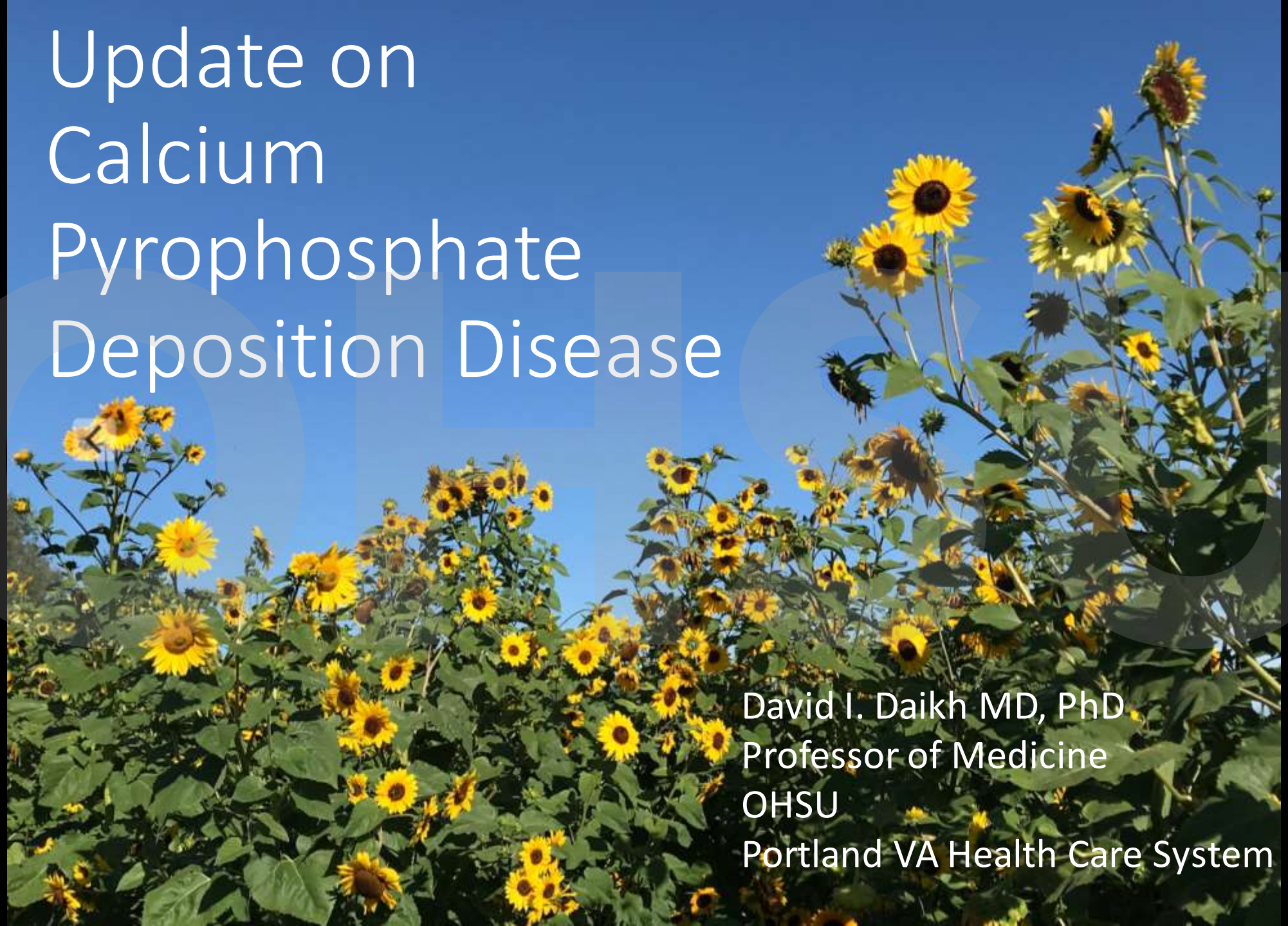
Update on Calcium Pyrophosphate Deposition Disease



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Disclosures

- None

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Learning Objectives

- Review and update of CPPD
- Know the most common joints involved by CPPD
- Recognize distinct patterns of inflammatory arthritis in CPPD
- Know risk factors associated with CPPD
- Understand treatment goals

Calcium Pyrophosphate Deposition Disease

CPPD CPPDD

"Pseudogout"

Why think about CPPD?

- A common cause of acute or chronic inflammatory arthritis in older individuals
- CPPD disease is a great imitator
  - Mimics Gout
  - Frequently co-exists and can cause Osteoarthritis
  - Mimics Rheumatoid Arthritis
  - Can look like meningitis

Calcium Pyrophosphate

- Clinical features
- Pathophysiology
- Treatment

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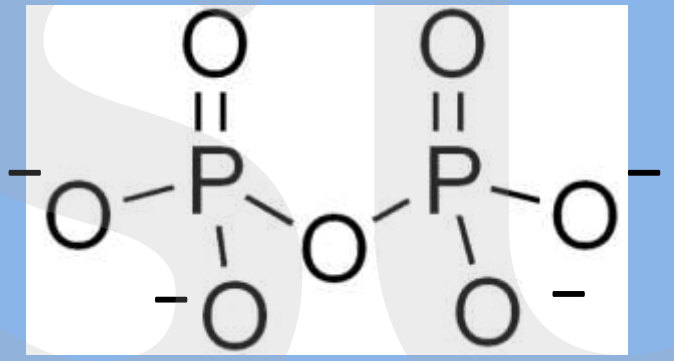
Calcium Pyrophosphate

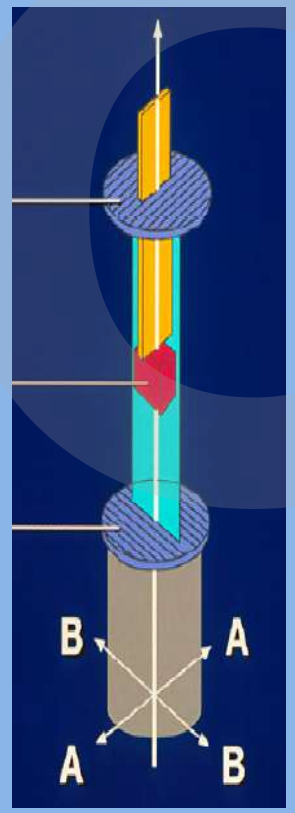
- Pyrophosphate P_2O_7 , PP_i
- ATP → AMP + PP_i
- Positively birefringent, rhomboid crystal
- CPP forms in pericellular matrix of cartilage

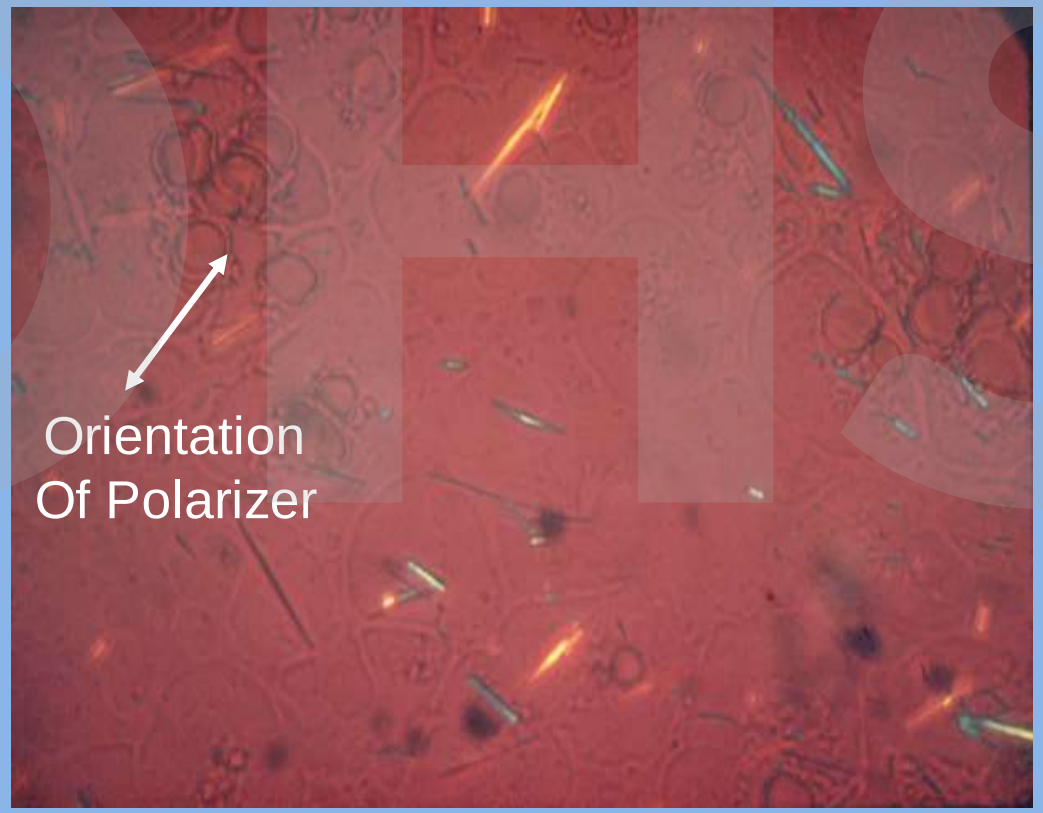


$Ca_2P_2O_7$

Polarized Microscopy

Demonstration of rhomboid-shaped crystals with positive birefringence on polarized microscopy





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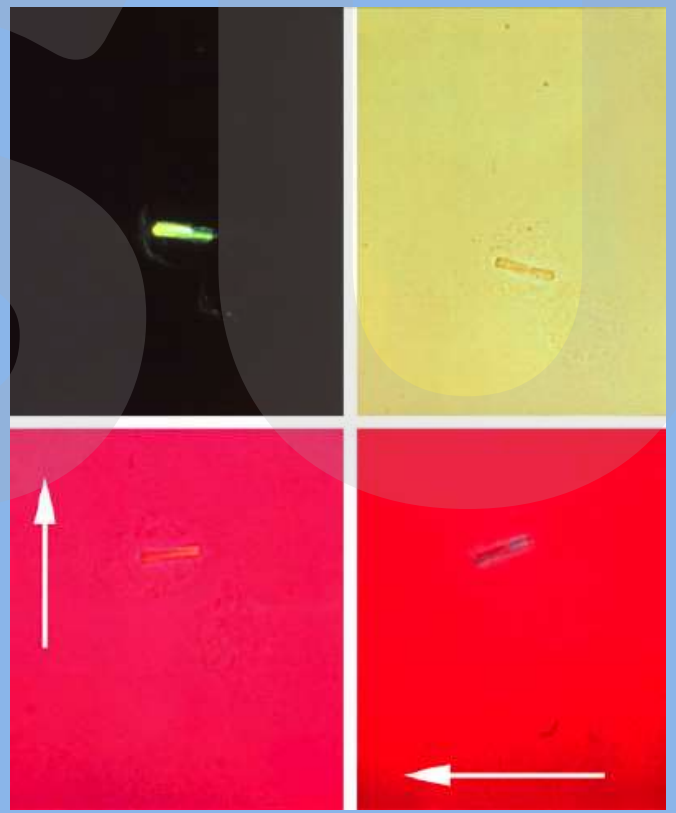
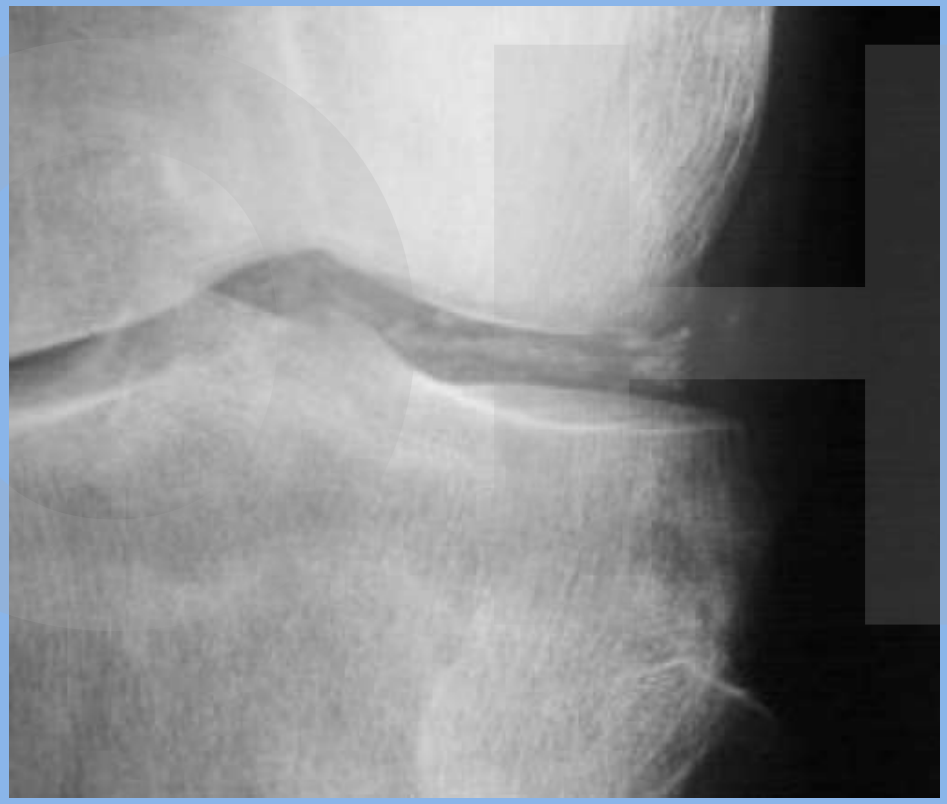
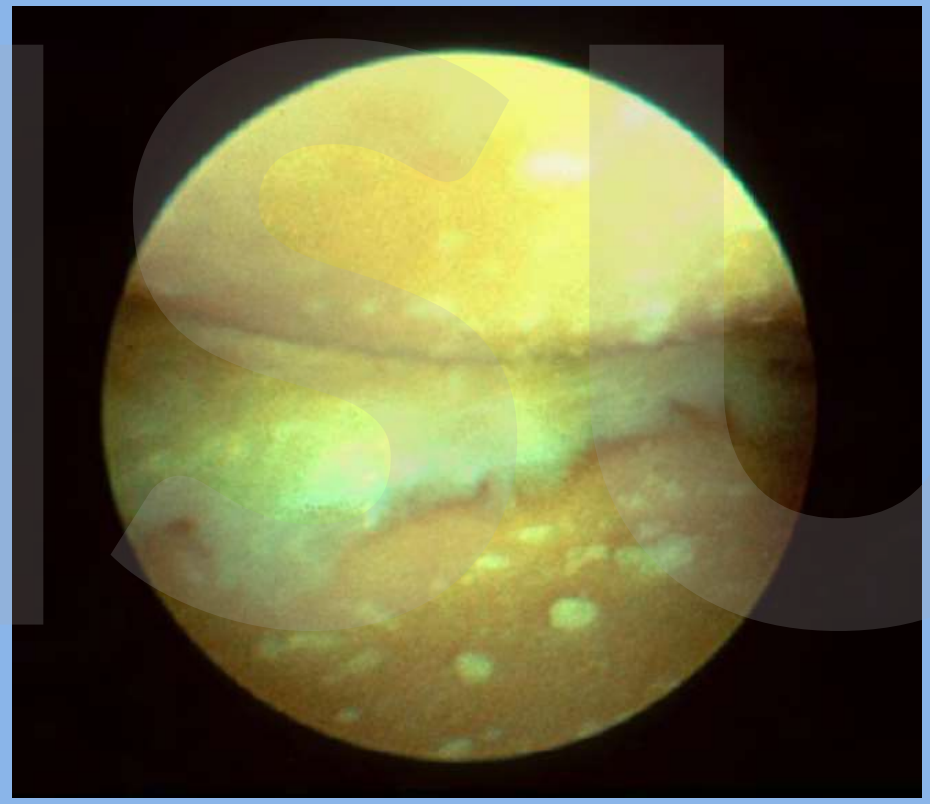


CPPD

Chondrocalcinosis





Radiographic vs Clinical disease

- Chondrocalcinosis is highly associated with clinical CPPD disease and precedes the development of clinical disease in familial CPPD.
- Clinical disease occurs in the absence of chondrocalcinosis
  - present in approximately 40% of patients)
  - difficult to visualize with severe cartilage loss
- Chondrocalcinosis may occur in patients without arthritis
  - non-CPP mineral (e.g. calcium phosphate dihydrate)
- Meniscus, fibrocartilage of wrist, symphysis pubis, AC joint, intervertebral disks and spinal ligaments

CPPD Disease is Common

- Prevalence is 4 to 7% in Europe and the United States
- Rare under age 60
- Prevalence doubles each decade
- 44% of patients > age 84
- Familial CPPD

Distinct Clinical Patterns

1. Acute inflammatory arthritis (gout like)
2. Chronic inflammatory arthritis (RA like)
3. Chronic degenerative arthritis (OA like)

- Severe destructive arthropathy (Charcot like)
- Spinal involvement
- Tumoral calcification

Acute inflammatory arthritis (Pseudogout)

- Acute monoarticular inflammatory arthritis
- Mimics acute gout and septic arthritis
- Knee is to pseudogout as great toe is to gout
- Pseudogout vs Gout
  - knee, wrist vs toe and ankle
  - weeks to months vs days to weeks

Chronic inflammatory arthritis (RA like)

- Chronic inflammatory oligo- or polyarticular inflammatory arthritis
- Synovitis typically present
- Frequently involving the hands and wrists (MCPs)
- CPPDD vs RA
  - Less symmetric
  - Sequential involvement of joints

➢ Chronic episodic inflammatory oligoarthritis

Pseudo-RA Pattern of CPPD Disease

Rosenthal AK and Ryan LA, CPPD, New Eng J Med, 374;2575-84

American College of Rheumatology Slide Collection

Pseudo-RA Pattern of CPPD Disease

American College of Rheumatology Slide Collection

Chronic degenerative arthritis (OA like)

CPPD:

- Causes OA
- Frequently co-exists with OA
- Is confused with OA
- CPPDD vs OA
  - Inflammatory features
  - Severe destruction
  - Specific Joint Involvement
    - Wrist, MCPs, Glenohumeral joint

Degenerative CPPD Arthritis

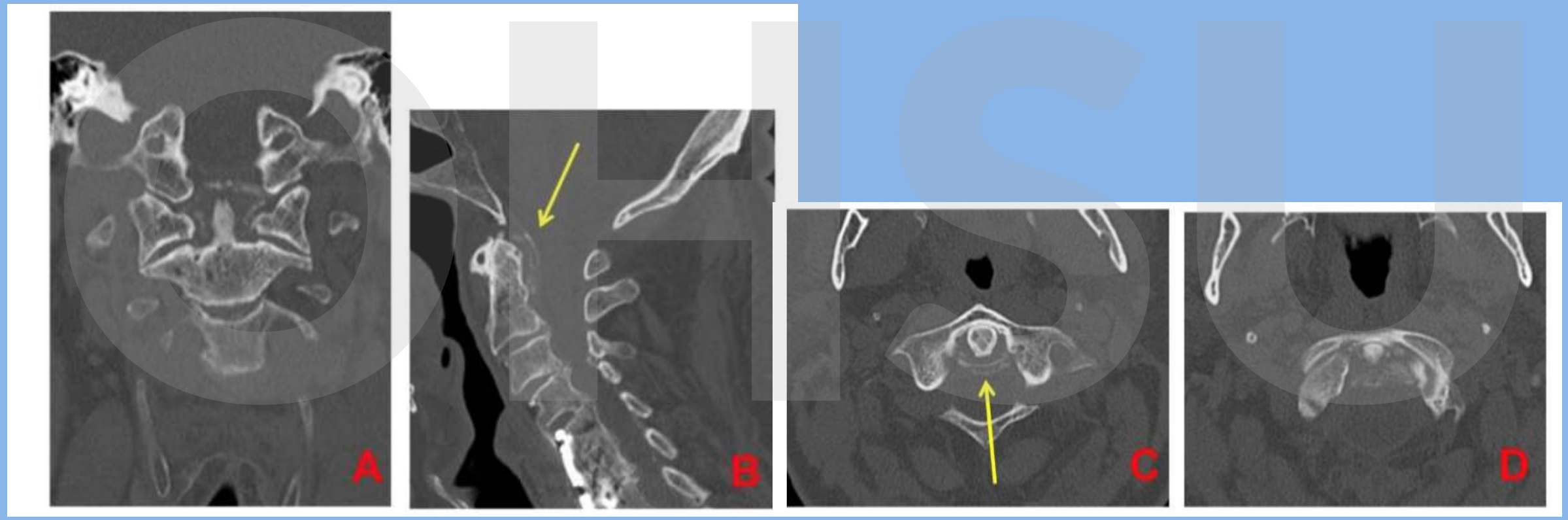
Resnick D, "Rheumatoid Arthritis and Pseudo-Rheumatoid Arthritis in Calcium Pyrophosphate Dihydrate Crystal Deposition Disease," Radiology, 140:615-21, 1980.

Patterns of Inflammatory Arthritis

Spine involvement

- CPP can deposit in intervertebral disks and along spinal ligaments
- Deposition and inflammation in and around C2 and C1 produces acute, severe neck pain, frequently with headache and fever. “Crown Dens Syndrome”
- High acute phase reactants
- Often confused with meningitis, epidural abscess or sepsis.

Crown Dens Syndrome



American College of Rheumatology Image Library

CPPD Disease

Associated Conditions

- Hemochromatosis
- Hyperparathyroidism
- Hypomagnesemia
- Hypothyroidism
- Hypophosphatasia
- Ochronosis
- Gout
- Diabetes

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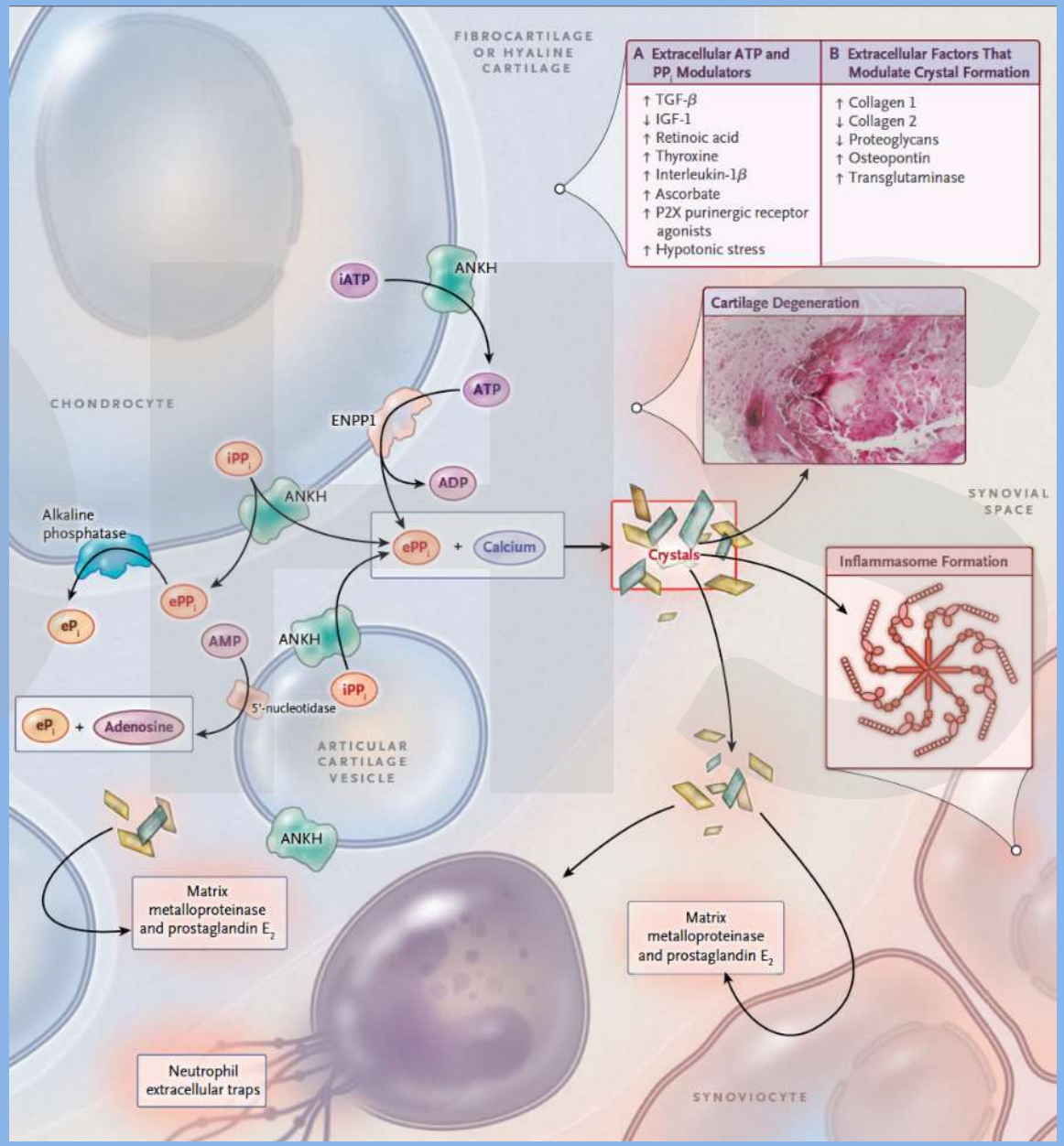
Pathophysiology of CPPD Disease

- formation of CPP crystals in the pericellular matrix of cartilage by chondrocytes in articular cartilage vesicles
- Extracellular ATP is a rate-limiting for PP_i formation
- ATP efflux regulated by membrane protein ANKH
- CPP crystals activate inflammatory responses and stimulate destructive metabolic changes that damage chondrocytes and synoviocytes

Pathophysiology of CPPD Disease



Rosenthal AK and Ryan LA, CPPD, New Eng J Med, 374;2575-84

Innate Immune Response in Gout

Liberation of uncoated MSU crystals

↓

C5 activated on crystal surface

↓

C5b-9 MAC

↓

Recognition by TLR2/4 → MyD88 signaling

↓

Induction of IL-1, TNFα and CXCL8

↓

Neutrophil infiltration

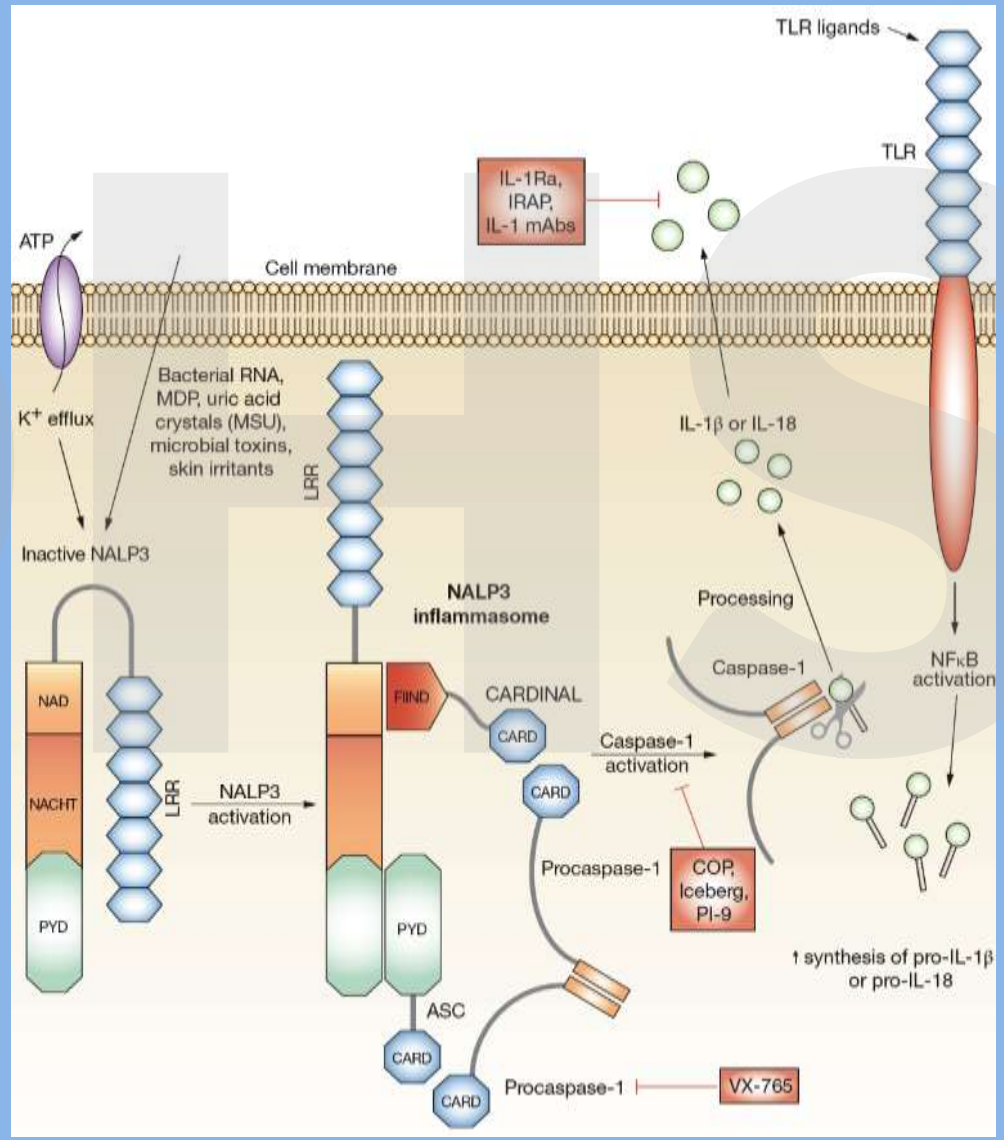
↓

MSU phagocytosis

↓

Release of chemotactic calgranulins

Induction of the NALP3 Inflammasome



Church LD, et al.,Nature Clinical Practice, 4:2008

CPPD "Pseudogout"

Typical Clinical Features

- Acute, inflammatory, gout-like attacks that occur secondary to calcium pyrophosphate dihydrate (CPPD) crystals.
- Patients are typically older (60's-70's).
- Male/female incidence is about equal
- Knee is to pseudogout as big toe is to gout (wrist also common).

Calcium Pyrophosphate Deposition Disease

Objective Findings

- Radiographs typically show linear deposition of calcium pyrophosphate dihydrate (CPPD) in hyaline cartilage or fibrocartilage.
  - triangular cartilage of wrist
  - menisci of knee
  - symphysis pubis
  - acromicoclavicular joint
- Inflammatory synovial fluid.
- Rhomboid shaped, weakly positively birefringent crystals.

Basic Calcium Phosphate Disease

- More likely in OA joint
  - Positive birefringent rod shaped crystals
  - knee> wrist> MCPs>
    hips, shoulders, ankles; frequently including tendons
- Chondrocalcinosis
- Neuropathic joint

Treatment Considerations

- Pseudogout - treat like gout
  - NSAIDS, steroids
  - colchicine
    - Start immediately
    - Acute gout regimen: 1.2 mg followed by 0.6 mg one hour later
  - anakinra
    - SQ daily for 3-5 day

Treatment Considerations

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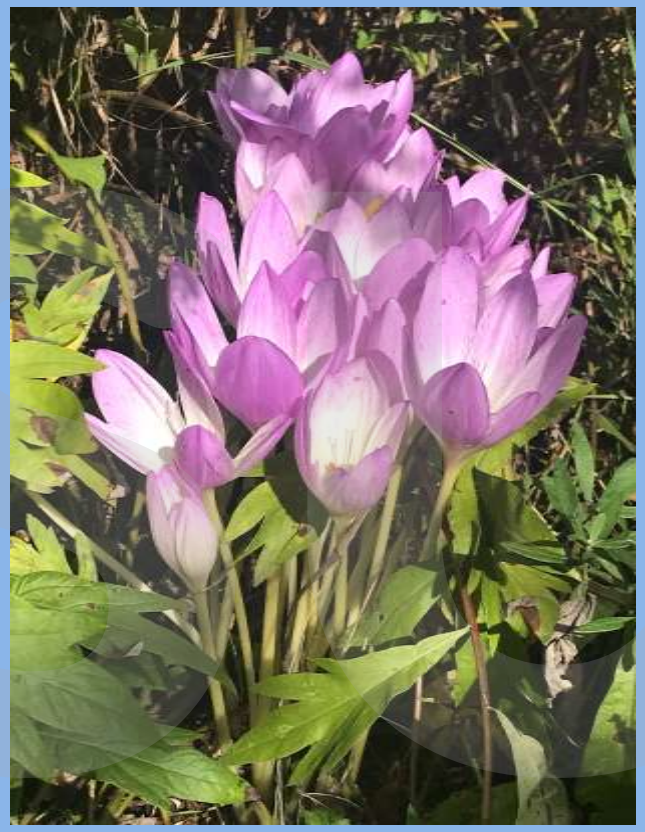
Colchicine

- Reversible inhibition of microtubule assembly
- Inhibits NALP3 inflammasome activation
- Now an expensive medication



Colchicum

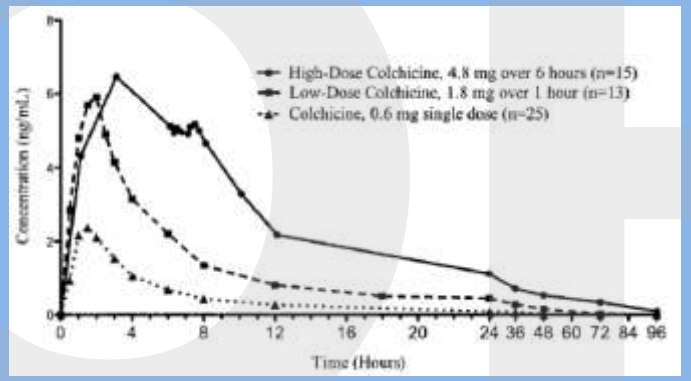
Colchicine - Side Effects

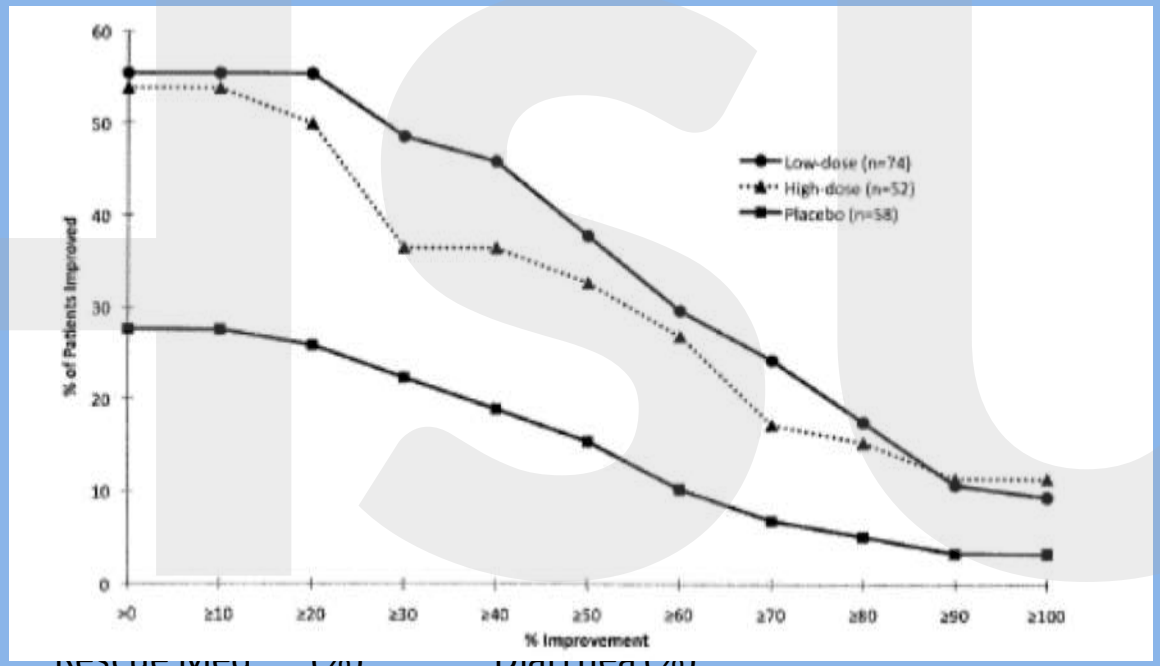
- Narrow therapeutic window
  - Neuropathy, myopathy, bone marrow suppression
- GI effects
  - Purgative effect
- IV colchicine
  - Tissue necrosis, acute renal failure, bone marrow aplasia
  - Don’t use it

AGREE Trial of Colchicine for Acute Gout

"Low-Dose" 1.8 mg over 1 hr (1.2 + 0.6)

"High Dose" 4.8 mg over 6 hrs (1.2 + 0.6/hr)





	Rescue Med (%)	Diarrhea (%)
Placebo	50.0	13.6
LD	31.1	23.0
HD	34.6	76.9

Terkletaub RA, et al., A&R 62:1060-1068, 2010

Treatment Considerations

Pseudogout

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- treat like gout
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  - **anakinra** (Kinaret)
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Treatment Considerations

Degenerative Arthritis (OA)

Consider metabolic risk factors

- Hemochromatosis
- Hyperparathyroidism
- Hypomagnesemia

GHSU

Treatment Considerations

Degenerative Arthritis (OA)

Consider metabolic risk factors

- **Hemochromatosis**
- Hyperparathyroidism
- Hypomagnesemia

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Hemochromatosis

- Clinical Manifestations
  - Liver function abnormalities – 75 percent
  - Weakness and lethargy – 74 percent
  - Skin hyperpigmentation – 70 percent
  - Diabetes mellitus – 48 percent
  - Arthralgia – 44 percent
  - Impotence in males – 45 percent
  - Electrocardiographic abnormalities – 31 percent

Niederau C, et al., "Epidemiology, clinical spectrum and prognosis of hemochromatosis."Adv Exp Med Biol. 356:293, 1994.

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Hemochromatosis

- Lab Testing/Screening
  - Unexplained liver function test abnormalities
  - High serum ferritin
    - eg, >300 ng/mL in men or postmenopausal women; >200 ng/mL in premenopausal women
  - High transferrin saturation
    - (>45 percent for men or >55 percent for women)
  - *HFE* gene mutation

UpToDate, Clinical manifestations and diagnosis of hereditary hemochromatosis

Treatment Considerations

- Degenerative Arthritis (OA)
  - Consider metabolic risk factors
    - Hemochromatosis
    - Hyperparathyroidism
    - Hypomagnesemia
  - Symptomatic treatment
    - acetaminophen
    - NSAIDs
    - consider gabapentin

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Treatment Considerations

- Chronic Inflammatory (pseudo-RA)
  - NSAIDs
  - Colchicine 0.6 QD – BID
  - Consider DMARDs
    - prednisone
    - hydroxychloroquine
    - methotrexate

CPPD Disease

- A common cause of chronic inflammatory and degenerative arthritis
- Appropriate treatment requires recognition of the distinct pattern of clinical disease
- Chronic inflammatory CPPDD is an unmet clinical need

Thank You