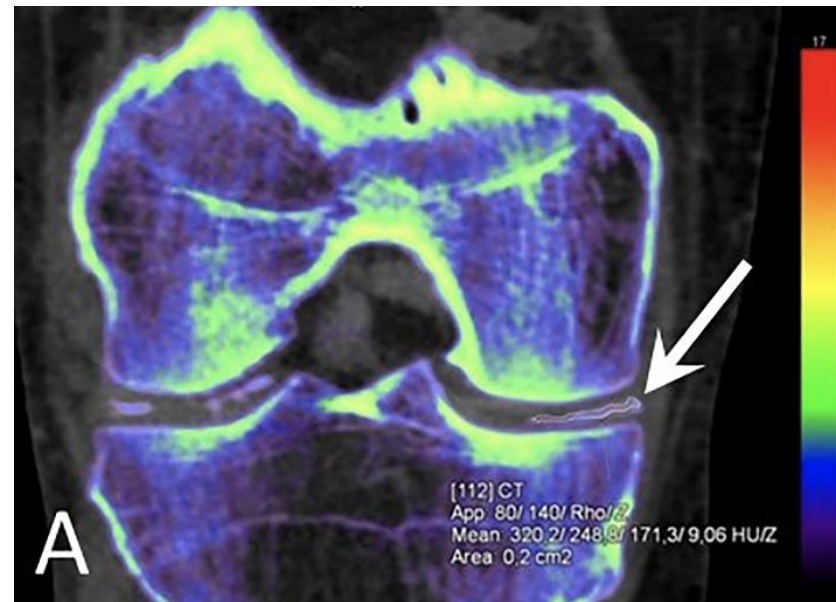


Ultrasound



CPPD within the cartilage

Computed tomography (CT) and dual-energy CT (DECT)



Chondrocalcinosis and joint symptoms

Osteoarthritis progression

- Unclear
- Two recent studies: chondrocalcinosis increases risk of new or progressive OA in the same knee compartment

Knee or hip replacement

- Not clearly associated with chondrocalcinosis

Joint pain

- Not clearly associated with chondrocalcinosis

Neogi T, et al. Arthritis Rheum 2006
Latourte A, et al. Arthritis Rheum 2020
Foreman SC, et al. Osteoarthritis Cartilage 2020
Ibad, et al. Osteoarthritis Cartilage Open 2023
Liew JW, et al. Arthritis Rheum 2024
Wu Y, et al. Ann Rheum Dis 2025



Pseudogout (acute CPP crystal arthritis) is associated with adverse outcomes outside of the joint

Cardiovascular events

- 25%-90% increased risk for non-fatal myocardial infarction, acute coronary syndrome, coronary re-vascularization in 2 large cohort studies

Fractures

- Osteopenia was associated with CPPD in two large cohort studies
- 80% increased risk for fracture of humerus, wrist, hip, or pelvis in patients with a prior episode of pseudogout



CPPD treatment depends on the manifestation

Pseudogout

- Oral prednisone*
- Colchicine*
- Intra-articular glucocorticoid
- IL-1 inhibitor
- Consider NSAID if no contraindications

Chronic CPP inflammatory arthritis

- Methotrexate
- Hydroxychloroquine*
- Colchicine
- IL-1 inhibitor
- IL-6 inhibitor

CPPD with osteoarthritis

- Treat like primary osteoarthritis (physical therapy, acetaminophen, NSAID)

* Supported by RCT data



Pseudogout treatment pearls

1. Short course prednisone was equivalent to colchicine for treating pseudogout flares
 - Prednisone 30mg x2d versus colchicine 1.5mg (day 1) + 1mg (day 2)
 - 65% met primary pain reduction endpoint in each group
2. About 25% of patients with an initial pseudogout flare will have recurrent episodes
 - Colchicine daily helps prevent recurrence in some but not all
 - Hydroxychloroquine, methotrexate, IL-1 inhibition (anakinra), or IL-6 inhibition (tocilizumab) used in patients with frequent recurrence



SUMMARY

- Start gout flare prophylaxis (e.g. colchicine) when starting urate-lowering therapy, and continue prophylaxis for at least 6 months
- Allopurinol can be used safely in nearly all patients with gout
- Gout flares are temporally associated with cardiovascular events and venous thromboembolism
- Pseudogout flares are associated with increased risk for cardiovascular events and fractures



MOC REFLECTIVE STATEMENT

- Start gout flare prophylaxis (e.g. colchicine) when starting urate-lowering therapy, and continue prophylaxis for at least 6 months
- Pseudogout flares are associated with increased risk for cardiovascular events and fractures



Key references

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