Crystallizing the Approach to Gout and Pseudogout

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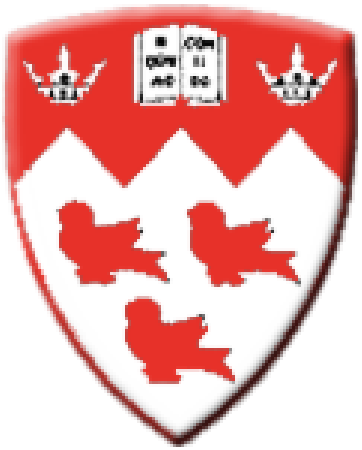


Mcgill Family Medicine Review Course

December 1, 2021

Disclosures:

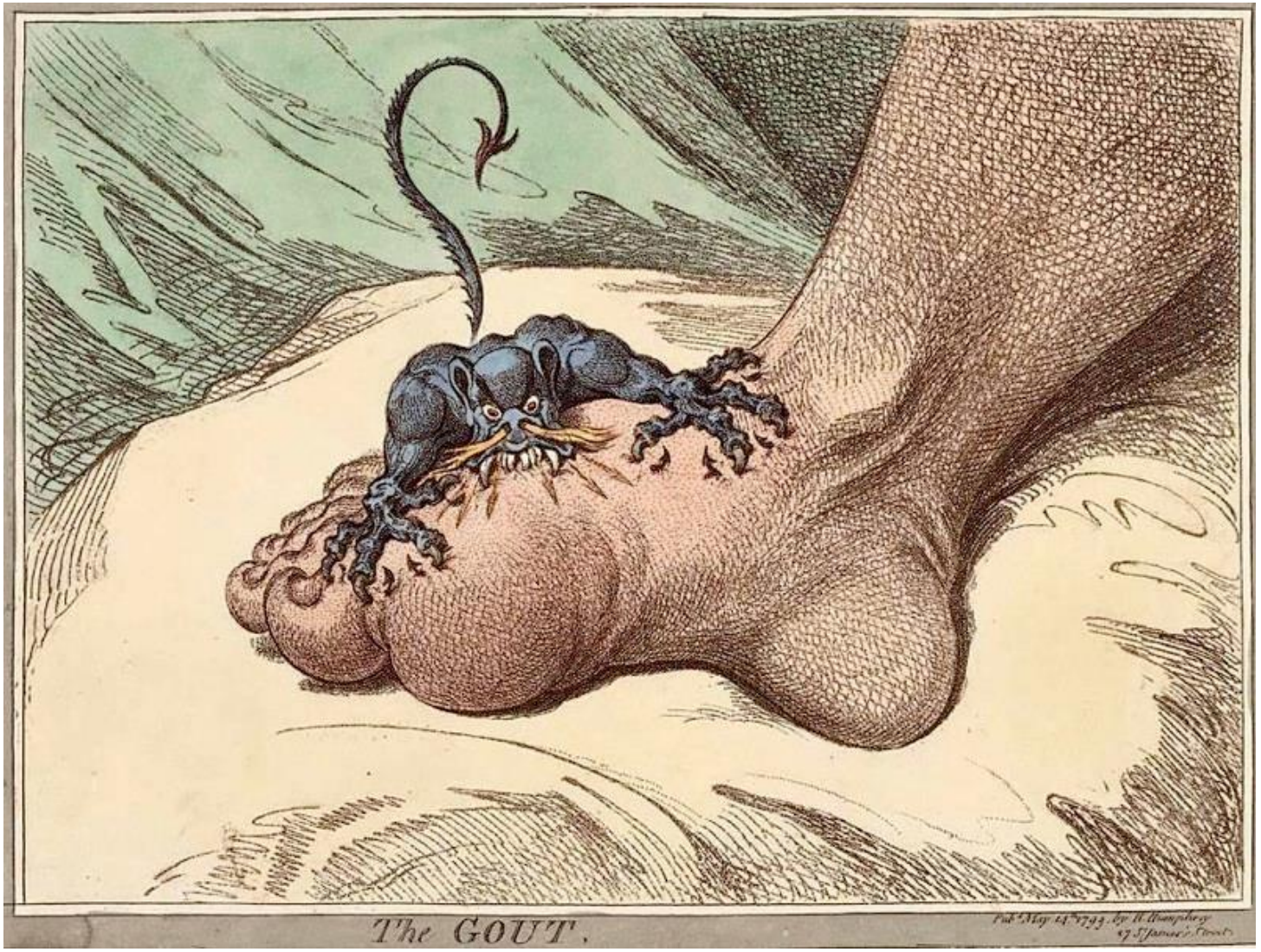
- None that affect the content of this lecture

Objectives

- To better understand the etiopathogenesis, predisposing factors and epidemiology of gout and pseudogout
- To improve skills in diagnosis and evaluation of crystal arthropathies
- To update current and emerging treatment options for gout and pseudogout management

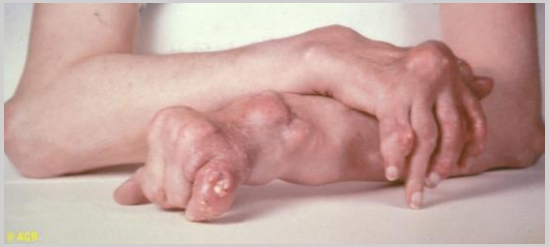
Gout History in Medicine : “A Disease of Kings”

“The Gout”



Gout

- Chronic disorder of urate metabolism
- Results in deposition of monosodium urate crystals in the joints, soft tissues, and other organs with accompanying inflammation and degenerative consequences[1]
- Most common form of inflammatory joint disease in men aged ≥40 years[1]
  - Overall prevalence: 1-15.3%[2]
  - Closely related to elevated sUA levels
  - sUA ≥540 µmol/L, cumulative incidence 22%[3]



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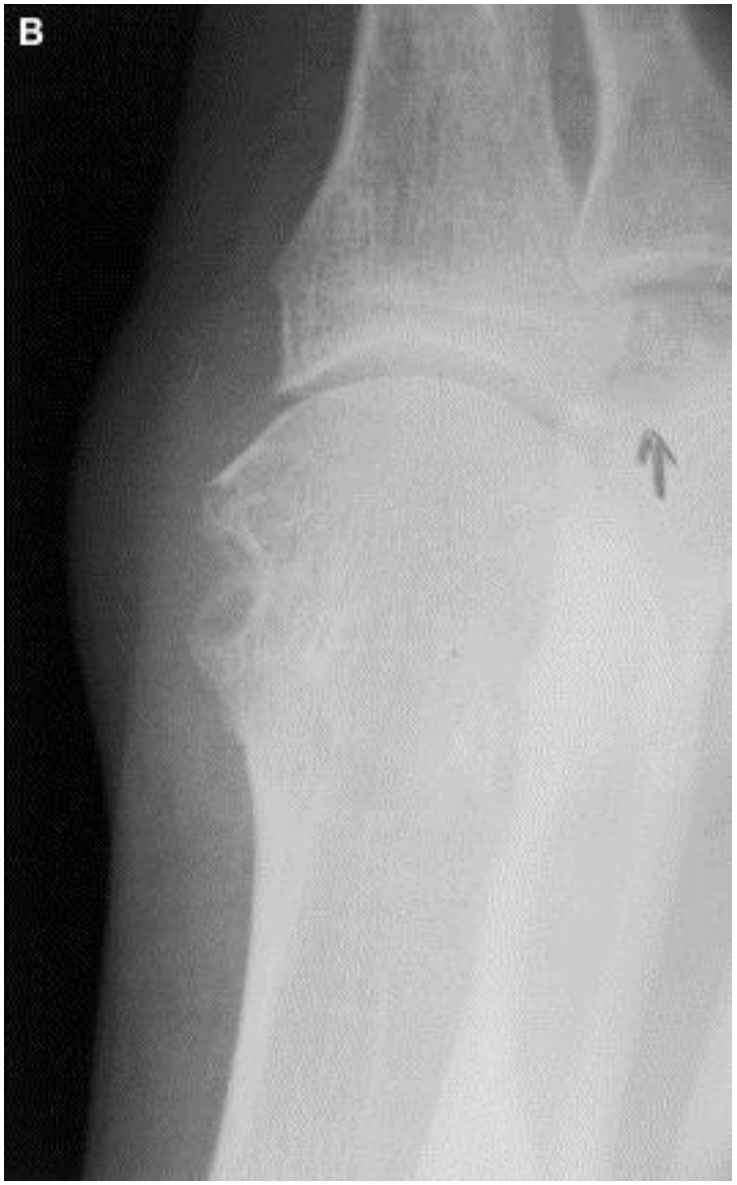
American College of Rheumatology.
ACR Clinical Slide Collection on the Rheumatic Diseases. Atlanta, Ga.
American College of Rheumatology; 1998.

1. Choi HK. *et al*. *Ann Intern Med*. 2005; 143: 499-516.
2. Worthmann PL, Kelly WN. In *Kelly's Textbook of Rheumatology*. 7th ed. 2005:1402-1429.
3. Campion EW. *et al*. *Am J Med.* 1987;82:421-6.

Complications: Gout

- Renal Failure
  - can be caused by chronic urate nephropathy
- Nephrolithiasis
- Destructive arthropathy
- Recurrent Gout
- Association with Cardiovascular Disease, CKD



Risk Factors and Associated Comorbidities

Comorbidities

- Hypertension
- Cardiovascular disease
- Chronic kidney disease
- Diab
- Dysli
- Metabolic syndrome

Medications

- Thiazide diuretics
- Low-dose aspirin
- Cyclosporine

Link between gout and higher risk of death from all causes including CVD

Lifestyle

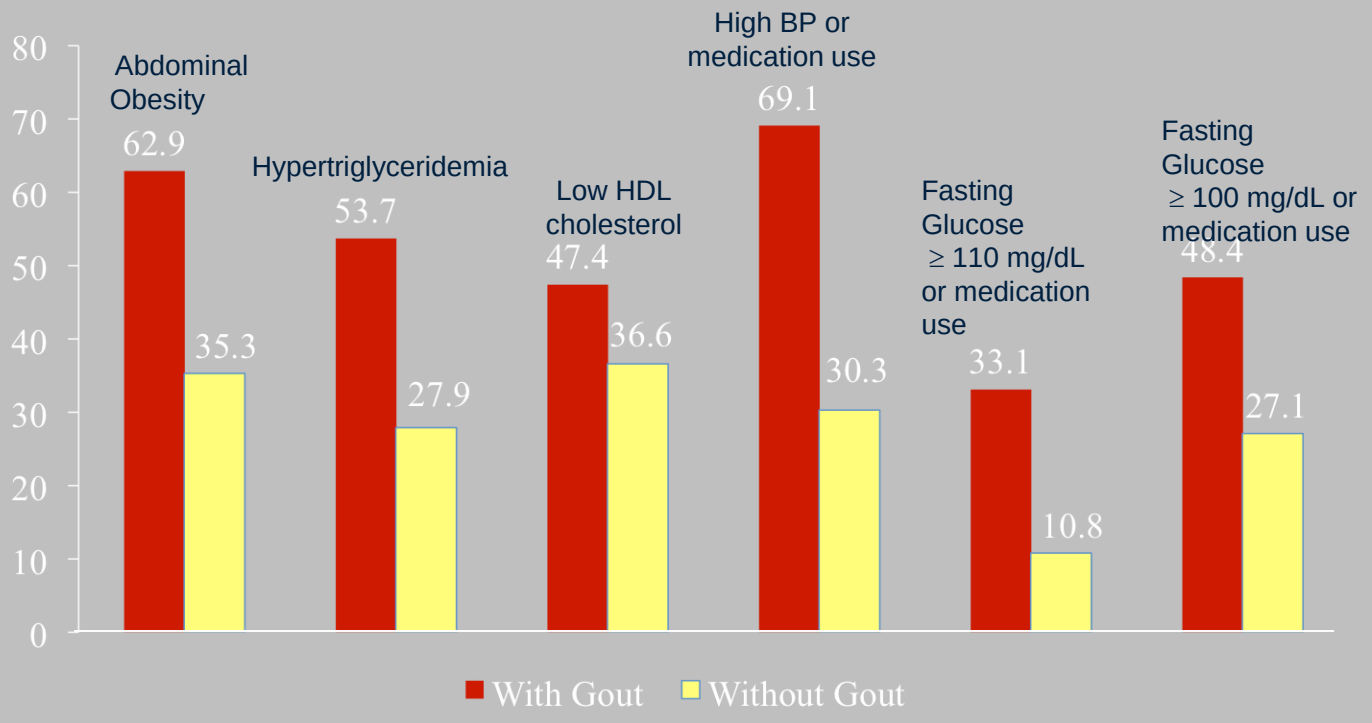
- Obesity (high BMI)
- Diet rich in meat and seafood
- High alcohol intake
- Frequent consumption of high-fructose corn syrup

Demographic Factors

- Advanced age
- Male
- Postmenopause in women

Choi HK, et al. *Ann Intern Med*. 2005;143:499-5161.
Kim SY. *et al*. *Arth Care & Res*. 2010; 62: 170–180.
Krishnan E. *et al. Arch Intern Med.* 2008;168:1104-1110.
Kou D-F.*et al*. *Rheumatology* 2010;49:141–146.
Kuo CF, et al. *Rheumatology (Oxford).* 2010;49:141-6

Higher Prevalence of Metabolic Syndrome in Patients With Gout



Choi HK, et al. Arthritis Rheum 2007, 57: 109-115

INCREASED GOUT PREVALENCE AND GOUT CLINICAL COMPLEXITY OVER THE LAST 20 YEARS:

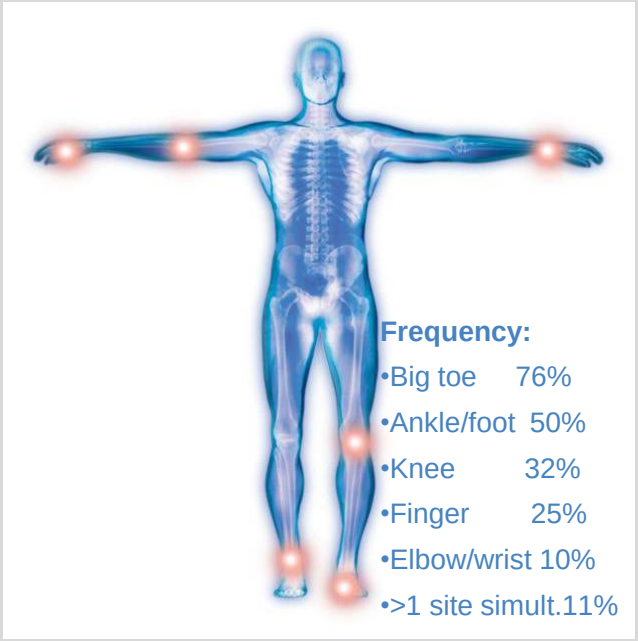
- **INCREASED LONGEVITY**
- **MORE HYPERTENSION**
- ***IATROGENESIS*: DIURETICS, ASA**
- **DIETARY TRENDS**
- **MORE OBESITY**
- **MORE METABOLIC SYNDROME, DM**
- **DEMOGRAPHIC TRENDS**
- **BETTER CAD, CHF, DM SURVIVAL**
- **INCREASED ESRD**
- **LIMITED NEW THERAPIES**

Presentation of Gout: Acute Flares

Common Characteristics

- Acute inflammation with rapid development of intense pain and tenderness, swelling, and with overlying shiny erythema
- Monoarticular ~90% of first attacks
- Podagra ~50% of first attacks
- Frequently involving lower extremities
- Often occurring at night
- As disease progresses, attacks occur more frequently and can become polyarticular and chronic

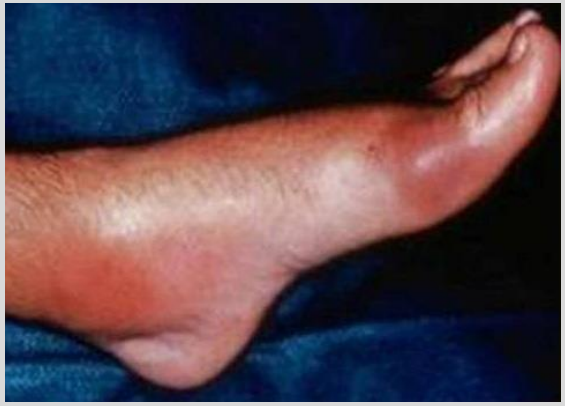
Common Sites



Mandell BF. *Cleve Clin J Med*. 2008;75:S5-S8.
Gibson T. In *Rheumatology*. 4th ed. Mosby Elsevier limited 2008:1829-1837

Acute Flares Often Become Recurrent as Gout Progresses

- Recurrence rates for flares
  - 60% within 1 year
  - 78% within 2 years
  - 84% within 3 years
- Some patients will develop severe tophaceous gout (mean 11.6 years)

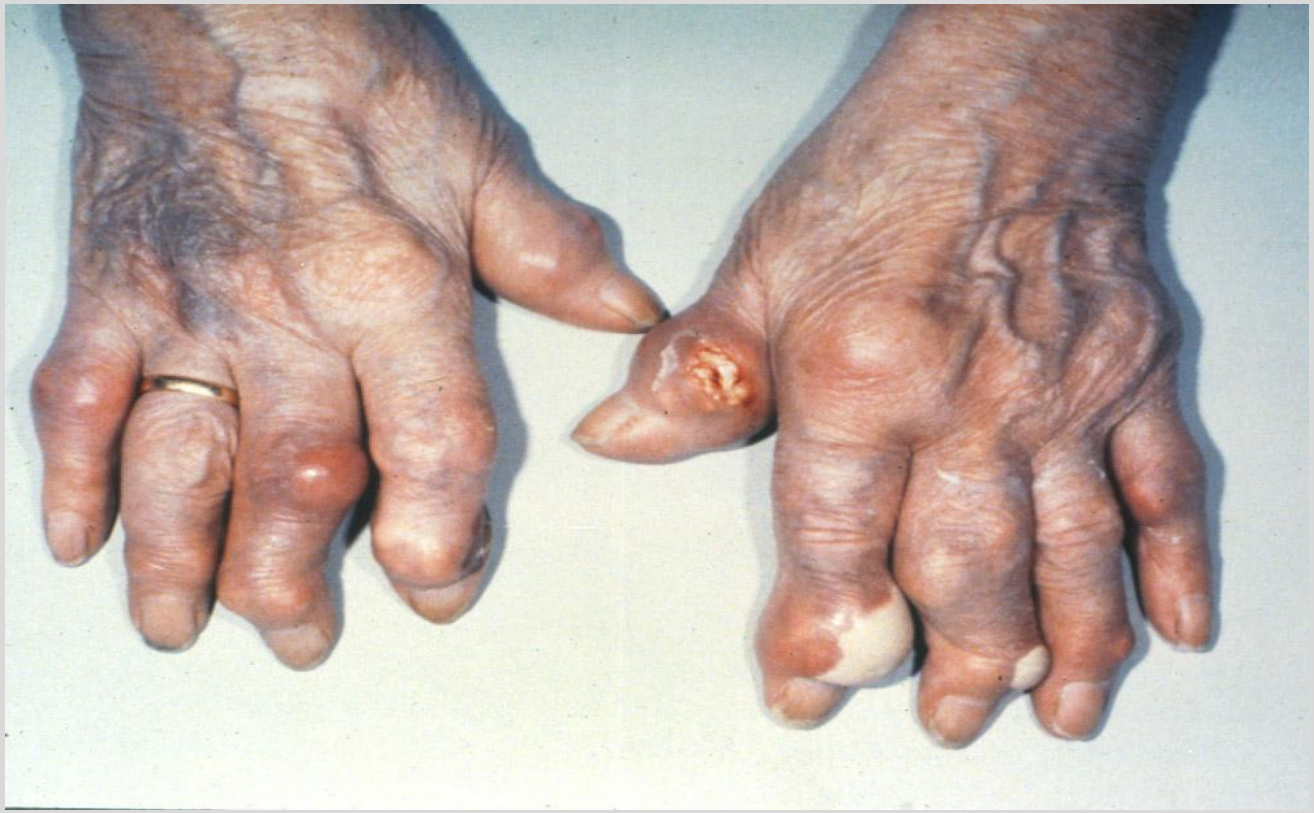


Podagra and acute Ankle synovitis

Courtesy of the American College of Rheumatology, Slide Collection on the Rheumatic Diseases, 1998.

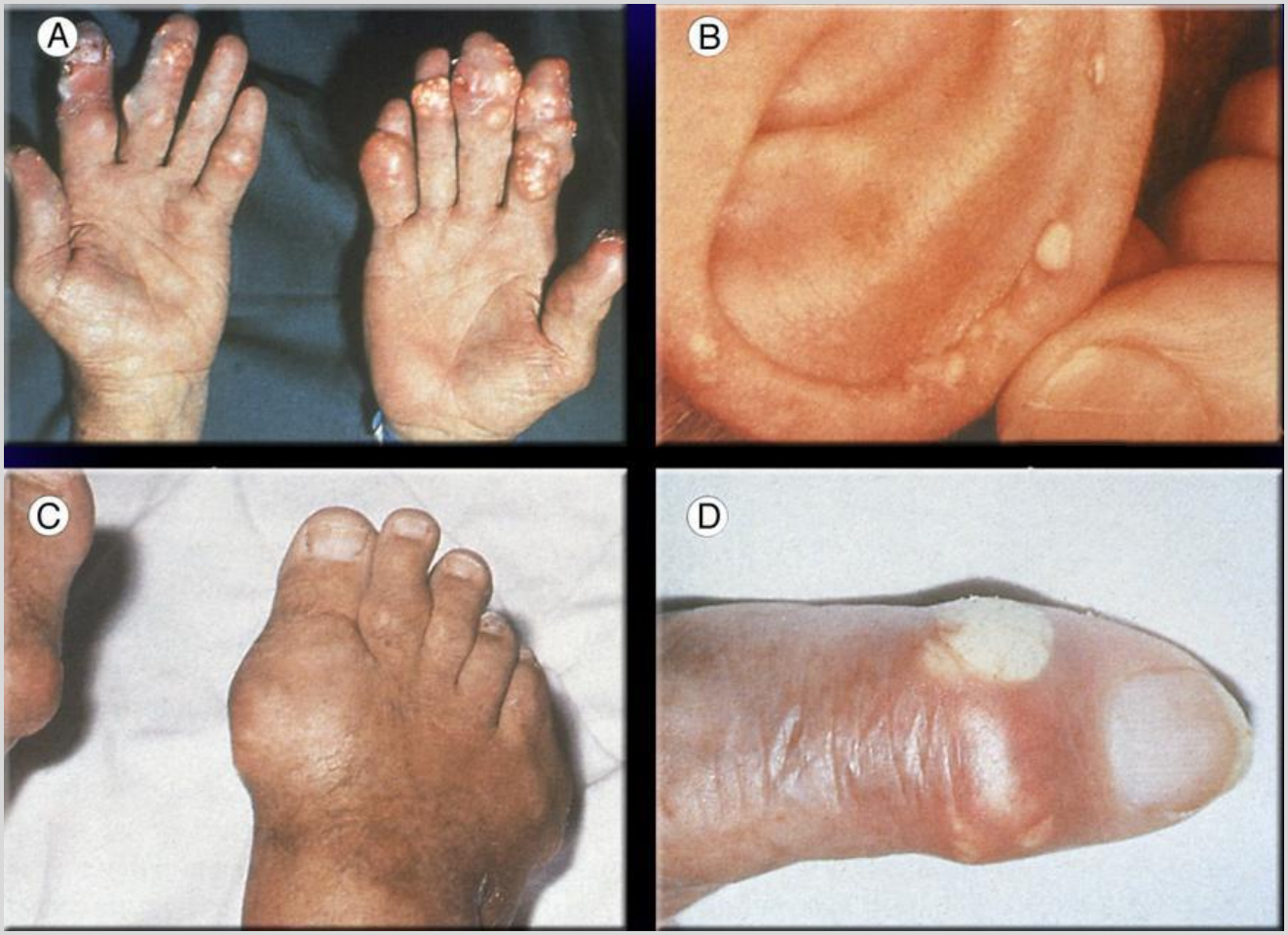
Mandell BF. *Cleve Clin J Med*. 2008;75:S5-S8.

Tophaceous Gout Hands



With Permission: Dr. M. Starr

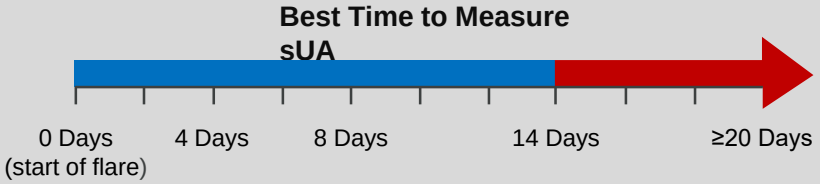
Tophaceous Gout



Kelley's Textbook of Rheumatology

sUA Levels as a Diagnostic Marker

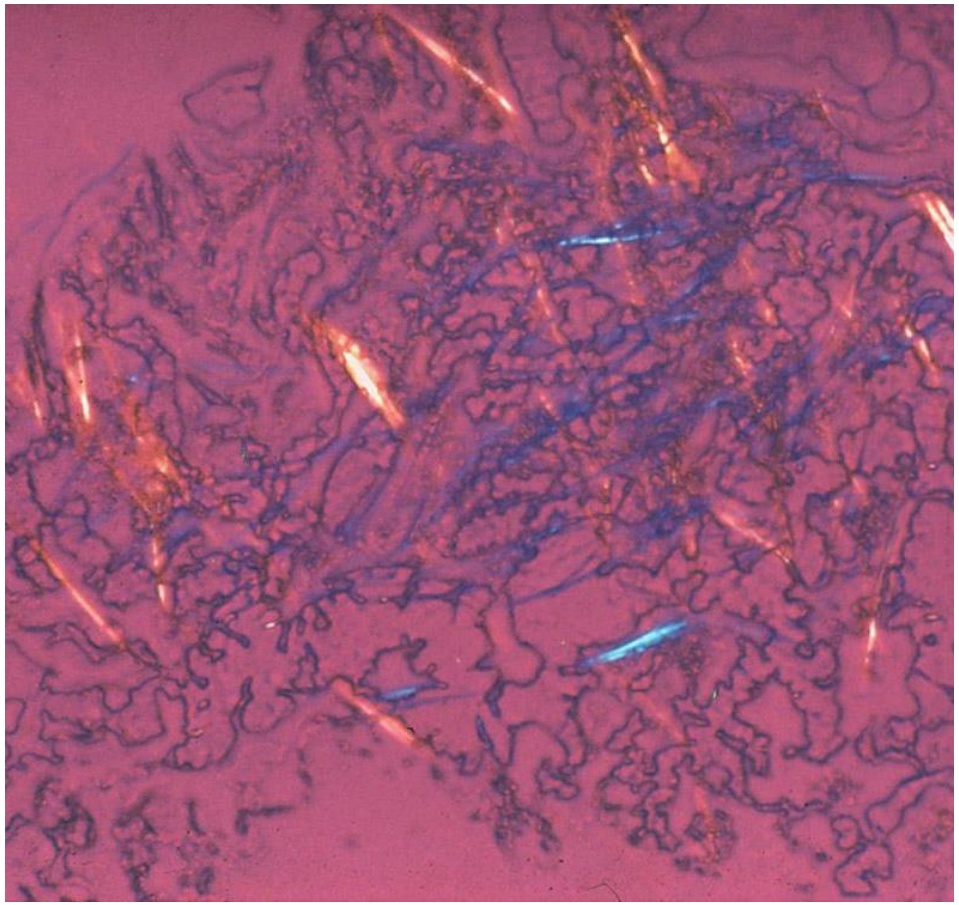
- sUA levels may be normal ~50% of the time during a flare
  - Normal sUA at the time of a flare does not rule out a gout diagnosis
- The best time to measure sUA is after a flare has resolved, which may take up to 2 weeks
- Laboratories often report hyperuricemia based on population norms
  - Population norms may be higher than biologically significant hyperuricemia (≥360 µmol/L)



Urano W. *et al. J Rheumatol*. 2002; 29:1950-3.

Zhang W. *et al*. *Ann Rheum Dis.* 2006; 65:1301-11.

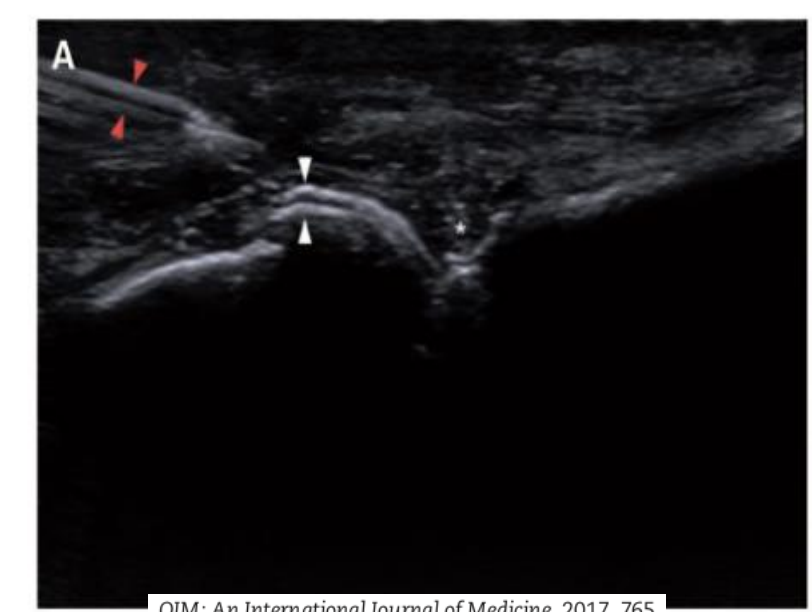
Crystal Identification on Polarizing Microscopy is the Gold Standard for Diagnosis of Gout



New: Ultrasound to Diagnose Gout

- Double contour sign and intrasynovial tophi have very good specificity
- Sensitivity depends on the severity of gout
- Not restricted to joints

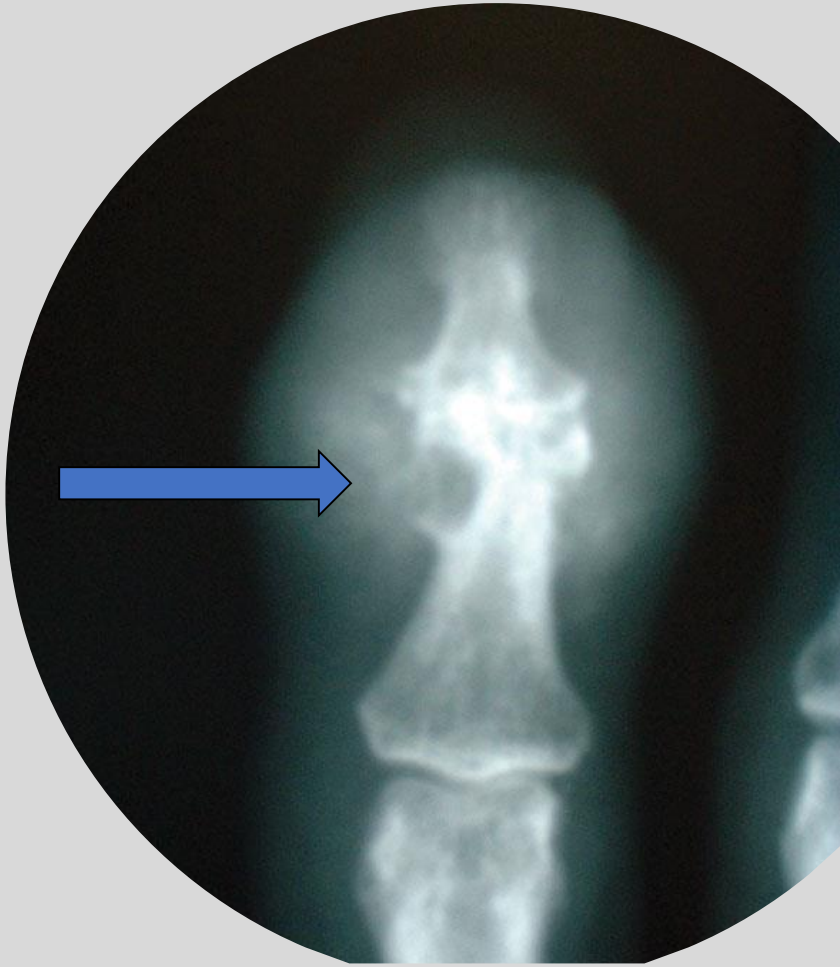
  Tendons are important



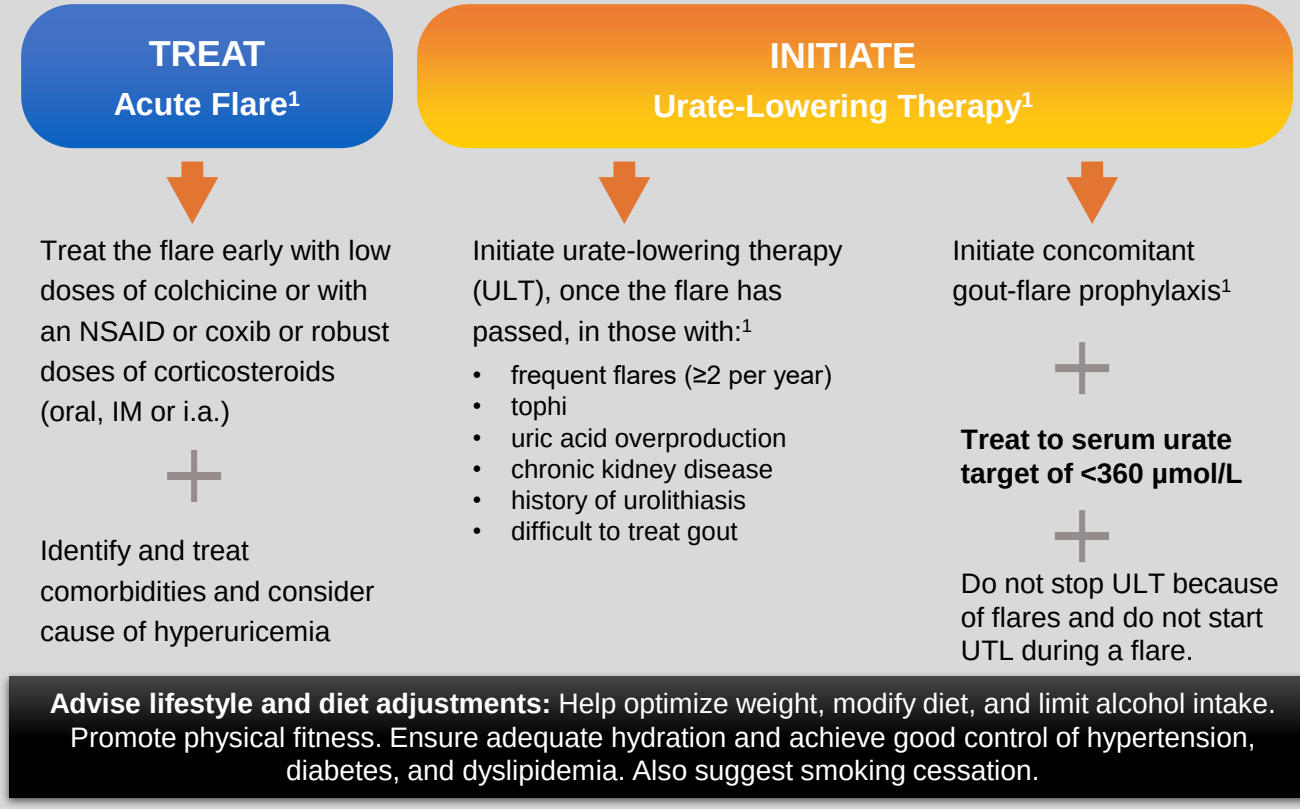
QJM: An International Journal of Medicine, 2017, 765

PREVENT THIS…..”Erosive” Gout

- Classic gouty erosion with “overhanging edge”



Gout Management Approach



1. Terkeltaub R, Edwards NL. Gout: Diagnosis and Management of Gouty Arthritis and Hyperuricemia. New York: Professional Communications Inc; 2010.

NSAID=Non-steroidal anti-inflammatory drugs; IM=intramuscular; i.a.=intra-articular

Treating to a Goal of <360 µmol/L[1]

- EULAR and ACR guidelines recommend maintaining sUA <360 µmol/L as the therapeutic goal of urate-lowering therapy.[1]

- Maintaining sUA <360 µmol/L can help promote the dissolution of crystals and prevent crystal formation[1]

- Periodically evaluate sUA in patients on therapy to ensure that the target level is achieved and maintained[2]

  - sUA levels should be monitored after an acute attack has subsided since it has been estimated that one third of patients have normal sUA levels during episodes of acute gout[3]

EULAR=European League Against Rheumatism; sUA=serum uric acid; ACR=American College Rheumatology

1. Zhang W, Doherty M, Bardin T, *et al*. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR standing committee for international clinical studies including therapeutics (ESCISIT). *Ann Rheum Dis* 2006;65(10):1312-1324.
2. Terkeltaub R, Edwards NL. Gout: Diagnosis and Management of Gouty Arthritis and Hyperuricemia. New York: Professional Communications Inc.; 2010.
3. Gibson T. Clinical features of gout. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, eds., *Rheumatology.* 3rd ed., Edinburgh: Mosby; 2003:1919-1928.
4. FitzgeraldJ, ACR 2020 Guidelines Gout Management, Arth Care Res, June 2020;1-17

Colchicine Dosing Guidelines for Acute Gout

- Colchicine tolerance depends on dosage, renal/liver function and drug interactions

- Terkeltaub (*Arthritis Rheum* 2010)

  RCT comparing 2 dosages *given early* (<12h)

  180 patients

  - 1.8 mg/d (1.2 mg, then 0.6 1h after) is as efficient and better tolerated than 4.8 mg/d (1.2 mg + 0.6 mg/h x 6)

Acute treatment Gout (cont'd):

- **Corticosteriods (PO,IM,IV)**
  - Patients who cannot tolerate NSAIDs, or failed NSAID/colchicine therapy
  - Daily doses of prednisone 20-50mg a day for 3-5 days then taper 1 week
  - Improvement usually seen in 12-24hr
- **ACTH**
  - Peripheral anti-inflammatory effects and induction of adrenal glucocorticoid release
  - 40-80IU IM followed by second dose if necessary
- **Intra-articular injection with steroids**
  - Beneficial in patient with one or two large joints affected
  - Good option for elderly patient with renal or PUD or other illness
  - Triamcinolone 10-40mg or Methylprednisolone 10-40 mg

- **<u>New</u>: Anti IL-1B sc (canakinumab)**
  Expensive, sc drug

Lifestyle Modification

Limit	Limit	Limit	Limit	Encourage
High fructose corn syrup (sweetened drinks)	Dietary purines- red meats, organ meats, seafood (sardines, anchovies, shellfish)	Even some veggies - asparagus, mushrooms, cauliflower, green peas	Alcohol consumption (beer especially)	Weight loss

Prophylaxis: Indications for urate lowering treatment (ULT)

- Frequent gout attacks 2-3x/year
- Urate overproducers (occurs in 10% of cases)
- Renal stones, urate nephropathy, CKD (after only 1 attack)
- Pre-chemotherapy
- Tophi development
- Erosive and destructive arthritis
- Uric acid > 540 ug/L (Japanese guidelines), but otherwise don't treat asymptomatic hyperuricemia

Fitzgerald J, ACR 2020 Guidelines Gout Management; Arth Care Res, June 2020;1-17

Prophylaxis: Urate Lowering Drugs

Goal is for serum urate concentration to 360 ug/dL or less

Start of therapy can precipitate acute attack; therefore, use colchicine 0.6 mg/day as long as six months

→Xanthine oxidase inhibitors (allopurinol and febuxostat)

- **Allopurinol**:
- Blocks conversion of xanthine to uric acid. Works for underexcretors and overproducers.
- Start typically 100 mg/day and titrate up 100mg until optimal urate levels achieved.
- Start even lower doses with renally impaired patients, rare hypersensitivity reactions (east Asia)
- **Febuxostat**:
- Fixed dose of 80 mg/day, can use in renally impaired, less hypersensitivity, increase MI (FDA black box)

→Uricosuric drugs

- **Probenecid** :
- increase renal clearance of uric acid by inhibiting renal transporters(URAT-1), blocks reabsorption
- Don’t use in overproducers (measure 24 hr urine uric acid) or if renal stones

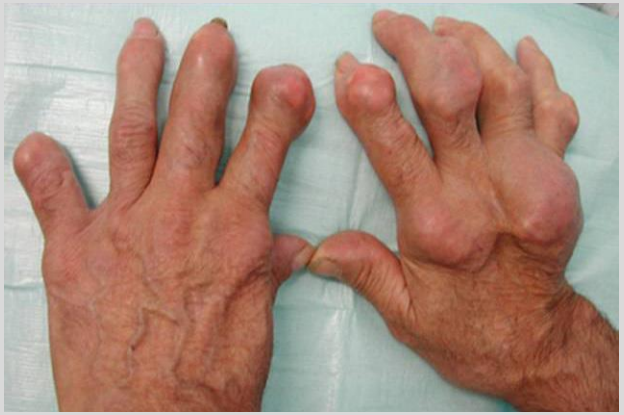
Newer Therapies: Gout

- **Lesinurad (Zurampic)**

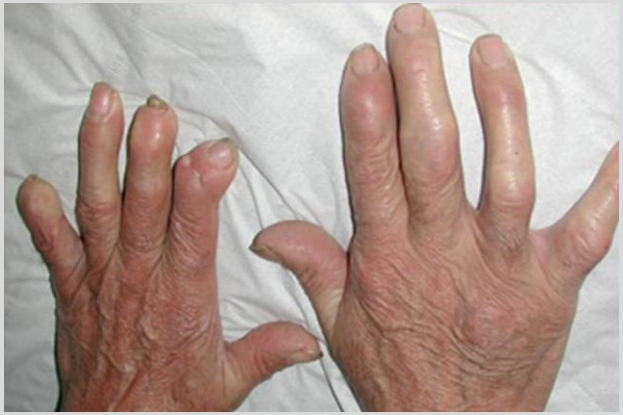
  - approved as add on to allopurinol. Prevents UA reabsorption by kidney- inhibits URAT-1 enzyme

- **Uricase iv (pegloticase, Krystexxa)**
  - Enzyme that oxidizes uric acid to a more soluble form
  - Severe refractory cases, resolution of tophi, expensive, iv drug q2 wks, immunogenicity issues,
- **Losartan**
  - ARB given as 50mg/dL can be uricosuric.
- **Fenofibrate**
  - Studies note when used in combo with Allopurinol produced additional lowering of serum urate

Benefits of Long-Term Urate-Lowering Therapy



Before Urate-Lowering Therapy
22 years with gout



After Urate-Lowering Therapy
1 year with sUA <240 µmol/L

Pearls for Successful Gout Management

- Encourage lifestyle modification- diet, alcohol, weight loss

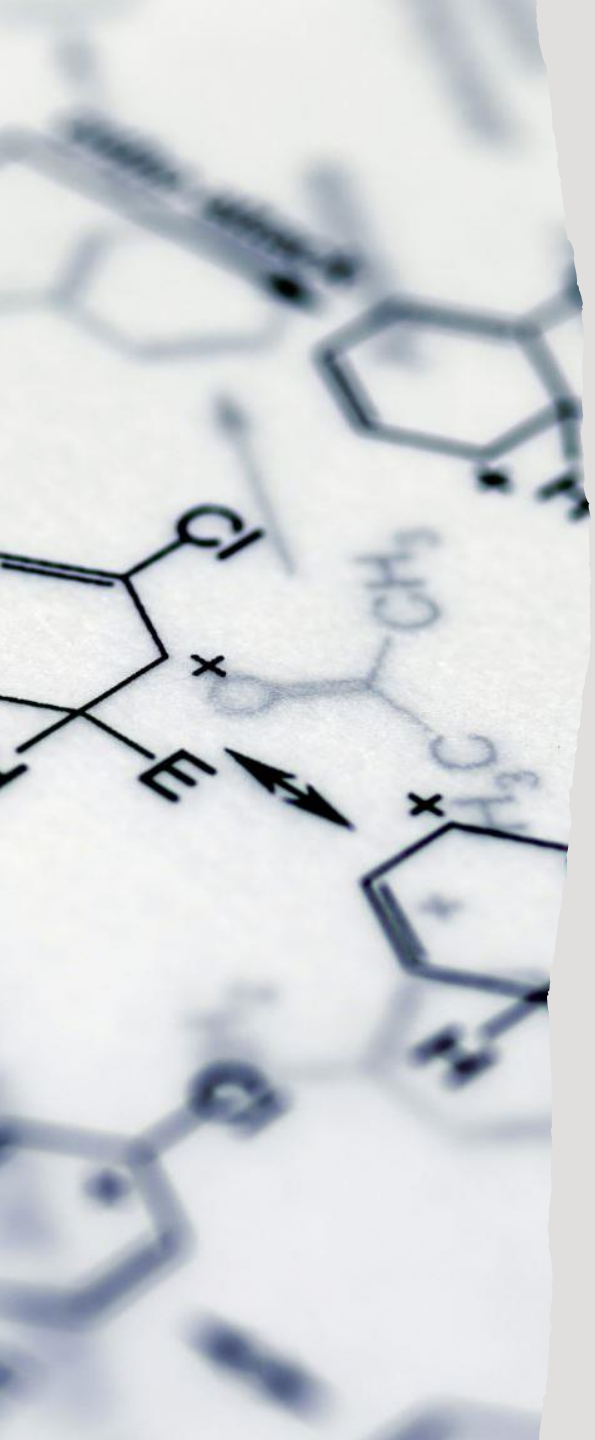
- For Acute Gout:

- NSAIDS, Colchicine , Corticosteroids – load upfront, taper over 5-7 days
- Continue 24-48 hrs after attack subsides

- For ULT:

Initiate urate lowering therapy in patients to reduce gout flares, tophi, and complications (erosion, cvs, renal)

- Allopurinol is drug of choice
- Always add colchicine for 3-6 months
- Start allopurinol low dose (usually 100 mg) and increase to reach target <360
- Don’t stop allopurinol during an attack
- Don’t increase allopurinol during a breakthrough attack
- Poor compliance is #1 reason for failure



- Calcium Pyrophosphate Deposition Disease (CPPD)

Calcium Pyrophosphate Deposition Disease (CPPD): Clinical Presentations

- Pseudogout- usually acute monoarthritis
  - frequent attacks after surgery, trauma
  - knee most commonly involved, then wrist
- Pseudo-rheumatoid arthritis
- Pseudo-osteoarthritis
- Pseudo-neuropathic joint

CPPD: Associated Diseases

- Definitely Associated
  - Hemochromatosis
  - Hyperparathyroidism
  - Hypophosphatemia
  - Hypomagnesemia
  - Wilson’s disease
- Possibly Associated
  - Hypothyroidism
  - Gout
  - Ochronosis

Think about it when you see OA in atypical joints not usually associated with primary OA (ex: shoulder, ankle, MCP’s) !

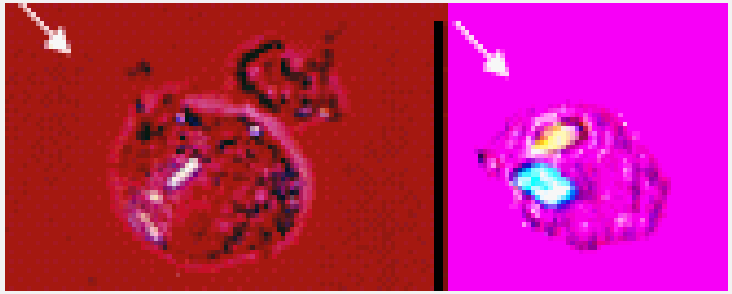
CPPD: Diagnosis

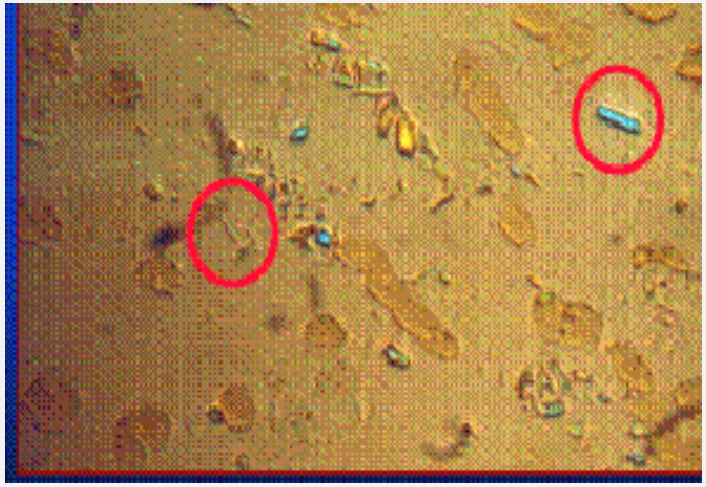
- Observation of calcium pyrophosphate crystals in synovial fluid leukocytes

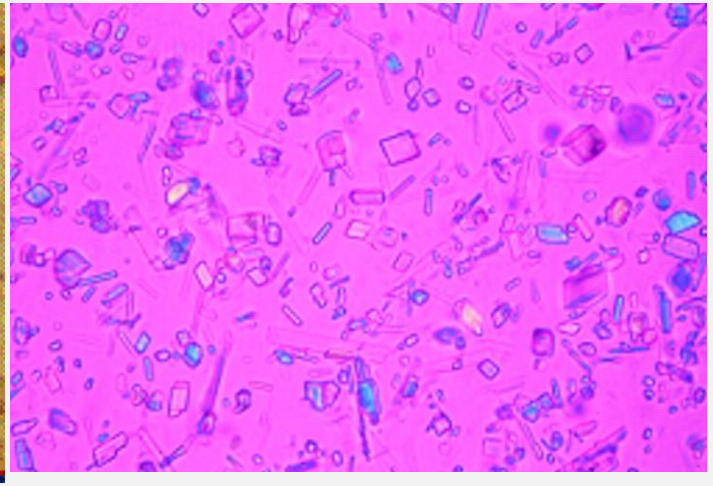
- CPPD crystals are
  - Rhomboid, or rod like
  - positively birefringent

  - (Gout crystals are needle shaped, negatively birefringent)

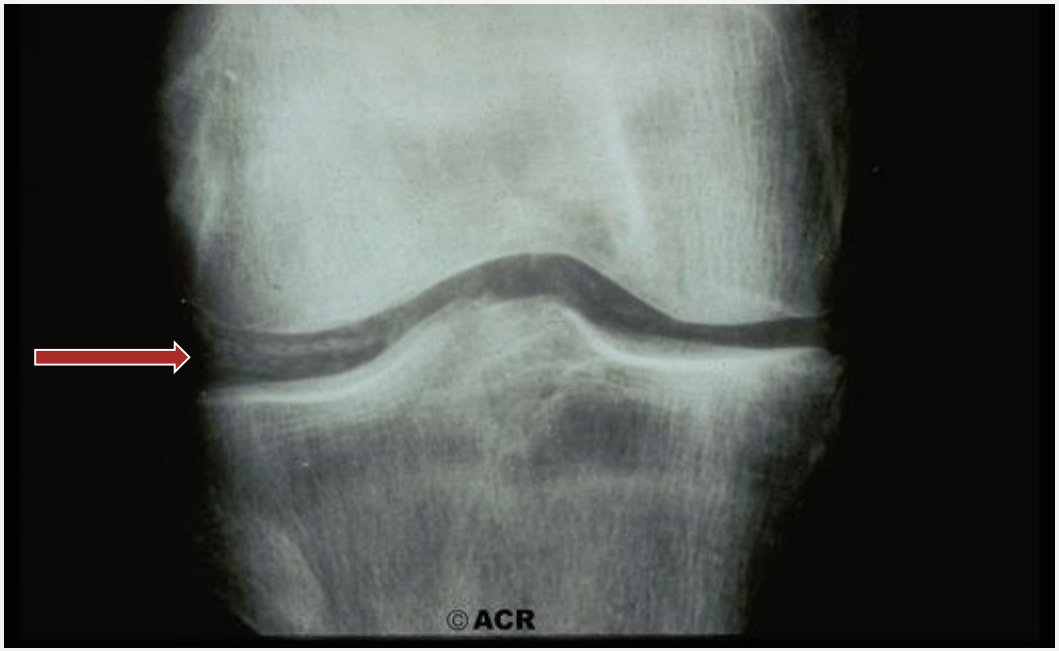
CPPD Crystals on Polarizing Microscopy



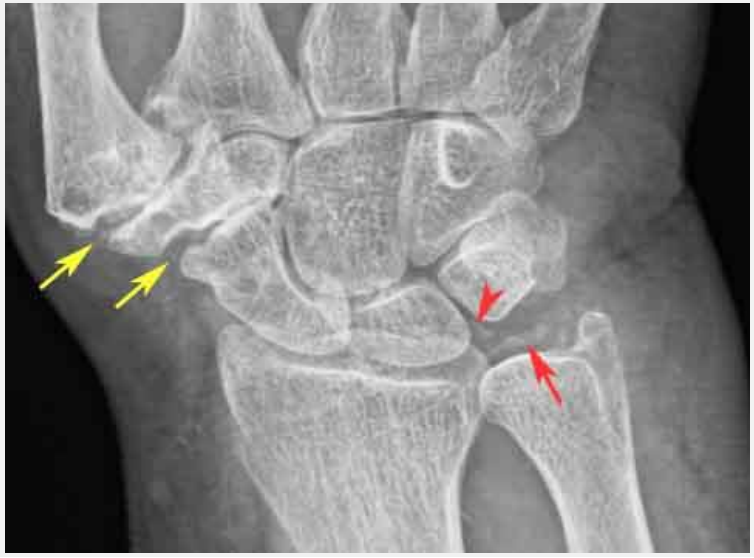




Chondrocalcinosis- Knee



Chondrocalcinosis: Wrist



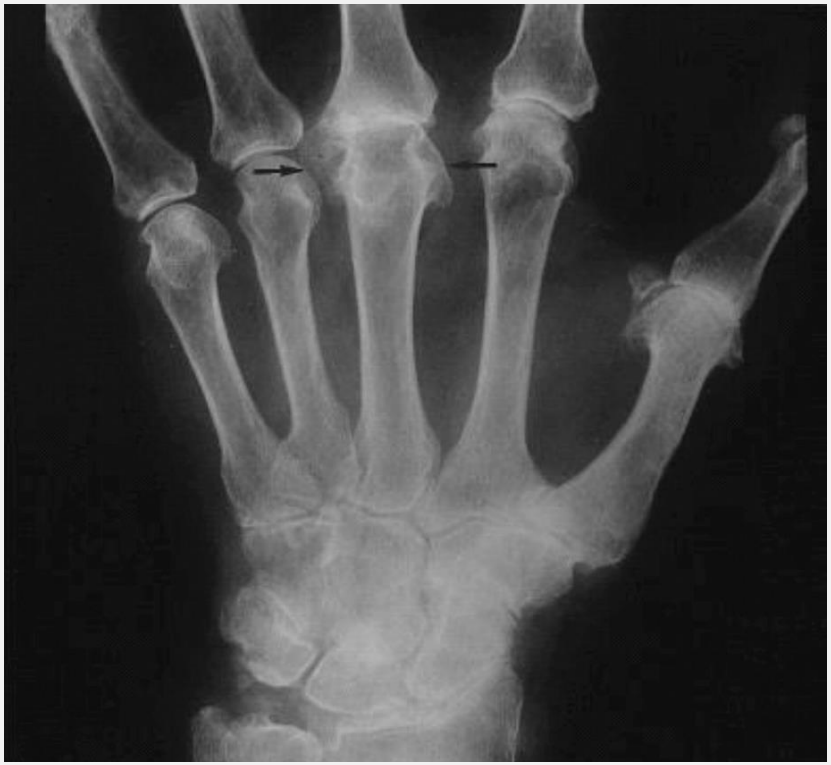
- *Fig.* Frontal radiograph of the wrist shows calcifications of the lunotriquetral ligament (arrowhead) and triangular fibrocartilage (red arrow). Joint space narrowing with sclerosis of the trapezioscaphoid and carpometacarpal joints (yellow arrows) are noted. Note absence of osteophytes.

  This patient presents with classic radiographic features of CPPD, which include:

- Chondrocalcinosis
- Degenerative change without apparent osteophytosis

CPPD Arthropathy Mimicking RA

- Diagnosis?
- Hemochromatosis



CPPD: Treatment Principles

- No definitive therapy for treatment of chronic CPPD
  - -- Colchicine – little data
  - -- MTX- 1 small study
  - -- Tx underlying disease- ? influences outcome

- Goals in managing acute attacks
  - reduce symptoms
  - identify and treat any associated or triggering illnesses
  - encourage mobility as inflammation subsides

CPPD: Treatment Options

- Joint aspiration
- NSAIDs
- Colchicine (not as effective as for gout)
- Steroids
  - oral
  - intra-articular
- Analgesics
- Surgery if necessary to preserve function

Take Away Points: Pseudogout

- Common crystal induced arthropathy , increases with ageing
- Great mimicker- can look like Gout, RA, OA, neuropathic joint
- Metabolic screening
  - For patients with:
    - Early-onset CPPD deposition; <55yrs
    - Florid polyarticular chondrocalcinosis
    - Frequent acute attacks without chronic arthropathy
    - Additional clinical/ radiographic features of predisposing disease
  - Tests to send:
    - Calcium, Alkaline phosphatase, Magnesium, Phosphate, Ferritin, Iron sat., LFT's

Thank You!