# (1) PHARMACOTHERAPY OF GOUT

# (ACUTE)

*DR SHAMS SULEMAN*

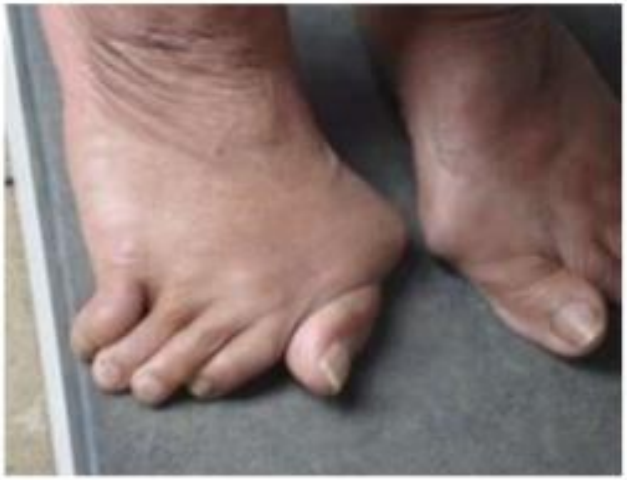
# LEARNING OBJECTIVES

- Classify drugs used to treat gout
- Describe the role of NSAIDs in the treatment of gout
- Describe the role of Glucocorticoids in the treatment of gout
- Describe the mechanism of action of various drugs (Colchicine, Probenecid, Allopurinol, Febuxostat) used in the treatment of Gout

# LEARNING OBJECTIVES

- Discuss the adverse effects of anti-gout drugs
- Describe the drug interactions of Allopurinol and Probenecid
- Enlist the drugs causing hyperuricemia
- Discuss the mechanism by which drugs causes hyperuricemia

# Physical Examination



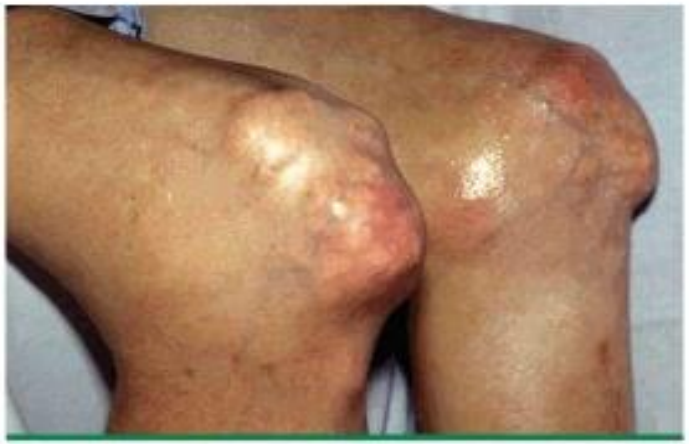
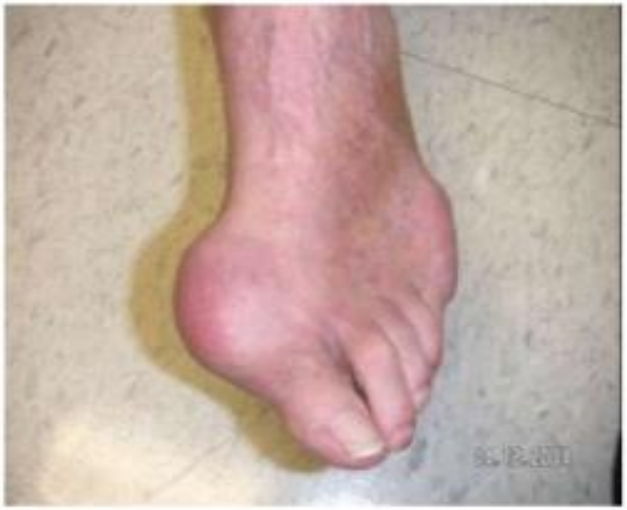
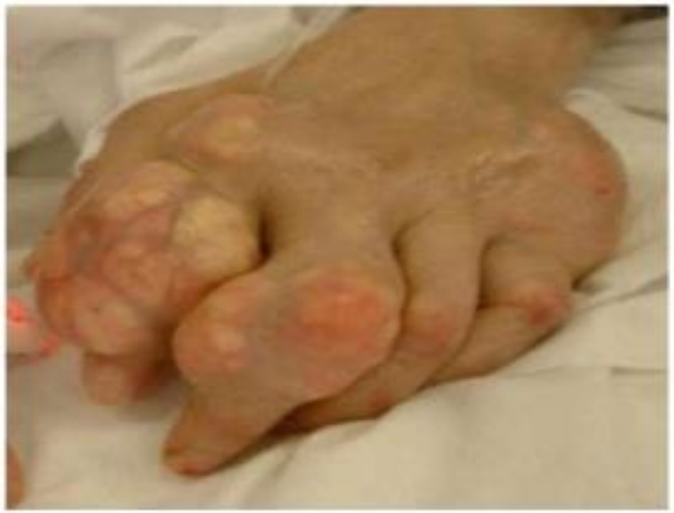
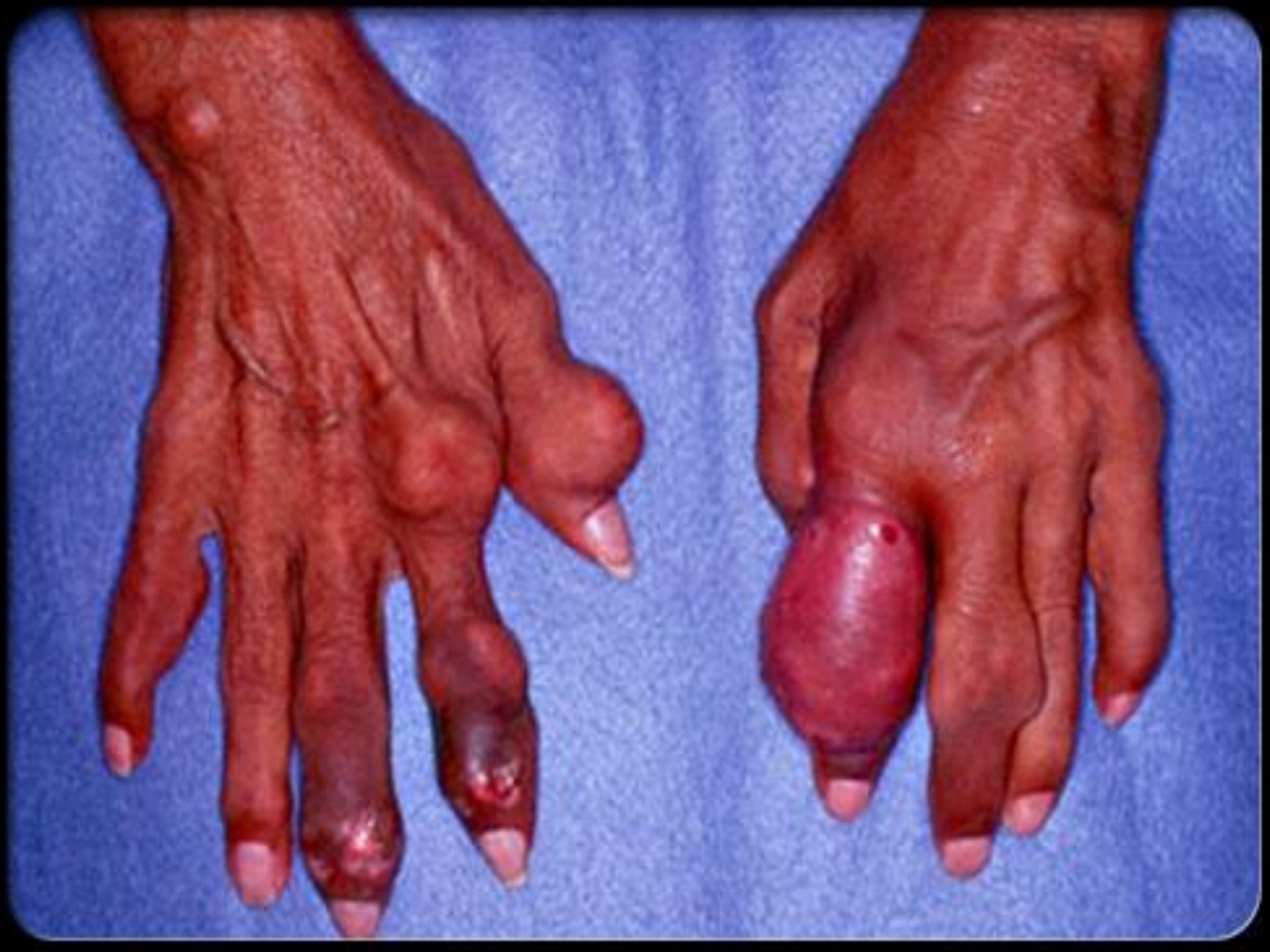


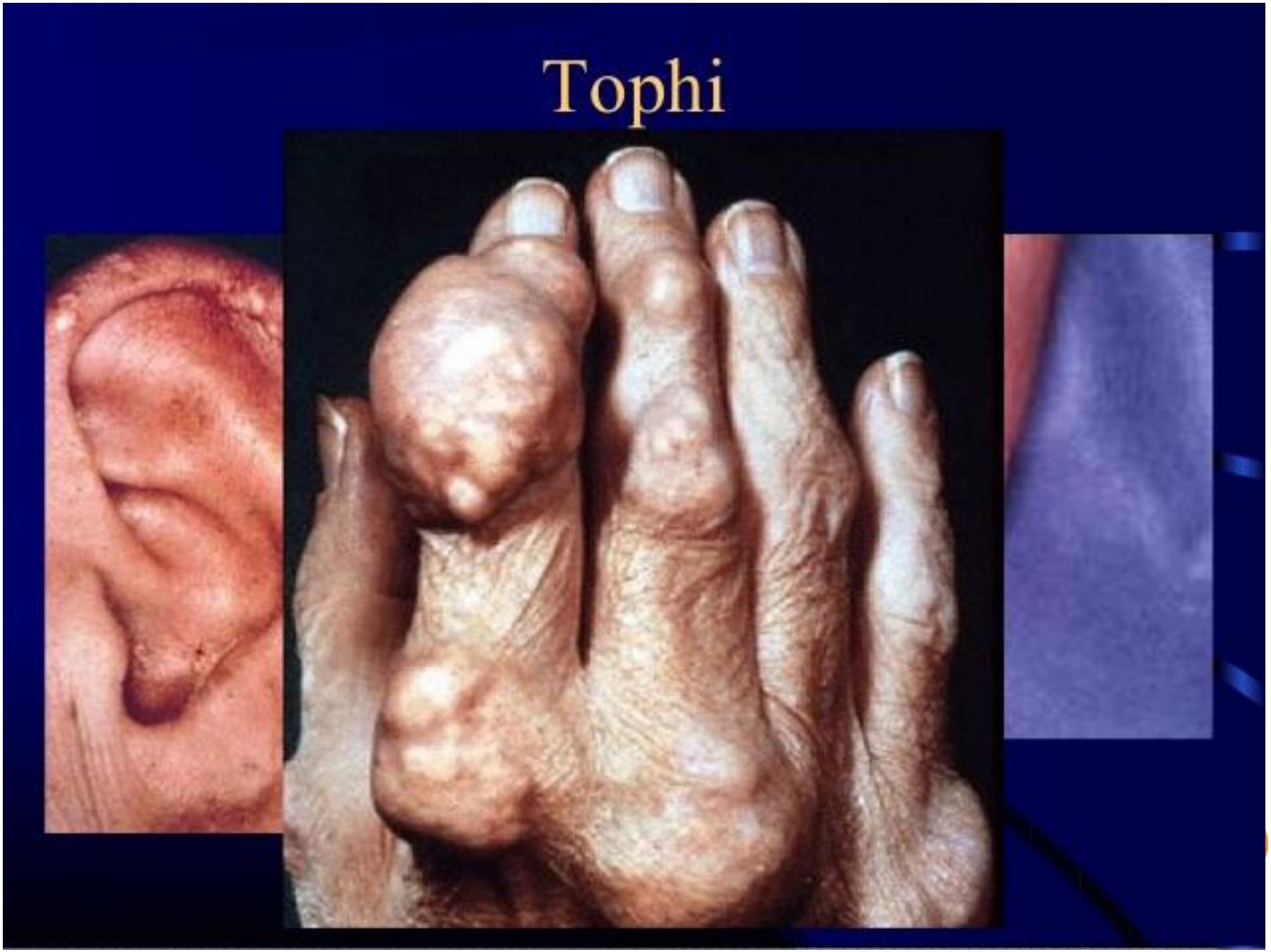
**FIGURE 2.** Multiple tophi overlying both knees in a patient with unrecognized gout.

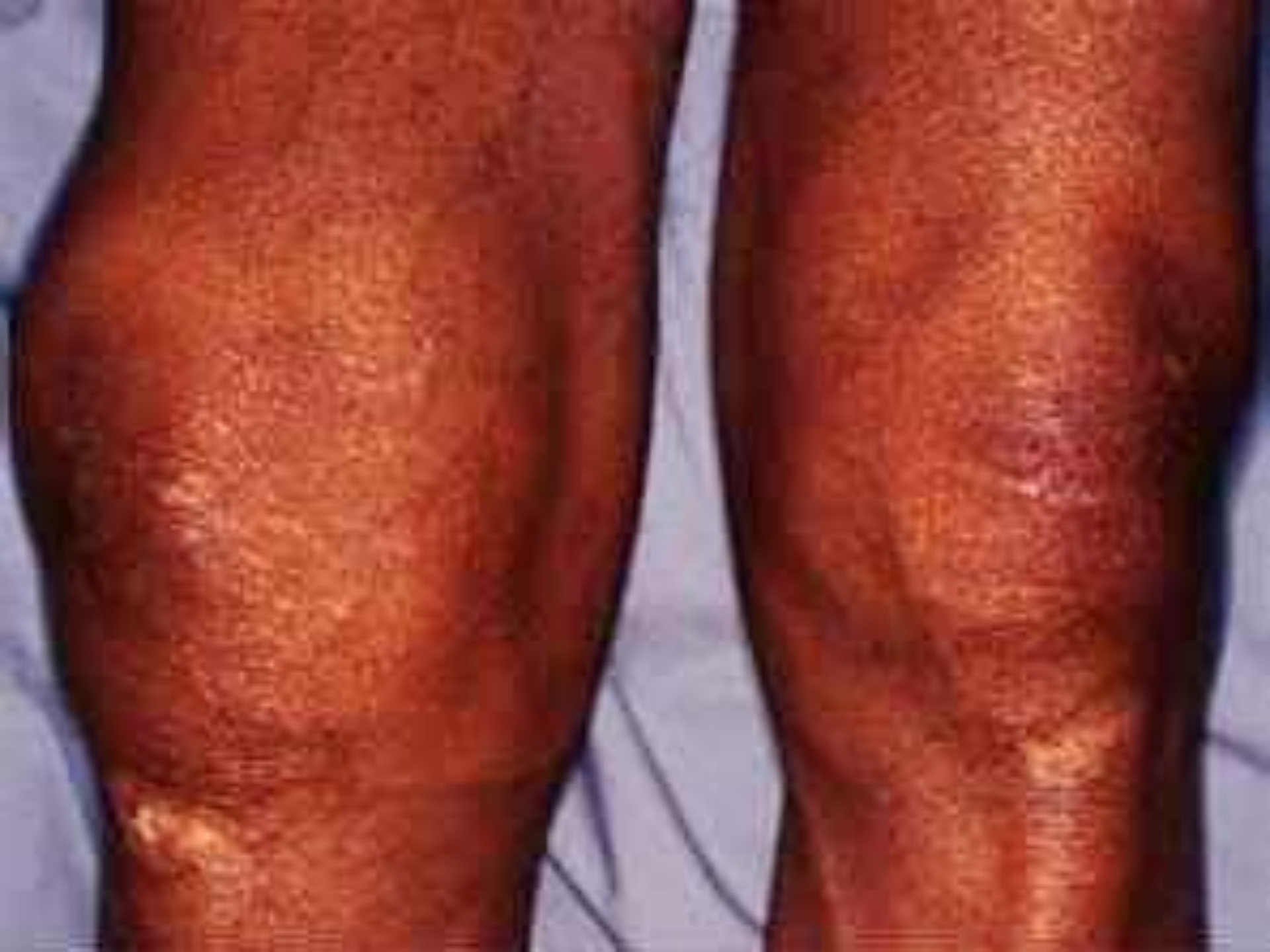


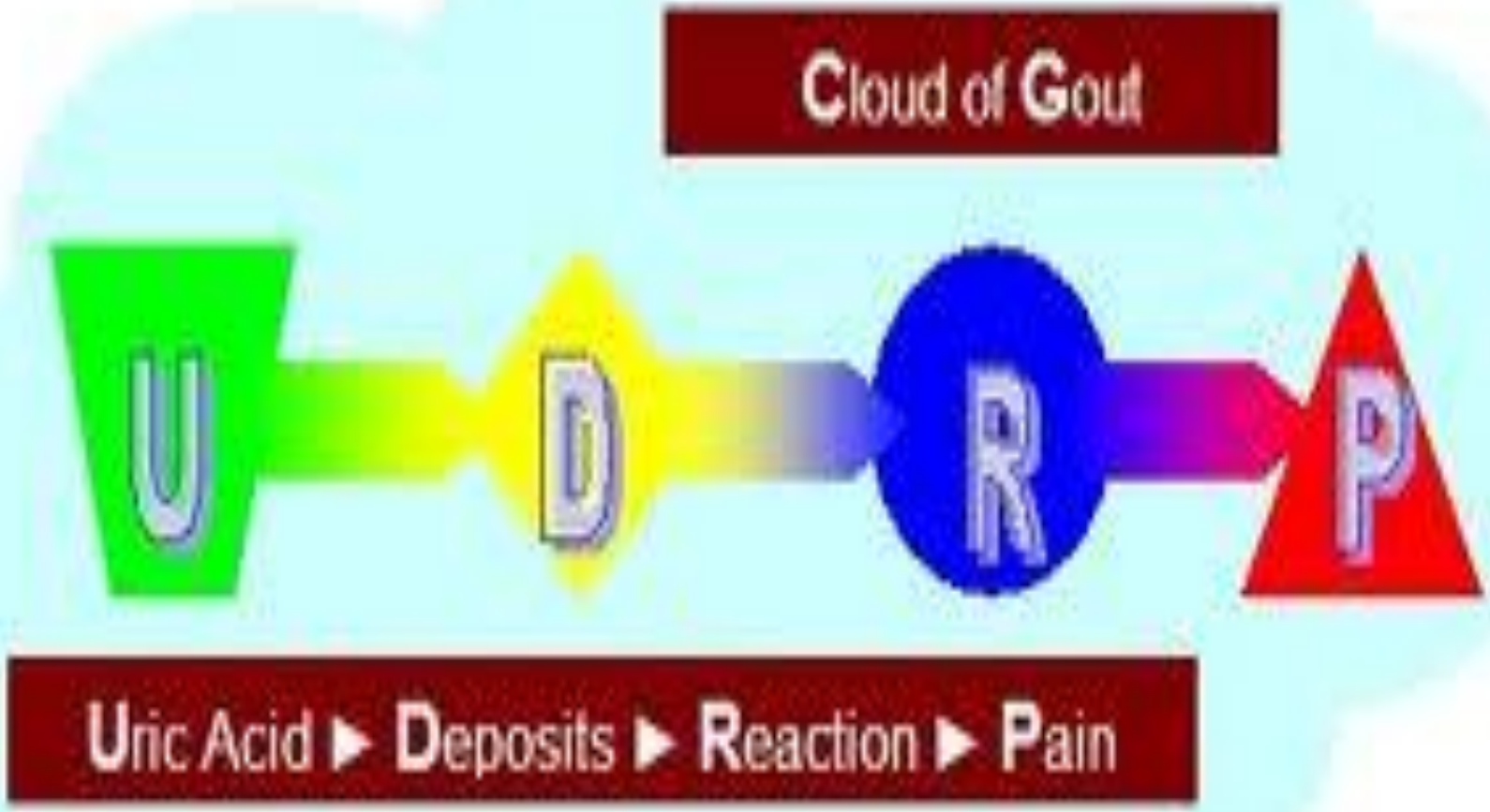




# Tophi






Cloud of Gout
U
D
R
P
Uric Acid ▶ Deposits ▶ Reaction ▶ Pain

# Key Points

- Gout is due to deposition of urate crystals in joints leading to inflammation.
- Diagnosis is by history and polaroid microscopy of synovial fluid.
- High serum uric acid does NOT mean the patient has gout.
- Gout is one of the most treatable arthritic conditions.
- Treat acute attack and then consider prophylaxis of future episodes.
- If untreated, can develop into chronic tophaceous gout.

# *Drugs Used in* **Gout**

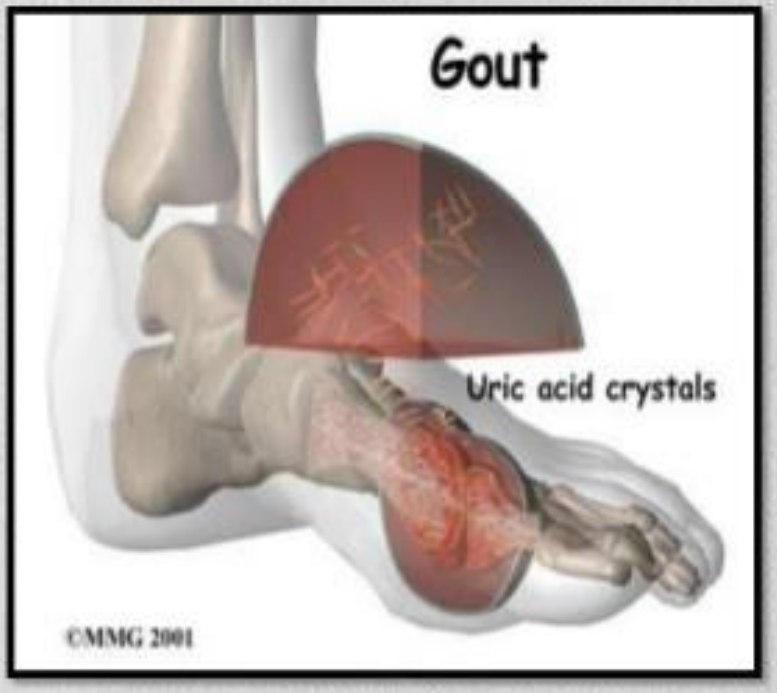
- **Gout** is a familial metabolic disease characterized by recurrent episodes of acute arthritis due to deposits of **monosodium urate** in joints and cartilage.
- Formation of ***uric acid calculi*** in the kidneys may also occur.
- It is usually associated with high serum levels of uric acid, a poorly soluble substance that is the major end product of purine metabolism.
- In most mammals, **uricase** converts uric acid to the more soluble **allantoin**; this enzyme is absent in humans.
- Treatment of gout is aimed at relieving the acute gouty attack and preventing recurrent gouty episodes and urate lithiasis.

# GOUT

## CLINICAL PRESENTATION

- Mono sodium urate crystals
- Allanoin
- Hyperurecemia and gout
- Joints and cartilages, tophi
- Renal calculi, interstitial nephritis
- Arthritis mutilans

# DEFINITION



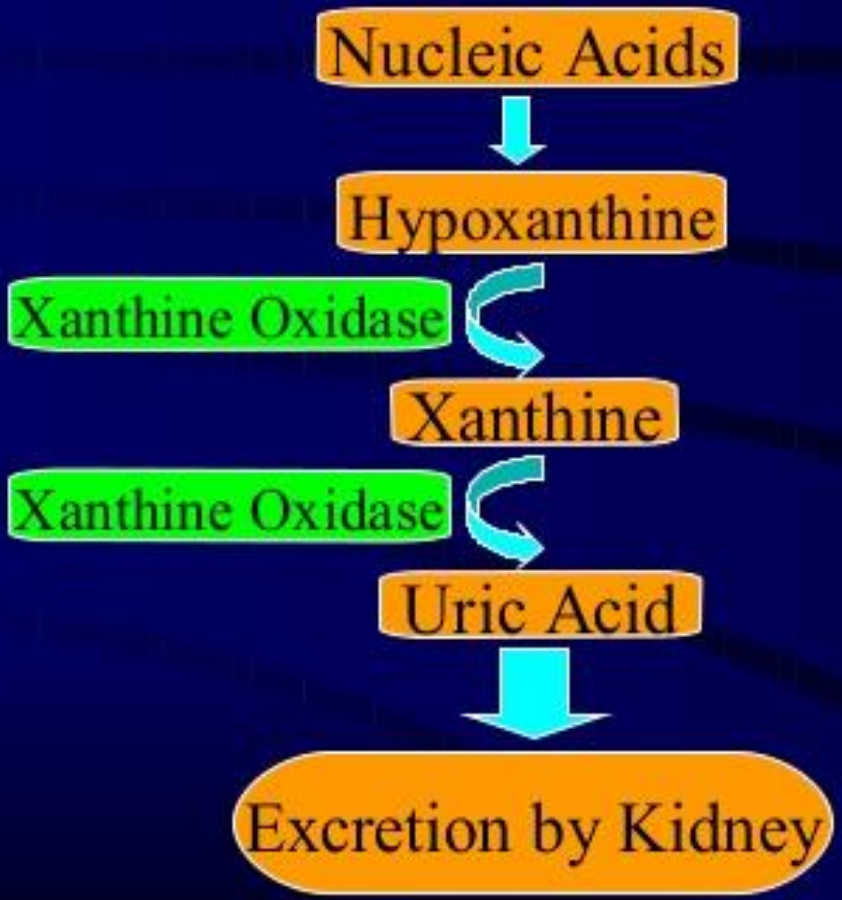

It is derived from the Latin word ***gutta***, meaning "a drop" (of liquid).

Gout is a metabolic disorder characterized by elevated serum uric acid levels and deposits of urate crystals in synovial fluids and surrounding tissues.

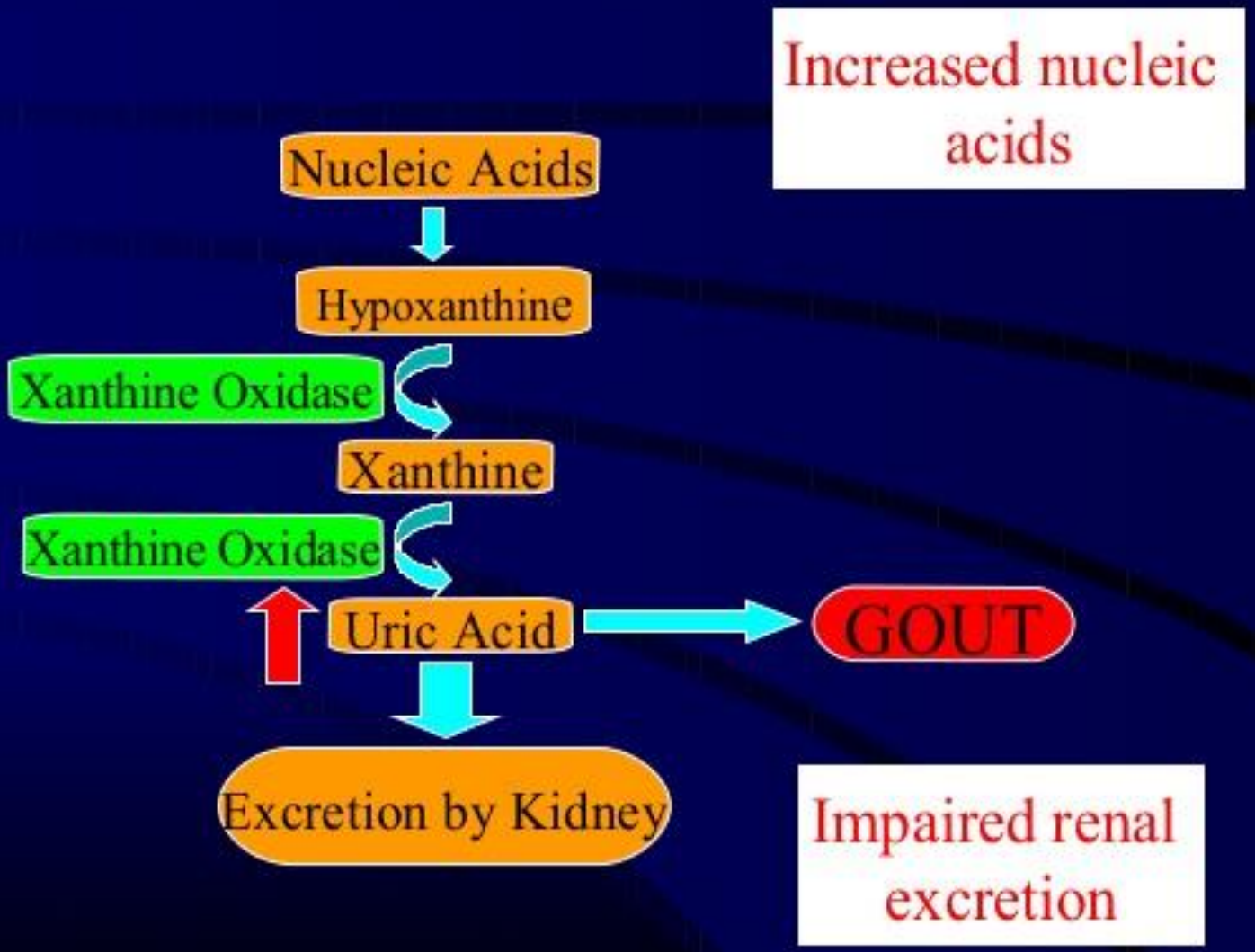
Gout also is a kind of arthritis that occurs when uric acid builds up in blood and causes joint inflammation.

- Acute
- Chronic

# Uric Acid Metabolism



# What goes wrong?



# Cause of hyperuricaemia

- 90% have decreased excretion
- 10% have increased production
- 1% have in born error of metabolism like HGPRT def or PRPP overactivity

## TABLE: DRUGS AND CONDITIONS THAT PREDISPOSE PATIENTS TO GOUT

| Drugs That Decrease Serum UA Levels | Drugs That Increase Serum UA Levels | Diseases Associated with Gout |
|---|---|---|
| • Allopurinol<br>• Diuretics (thiazide and loop)<br>• Febuxostat<br>• NSAIDs<br>• Probenecid<br>• Sulfinpyrazone | • Cyclosporine<br>• Ethambutol<br>• Ethanol<br>• Niacin<br>• Pyrazinamide<br>• Salicylates | • Alcohol abuse<br>• Chronic kidney disease<br>• Genetic or acquired cause of UA overproduction (eg, inborn error of purine metabolism or psoriasis, myeloproliferative, or lymphoproliferative disease)<br>• Hyperlipidemia<br>• Hypertension<br>• Metabolic syndrome<br>• Obesity<br>• Type 2 diabetes mellitus<br>• Lead intoxication |

NSAID = nonsteroidal anti-inflammatory drug; UA = uric acid.

Adapted from references 11, 14-17.

Table 2

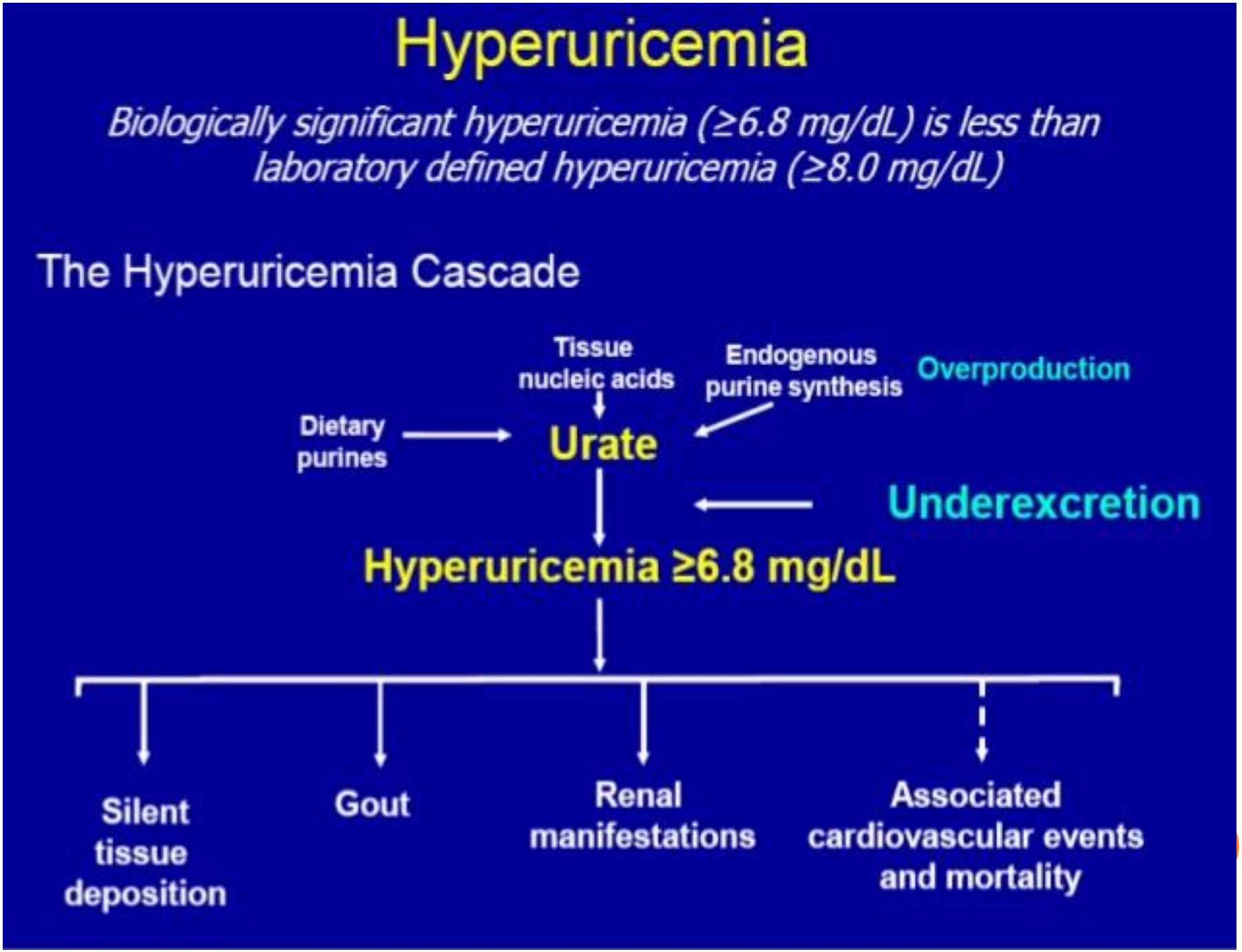
# Medications Associated With Risk of Hyperuricemia and Gout

| Uric Acid–Elevating Medications | Uric Acid–Decreasing Medications |
|---|---|
| ACE inhibitors/ARBs (excluding losartan) | Calcium channel blockers |
| Aspirin (low-dose) | Losartan |
| Beta-blockers | |
| Diuretics | |

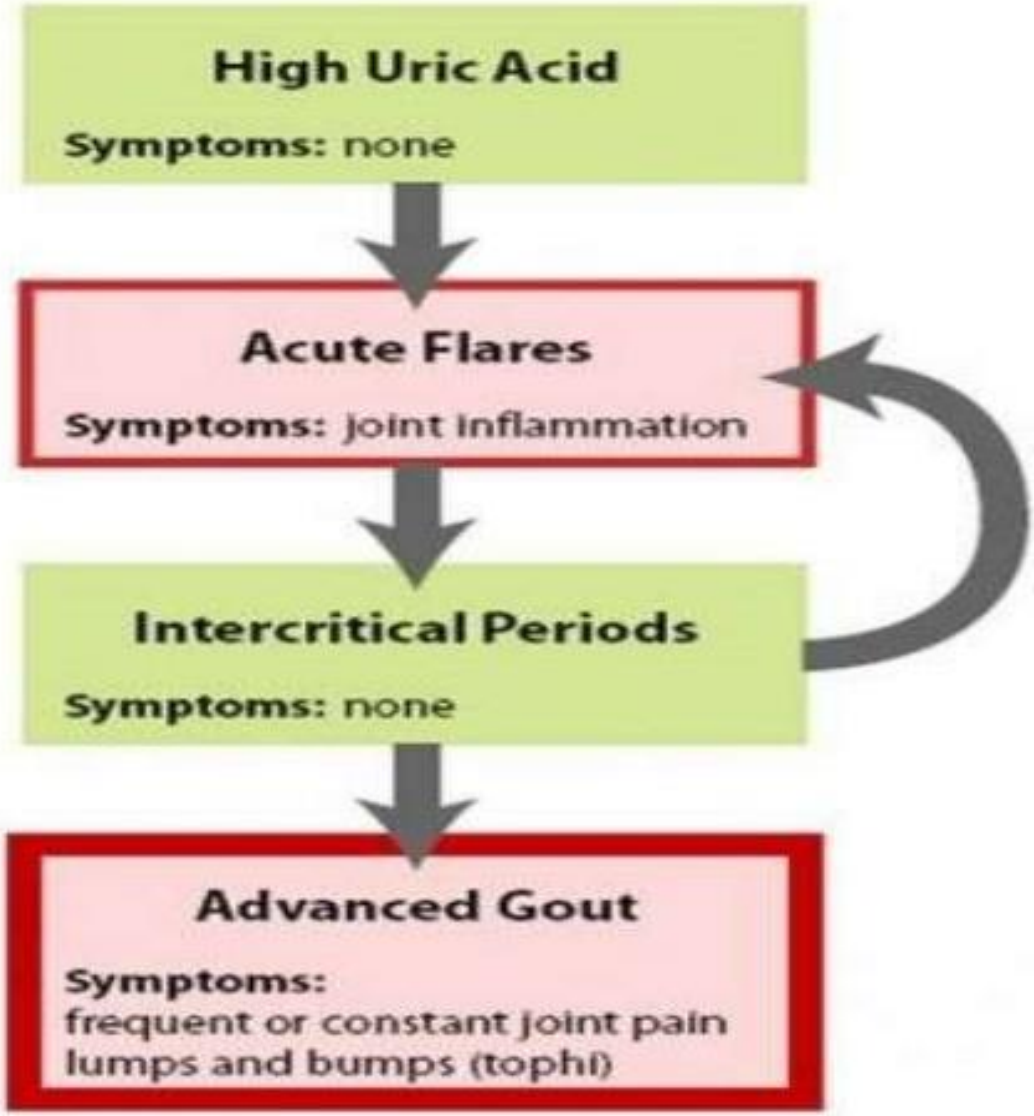
*ARB: angiotensin receptor blocker.*
*Source: References 18, 22-26.*

# Hyperuricemia

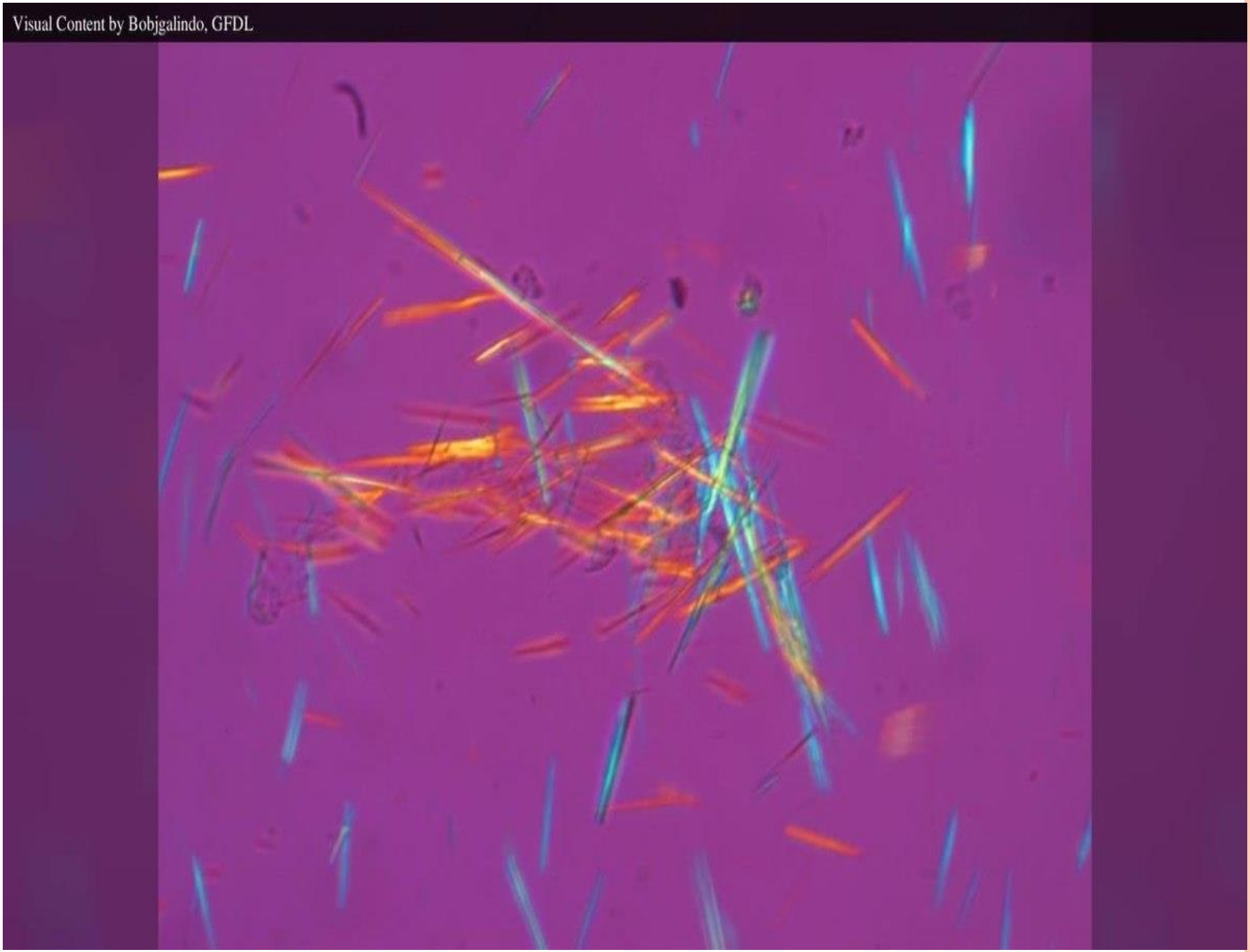
*Biologically significant hyperuricemia (≥6.8 mg/dL) is less than laboratory defined hyperuricemia (≥8.0 mg/dL)*



# Gout Stages


High Uric Acid
Symptoms: none
Acute Flares
Symptoms: joint inflammation
Intercritical Periods
Symptoms: none
Advanced Gout
Symptoms:
frequent or constant joint pain
lumps and bumps (tophi)

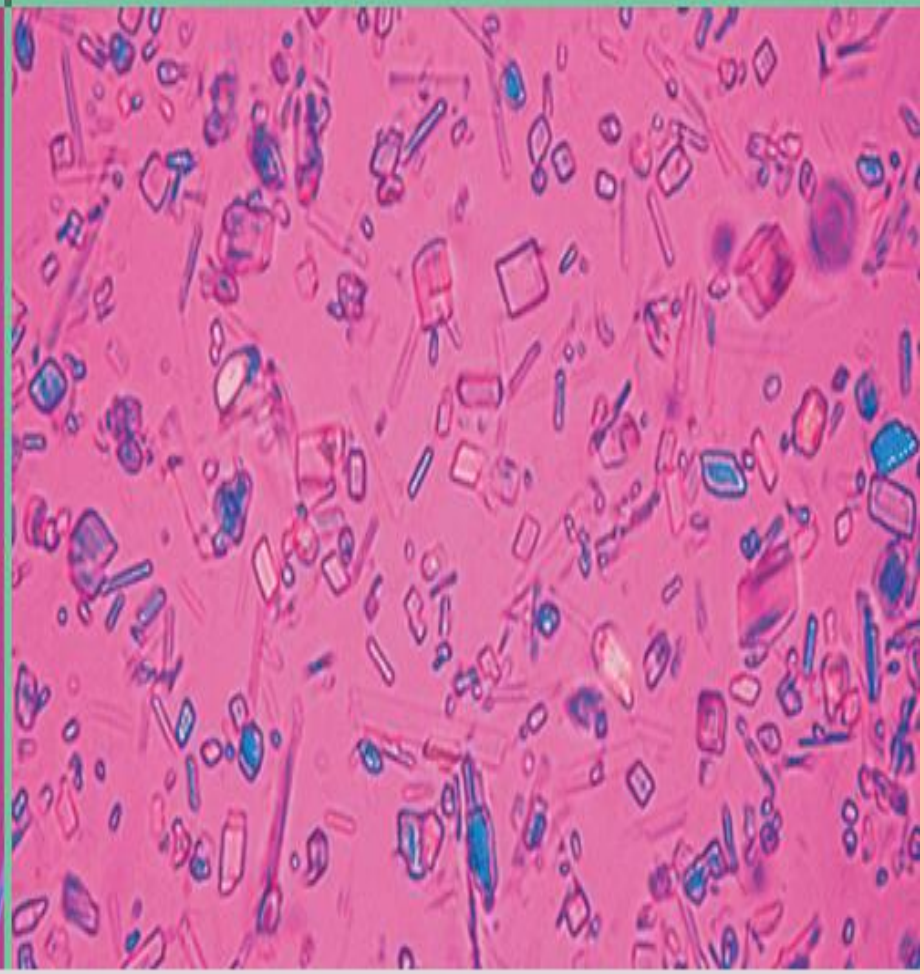

SCIENCEPHOTOLIBRARY


Visual Content by Bobjgalindo, GFDL

## Monosodium Urate (MSU) Crystals

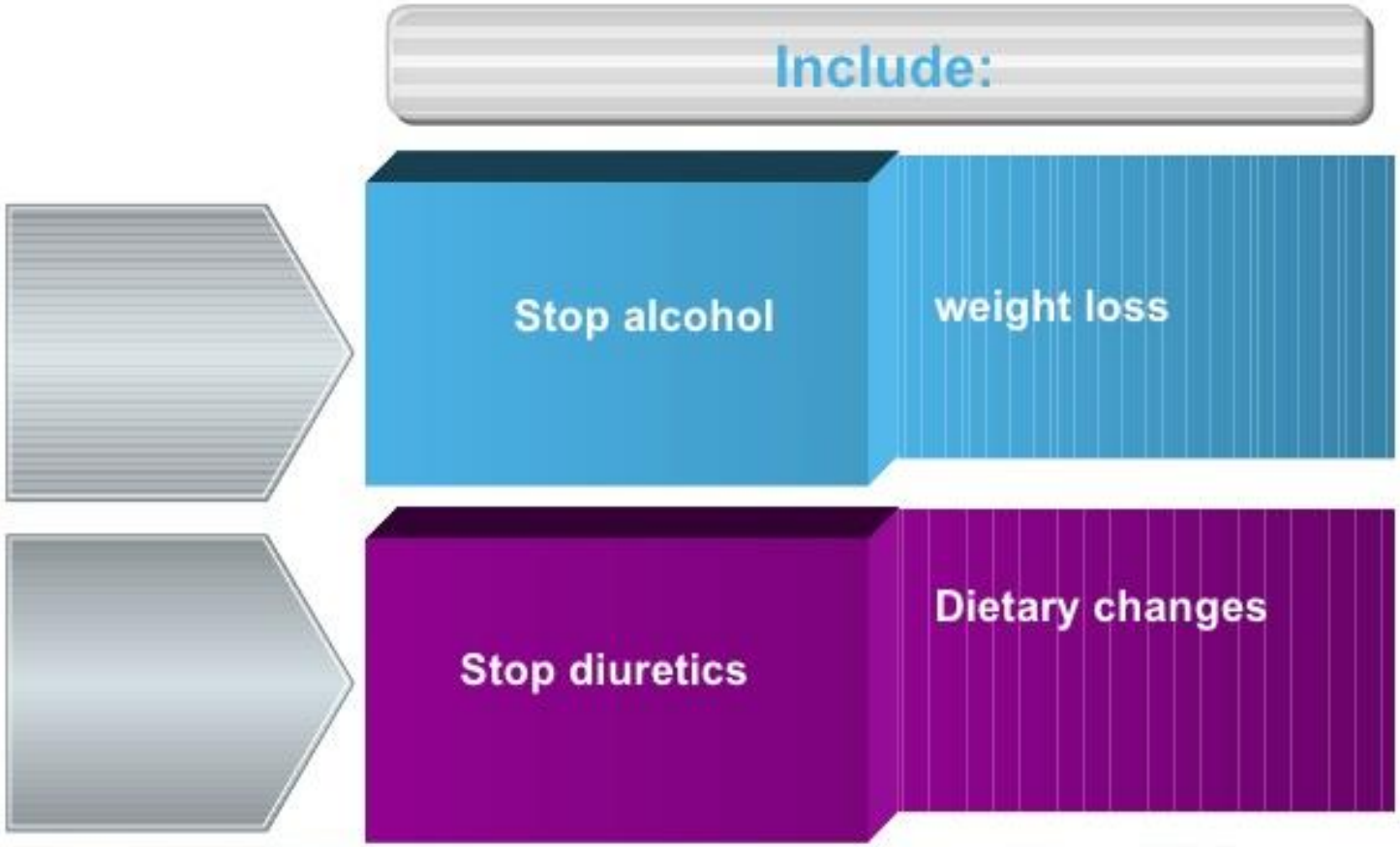
Needle shaped, strong negative birefringence
Yellow when parallel to compensator ray

## Calcium Pyrophosphate Dihydrate (CPPD) Crystals

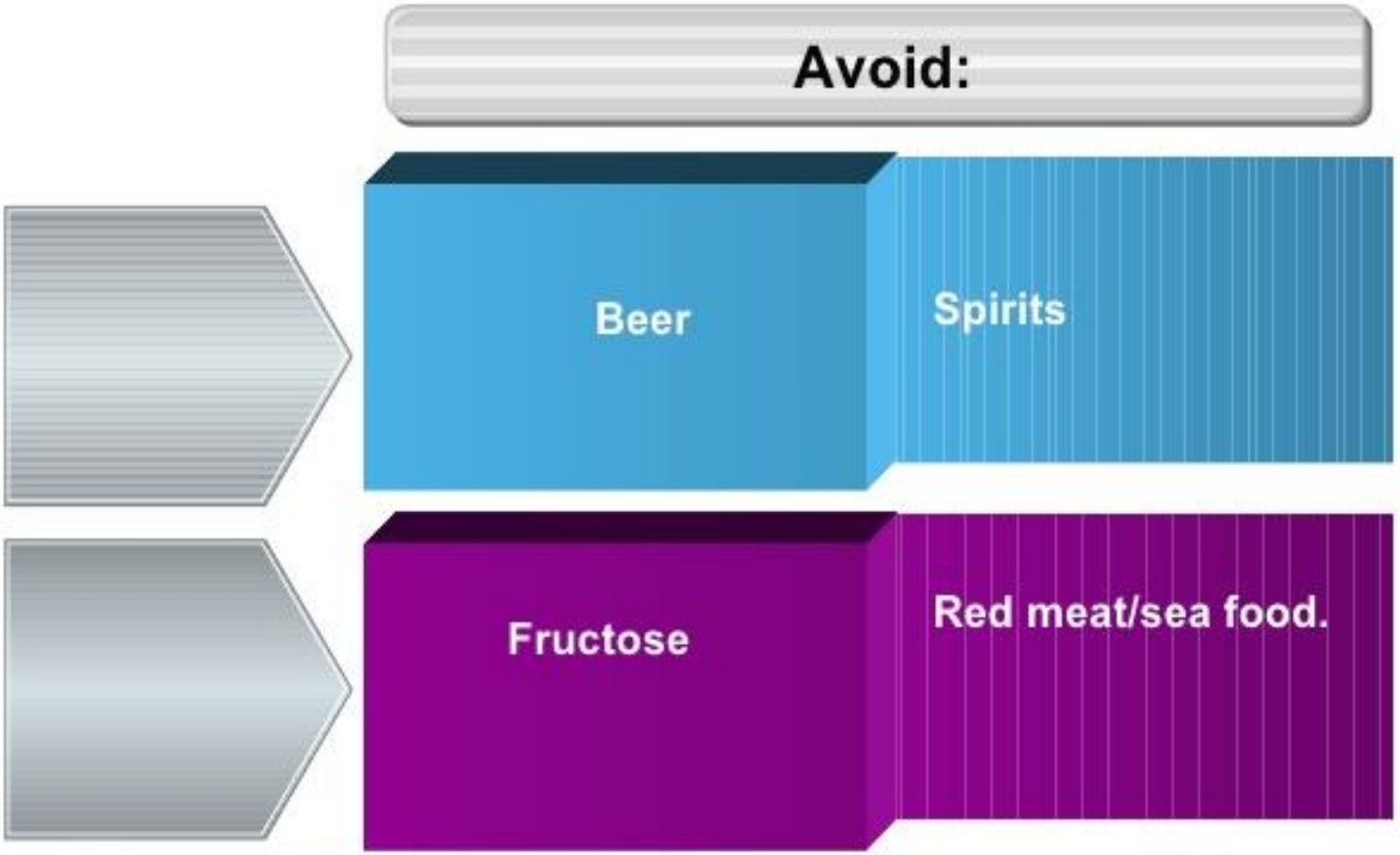


Rod or rhomboid, weak positive birefringence
Blue when parallel to compensator ray

# Non-drug Management:



# Dietary advices:



# Phases of Gout and Treatment Goals


Prevent gouty arthritis

Terminate flare

Prevent repeated flares
Reverse / prevent complications

# DRUGS FOR ACUTE GOUT

- NSAIDs
  - Nonselective Cox inhibitors
  - Selective Cox 2 inhibitors
- Corticosteroids
- Colchicine
- Anakinra

# DRUGS FOR CHRONIC GOUT

- **Uricosuric Agents**

  *(increase urinary excretion of uric acid)*

  - Probenecid
  - Sulfinpyrazone
  - Benzobramone
  - Lesinurad
  - ***Adjuvant drugs: not used primarily for gout***
    - ***Losartan***
    - ***Fenofibrate***
    - ***Atorvastatin***
    - ***Vitamin C***
    - ***Rilonacept***

# DRUGS FOR CHRONIC GOUT

- **Uricostatic agents**

  *(Decreasing Production Of uric acid)*

  - Allopurinol
  - Oxypurinol
  - Febuxostat

- **Uricolytic agents**

  - Rasburicase
  - Pegloticase
  - Polyethylene glycol uricase

# Treatment options for therapeutic goal

## Treatment of acute flares

- NSAIDs
- Colchicine
- Prednisolone
- Intra-articular corticosteroids
- Adrenocorticotropic hormone
- IL-1 inhibitors
  (canakinumab, rilonacept, anakinra)

Acute gout

## Prophylaxis against acute flares

- NSAIDs
- Colchicine
- IL-1 inhibitors
  (canakinumab, rilonacept, anakinra)

## Urate-lowering therapy for chronic gout

- Xanthine oxidase inhibitors
  (allopurinol, febuxostat)
- Uricosuric agents
  (probenecid, sulfinpyrazone, benzbromarone)
- Pegloticase

Chronic Gout

*Nat Rev Rheumatol.2011 Feb;7(2):77-8*

# Treatment of Acute Attack

**AIM- to reduce symptoms**

- NSAID
- Colchicine
  - GI side effects,
  - Most effective in 1st 24 hours
- Corticosteroid
  - If NSAID and colchicine contraindicated

# Preventing Flares

| COLCHICINE | NSAIDs | STEROIDS |
| --- | --- | --- |
| 0.5 mg OD-BID | Low doses + PPI<br>Naproxen 250 mg BID | Pred ≤10mg/d |

**WHICH EVER IS LONGER**

**DURATION**

- 6 months
- 3 months of achieving target SUA if with no visible tophi
- 6 months of achieving target SUA and resolution of visible tophi

Khanna D, Khanna PP, Fitzgerald JD, et al. 2012 ACR Guidelines for Management of Gout. Part 2. Arth Care & Res 2012; 64 (10): 1447-61.

# Starting urate -lowering drugs:

**Urate lowering drugs:**

- Started 1-2 weeks after resolution of the acute attack.

**Prevention of acute flares during maintenance trt:**

- Colchicin or NSAIDs for 3-6 months.

**Flares**

Should be treated without interruption of urate-lowering therapy.

# NSAIDS IN GOUT

**ALL can be used EXCEPT**

- ✓ Aspirin
- ✓ Tolmetin
- ✓ Salicylates

## COMMONLY USED AGENTS

- Indomethacin50 mg thrice daily
- Ibuprofen
- Flurbiprofen
- Oxaprazone = additionally excretes urates

# Treatment

- High Dose NSAIDs
- Rapid response
- Naproxen 750 mg initially then 500mg bid
- Diclofenac 75-100 mg intially then 50 mg bid or tid
- Indomemethacin 75 mg initially the 50 mg bid or qid

# NSAIDs

- Strong anti inflammatory drugs
- Use in patients without contraindication
- Use maximum dose/potent NSAID

  e.g., **Indomethacin** 50 mg po t.i.d.

  **Diclofenac** 50 mg po t.i.d.

  **Ketorolac** 10 mg q4-6hrsr,

  Napoxen, Piroxicam
- continue until pain/inflammation absent for 48 hours
- MOA: inhibit urate crystal phagocytosis and chemotatic migration of leukocytes into inflammed joints.
- NSAIDs are not recommended for long term.

- (Salicylates are not used , have tendency to raise uric acid)

# Aspirin in gout

- Aspirin is not used at low dose ≤ 2.6 g/d

  *( competes with physiological renal excretion of uric acid )*

- Aspirin can be used at high doses >3.6 g/d – Uricosuric action

# Corticosteroid

Use when NSAIDS/Cholchicine risky or contraindicated
e.g.,: elderly

hypertensive

peptic ulcer disease

renal impairment

liver impairment

use when • NSAIDS ineffective

Mode of administration –

- intra articular - Depomedrol 40-80 mg with lidocaine.
- Oral Prednisone 30-40 mg qd for 3-4 days, taper by 5 mg every 2-3 days & stop over 1-2 wks

# Glucocorticoids

- Reduce the migration of inflammatory cells
- Inhibit Phospholipase $A_2$
- Inhibit prostaglandins and leukotriene synthesis

**Oral Prednisone**

Dose is 30–50 mg/d for 1–2 days

Tapered over 7–10 days

**Intra-articular Triamcinolone injection**

10 mg (small joints)

30 mg (wrist, ankle, elbow)

and 40 mg (knee)

# COLCHICINE

- Alkaloid isolated from a plant, *Colchicum Autumnale*
- While NSAIDs are first-line drugs, colchicine is reserved for very severe acute attacks
- Relieves
  - the pain and inflammation of gouty arthritis in 12–24 hours
  - Without altering the production or excretion of urates.

# Colchicine

- Is neither analgesic nor anti – inflammatory, but it suppress gouty inflammation.
- It does not inhibit the synthesis or promote the excretion of uric acid, and has no effect on blood uric acid levels.

# Colchicine Pharmacokinetics

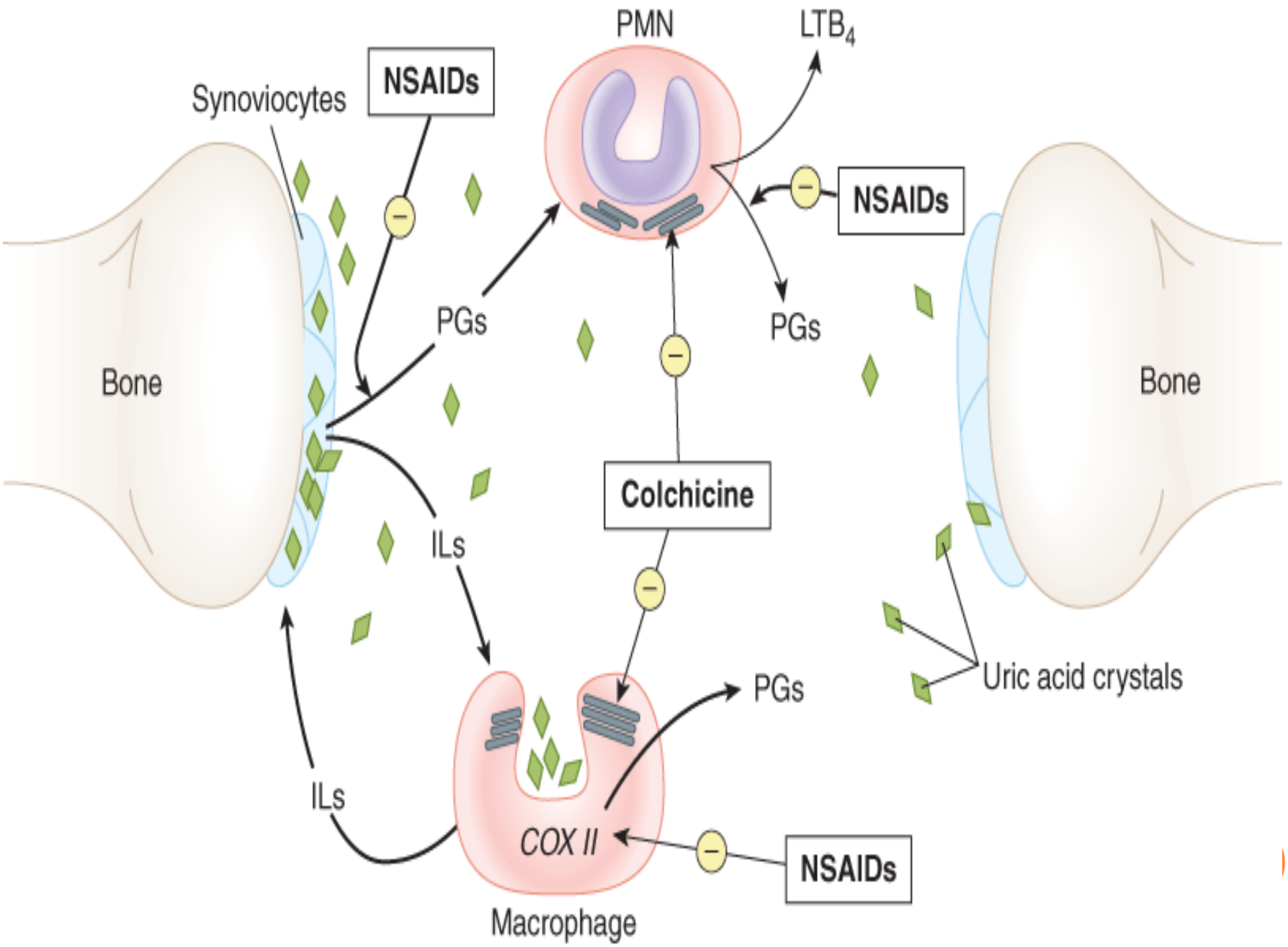
- Oral drug
- Half-life of 9 hours
- Excreted by intestinal tract & Urine

# COLCHICINE: MOA

- Inhibitor of microtubule assembly
- Binds to the intracellular protein tubulin
- Prevents its polymerization into microtubules
- Arrests structural moiety and the neutrophil are immobilized
- Leading to the inhibition of leukocyte migration and phagocytosis

# COLCHICINE: MOA

- Colchicine inhibit glycoprotein release
  - Other actions-
    - arrest of mitosis in metaphas "spindle poison"
    - increases gut motility.
    - Antipyretic , respiratory depressant
    - Inhibit histamine , Insulin release
    - hypertensive at high dose , Increase vasomotor tone
    - direct vasoconstrictor


PMN
$LTB_4$
NSAIDs
Synoviocytes
NSAIDs
PGs
PGs
Bone
Bone
Colchicine
ILs
PGs
Uric acid crystals
ILs
COX II
NSAIDs
Macrophage

# COLCHICINE DOSE

- **PROPHYLACTIC DOSE :**

0.6 mg 1-3 times daily.

- **DURING AN ACUTE ATTACK OF GOUT:**
  - Initial dose of 0.6 mg
  - Followed by 0.6 mg every 2 hours
  - Until pain is relieved or nausea and diarrhea appear.

Total dose can be given intravenously if necessary, but it should be remembered that as little as 8 mg in 24 hours may be fatal.

*(Intravenous use of colchicine is not recommended by FDA)*

# Colchicine: Indications

- Very high plasma levels of uric acid in patients with gout
- Several acute attacks of gouty arthritis in a short period of time
- Gouty tophi

# COLCHICINE ADVERSE EFFECTS

**Acute intoxication**:

- Burning throat pain
- Bloody diarrhea
- Hematuria
- Fatal ascending central nervous system depression

More common with parenteral therapy

Treatment is supportive.

Parenteral use = FDA disapproved in 2008

# COLCHICINE…..

## ADVERSE EFFECTS

- Diarrhea; rate and use limiting
- Hair loss
- Bone marrow depression
- Alopecia
- Acute renal failure
- Hepatic necrosis

## CHRONIC TOXICITY

- Agranulocytosis
- Peripheral neuritis
- Myopathy

* **Drug interaction with other drug:** Colchicine shows interaction with;

| Sr . No. | Category of drug | Example from class | Interaction |
|---|---|---|---|
| 1. | Cholesterol drugs | atorvastatin, fluvastatin, lovastatin, gemfibrozil | Serious muscle damage. |
| 2. | Antiarrhythmic drug. | Digoxin, | |
| 3. | HIV drugs, | indinavir, atazanavir, nelfinavir, saquinavir, or ritonavir. | |
| 4. | Antidepressressants | nefazodone. | |
| 5. | Antibiotics, | clarithromycin or telithromycin | |
| 6. | Antifungal drugs | ketoconazole or itraconazole. | Increases concentrationof colchicine |
| 7. | Calcium channel blocker | verapamil or diltiazem | stomach pain, constipation, diarrhea, nausea, or vomiting. |

# Interleukin-1 Antagonists (Canakinumab, Anakinra)

- MOA:
  - Anakinra: Competitively inhibits IL-1 from binding to the IL-1 type 1 receptors
  - Canakinumab: Recombinant IL-1β monoclonal antibody
- Dose:
  - Anakinra: 100mg SQ daily x 3 days
  - Canakinumab: 150mg SQ once
- Role in Therapy:
  - Canakinumab is approved in the EU for acute gout
  - FDA has not approved either in America for gout

# Prevention of Further Attacks

**AIM - Prophylaxis**

- Lifestyle changes – to minimise risk factors
- Drug therapies
  - Xanthine oxidase inhibitors e.g. Allopurinol
  - Uricosuric agents e.g. Probenecid
- Need to be taken for life
- Can precipitate an acute attack therefore give together with NSAID or colchicine for 2 months.

# REFERENCES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