MSS pharma lec 4: Gout النقرس

Summary done by: Dr Ahmad Almohtaseb

# Gout

- Gout: **the most common crystal-induced arthropathy**

- **Characterized** by **hyperuricemia(uric acid>7)** and **crystals deposition.** →**Inflammatory arthritis.**

- **Hyperuricemia does not always lead to gout**, **but gout is always preceded** by **hyperuricemia**; study of 990 vs 4200

- Lifestyle(sedentary people→**metabolic syndrome**)

- Genetics: SLC2A9, SLC22A12

- usually >30 yo

- "the disease of kings" or "rich man's disease"

## Gout: Pathophysiology

Uric acid:-

- **End product** of **purine** synthesis and metabolism

- **Eliminated** by **renal excretion**

**Primary hyperuricemia:**

due to uric acid:

1. **Overproduction** (rare genetic disorders)

2. **Underexcretion** (90%), usually **associated with metabolic syndrome**

**Secondary hyperuricemia :-**

Due to specific causes:-

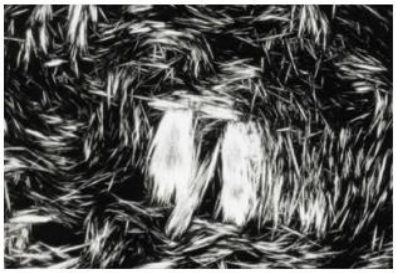
- Excessive alcohol consumption
- Diet rich in purines
- Nephropathy
- Starvation or dehydration
- Certain drugs

**Drugs That Increase Serum UA Levels**

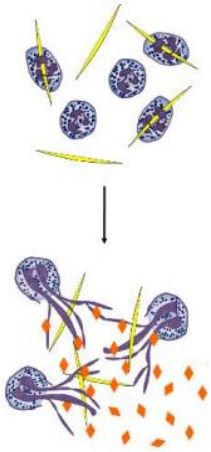
- Cyclosporine
- Ethambutol
- Ethanol
- Niacin
- Pyrazinamide
- Salicylates

- **Hyperuricemia→ precipitation of monosodium urate salts (needle-like crystals)** in **joints**

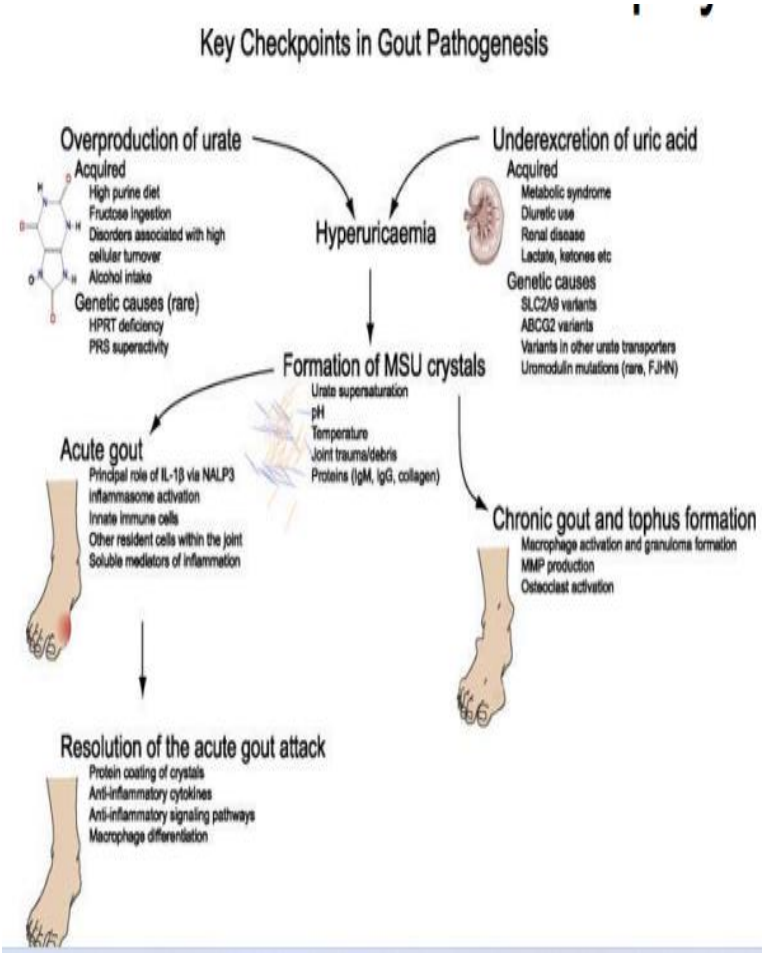
- Urate **crystal deposition in tissues triggers acute inflammatory response**: **infiltration of granulocytes(neutrophils) and production of leukotrienes**



Needles of urate crystals



Neutrophils attacking the urate crystals



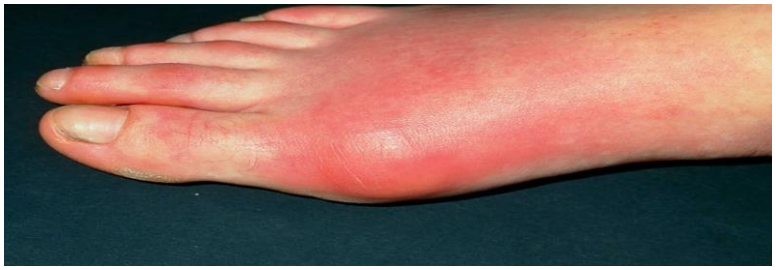

## Clinical features of gout:-

Gout has two types, **acute and chronic**:-

-**Acute gout S/S:** **Recurrent attacks** of a **red, tender, hot, and swollen joint(usually the big toe!!).**

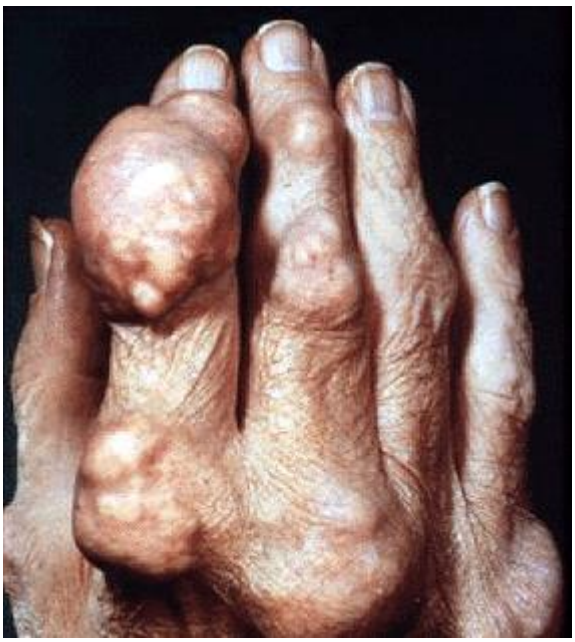
- The **pain is usually excruciating**(worst pains ever!)

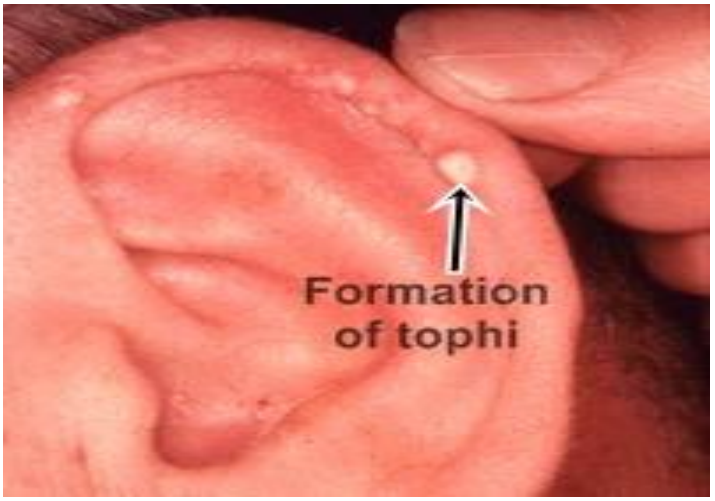
- **Rapid progression in <12h.(patient sleeps normally and wakes up next morning with gout**



**-Chronic gout :-**

**Accumulation of chalky masses called tophi over many years with destruction of bone and cartilage!!**






**Investigations:-**

**Arthrocentesis( collecting synovial fluid by a syringe is performed)-→ wbc 2000-50000, neutrophils(PMNs)>70,**

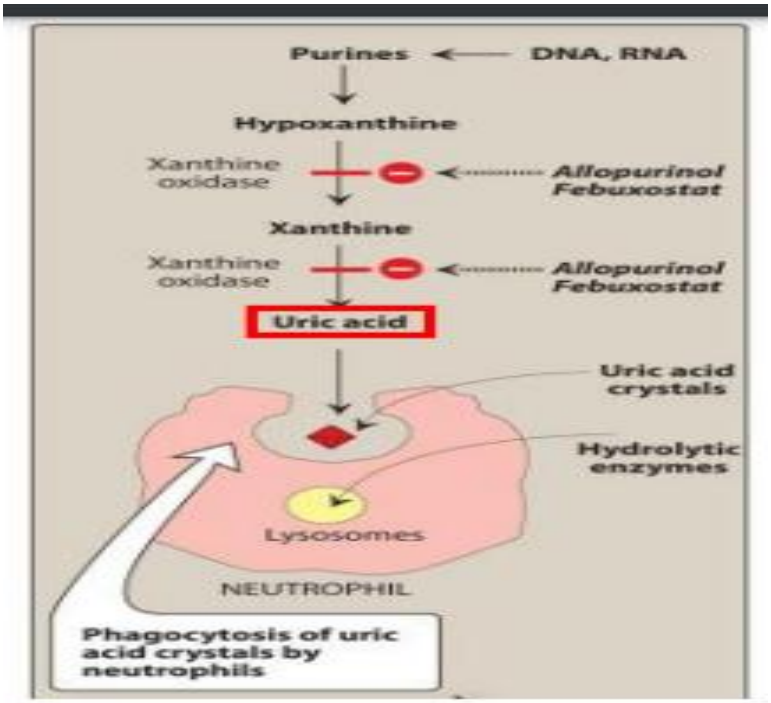
**When you use polarized light-→ needle shaped crystals that are negatively birefringent**

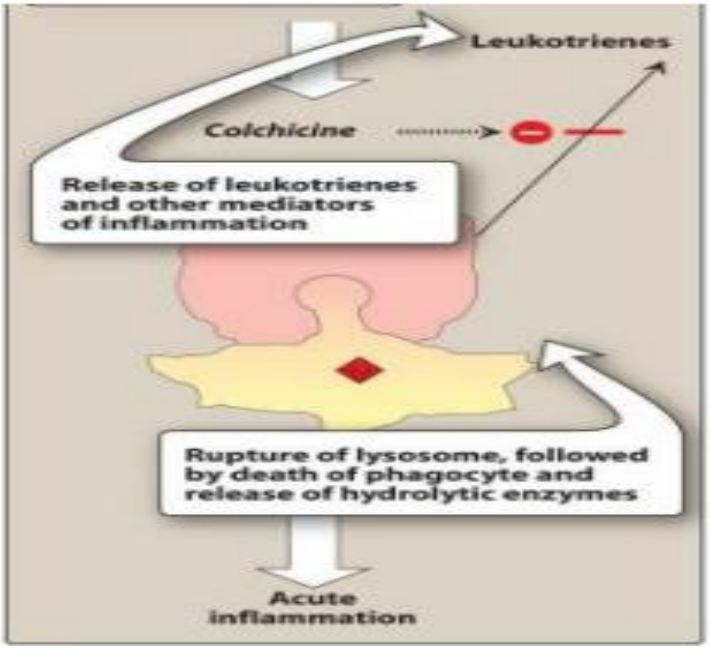
Clinical cases on gout:-

A 55-year-old woman presents to the emergency department with acute pain in the left proximal interphalangeal (PIP) joint of the second digit. She reports that the pain is excruciating and has happened once a few years ago but self-resolved over the course of 2 weeks. She states that she recently increased her alcohol and red meat consumption and was recently started on hydrochlorothiazide. On physical exam the PIP joint is swollen, erythematous, warm, and tender to palpation. Preparations are made for an arthrocentesis to be performed.

A 66-year-old man with a past medical history of coronary artery disease and obesity complains of left great toe swelling on the second day of his hospital stay for melena due to peptic ulcer disease. He describes significant pain at the metatarsal-phalangeal joint, and the radiographic findings are shown in Figure A. He also complains of chronic bilateral hip pain that has worsened during his admission. Temperature is 99.4°F (37.4°C), blood pressure is 142/91 mmHg, pulse is 92/min, respirations are 16/min. On examination, his left great toe is red, swollen and feels hot to the touch.

A 55-year-old man presents to the emergency department with right knee pain. He woke last night with sudden-onset, sharp, 10/10 non-radiating pain in his right knee. He denies recent trauma and he has no known medical problems. He denies tobacco use and will often drink 6-8 beers or spirits on weekend nights. His temperature is 98.6°F (37.0°C), pulse is 90/min, blood pressure is 140/90 mmHg, respirations are 16/min, and oxygen saturation is 97% on room air. Physical exam reveals an erythematous, edematous right knee. Passive extension of the knee is limited by pain. Synovial fluid aspiration is performed and sent for analysis, which reveals 20,000 leukocytes/mm^3, and no organisms visualized. Microscopic examination of synovial fluid shows negative birefringence.



# What Are The Approach Considerations?

Principles of gout management are :

- **Treatment** of **gout flares(acute attack)**

- **Urate-lowering therapy→decrease hyperuricemia(uric acid<saturation level of 6)→prevention of future acute attacks and chronic gout**

**Urate lowering therapy has certain indications, not any patient with gout has to be started on urate lowering therapy!!**(click here for considerations)

**Urate lowering therapy INITIALLY causes more crystal deposition in joints-→ increased risk of acute flares when starting urate lowering therapy, then after 6 months crystal deposition lessens and urate lowering therapy decrease hyperuricemia and exerts its beneficial actions.**

**Anti-inflammatory prophylaxis HAS to be given** when **starting urate-lowering therapy**(to prevent initial acute flares) and **continued for at least 6 months!**

- **Screening** and **management** of **comorbidities** associated with gout (Type 2 DM, cardiovascular disease, hypertension, hyperlipidaemia, etc

## Treatment of Acute Gout

**NSAIDs: e.g., indomethacin(NOT ASPIRIN!)**

**full dosage for 2-5 days**

**Stop 2 days after symptoms subside**

**Intra-articular/systemic corticosteroids**(if >2 joints)

**Colchicine(anti-neutrophilic agent)**

**Anakinra or Canakinumab (interleukin-1 receptor antagonist)**

# Colchicine:-

- **Plant alkaloid**

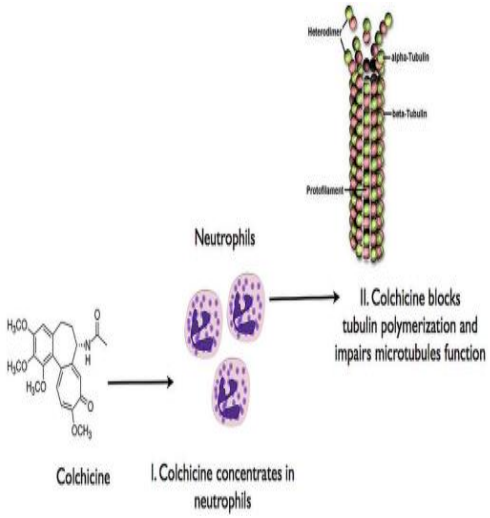
- **Not a uricosuric/not an analgesic** but **relieves pain** through **inhibiting inflammation**

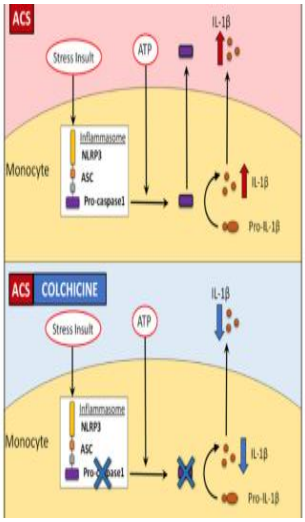
Mechanism of action:-

**1)Binds tubulin→depolymerization→Disrupts leukocyte migration**

3)**Blocks cell division(acts on mitotic spindles)→responsible for adverse effects**

2)**interferes** with the **inflammasome complex**(an organelle that synthesizes IL-1) **found in neutrophils and monocytes by blocking procaspase 1→ impaired inflammasome complex→ less IL-1 secretion**




Therapeutic uses

1. **Relieves acute gout pain** within 12 h (given 36 h after onset)

2. **Prophylactic agent against gout attacks in patients initiating urate lowering therapy.**

**Narrow therapeutic window**

Pharmacokinetics

- **Oral, rapidly absorbed → metabolized by hepatic CYP450 3A4** and other tissues.

**Recycles in bile(enterohepatic circulation) and a portion is excreted unchanged in feces and urine. exhibits high interpatient variability** in the **elimination half-life**

Other therapeutic uses:-

**ACS(acute coronary syndrome) pericarditis/post MI pericarditis, familial Mediterranean fever and recently trialed for Covid-19.**

Colchicine Adverse effects

- **N/V/D and abdominal pain**
- **Myopathy**
- **Neutropenia, aplastic anemia, agranulocytosis**
- **Alopecia**
- **Should NOT be used in pregnancy!(FDA;C, AU:D)**
- **Used with caution in patients with hepatic, renal disease,CVS disease**

**Dosage adjustments** are required in patients **taking CYP3A4 inhibitors** (for example, **clarithromycin and itraconazole) or P-gp inhibitors** (for example, **amiodarone and verapamil**) and those with severe renal impairment.

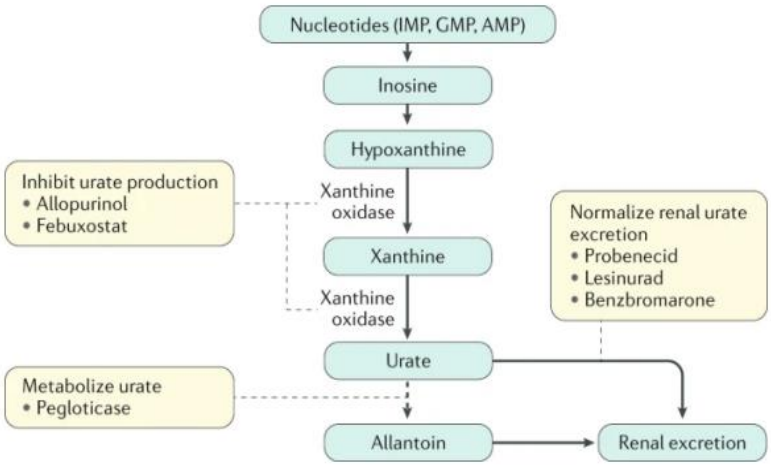
**NSAIDs have largely replaced colchicine** in the treatment of acute gouty attacks for **safety reasons**

## Treatment of Chronic Gout

- Aims to **reduce the frequency of attacks and complications of gout(tophi)**
- Options:-

**1)Xanthine oxidase inhibitors (allopurinol, febuxostat) first-line**

**2)Uricosuric agents (probenecid)**




## Indications for Uric Acid Lowering Therapy:-

**ACR and EULAR guidelines: Established diagnosis of gout with one of the following**

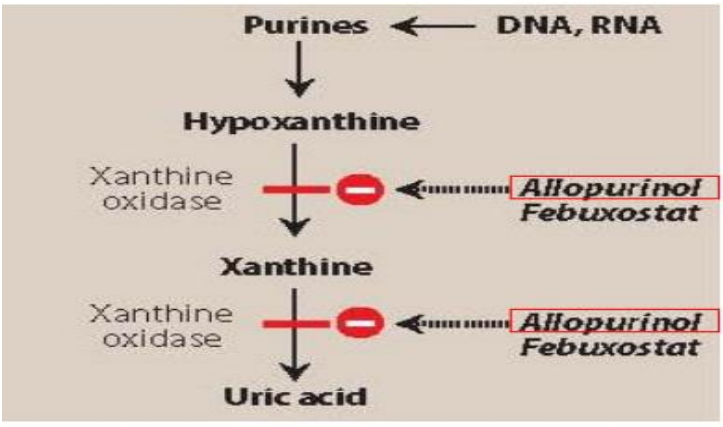
- **Frequent (2/yr) of acute gouty arthritis**
- **Tophus or tophi identified on clinical examination or imaging study**
- **Previous urolithiasis**
- **Chronic kidney disease (CKD) stage 2**

(for other gout considerations, click here):-

## Urate production inhibitors:Allopurinol

## Mechanism of action :-

- **Purine analog**
- **Xanthine oxidase compeitive inhibitor**
- **Interferes** with the **last two steps** in **uric acid biosynthesis**
- **Reduces uric acid production**



## Allopurinol Pharmacokinetics:-

- **Oral, completely absorbed**
- **Primary metabolite**: **alloxanthine (oxypurinol) (also active inhibitor) with Half-life 15-18 hours→once daily dosing**
- **Excreted in feces and urine**

Dose adjustment is needed if estimated glomerular filtration rate is<30

## Allopurinol Adverse effects:-

- **Hypersensitivity and skin rash(especially with renal impairment)**
- **Administered concurrently** with **NSAIDs, steroids or colchicine**. Why? **Because it increases crystal deposition and risk of acute attack initially**

## Urate production inhibitors :Febuxostat

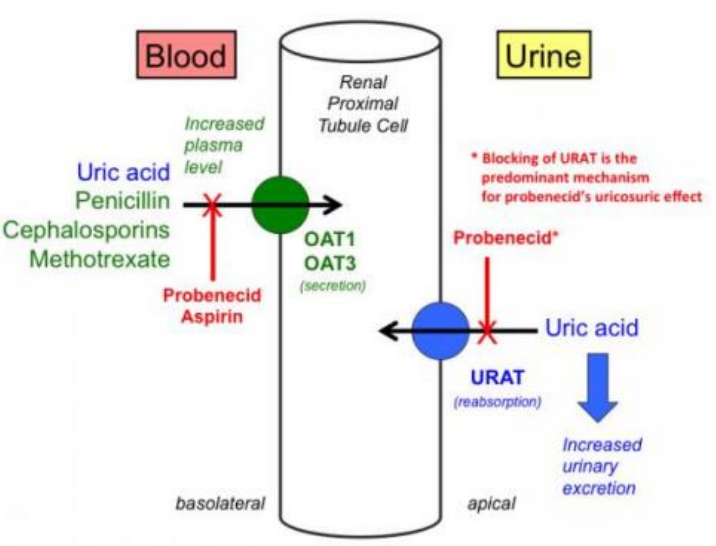
- **Xanthine oxidase inhibitor**
- **Structurally unrelated to allopurinol (non-purine)**
- Similar indication to allopurinol
- **Elimination.. Liver > kidney→ requires less adjustment** in **those with reduced renal function.**
- **Risk of hypersensitivity is less**
- **Reports of increased CVS events** lead to **limited use(use with caution in patients with CVS/stroke history**

## Urate excretion stimulants:- Probenecid

- **Uricosuric agent**
- **Weak organic acid**
- **Promotes renal clearance of uric [inhibits urate-anion exchanger]→Blocks tubular reabsorption of uric acid**

Probenecid **should be avoided** if the **creatinine clearance is less than 50 mUmin.**

- How does probenecid interact with aspirin/salicylates? **Aspirin competes with uric acid for secretion(from blood to urine)-→ uric acid accumulation in blood→antagonize probenecid effect**




## Pegloticase

- **Recombinant urate oxidase(uricase)**
- **Converts uric acid to allantoin**
- **Allantoin** is a **water soluble nontoxic metabolite excreted renally**
- **Indicated** for patients **who fail standard therapy**
- **Given as IV infusion**(because it is an enzyme) **every 2 weeks**

**Infusion-related reactions** and **anaphylaxis** **may occur** with pegloticase, and **patients should be premedicated** with **antihistamines and corticosteroids**

# Dietary Restriction

**Foods very high in purines:**

- Organ meats such as sweetbreads (eg, pancreas and thymus)
- Sardines
- Mussels

**Weight gain is a significant risk factor for gout (M), whereas weight loss reduces the risk**

**Avoid Alcohol and encourage vegetables**

**Foods moderately high in purines**

- Trout
- Anchovies
- Haddock
- Scallops
- Mutton
- Veal
- Live
- Salmon
- Kidneys
- Turkey

A 54-year-old man with gout is found to have an issue with renal excretion of uric acid. Which drug is an oral agent that would target the cause of his acute gout attacks?

A. Allopurinol B. Febuxostat C. Probenecid D. Pegloticase

Answer:C

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A 64-year-old man presents with signs and symptoms of an acute gouty flare. Which strategy is the least likely to acutely improve his gout symptoms and pain?

A. Naproxen B. Colchicine C. Probenecid D. Prednisone

Answer:C