Brigham and Women's Hospital
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# Advances in Gout and Crystal Deposition Disease

Sara K. Tedeschi, MD, MPH
Head, Crystalline Arthritic Diseases
Division of Rheumatology, Inflammation and Immunity, Department of Medicine, Brigham and Women's Hospital
Assistant Professor of Medicine, Harvard Medical School

# Sara Tedeschi, MD, MPH

Vanderbilt University School of Medicine
Harvard T. H. Chan School of Public Health
Medicine Residency @ BWH
Rheumatology Fellowship @BWH
Assistant Professor of Medicine @ HMS
Director, Giant Cell Arteritis Fast Track Program @ BWH
Head, Crystalline Arthritic Diseases @ BWH

- Clinical focus: giant cell arteritis and calcium pyrophosphate deposition (CPPD) disease
- Research focus: CPPD disease

# DISCLOSURES

Consulting for Novartis, Merck, Avalo Therapeutics, Alexion

# OBJECTIVES

1. To understand the importance of gout flare prophylaxis when initiating urate-lowering therapy

2. To recognize treatment strategies for treating a flare of acute calcium pyrophosphate crystal arthritis (pseudogout)

# Patient J.C.

53-year-old man who presents to establish care for gout

First gout flare at age 30 (1st MTP joint)

One flare per year for the past 20 years

Other medical issues:  Hypertension, GERD, glaucoma. No history of kidney stone

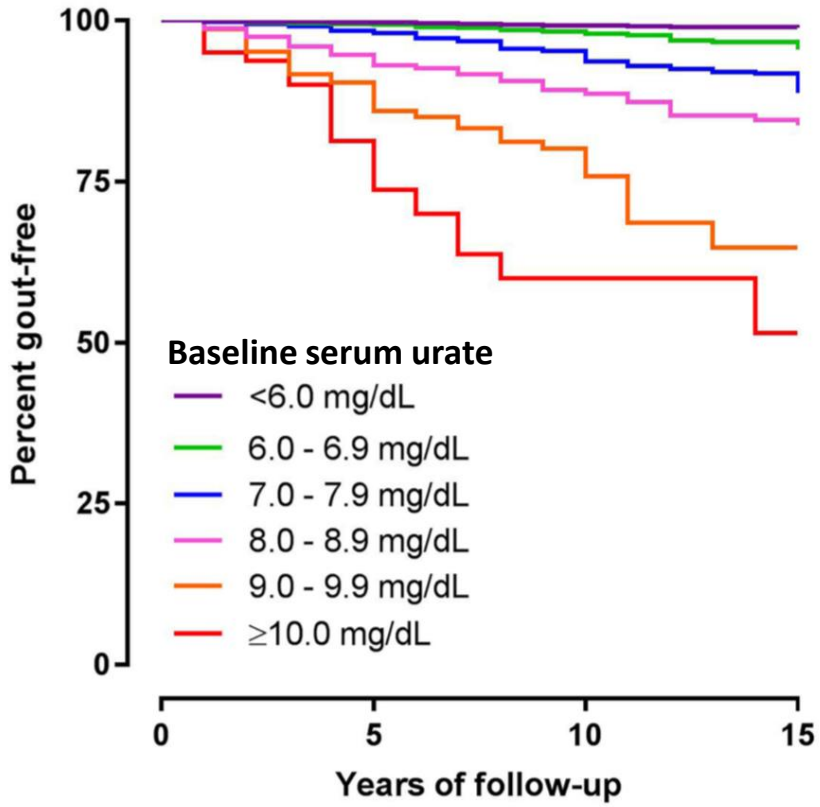
Wanted to try making dietary changes before starting medication for gout

# Gout is the most common inflammatory arthritis

8 million U.S. adults have gout (4%)

20% of U.S. adults have hyperuricemia

Gout risk increases exponentially with higher serum urate level




Dalbeth N, et al. Ann Rheum Dis 2018
Zhu Y, et al. Arthritis Rheum 2011

# Diet: how much does it influence gout flares?

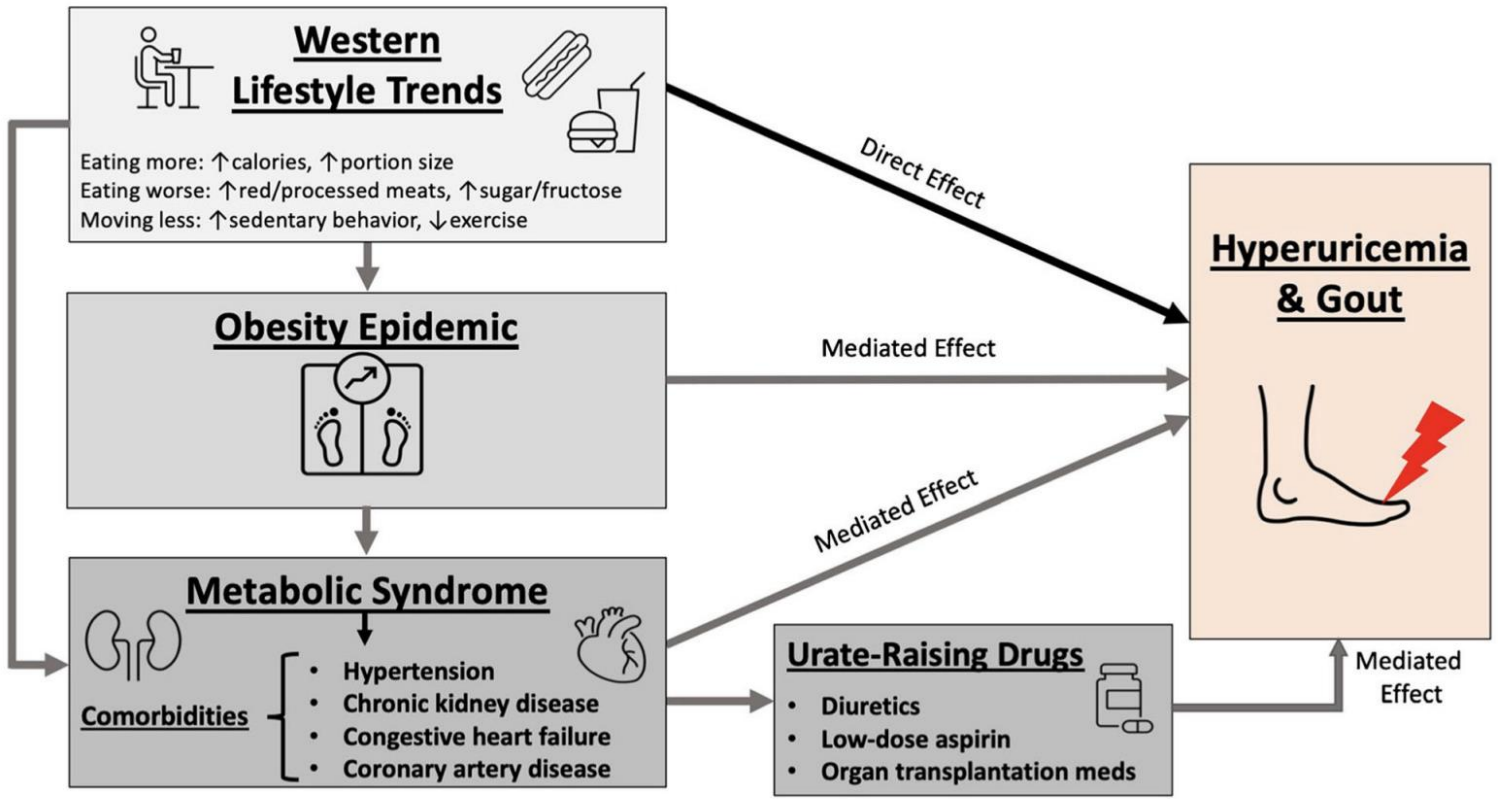
High-purine foods (red meat) can temporally associate w/flare

Alcohol intake had very small impact on longitudinal serum urate level in recent population-based study

DASH-style diet* tested in recent RCT in gout

- ✓ Mean serum urate reduction of **0.55 mg/dL** in DASH group

*5-7 servings of grains, 4 servings fruit, 4 servings vegetables, 1-2 servings poultry/fish, 2 servings low-fat dairy, <0.5 serving nuts/beans per day





Yokose C, et al. Curr Rheumatol Rep 2022
Fukui S, et al. Ann Rheum Dis 2024
Juraschek SP, et al. Nutrients 2021

# Which patients should be treated with urate-lowering therapy, per the American College of Rheumatology?

Definitely

2 or more gout flares per year

Tophus present

Gouty erosion on imaging

Possibly

>1 lifetime flare, but <2 flares per year

First-ever gout flare and any of the following:

- CKD stage 3 or worse
- Serum urate >9 mg/dL
- Kidney stone

Do not treat if asymptomatic hyperuricemia

# Why is gout flare prevention important?

- Patient quality of life
- Healthcare utilization
- Side effects of flare treatment

- Gout flares associated with **cardiovascular events** and **venous thromboembolism**
  - Among 60,000 patients with gout: those with myocardial infarction or stroke had odds ratio 1.9 for gout flare in prior 60 days
  - Among 300 patients with gout, venous thromboembolism rate was higher in 30 days after gout flare (incidence rate ratio 2.31) compared to the 2 years before gout flare

Cipolleta E, et al. JAMA 2022
Cipolleta E, et al. Arthritis Rheumatol 2023

# Patient J.C.

December 2022 physical exam notable for:

- R elbow olecranon bursa full
- R wrist thickened and tender
- R index finger PIP cannot flex
- Swan-neck deformity of left $4^{th}$ and $5^{th}$ digits
- Pads of three fingertips on right hand have pinpoint white nodules

Lab data:

- ESR 45
- CRP 2.9 mg/L
- uric acid 10.0 mg/dL
- creatinine 1.05 mg/dL
- rheumatoid factor and anti-CCP negative

# Gout diagnosis: best practices

Send synovial fluid aspirate for the 3 Cs

- cell count, crystals, culture (and gram stain)

Aspiration is especially important if never crystal-proven, or if known gout but symptoms are different

If aspiration is not performed or unsuccessful:

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

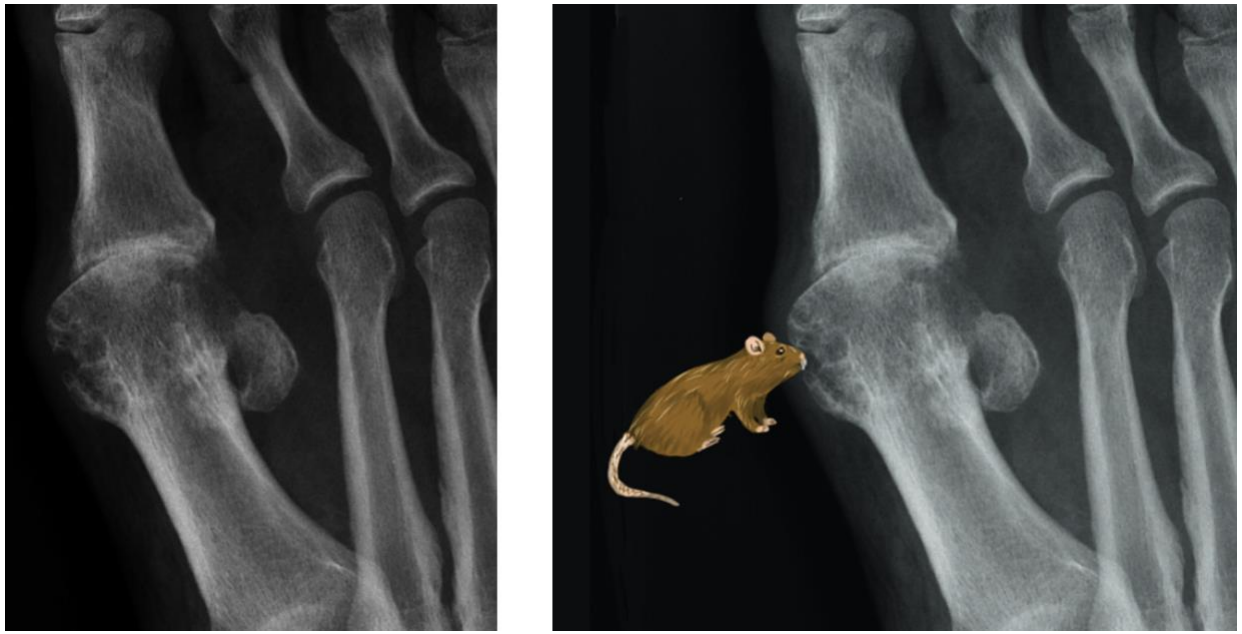
| Probability of gout | |
|---|---|
| ≤4 | low |
| >4 to <8 | intermediate |
| ≥8 | high |

Janssens HJ, et al. Arch Intern Med 2010

# Imaging studies can help diagnose gout

# X-ray in gout

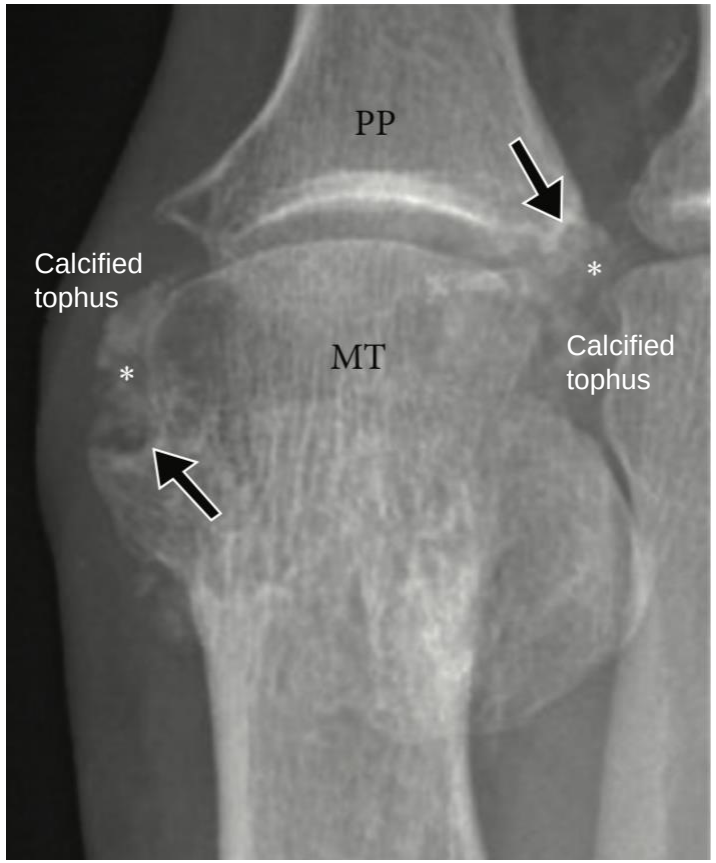
Gouty erosion



Ridley LJ, et al. J Med Imaging Radiat Oncol 2018

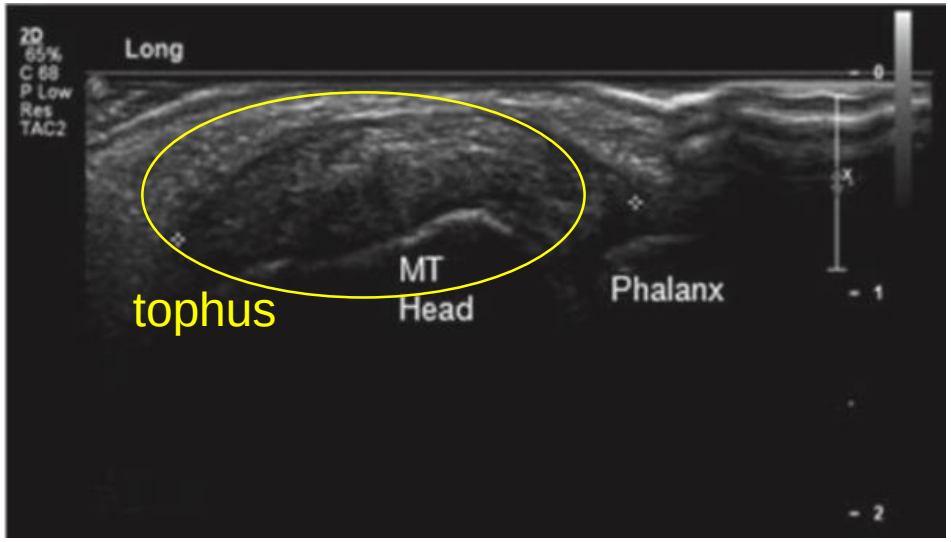
# X-ray in gout

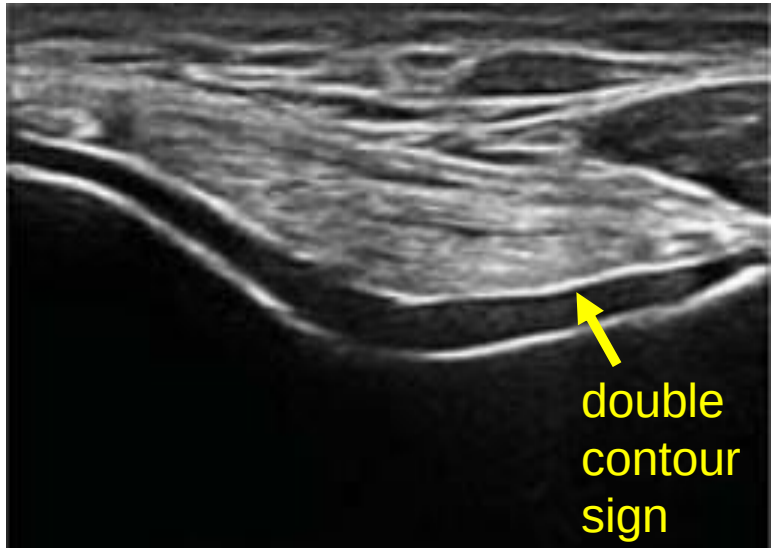
Gouty erosion
Tophus




Girish G, et al. Arthritis 2013

# Ultrasound in gout

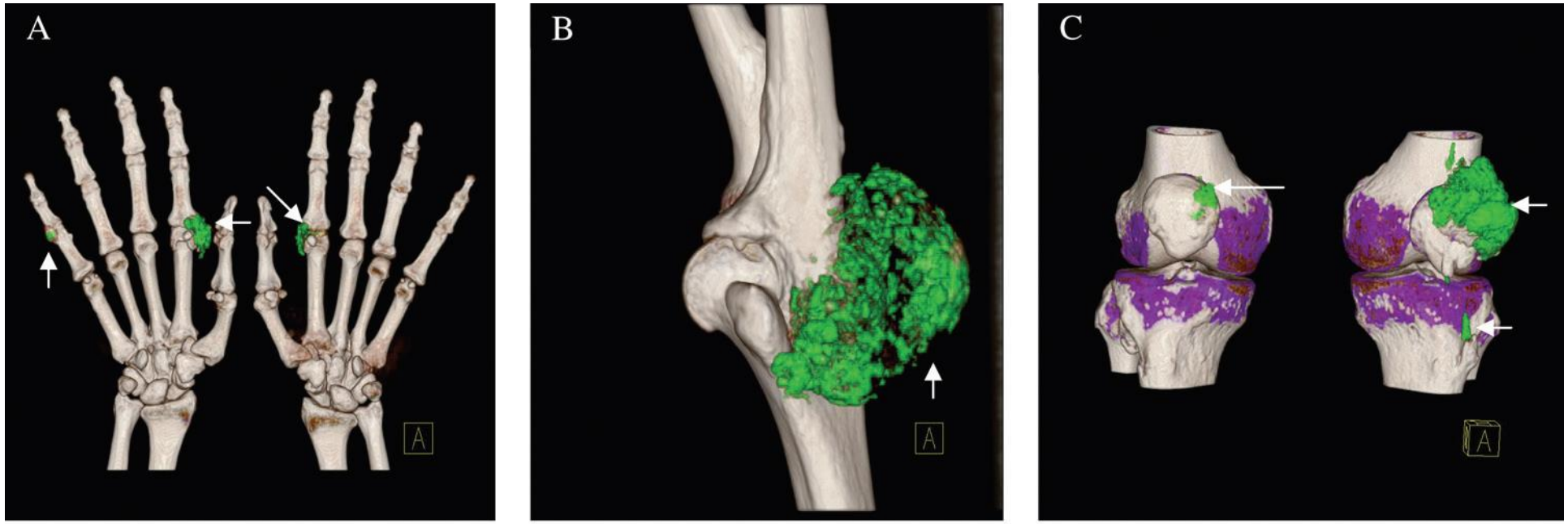



Sensitivity: 65%
Specificity: 89%

Dalbeth N, et al. Ann Rheum Dis 2010
Neogi T, et al. Arthr Rheum 2015
Lee YH and Song GG. Seminars Arthr Rheum 2018

# Dual-energy CT in gout




Sensitivity: 87%
Specificity: 84%

Choi HK, et al. Ann Rheum Dis 2012
Ogdie A. Ann Rheum Dis 2015

# Patient J.C.

X-rays in 2022 show large corticated erosions at left pinky finger PIP and DIP joints (“rate bite”) → confirms gout diagnosis

3 flares in 2022, treated with joint injections (patient’s preference)

# How should we treat a gout flare?

First-line

- NSAID (if no contraindication)
- Glucocorticoid (oral, intravenous, intra-articular, intra-muscular)
  - Specific dosing not indicated in guidelines
  - Typically prednisone 20-40mg daily x3d, then decrease by 10mg per day every 3 days
- Colchicine with loading dose (1.2mg followed by 0.6mg 1 hour later, then 0.6mg once or twice daily)
- Topical ice in addition to the above

Second-line

- Anakinra 100mg daily x3d (typically reserved for inpatient use / contraindications to the above)
- Canakinumab (long-acting IL-1b inhibitor) recently FDA approved for gout flares refractory to other treatments (q3 months)

Terkeltaub R, et al. Arthritis Rheum 2010
Blake KE, et al. Expert Opin Pharmacother 2022
Fitzgerald J, et al. 2020 American College of Rheumatology Guideline for the Management of Gout. Arthritis Rheumatol 2020

# Patient J.C.

Starts colchicine 0.6mg daily for flare prophylaxis

Agrees to start urate-lowering therapy

HLA B*58:01 testing ordered as he is of Han Chinese ancestry

# How do we pick a urate-lowering medication?

- Allopurinol
- Febuxostat
- Probenecid
- Pegloticase

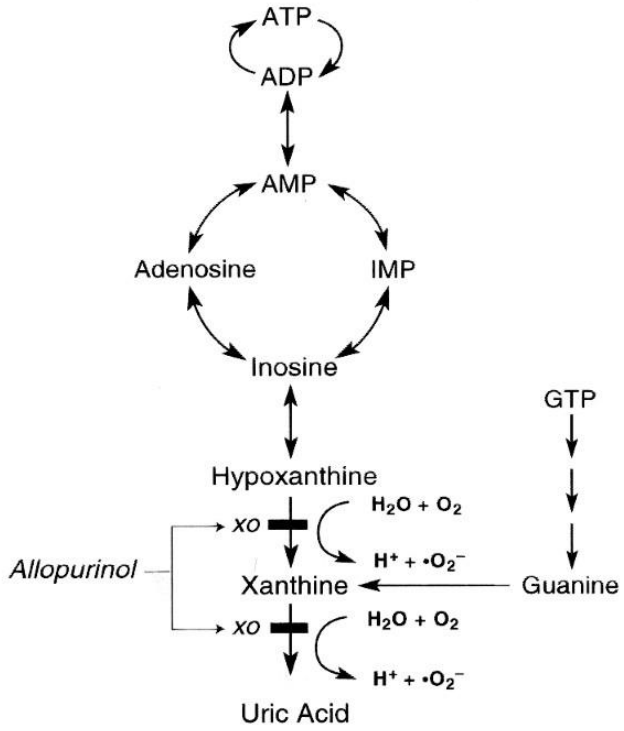


Mackenzie IS, et al. Lancet 2020

# How do we pick a urate-lowering medication?

**Xanthine oxidase inhibitors:  the front line**

- **Allopurinol** is first line.  Generally safe, including with CKD. Avoid if HLA B*58:01 present
  - Start 50mg daily if CKD stage ≥3, increase by 50mg every month until at goal (<6 mg/dL)
  - Start 100mg daily otherwise, increase by 100mg every month until at goal
  - Max 800mg daily per FDA (sometimes we use higher)






Marro P, et al. Nature Pediatric Research 1997

# How do we pick a urate-lowering medication?

**Xanthine oxidase inhibitors: the front line**

- **Allopurinol** is first line. Generally safe, including with CKD. Avoid if HLA B*58:01 present
  - Start 50mg daily if CKD stage ≥3, increase by 50mg every month until at goal (<6 mg/dL)
  - Start 100mg daily otherwise, increase by 100mg every month until at goal
  - Max 800mg daily per FDA (sometimes we use higher)

- **Febuxostat** is an alternative to allopurinol with similar potency
  - CARES trial (2018): febuxostat group had higher CV mortality (but not higher CV event rate) than allopurinol group
  - 2019: black-box warning about CV death
  - FAST trial (2020): febuxostat non-inferior to allopurinol in terms of CV events
  - Start 20mg daily, increase by 20mg (max 80mg) each month if not at goal

White WB, et al. NEJM 2018
Mackenzie IS, et al. Lancet 2020

# How do we pick a urate-lowering medication?

- **Probenecid** promotes renal urate excretion
  - Not as potent as xanthine oxidase inhibitors and can promote kidney stones
  - Start 250mg twice daily for 1 week, then 500mg twice daily
  - Increase by 500mg every month (maximum 2000mg daily) until urate at target

- **Pegloticase** is is reserved for severe tophaceous gout (intravenous, expensive, can generate anti-drug antibodies leading to inefficacy and anaphylaxis)
  - Methotrexate + pegloticase recently FDA-approved to reduce immunogenicity/decrease risk of inefficacy and anaphylaxis

- Start flare prophylaxis a few weeks before starting any urate-lowering therapy, and continue prophylaxis for 6 months after the target uric acid is reached



Mackenzie IS, et al. Lancet 2020

# What is HLA B*58:01, and when should this be tested in patients with gout?

HLA haplotype associated with increased risk for allopurinol hypersensitivity syndrome (drug reaction with eosinophilia and systemic symptoms [DRESS] or Stevens Johnson Syndrome)

- Allopurinol binds to the HLA B58*01 allele

American College of Rheumatology “conditionally” recommends testing for HLA-B*58:01 allele before starting allopurinol in patients of

1. Southeast Asian descent (e.g., Han Chinese, Korean, Thai) (prevalence ~7%)
2. African American patients (prevalence ~4%)

(rec against testing in other racial/ethnic backgrounds; prevalence <1% in White and Latino populations)

# Patient J.C.

HLA B*58:01 present → avoid allopurinol

Febuxostat 20mg daily prescribed 12/2022, continued colchicine 0.6mg daily for flare prophylaxis

Patient read about febuxostat online and did not want to start it

Probenecid 500mg twice daily prescribed in 2/2023, continued colchicine 0.6mg daily

Urgent clinic visit 4/2023 for gout flare. Reports he took probenecid for 1 week and then stopped it as he felt hesitant about taking urate-lowering therapy. Then took febuxostat 40mg daily for 1 week and stopped it. Took colchicine 0.6mg daily throughout this. During that time: gout flare in dorsal foot, several toes, 1st MTP, several PIPs (bedridden due to pain at one point). States “I have learned my lesson.”

# Patient J.C.

Impression and recommendations. I told him that an oral course of steroids is the best therapy to treat this polyarticular gout flare. He strongly does not want to take steroids as he is concerned about side effects. I did inject 3 joints as above although I told him this is unlikely to relieve his pain entirely. I suspect that the transient use of urate lowering therapies in the past month were the trigger for this flare.

I printed out a copy of the following plan for him:

**Patient Instructions**

1. Take colchicine 0.6mg (one tab) twice a day. This will be your dose for the next 6 months at least, unless I advise you otherwise.
2. On Monday, May 8, 2023, start taking febuxostat 20mg (half of a 40mg pill) once a day.
3. Take naproxen 500mg twice a day with food as needed for gout flare pain. Stop taking indomethacin

# Gout flare prophylaxis is important when initiating urate-lowering therapy

Initial weeks to months after starting urate-lowering therapy = high risk for gout flare

Is colchicine prophylaxis required with start-low go-slow allopurinol dose escalation in gout? A non-inferiority randomised double-blind placebo-controlled trial

Lisa Stamp [1], Anne Horne [2], Borislav Mihov [2], Jill Drake [3], Janine Haslett [1], Peter T Chapman [3], Christopher Frampton [1], Nicola Dalbeth [2]

Design: RCT in 200 patients with at least 1 gout flare in past 6 months with serum urate >7 mg/L, randomized 1:1 to colchicine 0.5mg daily or placebo for first 6 months of allopurinol ("start low go slow" dose approach)
Primary outcome: mean number of gout flares per month between 0 and 6 months (pre-specified non-inferiority margin 0.12 gout flares/month)
Results: Mean number gout flares/month: 0.35 (95% CI 0.22 to 0.49) in colchicine group versus 0.61 (95% CI 0.47 to 0.74) in placebo group, non-inferiority p=0.92. Serious adverse events: n=11 in colchicine group and n=3 in placebo group
Conclusion: placebo is non-inferior to colchicine in preventing gout flares in the first 6 months of allopurinol therapy

# What is calcium pyrophosphate deposition (CPPD) disease?

# CPPD disease represents a common crystalline arthritis

- Symptomatic arthritis caused by calcium pyrophosphate (CPP) crystal deposition
- Knee and wrist most common
- Affects 8-10 million U.S. adults
- No targeted therapies currently exist
- Prevalence will increase as the population ages

# Calcium pyrophosphate crystals:

- form around chondrocytes
- activate the NLRP3 inflammasome and neutrophil extracellular traps
- deposit in cartilage, which may cause mechanical damage

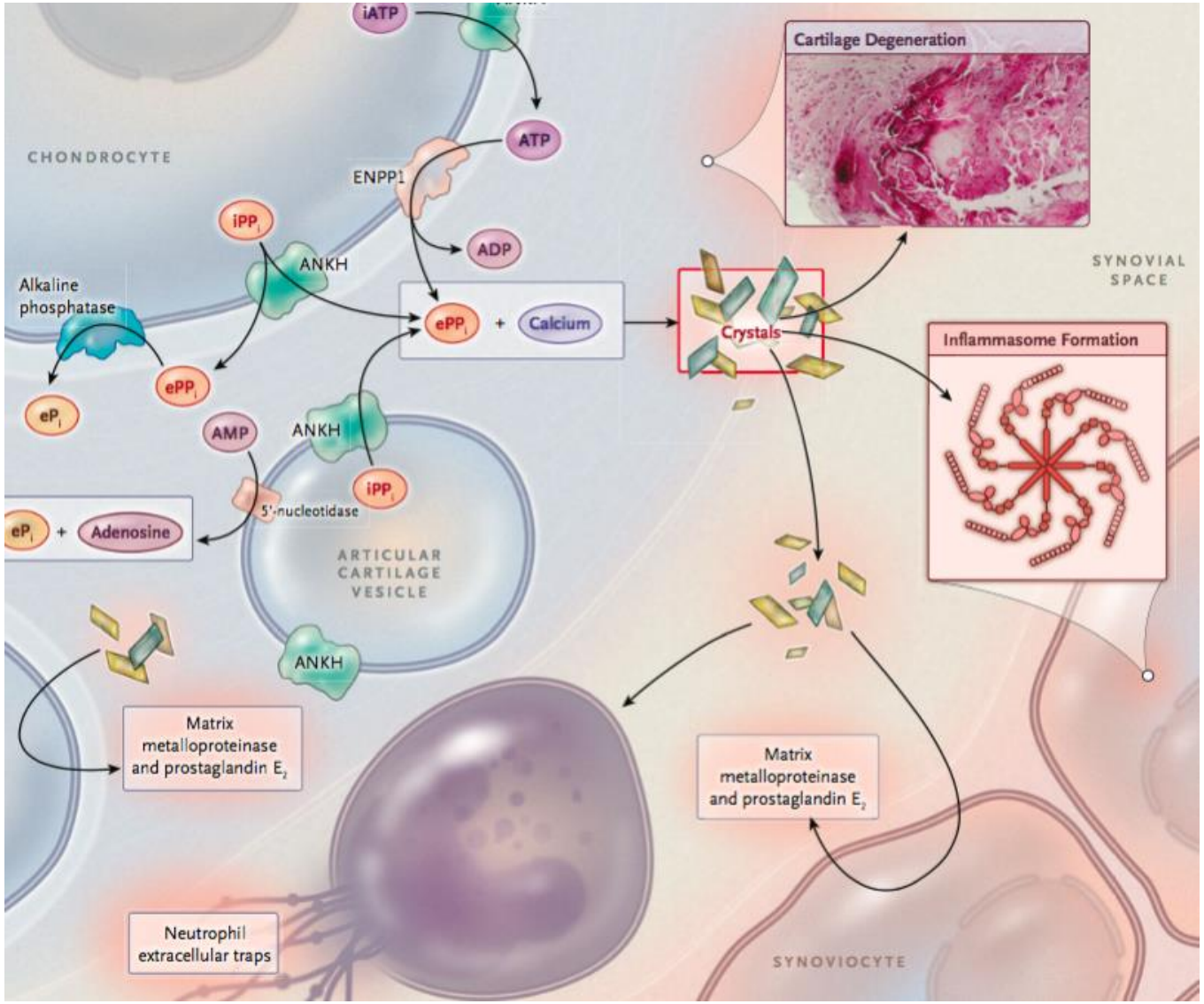
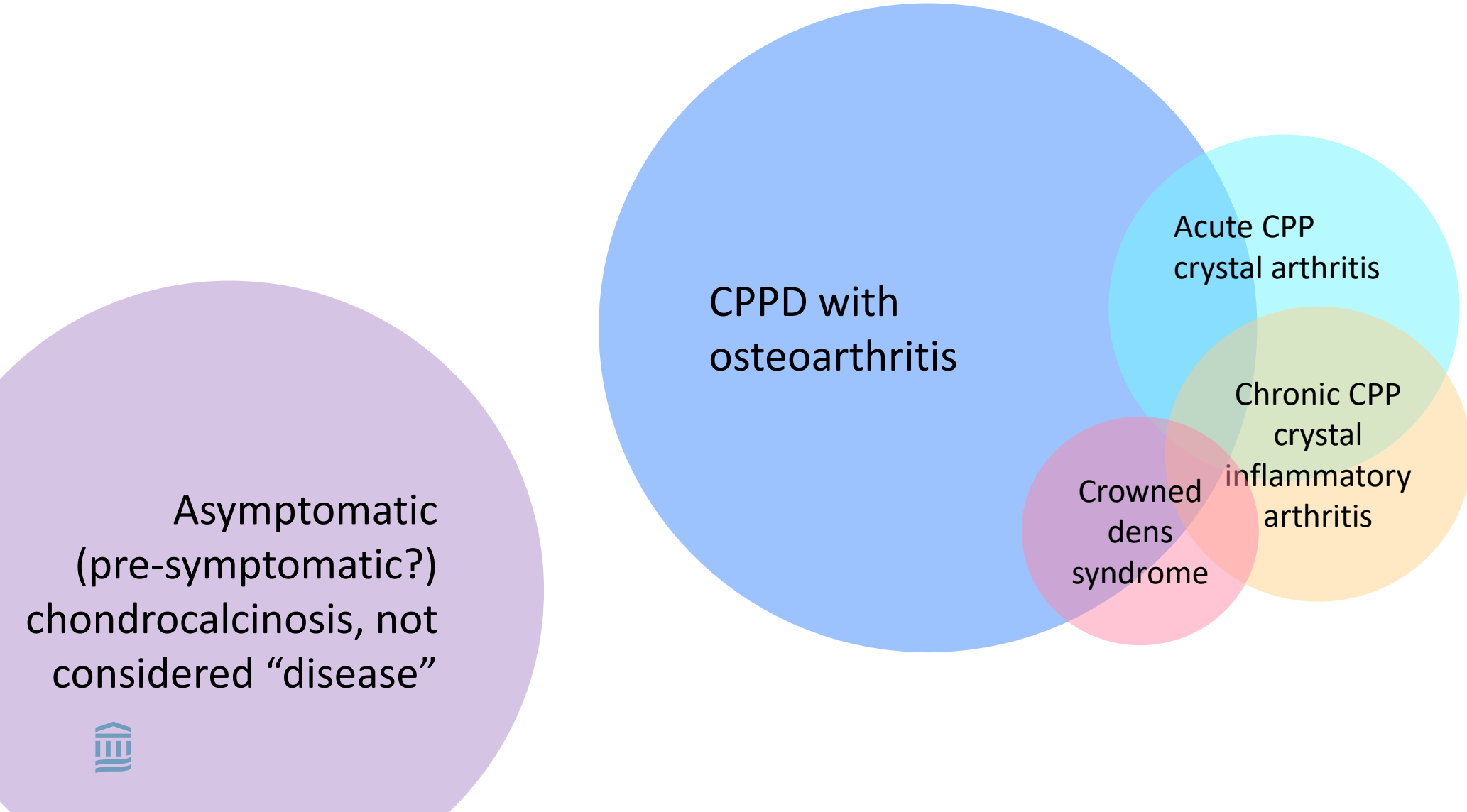



Figure 3 in: Rosenthal AK, Ryan LM. N Engl J Med. 2016 Jun 30;374(26):2575-84.

# CPPD disease has multiple clinical manifestations



# New: ACR/EULAR 2023 CPPD Disease Classification Criteria

Objective:  To develop a framework for identifying people with CPPD disease for entry into research studies, including clinical trials and observational studies

Outcome: A framework with very high specificity (93%) and sensitivity (99%) for CPPD disease

CPPD classification criteria calculator (to be used for research, not for clinical diagnosis): https://bblinks.live/acr-classification-criteria-for-cppd-disease

# What imaging modalities are most useful for identifying CPPD?

# Conventional radiography (x-ray)

- Commonly performed and easy to obtain
- High specificity (>90%) but only moderate sensitivity (~50%) for calcium pyrophosphate deposition

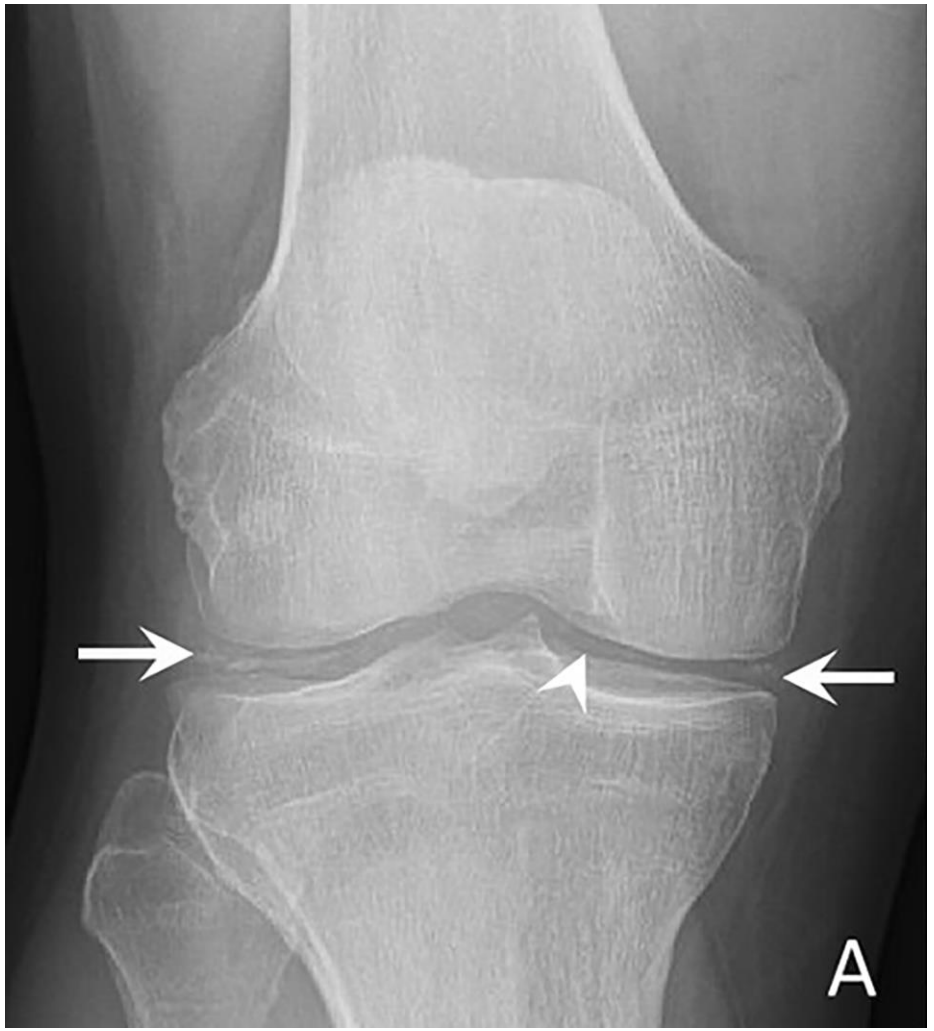



Figure 2 in: Tedeschi SK, et al. Arthritis Care Res. 2023 Apr;75(4):825-834.
Sirotti S, et al. Arthritis Rheumatol 2023

# Ultrasound

- Visualizes portions of hyaline and fibrocartilage (e.g., menisci) not obscured by bone
- High specificity (87%) and high sensitivity (85%) for calcium pyrophosphate deposition in meta-analysis of 26 studies

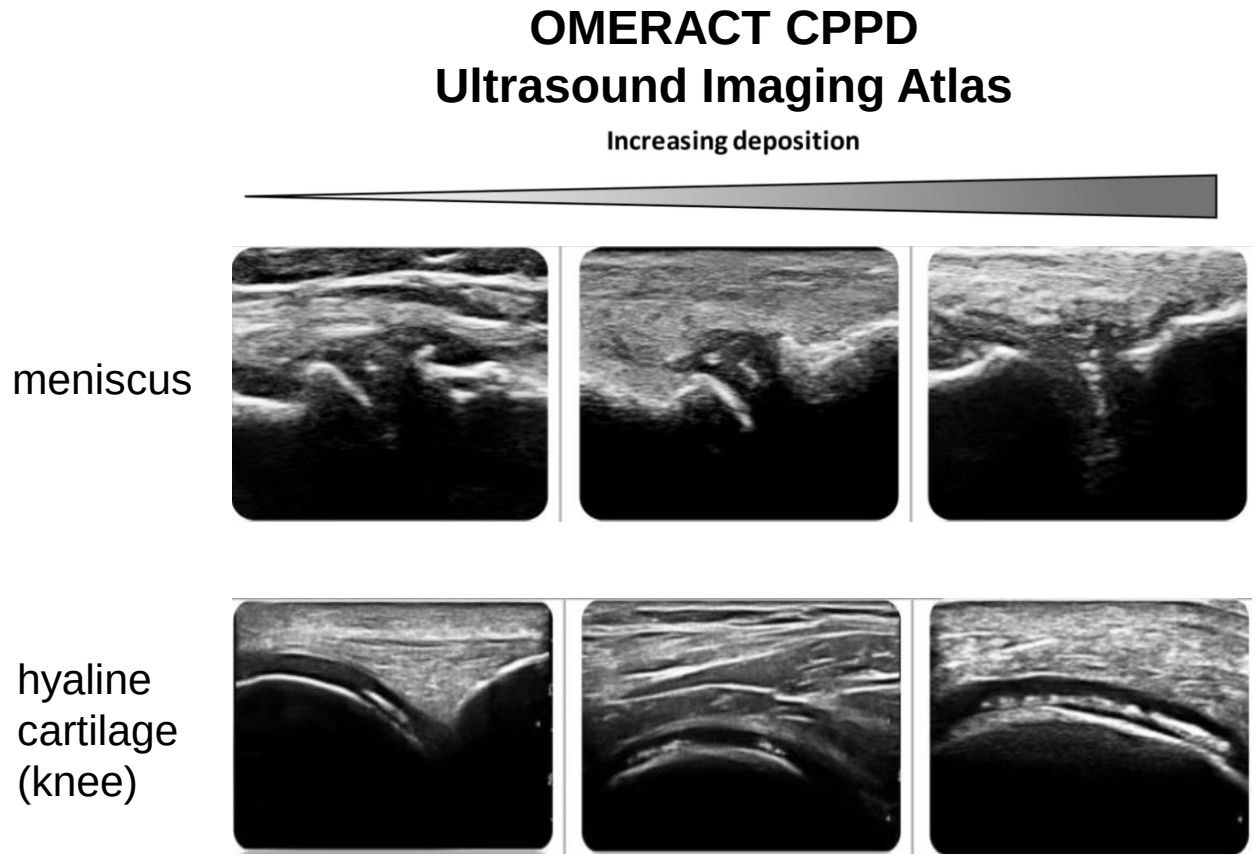
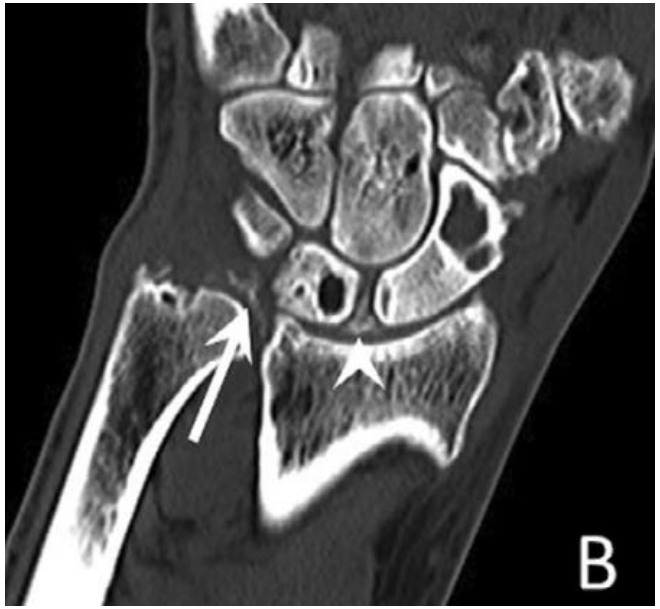
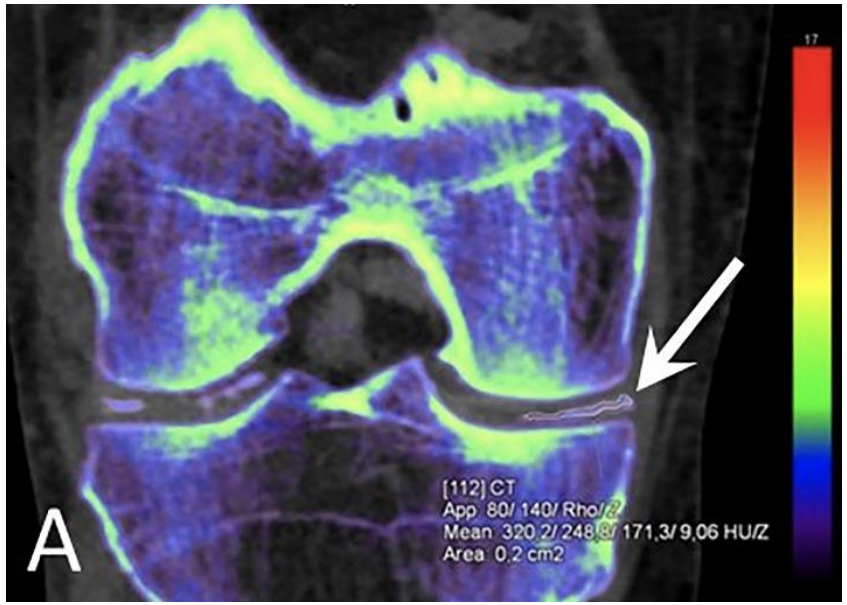



Figure 1 in: Filippou G, et al. Ann Rheum Dis. 2018 Aug;77(8):1194-9.
Cipolletta E, et al. Osteoarthritis Cartilage 2021

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

- Availability, cost, radiation considerations
- DECT sensitivity ~80-100% using histopathology or synovial fluid as reference
- May not provide additional info beyond CT




Figures 3 and 5 in: Tedeschi SK, et al. Arthritis Care Res. 2023 Apr;75(4):825-834.
Tanikawa, et al. J Ortho Surg Research 2018
Tedeschi, et al. Rheumatology (Oxford) 2020
Budzik, et al. Arthritis Rheumatol 2021

# Are individuals with CPPD disease at risk for complications

- within the joint?
- beyond the joint?

# Long-term outcomes in the joints of patients with chondrocalcinosis

**Osteoarthritis progression on MRI or x-ray**

- Conflicting results in 4 large cohort studies with 3-5 years follow-up, comparing patients with vs. without chondrocalcinosis on baseline x-ray

**Knee or hip replacement**

- Chondrocalcinosis on baseline x-ray not associated with this at 5 years

**Joint pain**

- Chondrocalcinosis on baseline x-ray not associated with WOMAC pain scores in KHOALA cohort
- Intra-articular mineralization on baseline knee CT was associated with more frequent, persistent, and worsening knee pain over 2 years in MOST cohort

Neogi T, et al. Arthritis Rheum 2006
Latourte A, et al. Arthritis Rheum 2020
Foreman SC, et al. Osteoarthritis Cartilage 2020
Liew JW, et al. Arthritis Rheum 2023

# Long-term extra-articular outcomes in patients with CPPD disease

## Cardiovascular events

- **25% increased risk*** for non-fatal myocardial infarction, acute coronary syndrome, coronary re-vascularization or stroke among ~23,000 patients with at least 1 diagnosis code for CPPD matched to ~87,000 comparators in nationwide VA medical center database

- **90% increased risk*** for these CV endpoints among 1200 patients with a prior episode of acute CPP crystal arthritis (pseudogout) matched to 3810 comparators in the Mass General Brigham healthcare network

*adjusted for traditional CV risk factors including age, sex, race, healthcare utilization, CV medications, glucocorticoids, colchicine, NSAID

Bashir M, et al. Arthritis Care Res 2021
Tedeschi SK, et al. Ann Rheum Dis 2022

# Long-term extra-articular outcomes in patients with CPPD disease

## Fractures

- Osteopenia and CPPD associated in two large observational cohort studies
- **80% increased risk*** for fracture of humerus, wrist, hip, or pelvis in patients with a prior episode of acute CPP crystal arthritis (pseudogout) versus comparators
  - Wrist fracture was the driver (**3.6x increased risk of wrist fracture**)

*adjusted for age, sex, race, healthcare utilization, body mass index, multimorbidity index, smoking, rheumatoid arthritis, hyperparathyroidism, hemochromatosis, hypothyroidism, hyperthyroidism, heart failure, cancer, proton pump inhibitors, glucocorticoids, osteoporosis treatment

Abhishek, et al. Ann Rheum Dis 2014
Kleiber Balderrama, et al. Arthritis Care Res 2017
Tedeschi, et al. Arthritis Rheum 2024

# What's the latest in treatment for CPPD disease?

# Treatment depends on the manifestation

## Acute CPP crystal arthritis

- 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 if no contraindication)

* Supported by RCT data

** Supported by open-label data

# Acute CPP crystal arthritis

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

## Evaluating the safety and short-term equivalence of colchicine versus prednisone in older patients with acute calcium pyrophosphate crystal arthritis (COLCHICORT): an open-label, multicentre, randomised trial

*Tristan Pascart, Pierre Robinet, Sébastien Ottaviani, Rémi Leroy, Nicolas Segaud, Aurore Pacaud, Agathe Grandjean, Hélène Luraschi, Thibault Rabin, Xavier Deplanque, Pierre Maciejasz, Fabien Visade, Alexandre Mackowiak, Nicolas Baclet, Sylvestre Maréchaux, Antoine Lefebvre, Jean-François Budzik, Thomas Bardin, Pascal Richette, Laurène Norberciak, Vincent Ducoulombier, Eric Houvenagel*

**Lancet Rheumatol 2023**

# COLCHICORT trial

First-ever RCT in acute CPP crystal arthritis

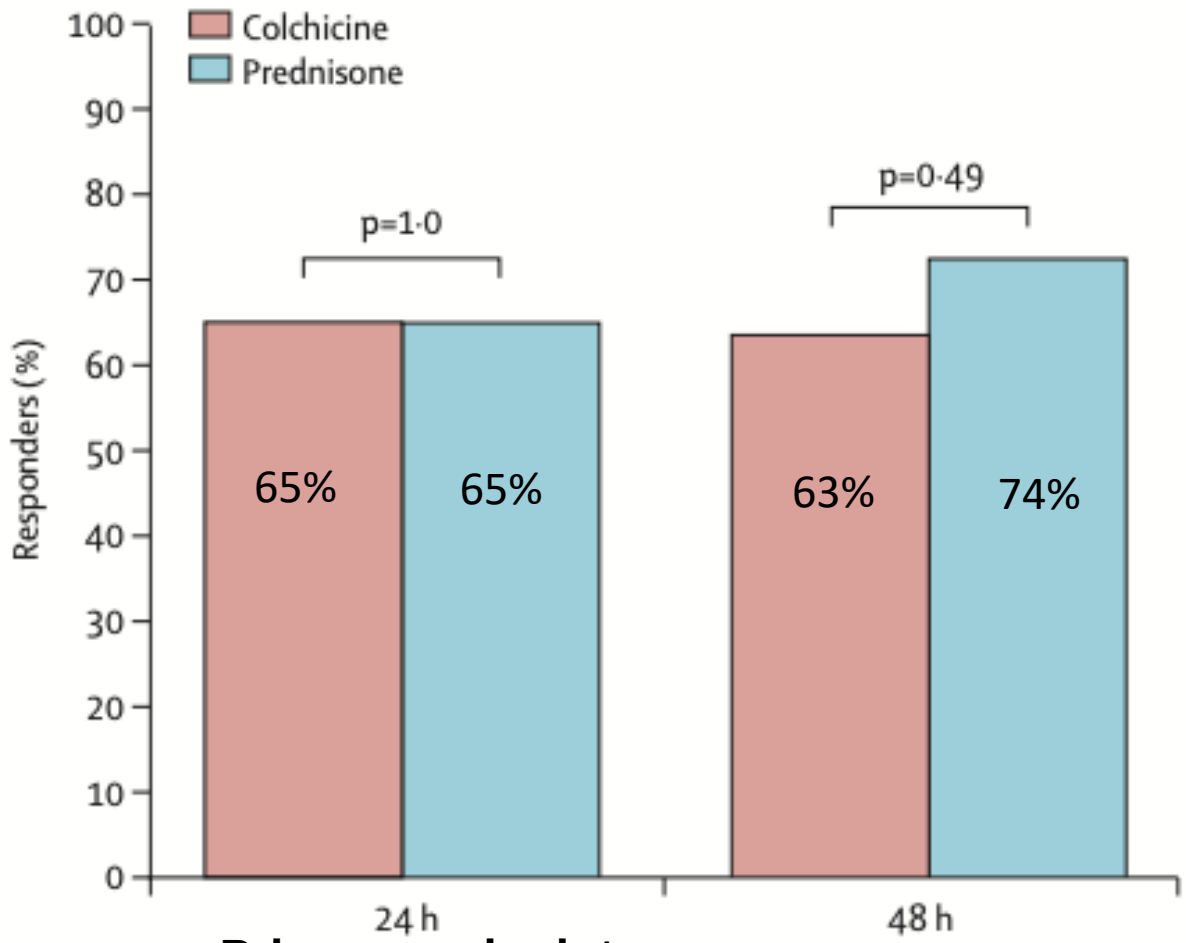
Interventions: randomized to **prednisone 30mg for 2 days** versus **colchicine load for 2 days** (1.5mg on day 1, then 1mg on day 2). All received acetaminophen and tramadol for 24h.

Study population: Adults >65 years old, hospitalized with acute CPP crystal arthritis, symptom duration <36h

Primary endpoint: pain VAS at 24 hours

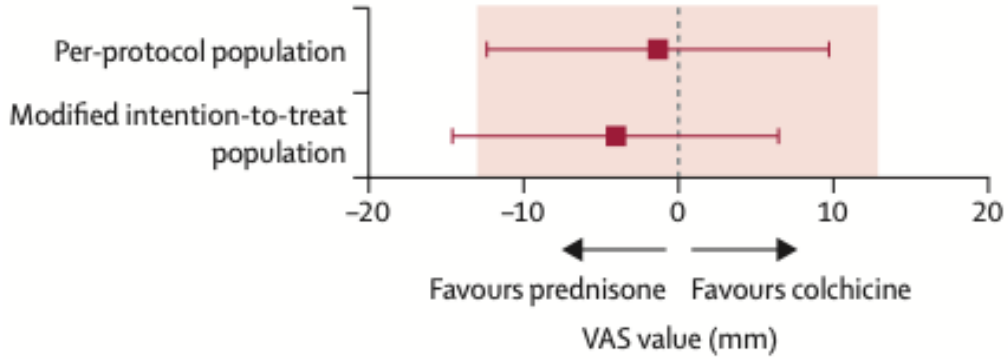
## Proportion achieving treatment response

*>50% reduction in pain VAS, or pain VAS <40 mm*




**Primary endpoint**

## Equivalence of prednisone and colchicine for primary endpoint



# Treatment for chronic CPP crystal inflammatory arthritis

**Methotrexate**: One double blind crossover RCT of MTX (7.5-15mg/week) vs. placebo (n=26)

- 3-month intervention
- No difference in pain scores or joint counts between study arms

**Hydroxycholoroquine**: One double-blind RCT of HCQ 400mg/day vs. placebo (n=36)

- 6-month intervention
- Percentage of responders (>30% reduction in tender and/or swollen joint count) significantly higher in hydroxychloroquine arm

Finckh A, et al. Arthritis Res Ther 2014
Rothschild, et al. Compr Ther 1997

# IL-1 and IL-6 inhibitors for CPPD disease

**Anakinra (IL-1 receptor antagonist):** case series in acute & chronic CPP inflammatory arthritis

- Anakinra 100mg daily x3 days for acute flare
- Daily chronic therapy may be an option for chronic symptoms

**Tocilizumab (IL-6 inhibitor)** for refractory acute & chronic CPP inflammatory arthritis

- Open-label study of tocilizumab IV or SC, N=11, requiring daily prednisone or had failed/contraindication to colchicine/NSAID/anakinra
- Patient Global Assessment decreased from median 60 to 15 mm at 3 months
- 2 patients had flares after >3 months of tocilizumab
- 3 patients had adverse events
- RCT is being planned in France

Andres M, et al. Curr Rheum Reports 2018
Dumusc A, et al. Joint Bone Spine 2021
Latourte A, et al. Ann Rheum Dis 2020

# KEY TAKE HOME POINTS

**GOUT**

- Start flare prophylaxis (e.g. colchicine) when starting urate-lowering therapy, and continue it at least 6 months
- Allopurinol can be used safely in nearly all patients with gout
  - Chinese, Thai, Korean, Black patients should undergo HLA B*58:01 testing
  - Start allopurinol at 50mg in patients with CKD stage 3 or worse
- Cardiovascular events and venous thromboembolism are temporally associated with gout flare

**CPPD DISEASE**

- Prednisone 30mg daily x2 days and colchicine load (1.5mg on day 1 and 1mg on day 2) provide similar relief for a flare of acute CPP crystal arthritis (pseudogout)
  - 2/3 of flares will improve with this regimen
- Cardiovascular events and fracture risk are increased in people with acute CPP crystal arthritis