The Crystals

Gout, Pseudogout and the others

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COI

- None.

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gout

> **BuzzFeed** @BuzzFeed · 9/29/21
>
> Fill in the blank: my kidnappers returning me back after listening to me talk about ____ for 2 hours

Objectives

- By the end of the session, learners will be able to:
  - Recognize the differential diagnosis for acute monoarthritis
  - Identify and diagnose gout and other crystal-induced arthropathies
  - Plan and initiate treatment for gout and pseudogout

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American College of Rheumatology
Empowering Rheumatology Professionals

ACR GUIDELINE FOR MANAGEMENT OF GOUT

2020 American College of Rheumatology Guideline for the Management of Gout

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Case

75 YO M with history of CKD, HTN, DM2 who presents with sudden onset of left foot pain, swelling, and erythema.

He is afebrile, HR 110, BP 110/70

His left foot is shown

WBC: 14,000, Sed rate 100

1st MTP aspiration: WBC 80,000, 50% neutrophils, with evidence of intracellular negatively birefringent crystals

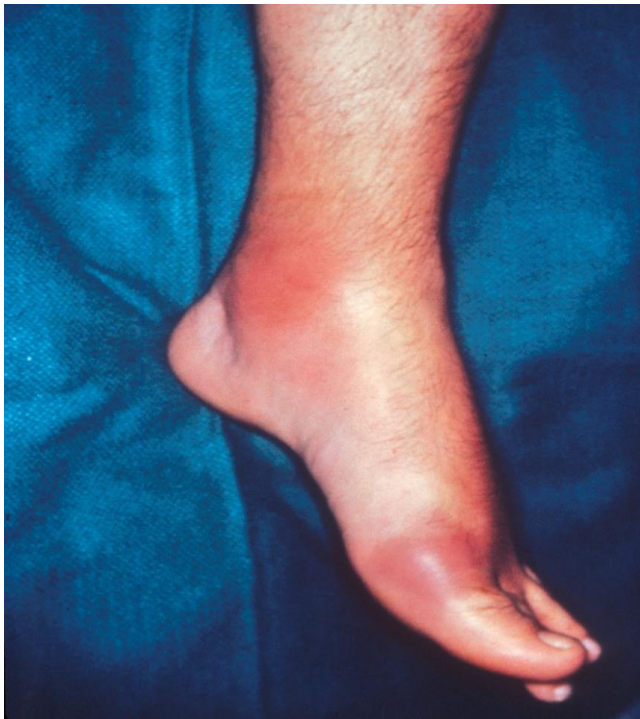
What is the most likely diagnosis?

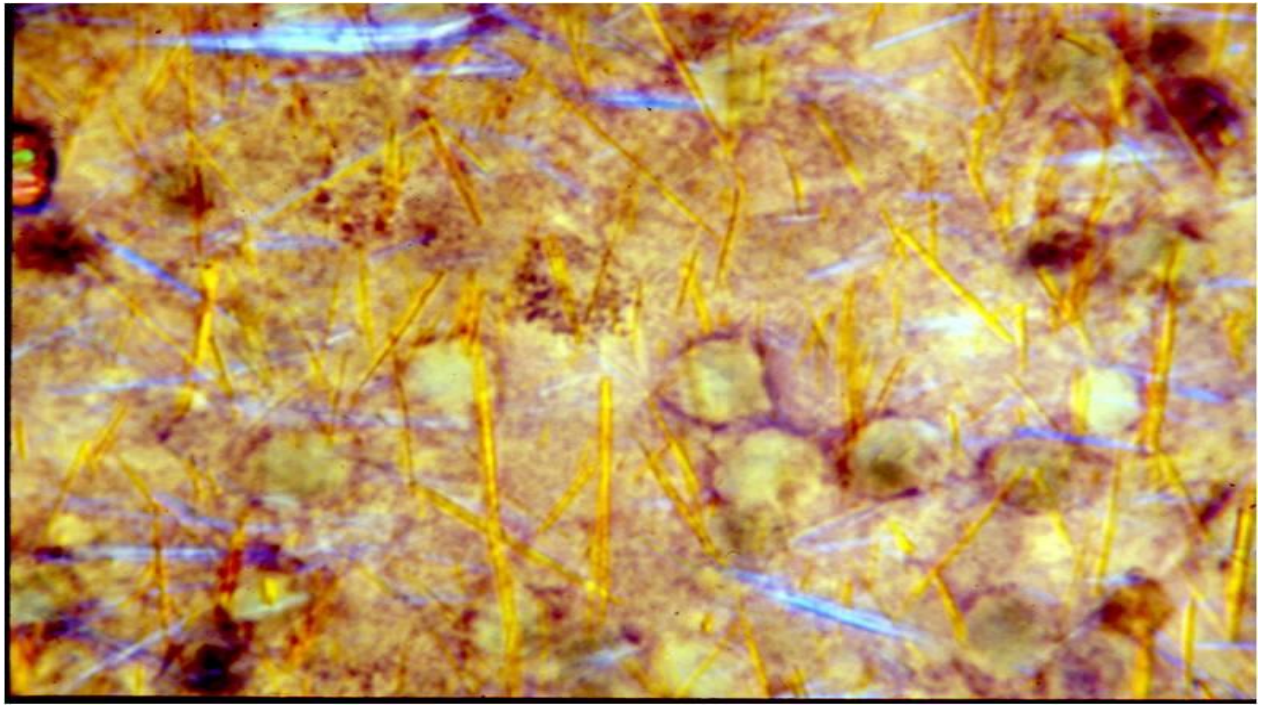
A. Osteoarthritis

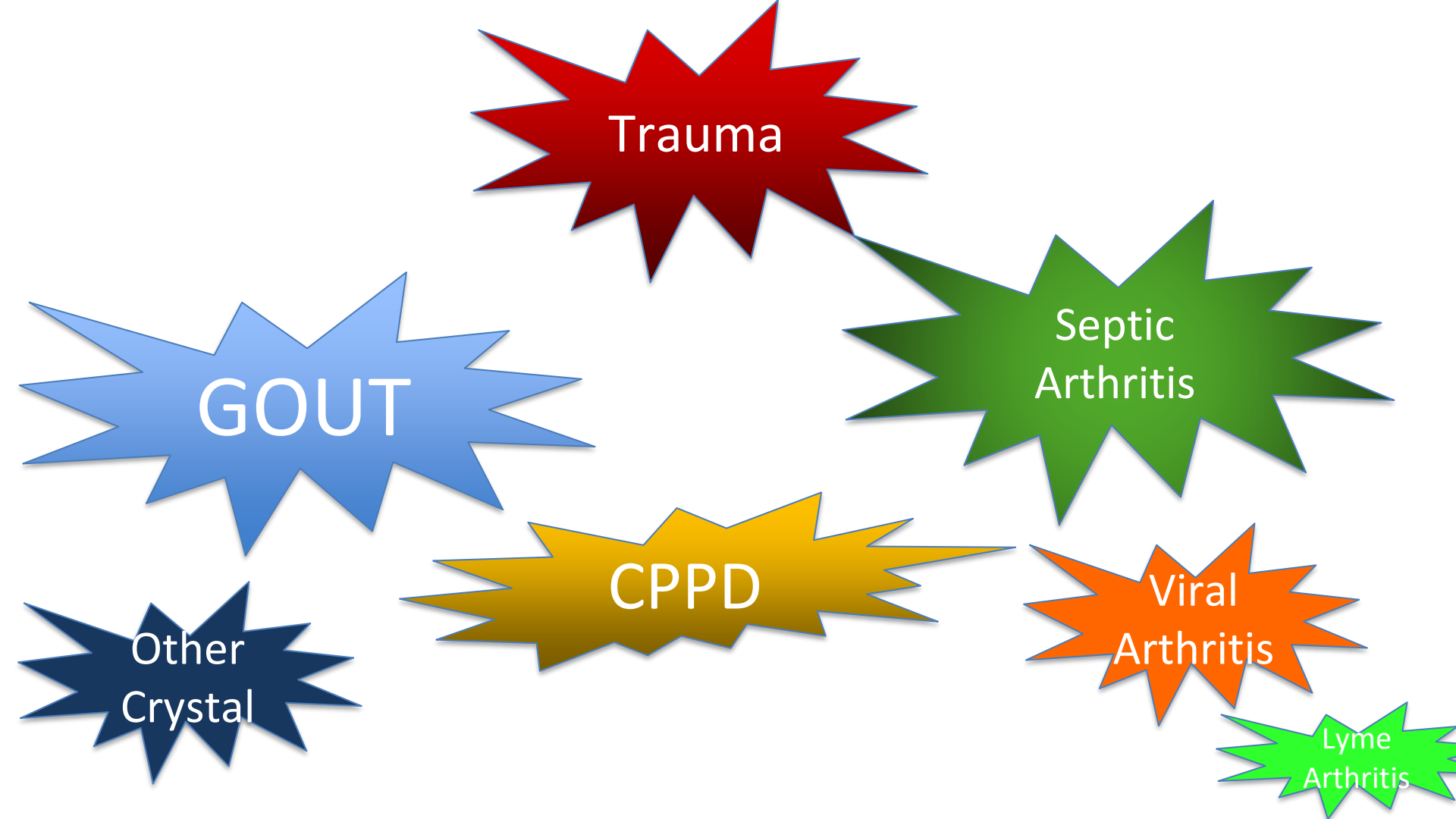
B. Gout

C. Septic arthritis

D. Trauma






Trauma
GOUT
Septic Arthritis
CPPD
Other Crystal
Viral Arthritis
Lyme Arthritis

Synovial Fluid Analysis

	Normal	Non-Inflammatory	Inflammatory	Septic	Hemorrhagic
Clarity	Transparent	Transparent	Transparent-opaque	Opaque	Bloody
Color	Clear	Yellow	Yellow	Yellow	Red
WBC	< 200	0-2000	>2000	>20,000	Variable
PMN	< 25	< 25	>75	>75	50-75

Monoarthritis

Diagnosis	Presentation	Diagnosis
Gout	Acute arthritis, Crescendo course, red/hot/swollen	Arthrocentesis, MSU crystals, (elevated uric acid)
Pseudogout (CPPD)	Sub-acute arthritis, wrist and knee are most common	CPPD crystals, x-rays with chondrocalcinosis
Septic arthritis	Acute arthritis, STI, Comorbidities, immunosuppression, trauma? Red/hot/swollen/fevers	Arthrocentesis, gram stain, culture, synovial fluid cell count
Reactive Arthritis	Sub-acute, Prior GI/GU infection, viral infection, 3-10 days prior, enthesitis, knees, ankles, feet	PCR Chlamydia, stool for enteric pathogens

Gout epidemiology

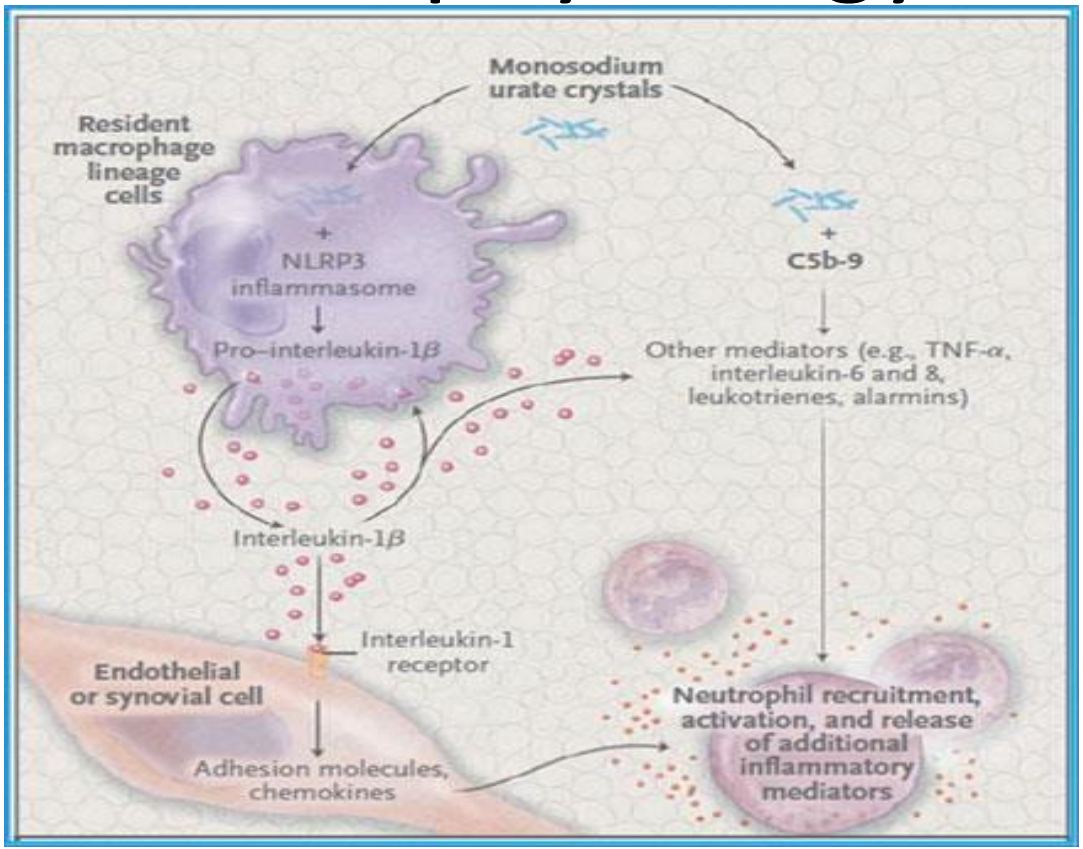
- 4% of US adults have gout
- Most common inflammatory arthritis
- You will see it often

https://pegsandtails.wordpress.com/2010/06/08/making-a-gout-stool-part-one/

What is gout?

- Uric acid is the end product of purine metabolism
- Monosodium urate crystals deposit in tissue due to hyperuricemia
  - Arthritis
  - Tophi
  - Uric acid nephrolithiasis and gouty nephropathy

Pathophysiology



Neogi T. Clinical practice. Gout. N Engl J Med. 2011;364:443-452.

Who gets gout?

- Increase in purines
  - Overproduction of urate
  - Under excretion of urate
  - Or both
- Increase incidence in older adults, obesity, other comorbidities (hypertension, diabetes, CAD, CKD)

- WHO DOES NOT GET GOUT?
  - VERY rare in young males and pre-menopausal women

Risk Factors

Overproduction (10%)

- **Defect in purine metabolism:** PRPP Synthetase overactivity, HPRT deficiency
- **Increased cell turnover:** leukemia, lymphoma, psoriasis, hemolytic anemia, polycythemia vera, tumor lysis

Under excretion (90%)

- Renal insufficiency, CKD
- Dehydration
- Lactic Acidosis
- Ketoacidosis
- **Drug induced**
- **Diet**

Clinical Manifestations

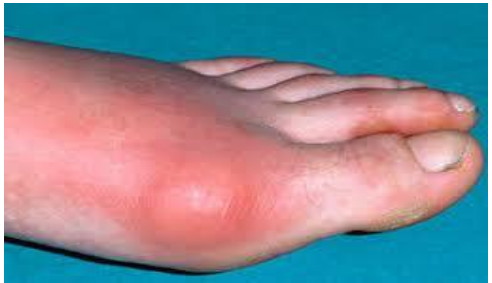
Acute Gout

First attack: Usually monoarticular

> 50% first MTP (in men), fingers affected by OA in women

Pain, swelling, redness and warmth

Start at night, and peak in 12-24 hours



Intercritical Gout

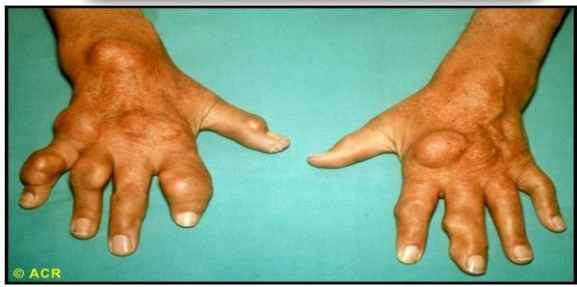
Between gout flares.

Long during early disease, shortens as progressively with time

Chronic Recurrent and Tophaceous Gout

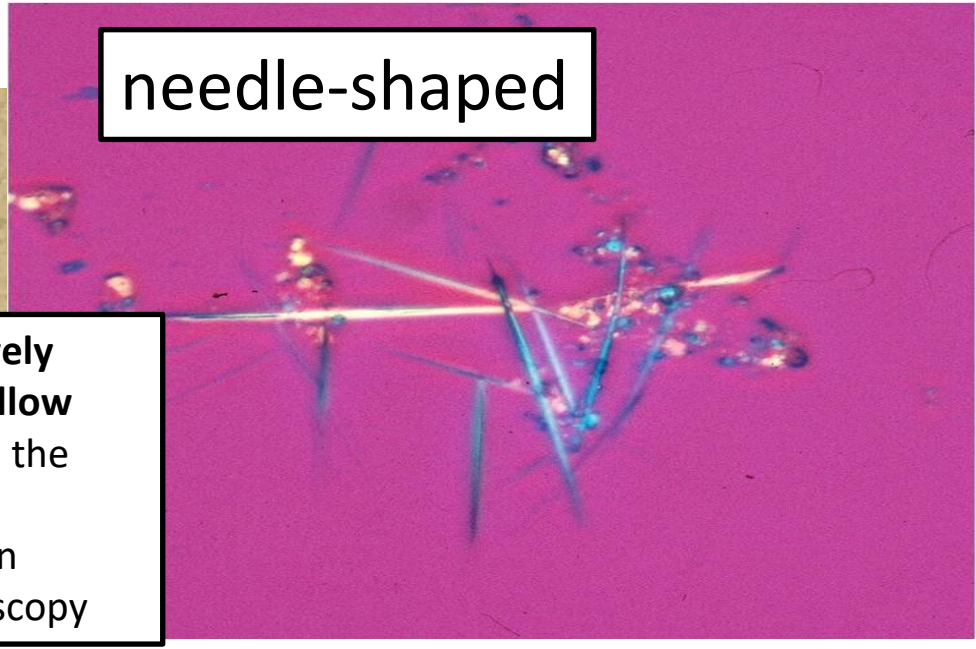
Increasing in frequency, severity and polyarticular flares

Tophi develops in long-standing gout



Diagnosis

- Synovial fluid showing monosodium urate crystals



strongly **negatively birefringent** (**yellow** when parallel to the axis of a red compensator) on polarized microscopy

Diagnostic Rule for Monoarthritis

Variable	Points
Male Sex	2
Previous arthritis attack	2
Onset within 1 day	0.5
Joint erythema	1
First MTP joint	2.5
Hypertension or > 1 CVD risk factor	1.5
Uric acid > 5.88 mg/dL	3.5
95% of patients do not have gout, consider an alternative diagnosis	≤ 4
Insufficient information to diagnose gout - **consider arthrocentesis**	5-7
85% of patients have gout	≥8

https://www.mdcalc.com/acr-eular-gout-classification-criteria

CASE

65 YO M with a history of HTN who presents after 1 episode of acute left knee pain, erythema and warmth. The symptoms resolved after 4-5 days, but his PCP is concerned that he has gout as his serum uric acid is 9. His only medication is hydrochlorothiazide.

What is your next step in management?

A. **Start allopurinol**
B. **Start colchicine**
C. **Recommend an alternative anti-hypertensive**
D. **Recommend dietary change to avoid purines**

Gout and Drugs

👎 Hydrochlorothiazide

- Loop Diuretics
- Cyclosporine
- Ethambutol
- Ethanol
- G-CSF

👍 Losartan

- Fenofibrate
- Atorvastatin

Each are uricosuric

Gout and Diet

Alcohol

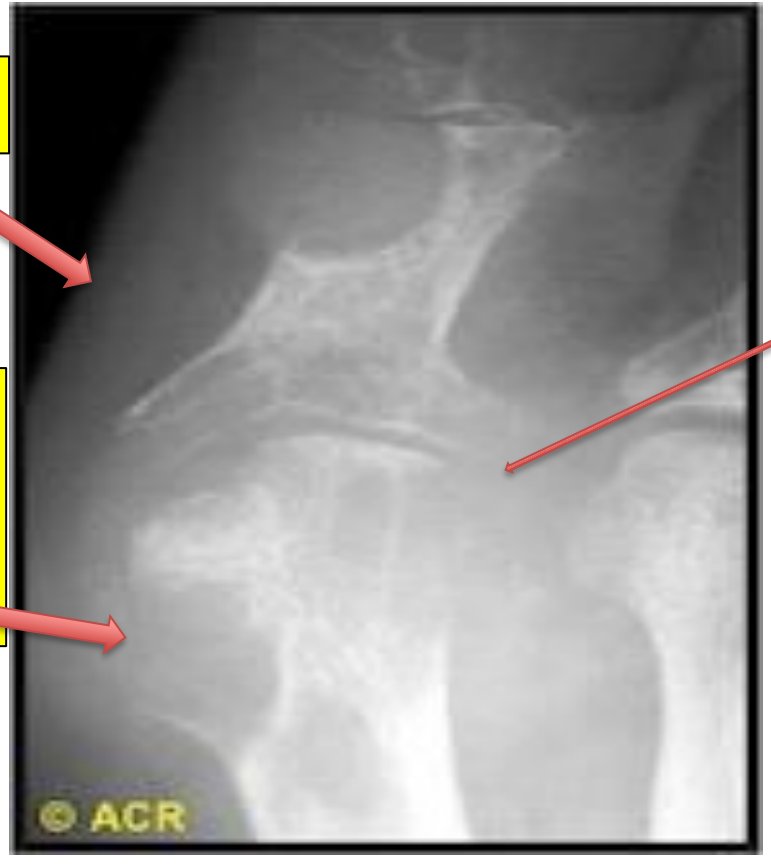
- Purines (red meat, shellfish, organ meat)
- High Fructose Corn Syrup
- Dehydration

Weight loss

Radiographs

Soft Tissue Swelling

Erosions: punched out, sclerotic margin and overhanging edges, “Rat Bite Erosion”

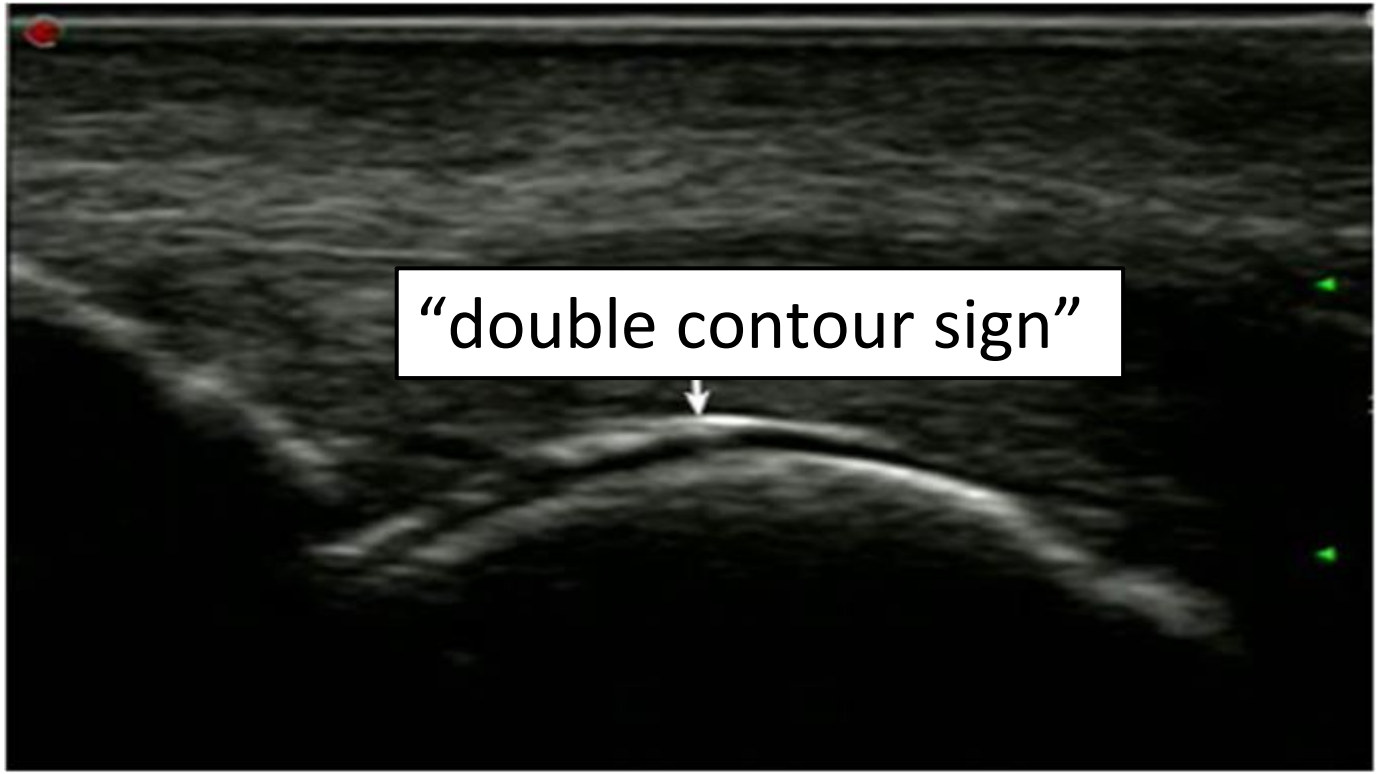


Joint space preserved

Role of Imaging

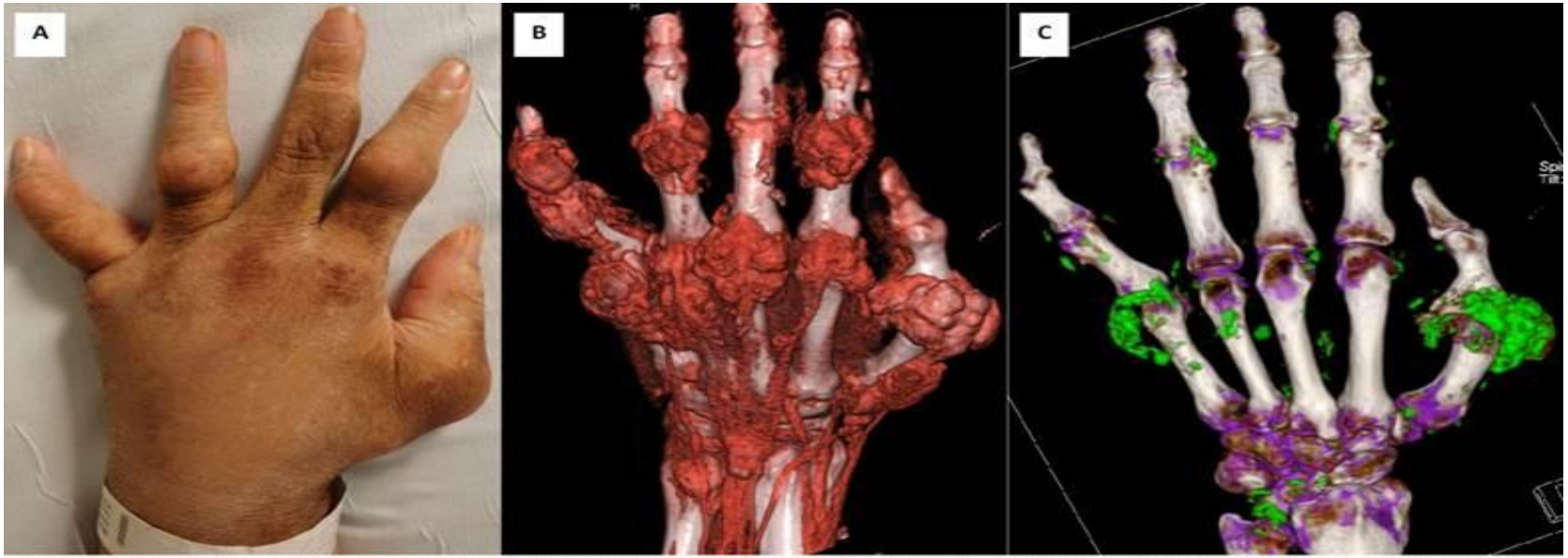
Ultrasound	Dual-energy CT
Recent onset of disease	Chronic
Single Joint, easily accessible	Multiple joints, Inaccessible joint or complex anatomy
Guidance for aspiration or injection	No target for aspiration or unsuccessful aspiration
Differentiation between soft tissue masses	OA or inflammatory arthritis concern for underlying gout.

Ultrasound



Sun, Chao, et al. "Risk factors for the formation of double-contour sign and tophi in gout." Journal of orthopaedic surgery and research 14.1 (2019): 239.

Dual Energy CT



Tophaceous gout: hand. Large tophi are evident in the fingers on clinical examination (panel A) and with 3D volume rendering (panel B). With DECT (panel C), MSU deposits (evident by their green color) conform to the areas of tophaceous deposits, but are sparse in some affected joints and absent in others (e.g. little finger DIP and long finger PIP).

Kurano, Tracie, et al. "Dual Energy CT Scanning: Variable Sensitivity for Gout in Non-Tophaceous and Tophaceous Disease and in Individual Erosions.: 2148." Arthritis & Rheumatology 66 (2014).

Case

42 YO M with right foot pain from recurrent attack of gout. First episode of gout was 3 months ago with acute inflammation of right great toe, synovial fluid confirmed the diagnosis. The symptoms subsided without any treatment. No past medical history.

On exam, 1st MTP and mid-foot are swollen and erythematous.

His pain is so severe that he is asking for some treatment.

What is the best initial treatment for this patient?

A. Acetaminophen
B. Prednisone
C. Naproxen
D. Hydrocodone
E. Allopurinol

Acute Gout Treatment

CKD

CKD

NSAIDS	Colchicine	Corticosteroids (PO, IV/IM or IA)	IL-1 receptor antagonist
Naproxen, indomethacin, ibuprofen	1.2mg PO, then 0.6 mg 1 hour later, then 0.6 mg BID or QD	Triamcinolone 40mg IA Prednisone 0.5mg/kg for 5-10d then taper over 7-10 days	Anakinra 100mg subQ x 3 days

Roddy, Annals of the rheumatic diseases 79.2 (2020): 276-284.

Case

45 YO M with gout, CKD 4, HFrEF (EF 20%), and DM Type 2 (A1c 14%) who is admitted for heart failure exacerbation. His allopurinol is stopped at time of admission.

2 days into his hospitalization he has bilateral knee pain and swelling. Serum uric acid is 9. You suspect polyarticular gout.

What is your best choice for treatment?

A. NSAIDs
B. Colchicine
C. Anakinra
D. Allopurinol
E. Prednisone

Indications for Urate Lowering Therapy

- One or more subcutaneous **tophi**
- Radiographic **damage** (any modality) due to gout
- Gout inflammatory activity as defined by
  - **Frequent** gout flares (> 2 flares/year)
  - First flare in presence of **CKD** > 3, SU > 9 mg/dL or urolithiasis
- NOT recommended for asymptomatic hyperuricemia or first flare and the absence of the above

Chronic Gout and Urate Lowering Therapy

- **Start with allopurinol**, even for patients with CKD > 3
  - Check **HLA B*5801** in Southeast Asian descent or African American patients, universal testing is not recommended
    - If HLAB*5801 +, use febuxostat
  - OK to start in a gout flare or right after
  - Febuxostat* not recommend in patients with CVD or new CVD event
  - Indefinite treatment
- **Use concomitant anti-inflammatory prophylaxis for 3-6 months**
  - Either colchicine, NSAID or low dose prednisone
- **Treat to a goal of serum uric acid < 6 mg/dl**
  - OR if you're the ACP, until they have no symptoms, which is usually less than 6.

Case

A 35-year-old man is referred to Rheumatology for evaluation of hyperuricemia. His father has gout that has been well controlled with allopurinol. The patient's family physician ordered a serum uric acid test because of the family history of gouty arthritis. The patient's uric acid value was elevated at 10.1 mg/dL (reference range: 3.0-7.0 mg/dL). The patient has never had any attacks of gout and has no knowledge of kidney stones or underlying kidney disease. He has hypercholesterolemia and uses atorvastatin 10 mg daily.

His physical examination is normal. No tophi are noted. His height is 59 inches, weight is 215 lb, blood pressure is 124/82 mmHg, and heart rate is 76 bpm. Additional laboratory tests reveal a normal serum creatinine level.

Which of the following is recommended for this patient at this time?

A. Allopurinol 100 mg daily
B. Colchicine 0.6 mg twice daily
C. Probenecid 500 mg twice daily
D. Lifestyle modification

Case

33 YO M with severe tophaceous gout.

He is on maximum treatment with allopurinol 300mg BID and febuxostat and remains hyperuricemic with polyarticular gout flares.

He requires multiple long steroid tapers per year.

Current serum uric acid is 10mg/dl.

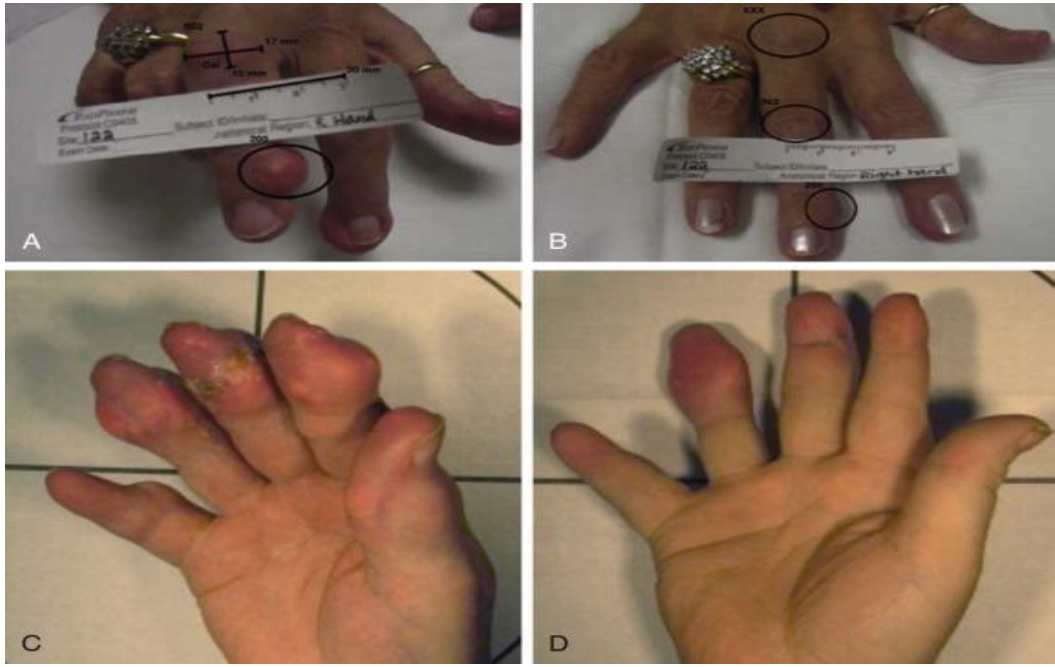
He is adherent to his home medications.

What would be your next treatment?

A. Increase allopurinol dose
B. Add prednisone 5mg daily
C. Start pegloticase
D. Refer to hand surgery

Pegloticase

- Krystexxa
- Recombinant porcine-like uricase
- Severe refractory gout
- Tophi reduction
- Contraindicated in G6PD deficiency
- Can form anti-pegloticase antibodies (7%)
- Check serum uric acid prior to each infusion to check for antibodies
- Don’t combine with ULT; can confound sUA levels



Schlesinger, Naomi, Uma Yasothan, and Peter Kirkpatrick. "Pegloticase." (2010): 17.

Long-term cardiovascular safety of febuxostat compared with allopurinol in patients with gout (FAST): a multicentre, prospective, randomised, open-label, non-inferiority trial

*Isla S Mackenzie, Ian Ford, George Nuki, Jesper Hallas, Christopher J Hawkey, John Webster, Stuart H Ralston, Matthew Walters, Michele Robertson, Raffaele De Caterina, Evelyn Findlay, Fernando Perez-Ruiz, John J V McMurray, Thomas M MacDonald, on behalf of the FAST Study Group**

- Prospective, randomized, open-label, blinded endpoint, non-inferiority multi-center trial of febuxostat vs allopurinol.
- Eligible patients were 60 years or older, had gout, required ULT and had at least one CV risk factor.
- Exclusion criteria: Patients who had a myocardial infarction (MI) or stroke in the previous six months, or class III/IV heart failure.
- A total of 6128 patients were randomized to receive allopurinol vs febuxostat.
- The primary outcome was a composite of **hospitalization for non-fatal MI or biomarker positive acute coronary syndrome, non-fatal stroke or death due to CV event.**
- The study showed that **febuxostat was non-inferior to allopurinol** with respect to the primary outcome as well as secondary outcomes including CV death, all-cause death, hospitalization for non-fatal MI or biomarker positive acute coronary syndrome, and hospitalization for heart failure or transient ischemic attack based on both intention-to-treat and on-treatment analyses.
- Is this enough evidence to remove the FDA blackbox warning?

Case

52 YO M presents to urgent care after injuring his left wrist while playing basketball with his son. Prior to the injury, he was having no joint pain. On exam, there is notable tenderness over the scaphoid. Otherwise the wrist is non-tender. There is no erythema or warmth. Neurovascular intact. Plain films without fracture, however, there is chondrocalcinosis of the fibrocartilage of the triangular ligament.

Which of the following is true?

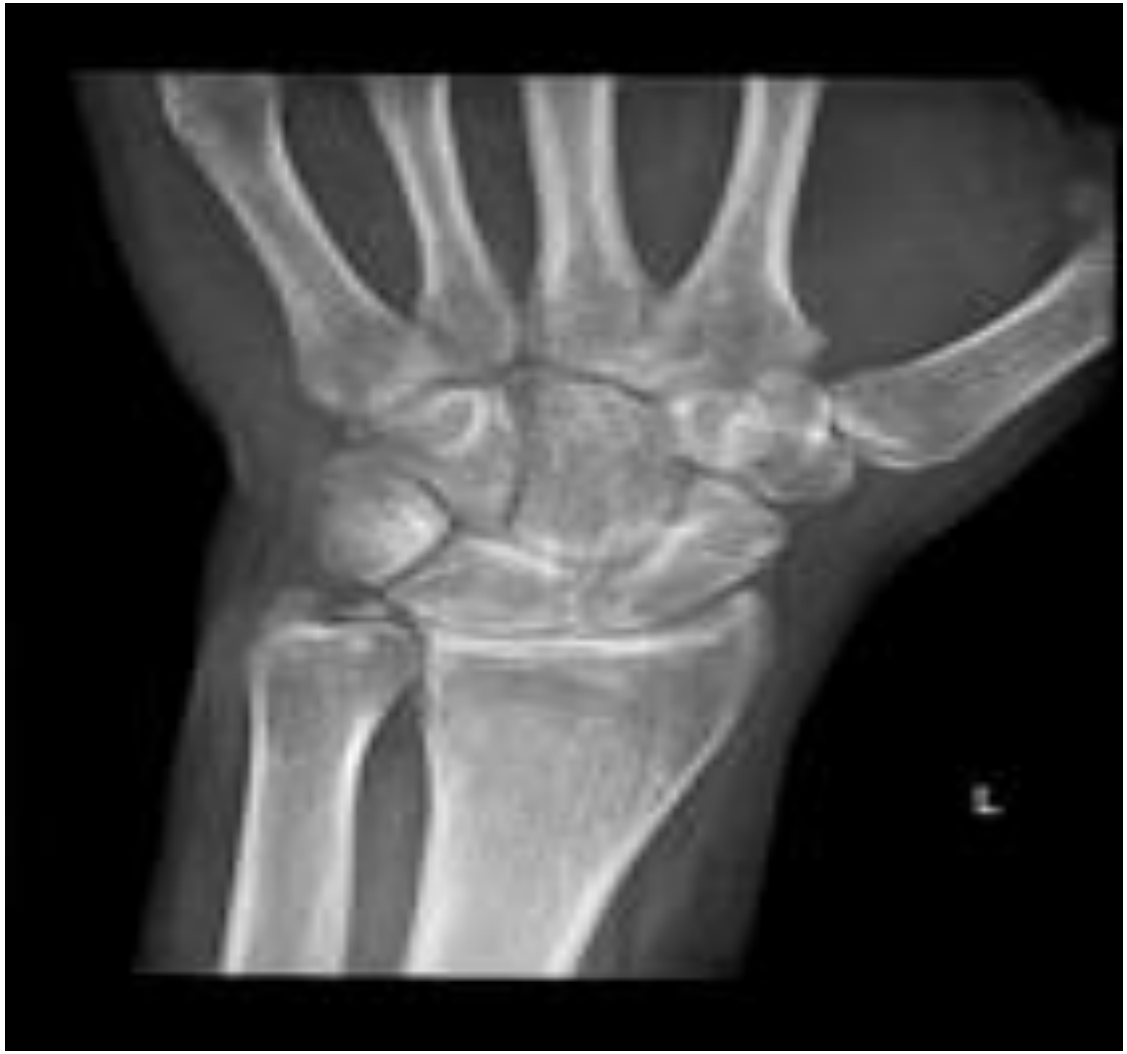
A. Most patients with his condition present with significant pain.

B. The patient needs urgent arthrocentesis.

C. This condition may present with signs and symptoms similar to osteoarthritis or rheumatoid arthritis.

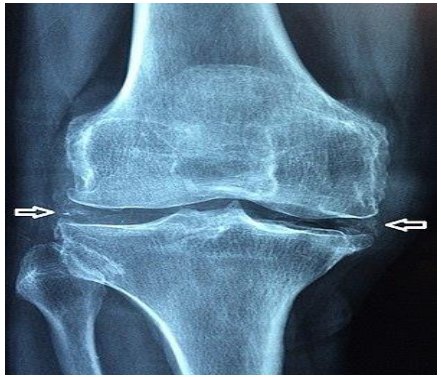
D. He should be started on prednisone immediately.

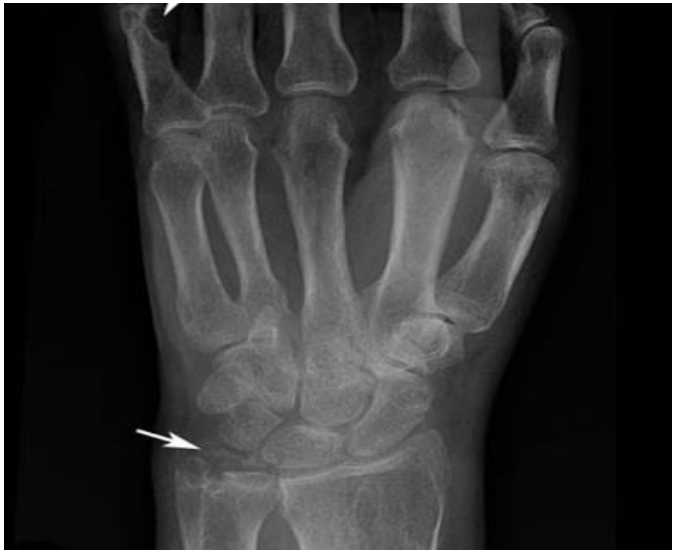
E. Treatment can reverse damage.


L

Calcium Pyrophosphate Disease (Pseudogout)

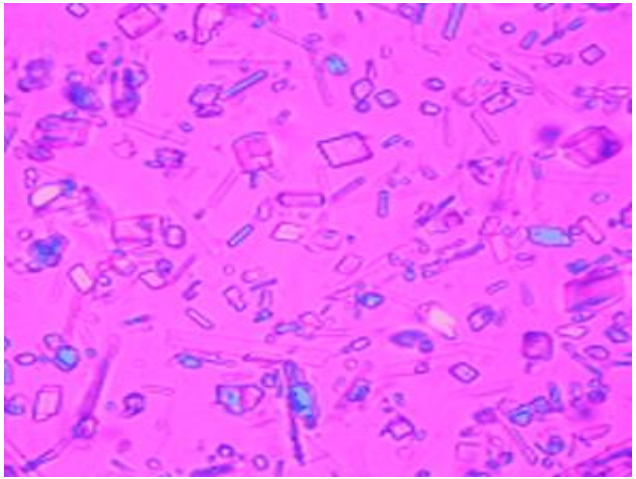
- Most common in older adults with prior joint damage
  - Younger adults: hyperparathyroidism, hemochromatosis, hypophosphatasia and hypomagnesemia
- Asymptomatic CPPD
  - Chondrocalcinosis on X-ray





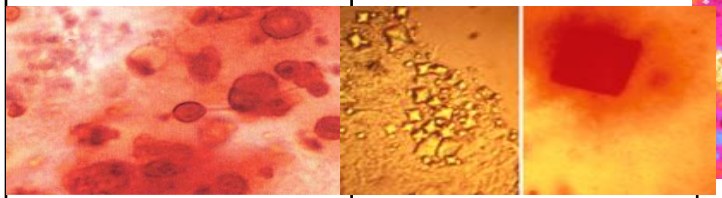
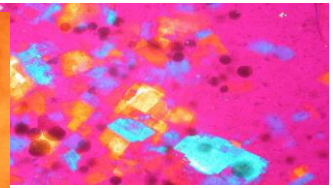
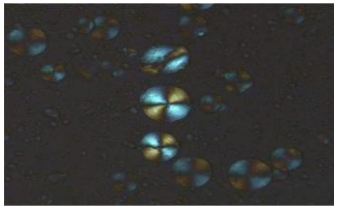
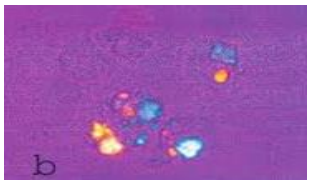
Acute CPPD Arthritis

- Similar to gout – sudden onset pain, swelling, loss of function, precipitated by illness/surgery
- Can persist for months
- Diagnosis: Synovial fluid with rhomboid shaped crystals that are positive birefringent
- Treatment: NSAIDs, Colchicine, steroids
- Prophylaxis: Low dose colchicine or daily NSAIDs



- Chronic CPPD Arthritis:
  - Treat the same as OA without CPPD – PT, NSAIDs/Acetaminophen and local steroids

The other crystals

Basic Calcium Phosphate	Calcium Oxalate Crystal	Cholesterol Crystals	Lipid Droplets	Steroid Crystals
Light microscopy: Shiny coins; Small Non-birefringent; Alizarin red S stains red with calcium	Light microscopy: Bipyramidal crystal; Weakly birefringent	Light microscopy: Polygonal plates with notched corners; Weakly birefringent	Light microscopy: Maltese Cross	Light microscopy: Small rectangular, irregular crystals; Positive Birefringent
Deposition of calcium hydroxyapatite; Milwaukee Shoulder	Primary oxalosis, ESRD, IBD patients	Chronic joint effusions, xanthomas in familial hyperlipidemia	Concern for fracture!	Steroid injection
				

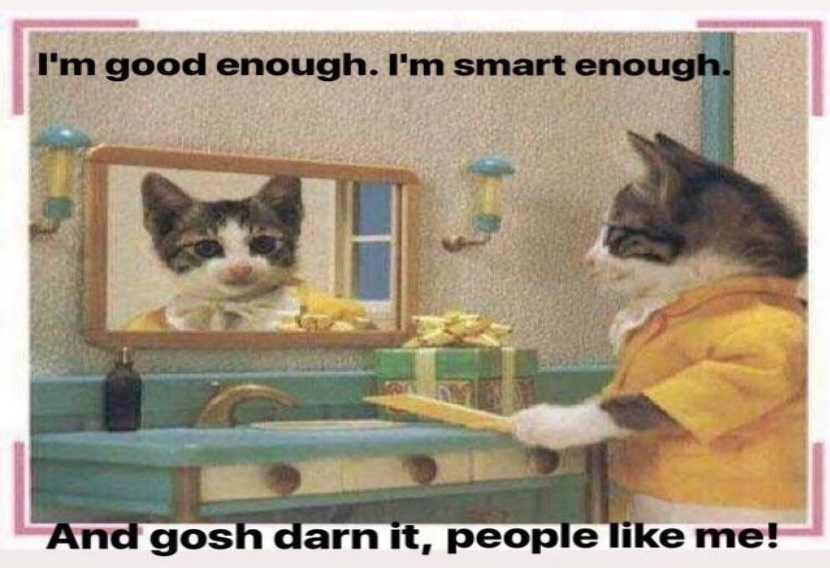
Selvi, Enrico, et al. "Arthritis induced by corticosteroid crystals." Journal of rheumatology 31.3 (2004): 622-622.

Final Thoughts

- Recognize the differential diagnosis for acute monoarthritis
- Identify and diagnose gout and other crystal-induced arthropathies
- Plan and initiate treatment for gout and pseudogout
- Do not stop allopurinol, unless there is a rash or other other concerning side effect

Rheumatologists when allopurinol is stopped.

Questions?



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