Gout

Definition and Overview

13th century beliefs  evil humour drop in the joint

nowadays science  Crystals blood ultra filtrate

Gout: 2 words hyperuricemia - inflammation
inflammatory disease due to hyperuricemia

Hyperuricemia ⟶ Inflammation ↓ Manifestations

- Hyperuricemic patients ⟶ small portion only develop Gout

> don't treat As. hyperuricemia
> but ~~control~~ life-style modification is required to ↓ risk

⟶ multiple steps
⟶ each step is influenced by multiple factors

OC

Hyperuricemia ↑uric acid serum ① ⟶ Crystal formation extra ¢ ② ⟶ Crystal deposition joint Kidney other ③ ⟶ Inflammatory reaction intra ¢ ✕ ④ ↓ Manifestations

Gouty arthritis (A)
Tophi (C)
Gouty nephropathy
Uric nephrolithiasis

* Hyperuricemia : ↑ serum uric acid [ ] > 6,8 mg/dl
exceeding it's threshould of solubility

→ Uric acid : end product of purines metabolism in humans
- Adenine
- Guanine

mid-CUT pyrimidines → 😐 😟 1 cycle
purely GA thered purines → 🙂 🙂 2 cycles

Humans	other species
Uricase ⊖, Gene is present but inactive	Uricase ⊕
uric acid → allantoin	
less soluble	less soluble → more soluble
but powerful antioxidant free radical scavenger	

Why do we - as clinicians - need these boring details?
Give me the clinical presentation and management strategy and go away !

Later on we will see :
- how goty attack triggers are related to purines
Adenine is a purine ATP is every where.
excessive ATP degradation → ↑purine catabolism → ↑uric acid
- Uricases are a therapeutic class in medication used in Gout.

Uricemia coming from purines
no uricase.

Hyper is due to a disorder in uric acid metabolism → metabolic
→ overproduction
→ under excretion
or both

They will be discussed later

P nitrogenous bases 2 rings

Gout

Prevalence >40y

Man - Toe (+ ankle, feet, knees)
Night - Sudden onset
Severe pain
Toe: red, swollen, tender = a toe with infection
Fever

Nicotinic acid
Binge drinking of alcohol } can precipitate acute gouty attack
Thiazides

Dg test: Best 1st → Arthrocentesis
Most accurate → Polarized light examination
negatively birefringent needle

⊖ birefr. needles

⊖ birefringence: horizontal and vertical have different colors

Pseudogout → Positive birefringent
Gout → negative

Presentation: Man, big toe inflammation, sudden onset at night
Dg test: arthrocentesis with fluid examination on polarized light
Work up of the patient:

Arthrocentesis: joint fluid examination
- Crystals ↑
- Cell count: WBC 2000 - 50 000 PMN ++
- Culture
- Protein level: don't really help

PE: extremity examination for tophi

ESR ↑, CBC (↑WBC)

Uric acid levels: may be normal or low during the attack.

X-Ray of the toe → early normal
→ late bone erosion

Trt: Gouty attack

NSAIDs
Best initial
CI: renal insufficiency

Steroids
NSAID, insufficient response
Contraindication
N^ve of joints involved
↑ → inj
X → PO or IV

Colchicine
first 24 h
you can't use both NSAIDs and steroids
Side effects: nausea diarrhea bone marrow suppression

Prevention of further gouty attacks

Diet	Xanthine oxidase inhibitors	Uricase ↓	↑ excretion
Weight loss ↙ water X alcohol X Soda X high purine food	① Allopurinol ② Febuxostat	③ Rasburicase Pegloticase	Probenecid Sulfinpyrazone

Stop thiazides, aspirin, niacin. Use losartan first for HTN

1 - Allopurinol treatment of choice
2 - Febuxostat if the patient doesn't tolerate allopurinol
3 - Uricase : if Allopurinol / Febuxostat are not enough
4 - Probenecid and sulfinpyrazone are rarely used for gout.

renal insuffisancy → ↙ excretion u.a ——→ gout ——→ Probenecid → ↑ excretion but this ↑ excretion in renal insuffisancy is CI

Lesinurad : blocks absorption of u.a in kidney tubules

Lesinurad + xanthine oxidase inhibitors

Do not start Allopurinol during an acute attack

if the patient is already on it you can continue it.

CPDD : Calcium Pyrophosphate Deposition Disease (Pseudogout)

Presentation
Joint : knee, wrist not the toes
Slower onset
Less important pain

Calcium disturbance profile : hemochromatosis
hyperparathyroidism
hypothyroidism
Acromegaly

Dg test : Tap the joint → examination → polarized light
Positive birefringent rhomboid shaped crystals

Trt NSAID, or steroids for acute management
Colchicine is not as effective

Chronic gout

Tophi : urate crystals deposition in tissues + foreign body reaction

* cartilage
* bone
* subcutaneous tissues
* kidneys

they take years to develop
can occur anywhere in the body

Chronic management

Stop thiazides, aspirin, niacin
Use Losartan first for HTN → it ↓ uric acid

Renal insufficiency CI : NSAIDs
Probenecid
Sulfinpyrazone.

Adverse effects with chronic trt

Allopurinol + Uricases : Hypersensitivity → rash
hemolysis
allergic interstitial nephritis

Allopurinol → Toxic epidermal necrosis

Colchicine → Bone marrow suppression
Nausea and Diarrhea

CPPD: Chondrocalcinose

Chondro - calcinose
cartilage ↓ calcium

Joint: large joints (knee)
Articular cartilage

Calcium containing salts deposition

Arthrocentesis : ⊕ birref. rhomboid shaped crystals ← most accurate
WBC 2000 - 50 000

x Rays : calcification of the cartilaginous structures of joints

~~Acid~~
Uric acid is normal
amp

Trt ① NSAID,
② Steroids : triamcinolone
③ Colchicine : prevention of subsequent attacks.

↑uricemia
- joints → Gout
- kidney → Urate nephropathy
  - uric acid nephropathy
  - uric acid nephro lithiasis

Gout: Joint inflammatory disease ✗ rope

Gout and Pseudogout

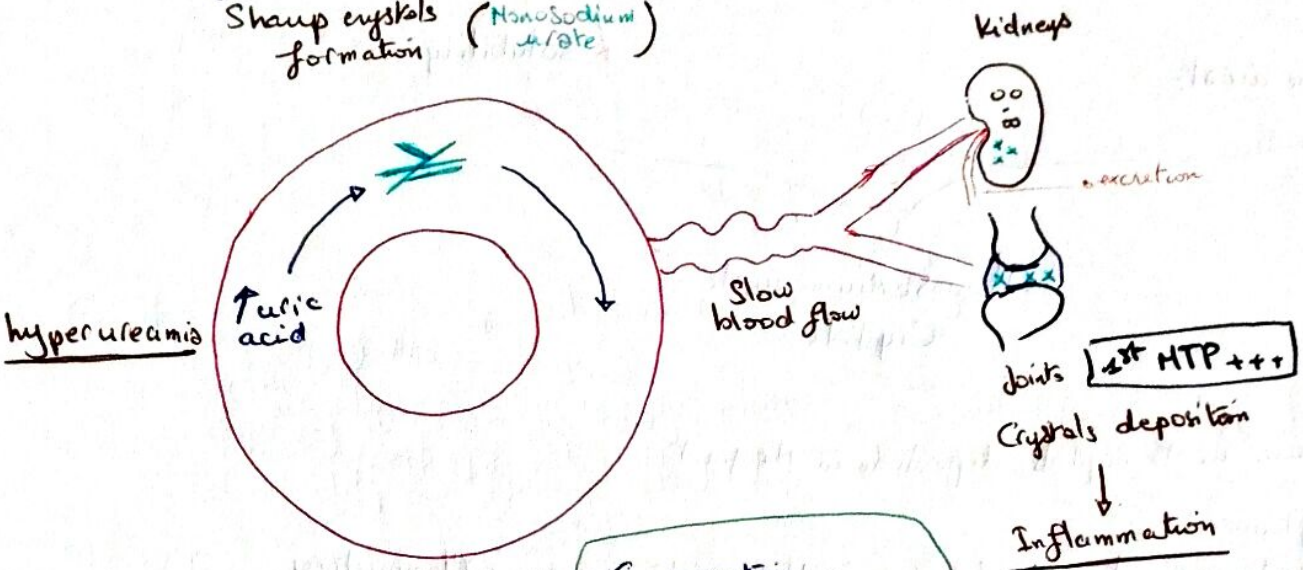
Gout: latin gutta = drop

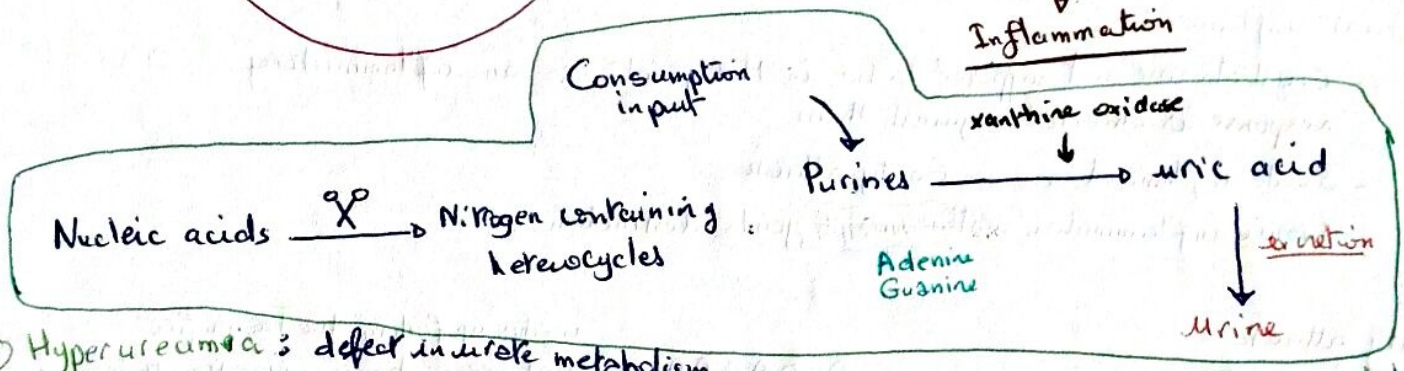
evil humor drop in the joint : 13th century thought

- Crystals
- blood ultrafiltrate (synovial fluid) in the joint : Nowadays

Gout: Inflammatory disease due to hyperuricemia

Sharp crystals formation (MonoSodium urate)





① Hyperuremia : defect in urate metabolism

Purines

↑ Consumption
- Red meat
- Organ meat
- Shellfish
- Anchovies

↗ Production
- ↑ Fructose
  - Corn syrup beverages
- ↑ Turn-over of cells
  - Chemotherapy and
  - Radiotherapy
  - Hemolysis

Uric acid

↙ clearance.
- Dehydratation
  - not enough water
  - alcohol consumption

Medications : Thiazides diuretics, Aspirin
Chronic kidney disease
Ketoacidosis Lactic acidosis

- Genetic predisposition
- Obesity and Diabetes (maybe the blood flow ?)

② Crystals formation

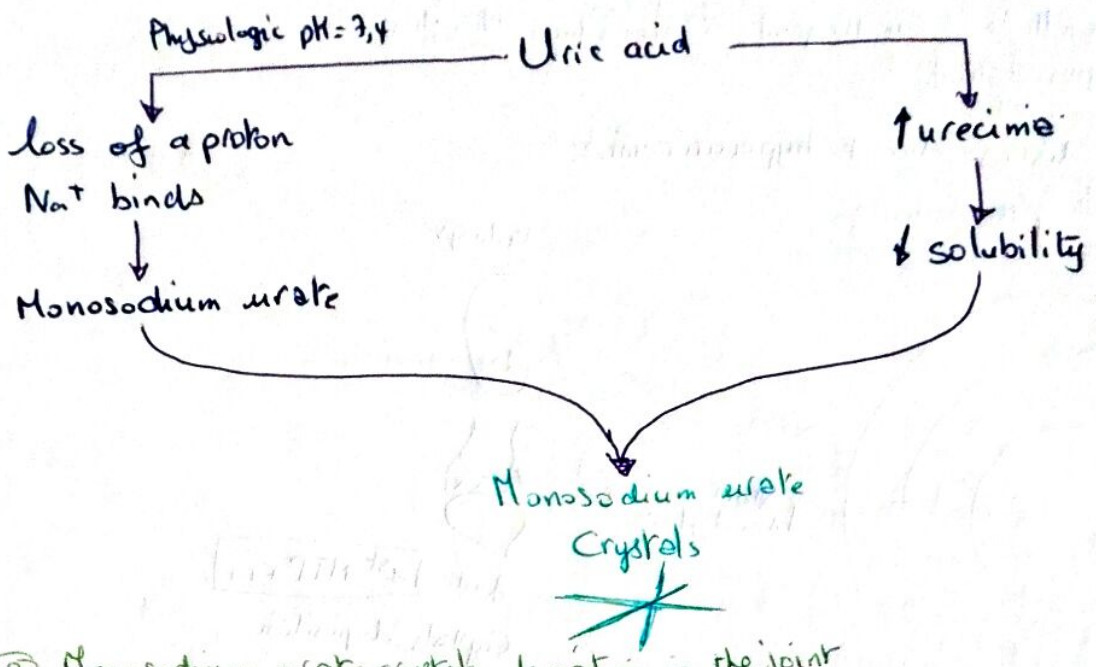
Uric acid has limited solubility in body fluids

Hyperuremia : uric acid level > its rate of solubility

At physiologic pH = 7,4 : uric acid looses a proton and binds to an Na^+ ion

Crystal formation

Physiologic pH = 7,4, uric acid looses a proton
Na^+ binds to uric acid
↑ uric acid → ↓ solubility
} ⇒ crystal formation



(03) Monosodium urate crystals deposition in the joint

(04) Joint inflammation
- crystals are not supposed to be in the joints so an inflammatory response is directed against them
- acute inflammation → Gouty attack
- chronic inflammation will lead to joints destruction

Gouty attack
Joint: 1st MTP of big toe → PODAGRA — wakes up feeling the Toe on fire, most severe hours after the attack, can last several days. weeks
Ankle, Knee
Wrist, Elbow

Repeated Gouty attacks → chronic gout — Tophi
Arthritis
Tissue destruction
↑ risk of [kidney stones : crystals in tubules
urate nephropathy : crystals in the interstitium

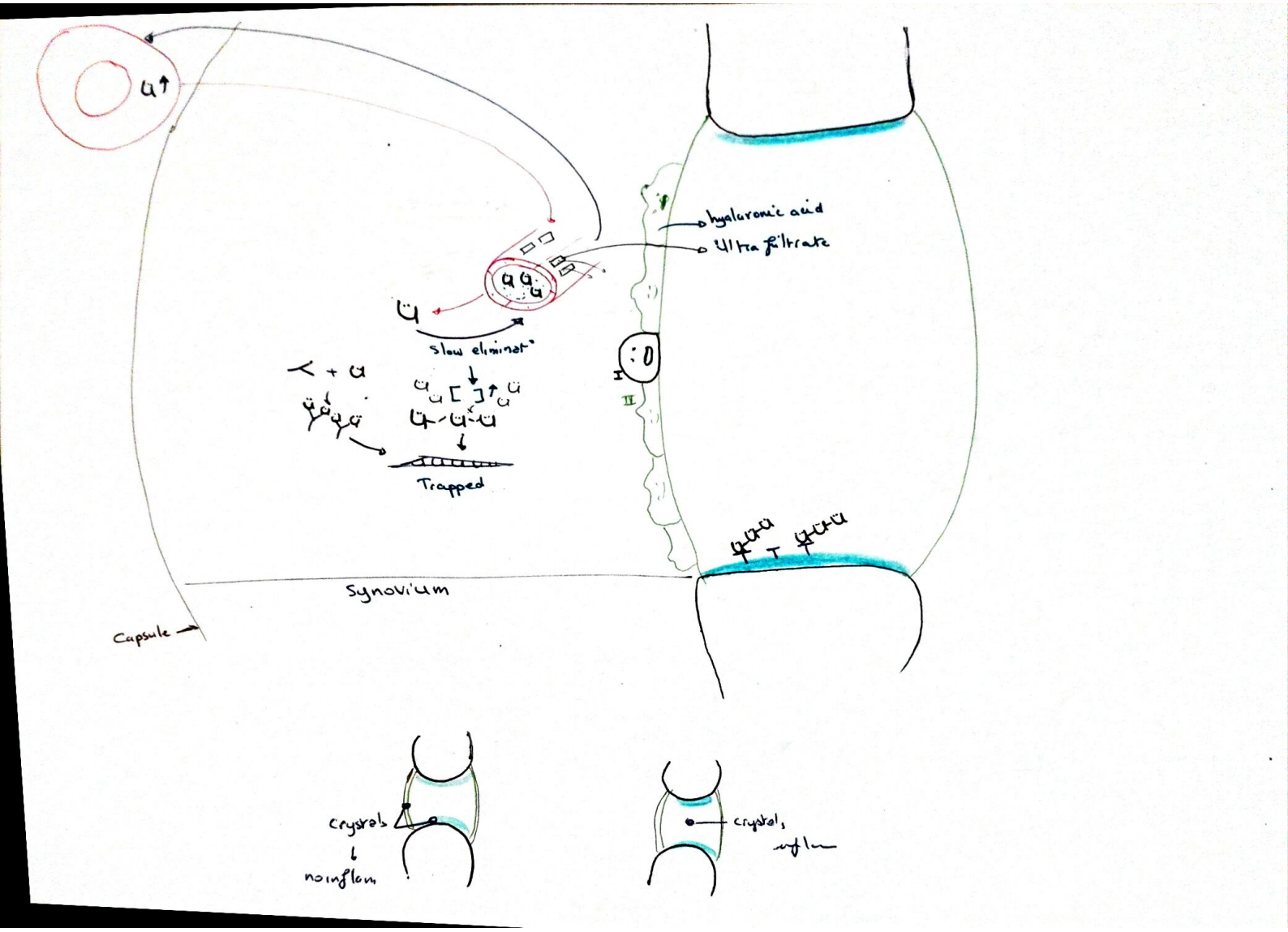
Treatment

↓ pain and swelling
NSAIDs
Corticosteroids
Colchicine : ↓ WBC migrat°

Underlying cause
Diet
Hydratation
Stay active (blood flow)

↓ uric acid
↓ production — Allopurinol
↑ excretion — probenecid

Allopurinol → xanthine oxydase inhibitor


hyaluronic acid
Ultra filtrate
slow elimination
Trapped
Synovium
Capsule

crystals
↓
no inflam
crystals,
inflam

Gout

Most common cause of inflammatory arthritis in ♂ > 40y
Should not occur in premenopaused ♀
Hyperuricemia and Gout are strongly associated with obesity
Dietry and lifestyle modification are recommended for management

01. What is gout? How was the name derived?

Gout from latin gutta = drop
13th century thoughts: Gout resulted from an evil humor drop is a vulnerable joint.

Gout:

hyperuricemia: MSU supersaturation of extra ↓ fluids

↓

MSU crystals

↓

Tissue deposition ⟶ inflammation

- Goty arthritis
- Tophi
- Gouty nephropathy

→ Uric acid nephrolithiasis

Gout = inflammatory disease due to MSU crystals deposition in tissues as a result of hyperuricemia.
Manifestations: • Gouty arthritis • Tophi • Gouty nephropathy
• Uric acid nephrolithiasis

02. Defining hyperuricemia

Serum uric acid concentration > mg/dl
- 7.0 → ♂
- 6.0 → ♀

Factors (predictors) associated with hyperuricemia and gout:
- alcohol intake
- BMI

Serum uric acid [ ]:
- age and sex dependent
- ↑ in association with
  - onset of puberty → ♂
  - menopause → ♀
- Gout onset

Women >60y

Men 40-50y

if <25y → inherited defect in purine degradation pathway
alcoholism
renal insufficiency
- familial juvenile hyperuricemic nephropathy
- medullary cystic kidney disease

03- Prevalence / Epidemiology

↑age → ↑ serum uric acid [] → ↑ gout prevalence (↑ more oxydative stress ?)

Most common inflammatory arthritis in ♂ >40 y

Over the past 2 decades, the prevalence ↑ due to:

- diet
- metabolic sd, obesity
- medications

♂ to ♀ ratio 2:1 to 7:1

Hyperuricemia —15%→ Gout but it ↑ the risk

25% gouty patients have family hx of gout.

04- Uric acid is the product of the metabolism of which group of nucleotides ?

→ Purines (A and G)

Humans

Absence of uricase enzyme

Presence of uricase gene but it is inactive

Uric acid sparingly soluble
- → powerful antioxidant
- → free radical scavenger

↑ risk of crystal deposition

Other species

Presence of uricase

uric acid (sparingly soluble) —uricase→ allantoin highly soluble

Allantoin highly soluble

05- Hyperuricemia mechanisms

Overproduction
- → exogenous : dietary purine precursors
- → endogenous

Underexcretion → abnormal renal handling of urate

Combination of the (2)

06- What test determines if the patient is overproducer or undersecreter ?

24h urine collection
- → uric acid
- → creatinine (to ensure adequate 24h collection)

24h urine collection uric acide

Overproducer

>800 mg/24h

Undersecretion

<800 mg/24h

07- Two (2) inherited enzyme abn. → overproduction

1) Overactivity of PRPP synthetase : Phosphoribosyl Pyrophosphate

2) Partial deficiency of HGPRT Hypoxanthine Guanine Phosphoribosyl Transferase

X linked early onset <25y ♂ ↑ incidence of uric acid nephrolithiasis

08. Acquired causes of hyperuricemia:

Urate

Overproduction

↑ dietary purine consumption:

↑ hepatic ATP degradation
- alcohol abuse
- fructose ingestion

↑ nucleotides
- myeloproliferative
- lymphoproliferative disorders

Undersecretion

Renal disease

Lead nephropathy (saturnine gout)

Inhibition of tubular urate secretion
anion competetion (keto- and lactic acidosis)

Miscellaneous:
- hyper PTH
- hypo TH
- respiratory acidosis

09. Drugs → ↓ urate renal excret° → ↑ uricemia

CAN'T LEAP

Cyclosporine	Lasilix (furosemide and other loop diuretics)
Alcohol	Ethambutol
Nicotinic acid	Aspirin (low dose)
Thiazides	Pyrazinamid

10. Why excessive alcohol consumpt° → ↑ uricemia + gout

Alcohol consumption accelerate hepatic ATP degradation

1) ↑ Alcohol → ↑ degradation of hepatic ATP → ↑ purine (A) → ↑ uric acid production

2) Alcohol consumpt° → lactic acid production → ↓ uric acid excretion

Beer has the higher risk
Contains a substantial amount of the purine guanosine

11. The 4 stage of gouty arthritis

Asx hyperuricemia

1) Asx hyperuricemia

↑ serum uric acid [ ]
without:
- gouty arthritis
- tophi
- uric acid nephrolithiasis

15% will develop gout (art) after 20 years of Asx ↑ uric.

Acute gouty attack

2) Acute gouty arthritis

1st attack
- Single joint 85-90%
- Polyarticular 15%

Intercritical gout

3) Intercritial gout

Asx [ ] between gouty attacks.

2nd attack
- within 1-2 y → 60%
- never → 5-10%

Chronic tophaceous gout

4) Chronic tophaceous gout

MSU crystal deposition in:
- synovium
- subchondral bone
- [illegible]
- subcutaneous tissue

12. Acute attack of gout

Gout / PseudoGout

Crystal deposition in the joint → MSU → Gout
→ CPP → PseudoGout

↓

Inflammation (crystals are not supposed to be in synovial fluid)

WBC recrutement, inflamatory mediators release.

♂ > ♀ ; black > white 30-60 y

↳ Urate metabolism related to xanthine oxydase
↳ genetic ♯

May be mistaken with by cellulitis

Gout

Monosodium urate crystals deposition in the joint ⟶ inflamation

1st, big toe
also ankle
knee
PIP
DIP
may be Polyarticular

Hx:
Midaged → older man
Overweight
Alcohol
Diuretics

Sudden onset of
excruciating
monoarticular
joint pain
at night
waking him up
Big toe +++

Sx
Swelling
Erythema
Tenderness
Nodules in soft tissue
Fever if polyarticular

Dx
Monoarticular inflamat° → Arthrocenthesis

if he had previous Gouty attacks
the Dg of a new flare can be made clinically

Needle shapped crystals
Negatively birefringent:
when it's ↳V → red
↳H → blue.

Gout attack → do not order ~~to~~ serum uric acid

Acute care

↙ Pain: NSAIDs

Prevent further attacks:
allopurinol
colchicine : ↑GI effects
Febuxostat:

Repeated Gout attacks:
24h ~~acid~~ uric acid collection
underexcretor? → probenicid

Podagra Tophi
Big toe. s/t

PseudoGout

Calcium Pyrophosphate Dihydrate CPPD } crystals → in the joint → single → at°
Calcium oxelate
Calcium hydroxy hapatite

Hx

Older patient
Pre existing joint disease
Metabolic/electrolyte disorders:
- ↑ parathyroidism → ↑Ca blood
- hemochromatosis
- ↓ phosphatemia
- ↓ magnesemia

Sx

Presentation identical to gout
Most common joints: Knee
also: ankle
wrist
shoulder

Dx: Arthrocentesis.

Rectangular / Rhomboid shaped
⊕ Birefringent

Tx: 1st NSAIDs

Consider workup for underlying cause
Calcium level
PTH

Low dose Colchicine to prevent attacks

Chondrocalcinosis

Synovial fluid / Urine → ultra filtrates

Urine is also an ultra filtrate

Synovial fluid is ultra filtrate of the serum, it will reflect what one's have in the serum.