Gout

This lecture relied 100% on the textbooks (kumar and davidson) in covering the objectives alongside the doctor's notes.

Objectives :

- ★ Describe clinical presentation of gout
- ★ Identify drug & non-drug risk factors for gout
- ★ Compare treatment options for acute gout attacks
- ★ Describe options for control of hyperuricemia / prophylaxis of gout attacks

Editing file

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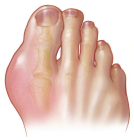
Gout النقرس



Gout

- Gout is an inflammatory-arthritis **associated with hyperuricemia** (it can occur if uric acid levels are normal) and reaction to intra-articular monosodium urate crystals

◀ Epidemiology

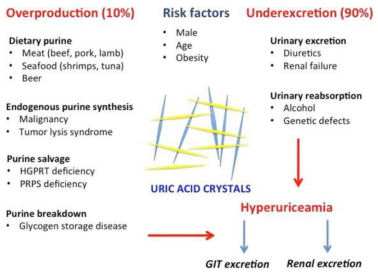
- Gout has become progressively more common over recent years in affluent societies due to the increased prevalence of **obesity and metabolic syndrome**
- Gouty arthritis in Saudi Arabia is not common, it's more common in Filipinos because of the genetic predisposition they have along with ethanol consumption.
- **Most common inflammatory arthritis in elderly:**
  - Increasing prevalence
  - Highest 75-85 y.o.
  - **Men** > women, (<65 y.o.) **90% of cases are found in men**
  - Postmenuposal women due to the loss of estrogen induced uricosuric effect (Estrogen promotes renal uric acid excretion, postmenopausal women have decreased estrogen levels and are thereforemore likely to develop gout)

i 24.41 Crystal-associated arthritis and deposition in connective tissue

Crystal	Associations
Common	
Monosodium urate monohydrate	Acute gout Chronic tophaceous gout
Calcium pyrophosphate dihydrate	Acute 'pseudogout' Chronic (pyrophosphate) arthropathy Chondrocalcinosis
Basic calcium phosphates	Calcific periarthritis Calcinosis
Uncommon	
Cholesterol	Chronic effusions in rheumatoid arthritis
Calcium oxalate	Acute arthritis in dialysis patients
Extrinsic crystals/ semi-crystalline particles:	
Synthetic crystals	Acute synovitis
Plant thorns/sea urchin spines	Chronic monoarthritis, tenosynovitis

◀ Risk Factors

- The risk of developing gout increases with **age** and with **serum uric acid (SUA) levels** (SUA levels are higher in men, increase with age and are positively associated with body weight)
- **Obesity & excessive weight gain** (especially in youth)
- High blood pressure, trauma and surgery



◀ Causes

Decreased Uric Acid excretion (under excretion) **Most common type 90%**	• **Abnormal kidney function (Renal failure)** Most common cause • Pre-renal azotemia (heart failure with renal failure) • Primary renal congenital or inherited diseases • Increased renal tubular reabsorption (usually genetic) • **Drugs: Thiazide** and loop diuretics, **Low-dose aspirin<1g/day?** , Cyclosporin, Niacin, Pyrazinamide & ethambutol Drugs associated with gout: **AS a Guy painfully walking THe NIce PYRamid LOOP trail:** aspirin, thiazides, niacin, pyrazinamide, loop diuretics • Lead toxicity • Hypertension • Lactic acidosis & Ketoacidosis • **Moderate to heavy alcohol intake (beer specially)** • **Postmenopause** Estrogen promotes renal uric acid excretion. Postmenopausal women have decreased estrogen levels and are therefore more likely to develop gout
Increased Uric Acid production (over production) **10%**	• High cell turnover: **Tumor lysis syndrome** "hypermetabolic state", chemotherapy, Hemolytic anemia, myeloproliferative and lymphoproliferative neoplasms, Psoriasis • Enzyme defects: **Lesch–Nyhan syndrome**[1], Phosphoribosyl pyrophosphate synthetase overactivity, von Gierke disease[2] • **High intake of Purine rich foods (Red meat)** (beef,pork,lamb), nutritional supplements, (Game, Offal , Seafood) • High fructose intake

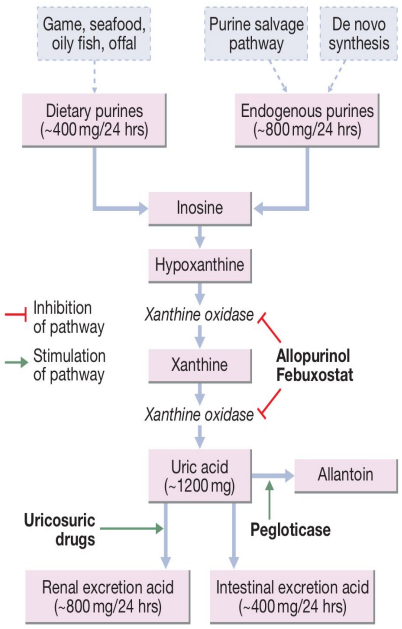
1-Lesch–Nyhan syndrome (HGPRT defciency) is an X-linked recessive form of gout that is also associated with mental retardation, self-mutilation and choreoathetosis. An **inherited cause** should be suspected if other clinical features are present or there is an **early age at onset with a positive family history**

2- A type of glycogen storage disorder caused by the def. of Glucose 6 phopshpate .

Gout النقرس

◄ Uric Acid Homeostasis:

- Urate is constantly near its limit of solubility, in a flux balance between production and elimination.
- Uric acid is the final product of endogenous and dietary purine metabolism in humans
- **Serum Uric Acid depends on the balance between** : purine synthesis, ingestion of dietary purines and the elimination of urate by the kidney (66%) and intestine (33%).
- **90% of people with gout have impaired excretion of uric acid** (10% have increased production due to high cell turnover and <1% due to an inborn error of metabolism).
- Renal excretion is coordinated by a group of secretory and reabsorptive **renal tubular urate transport molecules**, some of which are **targets of urate- lowering drugs.**



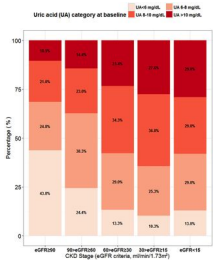
Production ⊕↑

- Breakdown of purines from nucleic acids
- Hypoxanthine converts to Xanthine which gets turned into uric acid by **Xanthine oxidase.**

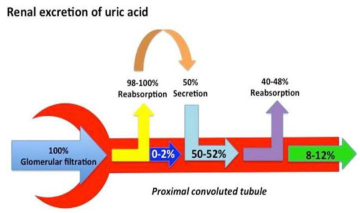
Elimination ⊖↓

Kidney - 10% of filtered load is excreted

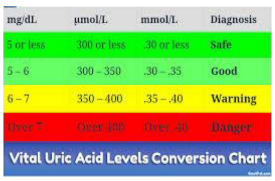
- Simultaneous reabsorption and secretion processes.
- Proximal tubule, reabsorb filtered urate anions in exchange for intracellular organic anions such as lactate or ketone bodies.



Deteriorating kidney function will eventually lead to higher uric acid levels



100% of uric acid will be filtered into kidney tubules. 90% will be reabsorbed and at the end only 10% will be excreted from the body.



◄ Hyperuricemia

- **For males > 7mg/dl, Females > 6.8 mg/dl, Or > 380 umol/L**
- Hyperuricemia in 90% caused by inadequate renal elimination.
- Above serum levels of 6.8 mg/dl (MSU) crystals are forming somewhere in the body. The higher the serum levels over time, the higher the probability of an eventual attack of gout.
- **CRYSTALLIZATION:** dependent on pH, nucleating partners and temperature.
- Urate is less soluble in synovial fluid and articular cartilage, especially in peripheral joints, is colder than adjacent tissue for lack of blood supply. Therefore, crystallization is likely to initiate in **small peripheral joints.**

Hyperuricemia may be asymptomatic or may cause:

- **Acute gout**, followed by an asymptomatic intercritical phase; a second acute attack is likely within 2 years.
- **Chronic interval gout**, with acute attacks superimposed on low-grade inflammation and potential joint damage.
- **Chronic polyarticular tophaceous gout**, which is rare and characterized by chronic joint pain, activity limitation, structural joint damage and frequent flares.Urate renal stone formation

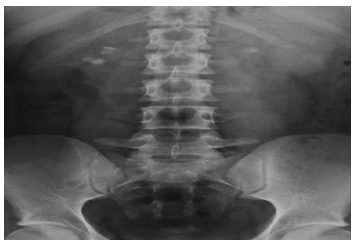
1-Although hyperuricaemia is strong risk factor for gout, only a minority of hyperuricaemic individuals actually develop gout.
2- Opsonin molecules include: Antibodies, Complement proteins,Circulating proteins.

Gout النقرس

Pathophysiology

Precipitation of monosodium urate crystals in avascular tissues
- Cartilage, epiphyseal bone, periarticular bone
- Hyperuricemia likely asymptomatic for years[1]

The acute attack - crystals activate plasma proteases
- Can activate factor XII & C5
- Can adsorb opsonins[2] in area, attracting phagocytes!

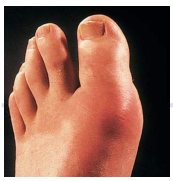


Can manifest as kidney stones mostly radiolucent but sometimes there are deposits of Ca-oxalate and Ca-carbonate making it radiopaque.
Diagnosed with US

Clinical Features

Characteristics of gouty arthritis: (GOUT)

- ★ Recurrent attacks which resolve spontaneously without intervention within 4-6 weeks, so when there is a history of recurrent attacks that are resolved without intervention THIS IS very suggestive of gout
- ★ Involvement of the first MTP joint (Great toe) + Cellulitis like picture "the inflammation is not only restricted to the joints but it also involving the skin and the soft tissue"
- ★ One joint only in 75%
- ★ Renal stones (Urolithiasis)
- ★ Tophi



1 Acute Gout

- Acute gout presents typically in a middle-aged male with a sudden onset of agonizing pain, swelling and redness of the first MTP joint. The attack may be precipitated by excess food, alcohol, dehydration or diuretic therapy.
- The classical presentation is with an **acute monoarthritis**, which affects **the first MTP joint of the big toe** in over 50% of cases. Other common sites are the **ankle**, **midfoot**, **knee**, **small joints of hands**, **wrist** and **elbow**. The axial skeleton and large proximal joints are rarely involved.

Typical features include:

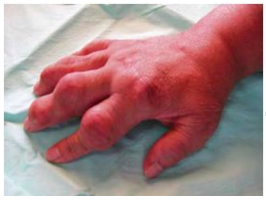
- **Rapid and sudden onset**
- **Severe pain**. often described as the 'worst pain ever'
- **Extreme tenderness**. patient is unable to wear a sock or to let bedding rest on the joint
- **Marked swelling** with overlying red, shiny skin
- **Self-limiting** over 5–14 days, with complete resolution
- There may be accompanying fever, malaise and even delirium, especially if a large joint such as the knee is involved.
- As the attack subsides, pruritus and desquamation of overlying skin are common giving the impression of cellulitis
- Symptoms are more likely to occur at night, typically waking the patient.
- Asymmetrical distribution is common if more than one joint is affected
- If a pt presented to you with acute monoarthritis, how can you differentiate between gout and septic arthritis by history and physical examination?

→ Chills and rigors are in favor of septic.

→ Unlike septic arthritis, gouty arthritis usually starts as cellulitis, inflammation of the skin and soft tissue, erythema, induration, and edema.

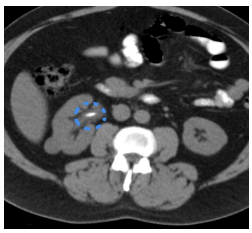
1-Although hyperuricemia is strong risk factor for gout, only a minority of hyperuricemic individuals actually develop gout.
2- Opsonin molecules include: Antibodies, Complement proteins,Circulating proteins.

◄ Clinical Features Con.



2 Chronic tophaceous gout

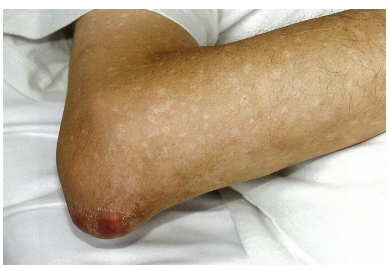
- Individuals with persistently high levels of uric acid can present with chronic tophaceous gout, as sodium urate forms smooth white deposits (tophi) in skin and around joints, on the ear, fingers or the Achilles tendon. Large deposits are unsightly and ulcerate .
- Patients with uncontrolled hyperuricemia who suffer multiple attacks of acute gout may also progress to chronic gout.
- There is **chronic pain and joint damage**, and occasionally severe deformity and functional impairment
- **Characterised with Tophi:** irregular firm **white nodules** produced when crystals are deposited in the soft tissue. These have a predilection for the **extensor surfaces** of **fingers**, **hands**, **forearm**, **elbows**, **Achilles tendons** and sometimes the **helix of the ear most commonly.**
  - Bone tophi: urate crystal deposition in bones (e.g., elbows, knees, extensor surfaces of forearms)
  - Soft tissue tophi: urate crystal deposition in the pinna of the external ear, subcutis , tendon sheaths (e.g., at the Achilles tendon), or synovial bursae.
- Tophi can **ulcerate**, **discharging white gritty material and become infected.**
- In patients with chronic tophaceous gout who are on **diuretic therapy**, the hyperuricemia may be complicated by renal stone formation (nephrolithiasis) and, if severe, **renal impairment** due to the development of interstitial nephritis as a result of urate deposition in the kidney.
- Whenever possible, **stop the diuretics or change to less urate-retaining ones, such as bumetanide**



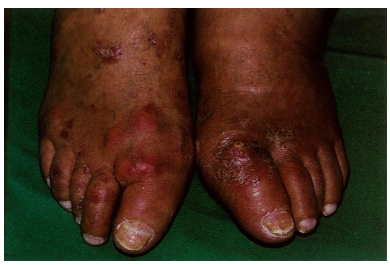
Chronic gout can cause urate renal stones which are radiolucent by x-ray. Best imaging modality for radiolucent stones is **US** since that there is no radiation and it does not require any contrast, but we prefer to do CT without contrast cause it gives more details about:

- ➔ The anatomical structure
- ➔ The size and diameter of the stones

Thus CT helps in determining the appropriate intervention whether hydrate and observe or shock wave. X-ray can also help in diagnosing urate stones and that's why we start with it, cause whenever we have a negative x-ray for a stone, with a positive CT this is urate stone unless proven otherwise



Soft tissue typhi



Multiple gouty tophi (in this patient secondary to increased uric acid production in psoriasis)

◀ Diagnosis

The clinical picture is often diagnostic, as is the rapid response to NSAIDs or colchicine.

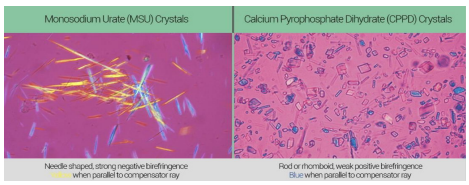
1 Biochemical screen

It includes renal function, uric acid, glucose and lipid profile, should be performed because of the association with metabolic syndrome.

- Acute gout is characterised by an **elevated ESR and CRP** and with a **neutrophilia**, all of which return to normal as the attack subsides.
- Serum urea, creatinine and estimated glomerular filtration rate (eGFR) are monitored for signs of renal impairment.
- **Hyperuricemia** is usually present in gout but levels may be normal or even low during an attack because serum urate falls during inflammation.

2 Joint fluid microscopy

- Most specific and diagnostic test but is technically difficult (gold standard)
- **Joint aspiration** should only be performed if polarized light microscopy is available
- Indications: To exclude septic arthritis and to confirm the diagnosis
- Uric acid crystals are often intra-cellular and appear **needle-shaped** and **yellow parallel** (negatively birefringent) When examined with a polarizing filter and red compensator filter, they are yellow when aligned parallel to the slow axis of the red compensator but turn blue when aligned across the direction of polarization (i.e. they exhibit negative birefringence).
- Polarized microscopy helps also in differentiating gouty crystals **"MSU- needle shaped"** from pseudogout crystals **"CPPD-triangular"**
- In acute gout, the synovial fluid may be turbid due to an elevated neutrophil count. In chronic gout, the appearance is more variable but occasionally the fluid appears white due to the presence of urate crystals. Between attacks, aspiration of an asymptomatic first MTP joint or knee may still reveal crystals
- Synovial fluid cell count: **WBC > 2000/μL with > 50% neutrophils**



3 X-ray

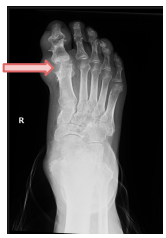
- **Normal** in acute gout
- Well-demarcated **erosions** may be seen in patients with chronic or tophaceous gout.

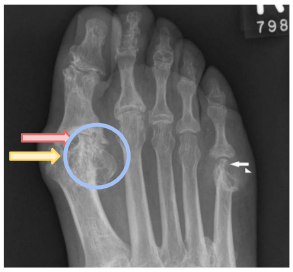
In Gouty arthritis the bone density is usually preserved unless in advanced stages.

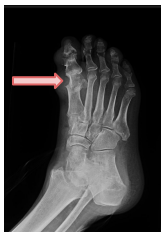
1- Punched out intra-articular erosions

2- Periarticular erosions

3- Hypertrophy of the distal metatarsal bone with subchondral cysts.







Even if you don't know the history and you saw this you can say it is gout, **Why?**

- **MTP**
- **Punched out erosions** مأكول العظم **(Aka: Rat-bite erosions)**
- **Periarticular erosions**
- **Preserved joint space**

◀ Principles of Management

01 **Terminate acute attacks** NSAIDs - Colchicine - Corticosteroids

02 **Prevent recurrence & reverse complications** Eliminate urate crystals from joints & tissues

03 **Address co-morbid conditions** Obesity, Hypertriglyceridemia, Hypertension, Diabetes mellitus, Excessive alcohol

Management should focus on first dealing with the acute attack and then giving prophylaxis to lower SUA and prevent further attacks

EXTRA

Treatment of Gout

Acute gouty attack

- Treat pain "Anti inflammatory"
- NSAIDS, Glucocorticoids "intraarticular,systemic", Colchicine "low dose"
- We don't ↓uric acid in acute setting or when patient is in pain (you'll make things worse"

Chronic gout "prophylaxis"

- Prevent attacks from occurring
- ↓uric acid but not so rapidly as it can lead to acute gout
- Goal :

- ↑ **excretion of UA:** Xanthine oxidase inhibitors, uricosuric agens, uricase DO NOT USE THESE DRUGS DURING THE ACUTE ATTACK
- ↓**production of UA:** weight loss, decrease intake of meat, seafood and beer, manage HTN

- Patient presenting with acute monoarthritis: **Give Antibiotics** on presentation and do not discontinue the Antibiotic even if the crystals were seen. You only stop the antibiotic when the culture comes back negative, there might be coexistence of septic arthritis and crystal induced arthritis.
- Antibiotics are always given first in cases of acute monoarthritis because septic arthritis is the most dangerous, as it may lead to septicemia, septic shock and death eventually unlike gout which usually resolves by itself within 2wks even without treatment, but we usually give anti-inflammatory meds to abort the attack quickly
- Can high WBC exclude gout? NO, gout pts may also present with high WBC.
- Treatment of acute attacks is different from the treatment of chronic gout.
- Goals of managing the acute gouty attacks: to relieve the pain, reduce inflammation, and avoidance of risk factors (e.g. red meat, diuretics …etc). While the goal of chronic gout treatment is to lower the uric acid levels and to prevent further attacks.
- Not all patients with high uric acid will be treated by urate lowering agents.

1. Terminate acute attacks[1]

- Directed at WBC inflammatory response
- The first dose should be taken at the first indication of an attack. After 24–48 hours, reduced doses are given for a further week.
- **Options: 1- NSAIDS 2- Colchicine 3- Corticosteroids**
- Choice depends on:
  - **co-morbidities & history**
  - **More importantly** - rapidity of treatment selection!
    - Keep agent close at all times; start as soon as possible as needed
    - Especially with poor renal function, slower response = increased drug exposure over course of a flare.

Doctor's notes (439):

➔ A **30** years old young lady came to ER with knee effusion and cellulitis like presentation, what is the first possibility she has? gout?
NO wrong (Never say gout in young lady cause gout is extremely rare in women who are in fertility age, but the likelihood increases in post menopausal women as the frequency of gout will become equal in males and females). So it is (Septic Monoarthritis)

➔ A young man who underwent a polarized microscopy, and we found that he has urate crystals with no sepsis. **How will you manage him?**
Acute attack = We can use Colchicine "better" or NSAIDs

- **NSAIDs : make sure he don't have renal or liver impairment.**
  1- Effective at any time
  2- No narrow therapeutic to toxicity ratio.
- **Colchicine :**
  1- Very effective as an anti-inflammatory but only **effective in the first 12 hours** (24 may be effective).
  2- Has a very narrow therapeutic to toxicity ratio.

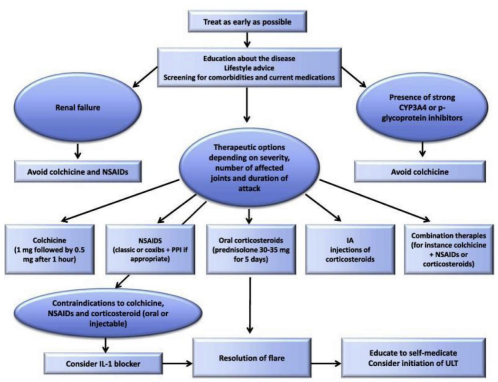
Doctor's notes (438):

In renal impairment:

- **Steroids:** preferred, either intra-articular or systemic.
- **Colchicine:** if needed, can be used in mild renal impairment (Cr clearance >70)
- **NSAIDs:** should be avoided
- **Cr clearance < 50: Colchicine and NSAIDs are contraindicated.**

Joint involvement:

- **Monoarthritis:**
  - Intra-articular steroid injection is preferred NSAIDs and colchicine also can be used. Recall: Intra-articular steroids are contraindicated in septic arthritis
- **Polyarthritis:**
  - NSAIDs or Colchicine



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1.NSAIDS

1- Fast onset of action (within 1 hour)
2- Effective even after a few days of symptoms onset prefered over Colchicine if the pt presented after 24hrs of onset of symptoms
Choose based on: toxicity, Cost, Convenience

- CrCL
  - Avoid in **CKD**
- Risk of ADRs
  - (Nausea, vomiting, diarrhea, GI bleed, fluid retention, acute renal failure, etc)
- Cost & availability
  - Rx vs Over the counter
- For elderly: Choose shorter half-life (t ½)
  - Ibuprofen (2-4 hrs); **diclofenac (2 hrs);** indomethacin (4.5 hrs);
  - **Avoid in CHF, CKD, peripheral edema, PUD/GERD**
- N.B. increased risk of GI bleed with concurrent ASA, even 81 mg!
  - Consider adding a PPI

2.Colchicine

- Slower onset (around 6-8 hours)
- Weak effect after 24-36 hours after symptoms onset
- Most specific agent in use, Used for centuries.
- **OVERALL EFFECT:**
- **if given in high doses it can lead to bone marrow suppression (neutropenia)**
- **Decreases leukocyte motility**
  - - Binds to tubulin and inhibits microtubule formation, arresting neutrophil motility
  - Decreases phagocytosis in joints
  - Decreases lactic acid production
  - Interruption of inflammatory process
- PO or IV
  - Avoid IV - **Potentially fatal** if mis-dosed
  - Risk of **Arrhythmia**
- **Alternative regimens**
  - 1 mg loading dose, then 0.5 mg q 2-6 hrs
  - OR 0.5 - 1 mg TID
  - OR 1.2 mg initially, then 0.6 mg BID
- Most effective w/i first 12 hrs of attack
- Dose low! Try TID dosing first
- Narrow therapeutic index (neurotoxicity, myotoxicity and GI upset)
- **D/C if GI distress develops e.g. diarrhea or colicky abdominal pain**

3.Corticosteroids

- **Reserved for:**
  - Intolerant of NSAIDs or colchicine
  - Comorbidities that prohibit use of other meds
- Good alternative for **elderly w/ poor renal function**
  - Few trials - choice is empiric
  - Eg. Prednisone 20-60 mg/day PO
  - Are low doses less effective?
  - Noted flares in transplant patients on 7.5-15 mg/day
- **Methylprednisolone** 125 mg/day IV or IM q 1-4 days prn
  - Use smallest gauge needle (esp if on Warfarin).
- **Routes of administration:**
  1- Oral
  2- Intra-articular: used only when single or few joints are affected.
- **When to use corticosteroids?** For ex. Patient who have advanced HF and renal failure along with PUD and he came with multiple joints arthritis. NSAIDs and Colchicine is contraindicated and we can't use intra-articular steroids cause it is not monoarthritis. So we should give him systemic steroids.

2. Prevent recurrence & reverse complications

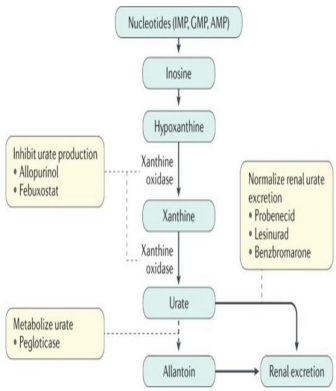
Recommendations: Urate Lowering Therapy

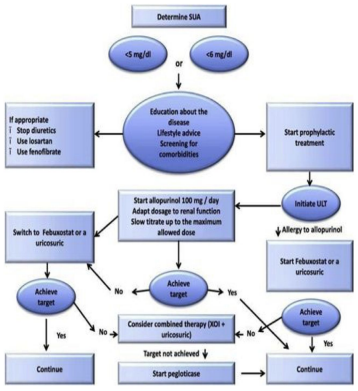
- **EULAR:**
  - "with recurrent attacks, arthropathy, tophi or radiographic changes"
- **US Panel:**
  - "if tophaceous deposits, erosive changes on X-ray, or >2 attacks per year"
- **Others:**
  - "After first attack" → Disease declared, high rate of recurrence
  - "Based on frequency of attacks" → Since second attack may not occur for years

- **Must eliminate excess body urate**
  - Else tophi may continue to enlarge
  - Destructive, chronic mononuclear cell inflammatory responses that destroys cartilage and bone, resulting in chronic arthritis
- High likelihood of recurrence
  - 62% w/i 1 yr
  - 78% w/i 2 yrs
  - 90% w/i 5 yrs

- **Recommended urate levels <360 umol/L**
  - Normal range 140-340 (Dynacare)
- At > 360 umol/L, fluids are supersaturated and crystal can **precipitate**
- At < 360 umol/L, deposits dissolve, mobilize and are **eliminated**

- **Recall**: Lowering urate can precipitate a flare!
- Acute flares of gout often follow initiation of urate-lowering therapy. The patient should be warned about this and **told to continue therapy**, even if an attack occurs. The risk of flares can be reduced by prophylaxis with oral colchicine or an NSAID for the first few months. Giving prophylaxis to the prophylaxis ..
  - Increased risk w/ more rapid & severe changes
  - ~25% of patients
- **Start 2-3 weeks after flare resolved**
  - Uricosuric agents- increase excretion (2nd line)
    - **Probenecid**
    - **Sulfinpyrazone**
  - Xanthine Oxidase Inh.- decrease production (1st line)
    - **Allopurinol** - agent of choice
    - **Febuxostat** - new agent (ULORIC ™)
  - **Pegloticase**





Allopurinol:
- First choice (In patients with any kidney problem we should use febuxostat because it is metabolized by the liver)

Febuxostat:
- There is a concern about sudden cardiac death

Pigloticase or Rasburicase:
- Used in tumor lysis syndrome due to chemotherapy

Urate drugs:
- Have weaker action

Gout النقرس

Xanthine oxidase inhibitors

Allopurinol

1. The drug of **first choice**
2. Treatment is not started within 1 month after an acute attack and NSAIDs or colchicine are given for 4 weeks before and after starting allopurinol

Start Allopurinol at **low dose** and titrate up **to avoid precipitating event**

GOAL: lowest dose to target urate < 360 umol/L

N.B Dose adjust for renal function

- Dosing according to CrCL may not attain control

ADRs: (well tolerated)

- **Common:**
  - GI upset,
  - Rash, esp if on Amox/Amp or Cyclophosphamide)
- **Rare:**
  - Blood dyscrasias
  - Jaundice
  - TEN
  - Hypersensitivity Syndrome (including rash)
- **If mild rash occurs, hold and re-challenge**

After giving the acute measures therapy and the attack is now aborted, what is the next step?

-Allopurinol is the best first line (small dose then upgrade it)

-Unlike febuxostat which is available as IV only, allopurinol is available in different modalities oral and IV

Febuxostat (ULORIC ™)

- A non-purine, selective xanthine oxidase inh.
- **More potent than allopurinol**

Efficacy vs Allopurinol:

- **Lower** frequency of gout **flares**
  - N.B. Higher frequency of flare with initiation at higher doses! commonly provokes acute attacks when therapy is initiated
- Improved serum urate lowering effect
- Limiting RCTs - need more evidence in:
  - Renal dysfunction, concominant use of urate raising drugs (eg. ASA, thiazides), comparison against non-fixed doses of Allopurinol
- undergoes **hepatic metabolism** and no dose adjustment is required for renal impairment
- **CrCL > 30 mL/min - no dose adjustment**
- **CrCL < 30 mL/min - unstudied - avoid**

Side effects:

- Rash (1% to 2%)
- Liver function abnormalities (5% to 7%)
  - F/U LFTs in 2 & 4 months after starting tx
- Arthralgia (1%)

Cost: 80 mg tabs ~ $65/month;

- (no ODB coverage)

Treat the same as allopurinol

- More expensive than allopurinol

- Start **prophylaxis before** urate lowering therapy
  - Eg. Daily, low dose NSAID or colchicine 2-3 weeks before allopurinol
  - Eg. Indomethacin 25 mg bid
- Continue 3-6 months and/or [urate] < 360 umol/L

Note Bene (N.B.)

- Acute flare prevented but crystal deposition in tissue continues!
- Hence no warning signs of continues cartilage and bone damage and deposition in organs, especially kidneys!
- **Remember**: Colchicine is NOT uricosuric

Gout النقرس

Uricosuric Agents	
Probenecid	**Sulfinpyrazone**

• 500 mg to 3g/day divided bid-tid
• Start: 250 mg BID
  ○ Increase by 500 mg q4wk
• May decrease by 500mg q6mo if stable >6 mo till urate starts to rise
• ADRS: GI upset, rash
	• Up to 800 mg/day divided bid
	• Start: 100mg BID
	  ○ Increase q1wk
	• May decrease to 200 mg/d once urate controlled
	• ADRs: GI upset, rash

Pegloticase
A biological treatment (a conjugated uricase enzyme) a. It is indicated for the treatment of **tophaceous gout resistant to standard therapy** (Standard therapy is allopurinol and/or uricosuric agents) and is administered as an intravenous infusion every 2 weeks for up to 6 months. It is highly effective at controlling hyperuricemia and can cause regression of tophi. b. Used preventatively in people undergoing chemotherapy for **malignancies (tumour lysis syndrome)** **c. The main adverse effects:** **i.** Infusion reactions (which can be treated with antihistamines or glucocorticoids) **ii.** Flares of gout **iii.** Development of antibodies to pegloticase.

★ **Don't start urate lowering agents till the acute attack is resolved.**

★ **When to start urate lowering agents?**

- Uric acid ≥ 9 mg/dl or 650 umol/L
- More than two attacks per year
- Presence of tophi
- Presence of renal stones
- If there is organ destruction or joint involvement (erosion as we saw in x ray

Dr's case: a young man who used to come to you two times a year for his severe arthritis and cellulitis. How will you manage him? start Allopurinol? Wrong answer! **It should be more than 2 attacks a year to start urate lowering agents.**

Summary of Gout Prevention:

- High likelihood of recurrence
- Eliminate excess body urate to prevent chronic destructive changes
  - Colchicine is **not** uricosuric!
  - No prophylaxis without urate lowering therapy!
- Manage risk factors
  - Drugs, diet, comorbidities
- Allopurinol - drug of choice
  - Start low, go slow
  - May have to push dose to attain

3. Address co-morbid conditions

- Obesity
- Hypertriglyceridemia
- Hypertension[1]& Diabetes mellitus
- Excessive alcohol

Obesity & Hypertri-glyceridemia 	• Weight loss independently lowers urate levels
	• Decreased alcohol consumption, regular exercise and weight reduction will lower TGs
	  ○ Fibrates
	  ■ Especially fenofibrate - mild uricosuric effect

Diet restrictions 	• Highly restrictive diet is not necessary
	• Total diet restriction only lowers urate levels by ~52.9 umol/L (1 mh/dL)
	  ○ Very unpalatable
	  ○ Poor compliance
	• Purine sources matter
	  ○ Increase with meat & seafood
	  ○ Decrease with dairy
	  ■ Daily consumption lowers urate levels
	  ○ Oatmeal and purine rich vegetables do not increase risk of gout
	  ■ Peas, mushrooms, lentils, spinach, cauliflower

Dietary sources 	**Avoid if Possible:-** Organ Meats – liver, kidney, heart, sweetbreads, tripe, brain and tongue **Limit:-** Beef. Chicken.camel. Seafood sardines , Tuna , Lamb..lard or pork pig, mushrooms[fungi] **vegetable:-** high purine content include cauliflower, spinach, Chickpeas, Soy beans, Peanut, high fructose corn syrup, sweetened soda (high in fructose which increases the production of UA , also in the long term it will affect kidney function decreasing UA secretion).

EXTRA

Pseudogout (pyrophosphate arthropathy) (CPDD)

Definition:

- Calcium pyrophosphate deposits in hyaline and fibrocartilage produce the radiological **appearance of chondrocalcinosis**. Shedding of crystals into a joint precipitates acute synovitis which resembles gout, except that it is more common in elderly women and usually affects the knee or wrist. The attacks are often very painful. In young people it may be associated with **haemochromatosis, hyperparathyroidism,** Wilson's disease or alkaptonuria.
- It differs from gout in that large joints such as the knee, and wrist are affected, but not particularly the first MCP of the foot. **It different from DJD in that the DIP and PIP are not affected.**

Diagnosis:

- The diagnosis is made on joint fluid microscopy demonstrating small brick-shaped pyrophosphate crystals which are positively birefringent under polarized light (compare uric acid) or deduced from the presence of chondrocalcinosis (Ca+ phosphate deposition) on X-ray.

Treatment: Joint aspiration and NSAIDs or Colchicine.

1. If possible, substitute the antihypertensive drugs that increase uric acid (e.g. thiazides, β-blockers and ACEI) with losartan which has uricosuric effect

Take home Messages

- **Gout can be caused by decreased excretion or over production of Uric acid**
- **Gout is characterized by:** Recurrent attacks that resolve spontaneously which usually happens in the first MTP joint along with Cellulitis like picture and if chronic there will be tophi and renal stones.
- **Acute attacks** are treated by NSAIDs or colchicine
- **Start urate lowering agents when:** Uric acid ≥ 9 mg/dl or 650 umol/L, or when there are more than two attacks per year, or whenever there is tophi, stone, or joint destruction by x-ray.
- When a patient presents with an acute gouty attack start with colchicine then urate lowering therapy. Never initiate Urate lowering therapy first, the acute attack must subside.

Doctor's Take home messages:

- **When you are considering the diagnosis of gout you must rule out septic arthritis first.**
- **Gout is extremely rare in young females.**
- **You have to memorize the indications for urate lowering agents.**
- **You should know the acute and chronic management**

◀ Summary

Characteristic	Gout	Pseudogout
Crystal composition	monosodium urate "Uric acid"	Calcium pyrophosphate
Crystal shape	Needle-like	Rhomboid
Birefringent	Negative	Positive
Most common joint affected	1st metatarsophalangeal joint	Knee
Radiography	Rat-bite erosions	Chondrocalcinosis

Summary

	Gout & Pseudogout
Pathogenesis	an inflammatory reaction to **monosodium urate crystals**. (Most common inflammatory arthritis in elderly)

Predisposing factors	• Purine rich foods
	• Drugs
	  ○ **Thiazides**
	  ○ **Low dose ASA**
	  ○ Niacin
	  ○ Cyclosporin
	  ○ Pyrazinamide & ethambutol
	• Obesity
	• Moderate to heavy alcohol intake
	• High blood pressure
	• Abnormal kidney function
	• Leukemias, lymphomas, and hemoglobin disorders
	• Tumor lysis syndrome
	• Trauma & Surgery

Presentation	• Sudden onset of exquisite pain. • Wakes the patient from sleep, • Classically affects the **big toe (podagra).** • Pain & cellulitic changes (Erythema, swelling, tenderness, and warmth)
Investigations	• Clinically or by rapid response to NSAIDs or Colchicine • Joint aspiration (Synovial fluid analysis) → Cell count, polarized microscopy and culture **to exclude septic arthritis** and confirm the diagnosis.
Treatment	• Patient presenting with acute monoarthritis: **Give antibiotics and do not stop until the culture comes back negative.** • Terminate acute attacks (NSAIDs , Colchicine , Corticosteroids (last) • Prevent recurrence & reverse complications by eliminate urate crystals from joints & tissues • Lifestyle modification (weight reduction , diet restriction , manage DM & HTN)
Pseudogout	• **Calcium pyrophosphate** deposits in hyaline and fibrocartilag (most common in elderly women and usually affects the knee or wrist • produce the radiological appearance of chondrocalcinosise • small brick-shaped pyrophosphate (rhomboidal) crystals which are positively birefringent under polarized light

Lecture Quiz

Q1: A 74-year-old woman presents to accident and emergency with sudden onset pain and swelling in the left knee. On examination, she is apyrexial and the left knee is swollen. There is reduced range of movement in the knee due to swelling and pain. X-ray of the right knee shows chondrocalcinosis. Microscopy of the fluid aspirated from the joint is most likely to show:

A- Rhomboidal, weakly positively birefringent crystals under polarized light microscopy
B- Needle-shaped negatively birefringent crystals under polarized light microscopy
C- Atypical mononuclear cells
D- Reed Sternberg cells
E- Tophi

Q2: A 53-year-old man comes to the emergency department for severe left knee pain for the past 8 hours. He describes it as an unbearable, burning pain that woke him up from his sleep. He has been unable to walk since. He has not had any trauma to the knee. Ten months ago, he had an episode of acute pain and swelling of the right great toe that subsided after treatment with indomethacin. He has hypertension, type 2 diabetes mellitus, psoriasis, and hyperlipidemia. Current medications include topical betamethasone, metformin, glipizide, losartan, and simvastatin. Two weeks ago, hydrochlorothiazide was added to his medication regimen to improve blood pressure control. He drinks 1–2 beers daily. He is 170 cm (5 ft 7 in) tall and weighs 110 kg(242 lb); BMI is 38 kg/m2. His temperature is 38.4°C (101.1°F). Examination shows multiple scaly plaques over his palms and soles. The left knee is erythematous, swollen, and tender; range of motion is limited by pain. Which of the following is the most appropriate next step in management?

A- Serum uric acid level
B- Oral colchicine
C- Arthrocentesis
D- X-ray of the knee
E- Intra-articular triamcinolone

Q3: A 70-year-old woman presents to accident and emergency with sudden onset pain and swelling in the right knee. Her past medical history includes hypertension and hypercholesterolaemia. She is currently taking aspirin, ramipril and simvastatin. On examination, she is apyrexial and the right knee is swollen. There is reduced range of movement in the knee due to swelling and pain. X-ray of the right knee shows chondrocalcinosis. What is the most likely diagnosis?

A- gout
B- psuedo-gout
C- septic arthritis
D- reactive arthritis
E- osteoarthritis

Q4: A 53-year-old man, who works as a chef, presents to accident and emergency with sudden onset severe pain, tenderness and swelling of the first metatarsophalangeal joint. The pain is making it difficult for him to mobilize. He has had two previous similar episodes. Blood tests reveal a raised serum urate level. The most likely diagnosis is:

A- gout
B- psuedo-gout
C- septic arthritis
D- reactive arthritis
E- osteoarthritis

Q5: A 59-year-old man presents to his GP with sudden onset severe pain, tenderness and swelling of the first metatarsophalangeal joint. He is known to suffer from acute gout and has had several previous similar episodes. What is the most appropriate treatment?

A- Allopurinol
B- NSAIDs
C- Conservative measures including reduced alcohol intake and weight loss
D- Intra-articular steroid injection
E- methotrexate

Answers: Q1:A | Q2:C | Q3:B | Q4:A | Q5:B

Answers Explanation File!

GOOD LUCK !

This work was originally done by ***438 Medicine team:***

Team Leaders

- *Raghad AlKhashan*
- *Amirah Aldakhilallah*
- *Mashal AbaAlkhail*
- *Nawaf Albhijan*

Member : Ghada Alsadhan, Razan alzohaifi, Amirah Aldakhilallah, Deana Awartani

Note taker : Sarah Alhelal

Edited by ***439 Medicine team:***

Team Leaders

- *Shaden Alobaid*
- *Ghada Alabdi*
- *Hamad Almousa*
- *Naif Alsulais*

Member : Rima Alomar

Note taker : Ahmed Alhawamdeh

CONTACT US THROUGH OUR EMAIL :
MEDICINE439@GMAIL.COM