

Gout and CPPD Disease

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

DISCLOSURES

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

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?

1. Joint aspiration and synovial fluid crystal analysis
2. X-ray of the 1st metatarsophalangeal joint
3. ESR and CRP
4. Serum uric acid



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

1. Joint aspiration and synovial fluid crystal analysis **crystals*
2. X-ray of the 1st metatarsophalangeal joint **erosions*
3. ESR and CRP **not specific*
4. 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!)



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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



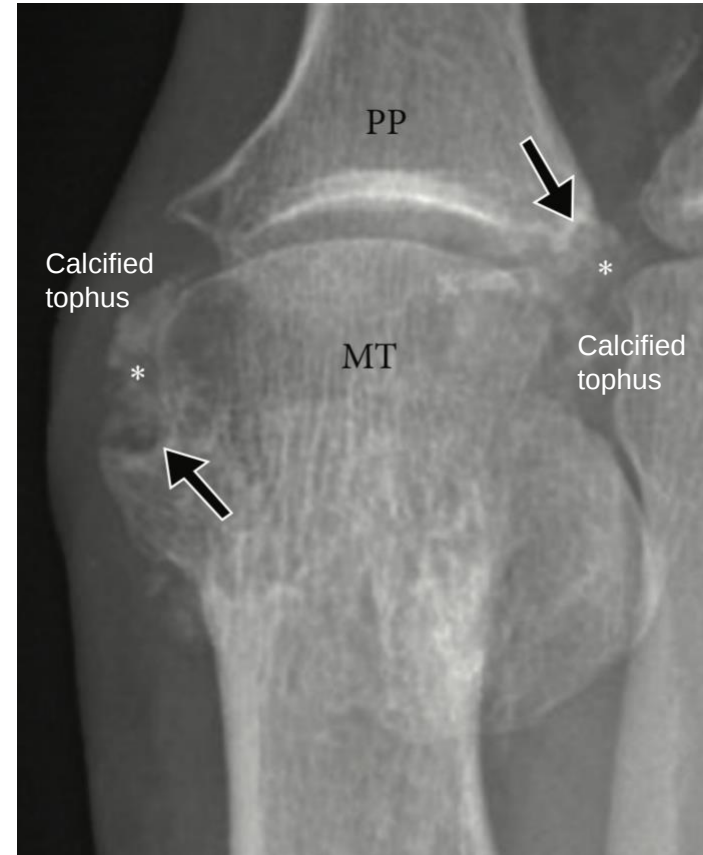
X-ray in gout

Gouty erosion

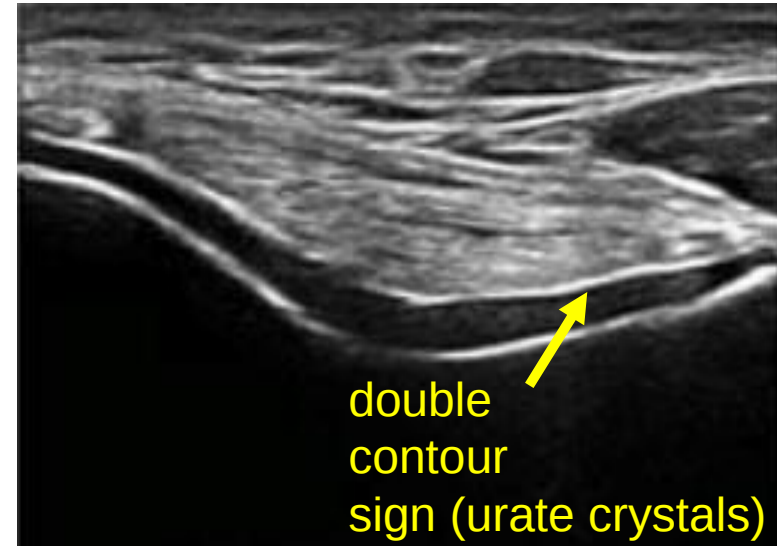
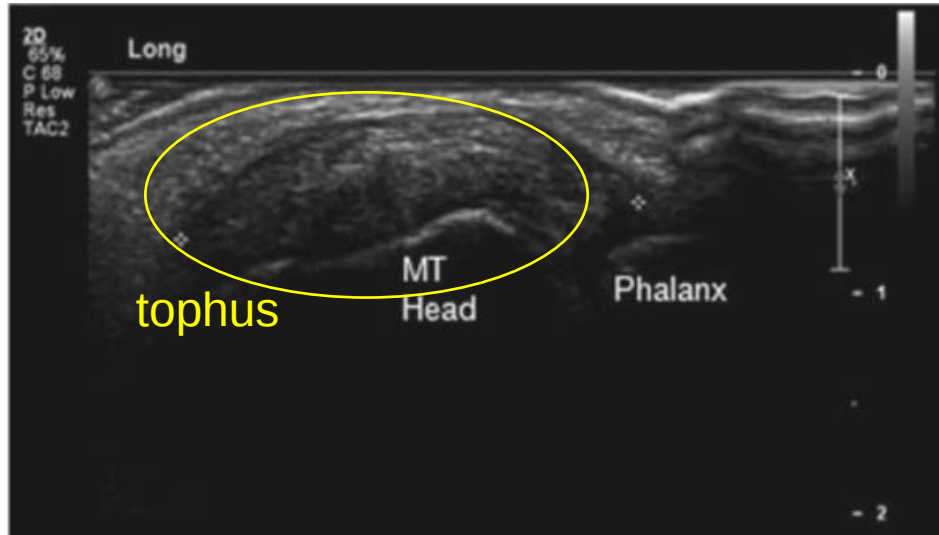


X-ray in gout

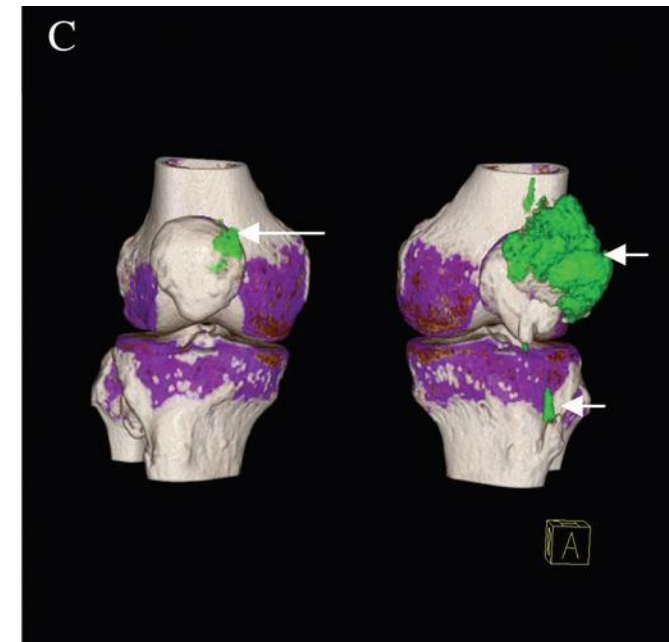
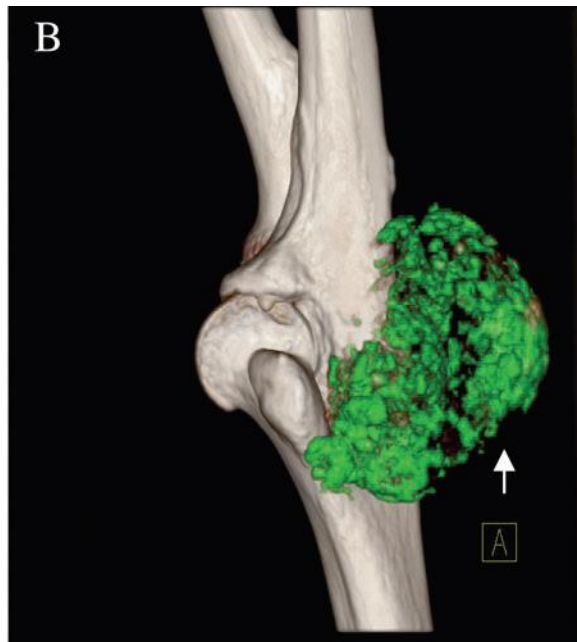
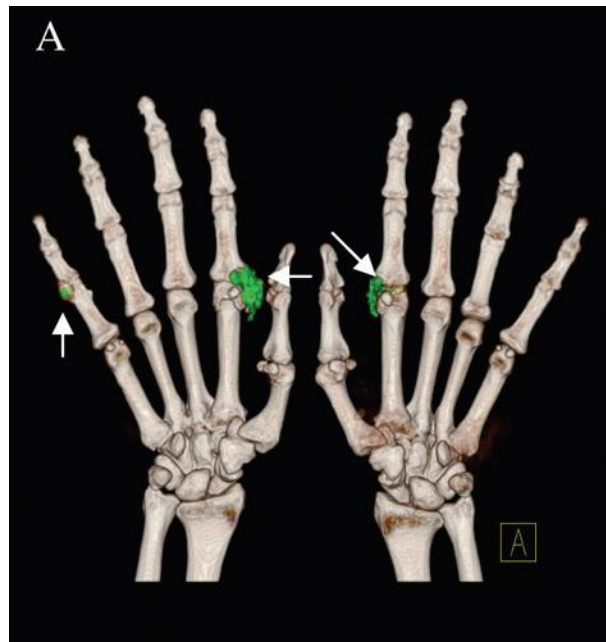
Gouty erosion
Tophus



Ultrasound in gout

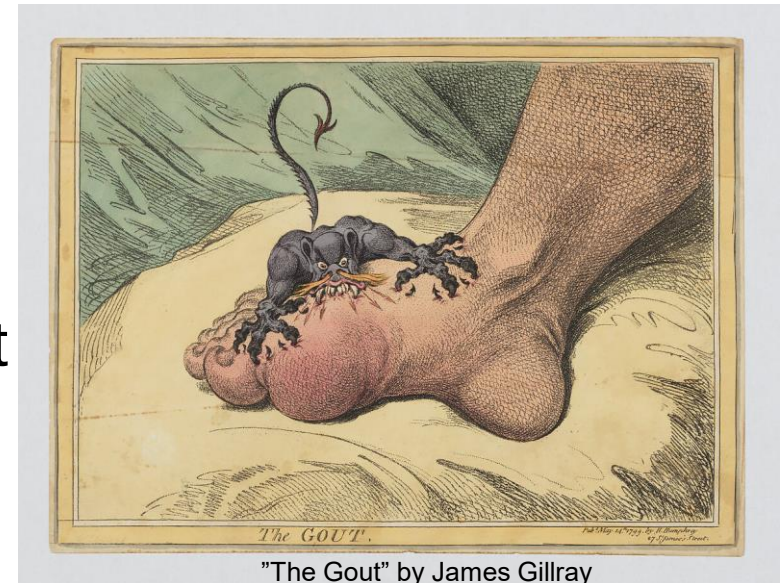


Dual-energy CT in gout



Why do gout flares happen?

- Often no known trigger
- For some patients, triggers include
 - Fluid shifts, e.g., surgery, diuretics
 - Stopping allopurinol! (e.g., patient's decision, ran out of refills, fell off the med list at hospital discharge....)
 - High-purine diet: alcohol, red meat, shellfish
- Common joints:
 - 1st MTP (podagra = foot trap), knee, ankle, midfoot
 - Can also affect upper extremity joints



"The Gout" by James Gillray



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

- 2x greater odds for myocardial infarction or stroke if flare in past 2 months

Venous thromboembolism

- 2x higher incidence of venous thromboembolism if flare in past 1 month



Let's treat this patient's gout flare



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** (1.2mg followed by 0.6mg 1 hour later, then 0.6mg once or twice daily)
 - Lower dose if CrCl 30-60 mL/min
 - Avoid if CrCl <30 mL/min
 - Oral only (IV is unsafe)

Second-line: IL-1 inhibitors

- Anakinra
- Canakinumab

Don't stop a patient's allopurinol during a gout flare!



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)

1. Switch from hydrochlorothiazide to losartan
2. Start colchicine 0.6mg daily
3. Start allopurinol 100mg daily
4. Start febuxostat 40mg daily



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

1. Switch from hydrochlorothiazide to losartan
2. Start colchicine 0.6mg daily **pharmacy may flag atorvastatin – let's discuss!*
3. Start allopurinol 100mg daily
4. Start febuxostat 40mg daily



Who should be treated with urate-lowering therapy (ULT)?

Definitely

- 2 or more gout flares per year
- Tophus
- Gouty erosion on imaging

Possibly

- >1 lifetime flare, but <2 flares per year
- First-ever gout flare and has:
 - CKD stage 3 or worse
 - Serum urate >9 mg/dL
 - Kidney stone

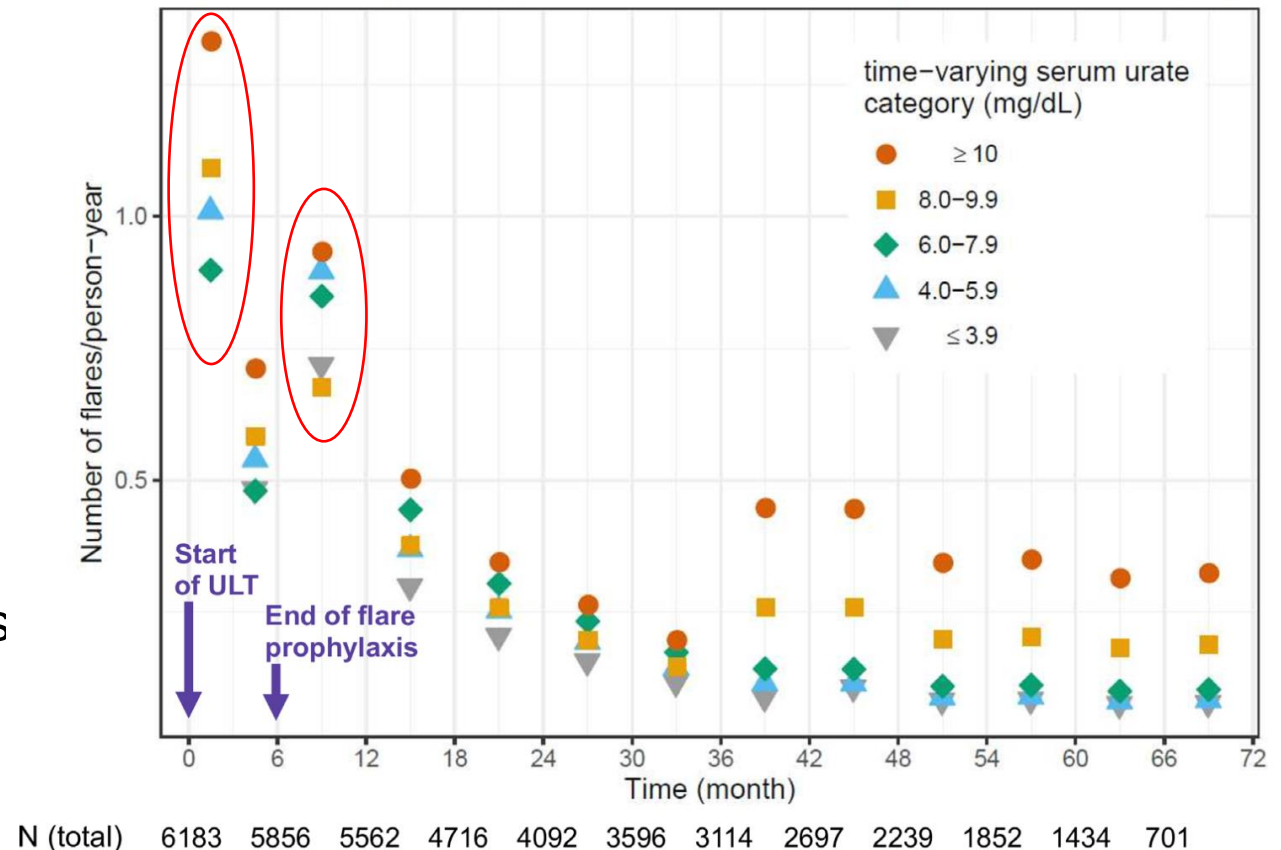
You have a “captive audience” during a gout flare.

The American College of Rheumatology recommends starting ULT during a gout flare, rather than waiting until the flare resolves, if the plan is to start ULT.



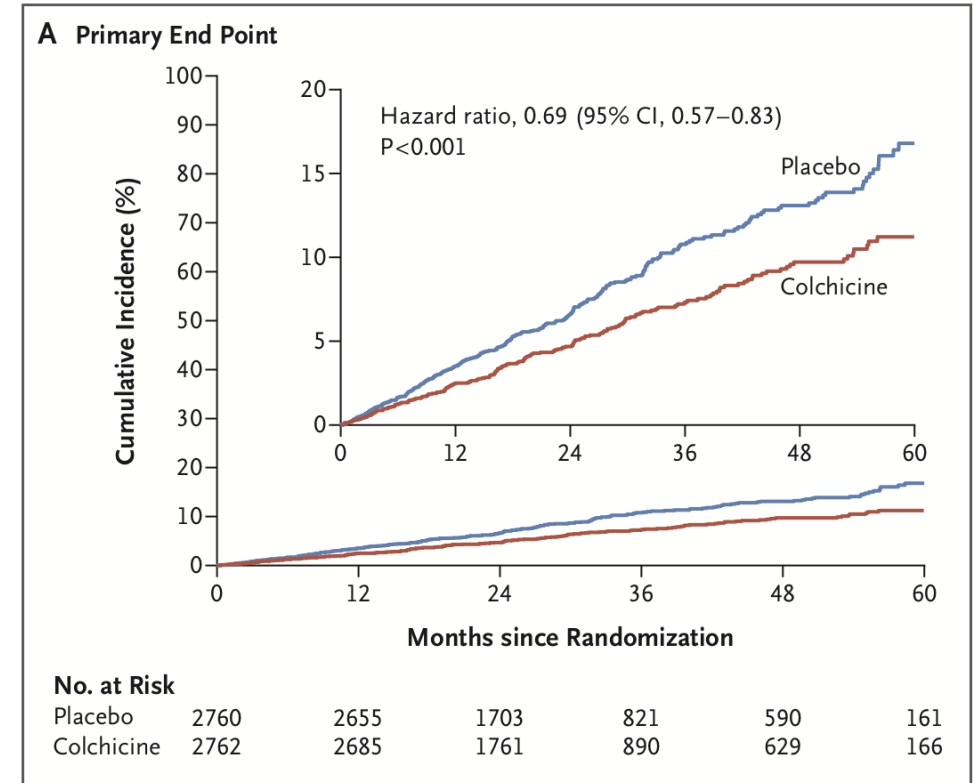
Gout flare prophylaxis is important when starting ULT

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**
 - 0.6mg once daily (CrCl >60)
 - 0.6mg every other day (CrCl 30-60)
 - Avoid or lower dose if CrCl <30
 - NSAID or low-dose prednisone
3. Continue prophylaxis for at least 6 months after achieving serum urate <6 mg/dL
4. Gout flare risk increases after stopping prophylaxis



Colchicine updates

- Recent FDA approval for secondary CV prevention
- 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 use
- Pharmacy may call you to flag an interaction with atorvastatin (CYP3A4 inhibitor)
- But, in 2 large RCTs including >10,000 patients with cardiovascular disease:
 - >90% were taking a statin
 - Neutropenia, myotoxicity, hospitalization for GI reason very rare; similar in colchicine and placebo groups



Nidorf, et al. *NEJM* 2020

Tardif, et al. *NEJM* 2019



Pearls for picking and starting urate-lowering therapy

1. Xanthine oxidase inhibitors are 1st line ULT

- Allopurinol is 1st choice for most; safe in CKD!! (start at a lower dose if CKD)
- Febuxostat is 2nd choice; controversy about cardiovascular safety
- **HLA-B58*01 haplotype**
 - Allopurinol binds HLA-B58*01 allele → risk of allopurinol hypersensitivity syndrome
 - American College of Rheumatology recommends to test in patients of Southeast Asian or African American descent and avoid allopurinol if present (can use febuxostat)

2. Probenecid (URAT1 inhibitor) is a less potent ULT option

- Avoid if prior uric acid kidney stone

3. Pegloticase is a very potent ULT infusion

- Missed doses of pegloticase 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)



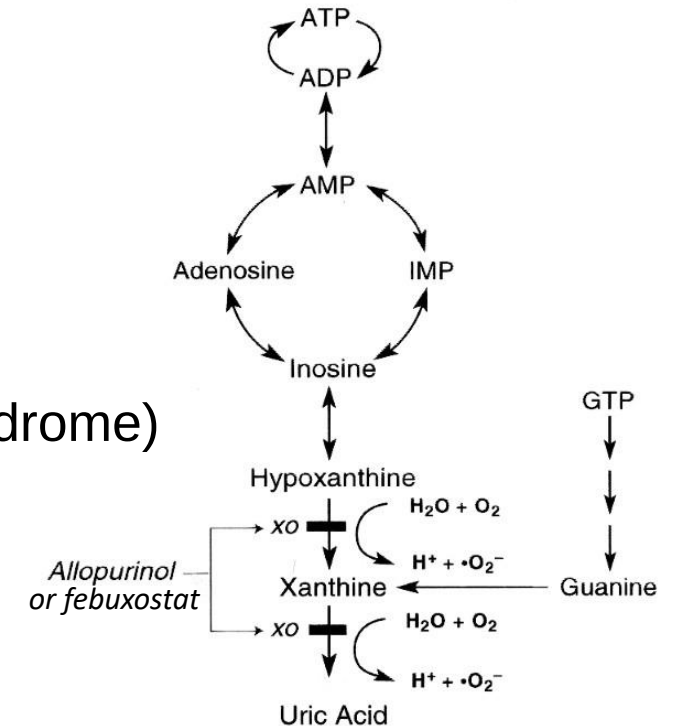
How to dose allopurinol and febuxostat

Allopurinol: maximum dose can be >900mg!

- If normal renal function:
 - 100mg daily to start
 - Check serum urate, ALT, AST, CBC after 1 month
 - Increase by 100mg every month until serum urate <6 mg/dL
- If CKD stage ≥ 3
 - 50mg daily to start (to reduce risk of allopurinol hypersens. syndrome)
 - Labs as above
 - Increase by 50mg every month until serum urate <6 mg/dL
 - Do not stop at 300mg daily! You can go higher!

Febuxostat: maximum dose 80mg

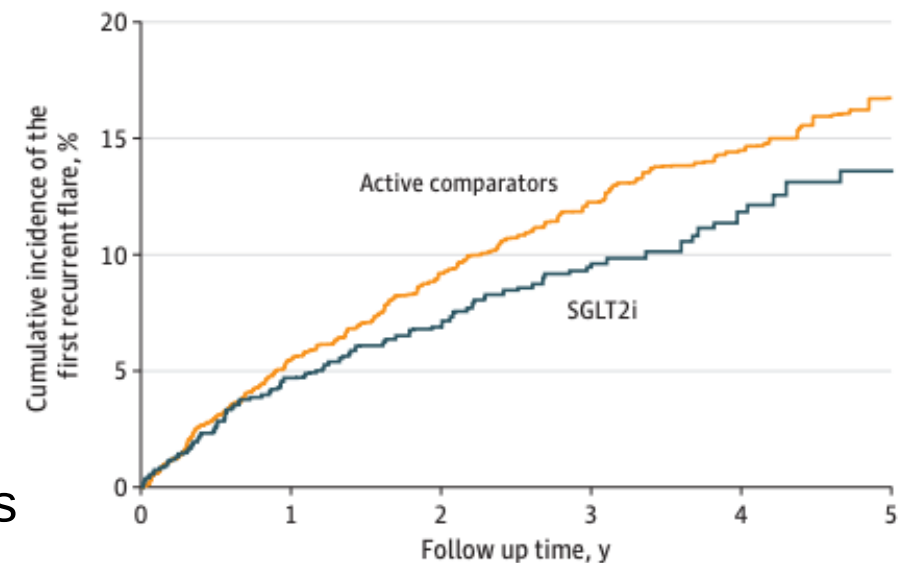
- 20mg daily to start
- Labs as above
- Increase by 20mg every month until serum urate <6 mg/dL



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

- **Gout incidence rate** in patients with type 2 diabetes was
 - 36% lower among SGLT2i vs. GLP1-RA initiators
 - 11% lower among SGLT2i vs. DPP-4i initiators
- After initiating SGLT2i in patients with type 2 diabetes & gout
 - **20% lower gout flare rate**
 - **30% lower risk of mortality**...compared 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 lasting 4-206 weeks)

Cumulative incidence of 1st recurrent gout flare after initiating SGLT2i or active comparator (GLP1-RA or DPP-4i)



Fralick M, et al. Ann Int Medicine 2020
Chung M-C, et al. JAMA Network Open 2021
Wei J, et al. JAMA Network Open 2023
Mikuls TR. NEJM 2022





Calcium pyrophosphate deposition (CPPD) disease

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

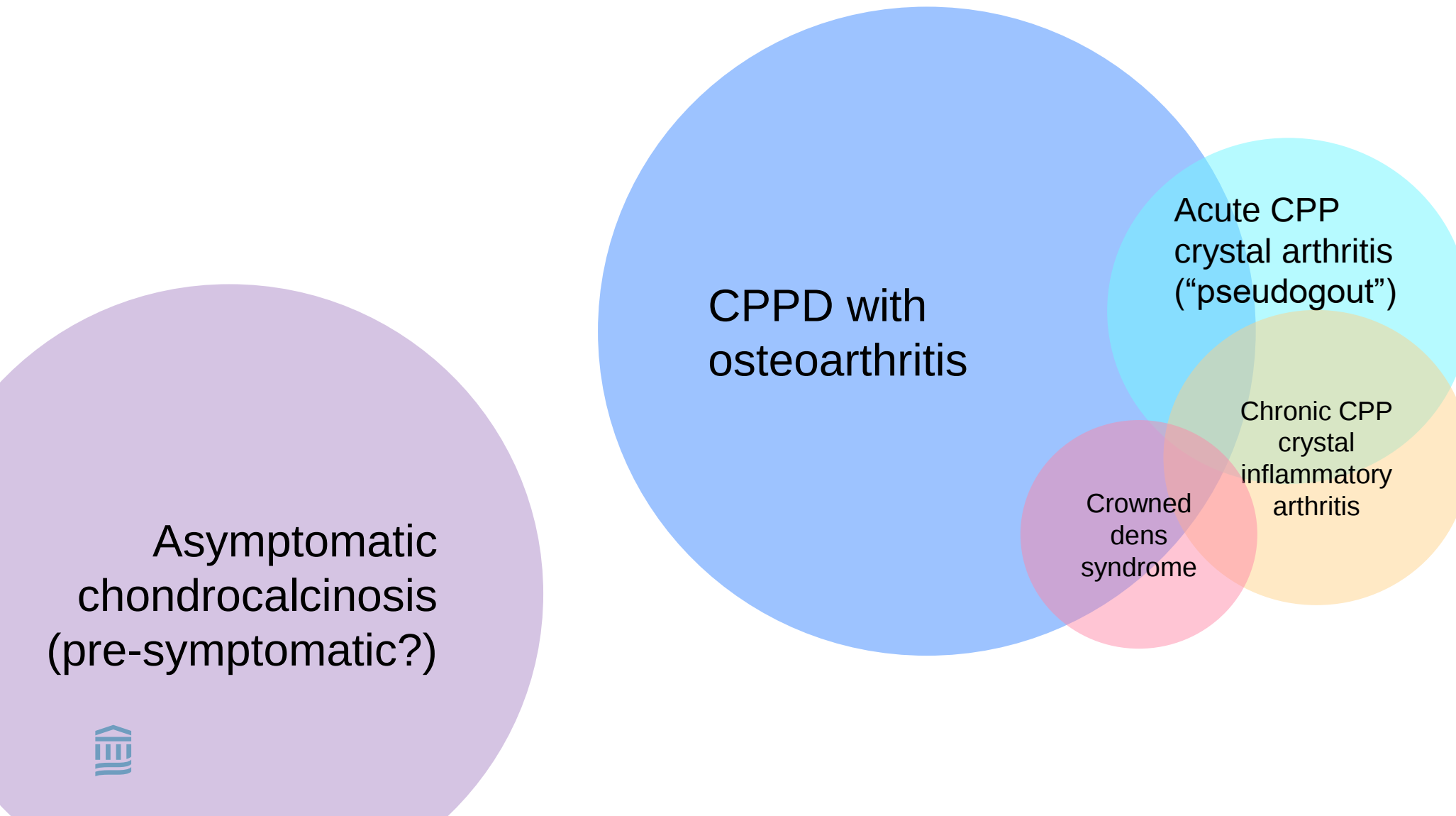


Calcium pyrophosphate deposition (CPPD) disease represents a common crystalline arthritis

- 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
- Modifiable
 - Bisphosphonates, diuretics, PPIs (all possible, not conclusive)
- CPPD and gout can co-exist (about 5%)



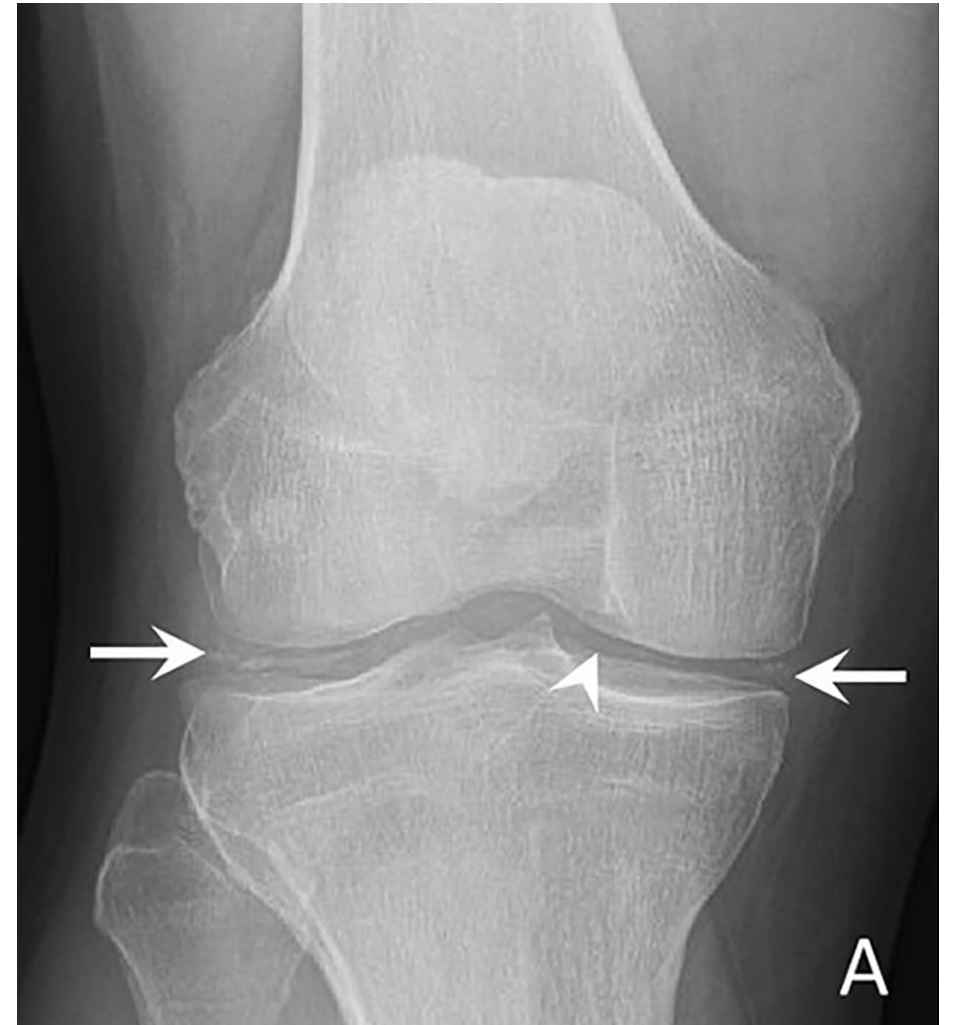
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Tedeschi SK, et al. *Arthritis Care Res* 2021
Kleiber-Baldarrama C, et al. *Arthritis Care Res* 2017
Hamilton E. *Arthritis Rheum* 1970

Imaging studies to identify CPPD

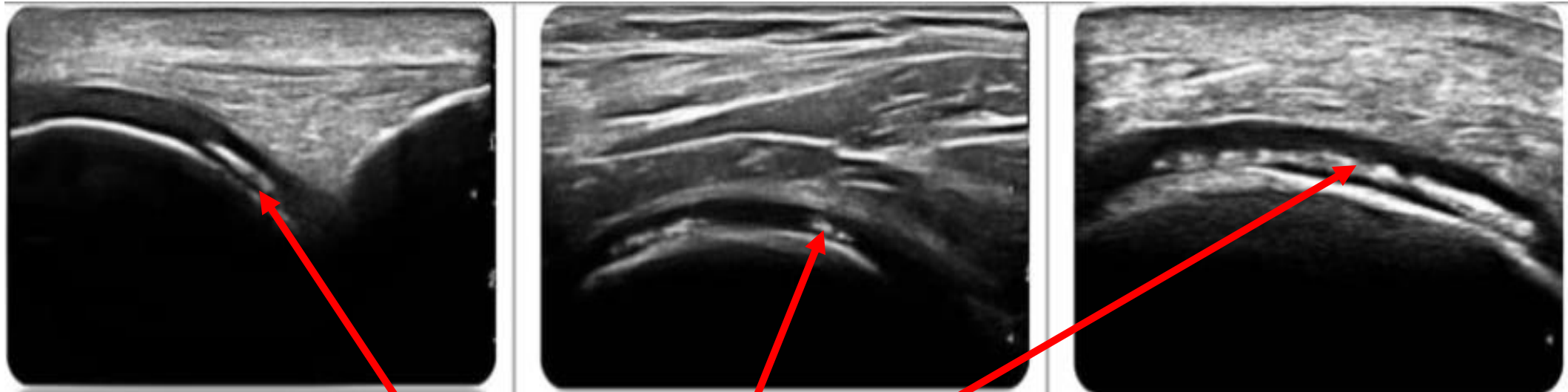


Conventional radiography (x-ray)

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

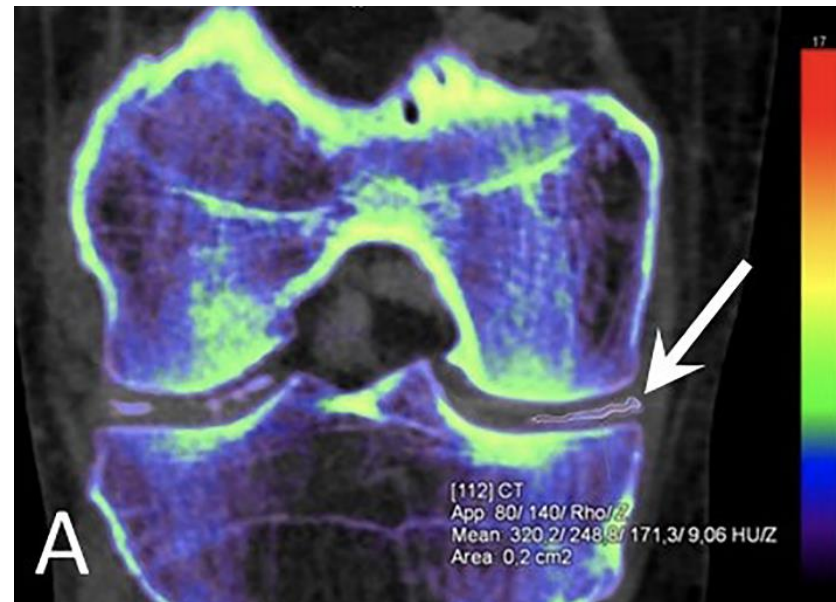


Ultrasound



CPPD within the cartilage

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



Case 2

A 64-year-old woman comes to see you after an emergency room visit for a warm, swollen knee. Synovial fluid aspiration was positive for calcium pyrophosphate crystals and she was given an oral prednisone taper. This is the first she's ever heard of "pseudogout" and she wants to know more about it.

Which of the following is true?

1. Pseudogout is associated with increased risk for cardiovascular events
2. Pseudogout is associated with increased risk for fractures
3. About 25% of patients with pseudogout will have recurrent acute episodes
4. All of the above



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Chondrocalcinosis does not clearly associate with joint symptoms

Osteoarthritis progression

- Unclear
- Chondrocalcinosis might increase risk of OA progression if <60 years old

Knee or hip replacement

- Not clearly associated with chondrocalcinosis

Joint pain

- Not clearly associated with chondrocalcinosis
- But, *persistence* or *worsening* of knee pain was associated in one study



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
 - IL-6 inhibition (tocilizumab) helps in some but not all



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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