GOUT
AND HYPERURICEMIA

INTRODUCTION

Gout "disease of the kings" is a disease spectrum including:

- hyperuricemia,
- recurrent attacks of acute arthritis,
- deposits of monosodium urate crystals in tissues (tophi), interstitial renal disease, and uric acid nephrolithiasis

Hyperuricemia may be an asymptomatic condition, with an increased serum uric acid concentration only.

A urate concentration greater than 7.0 mg/dL is abnormal and associated with an increased risk for gout.

INTRODUCTION

- The incidence and prevalence of gout continue to increase due to numerous factors like **dietary habits, and increasing prevalence of obesity.**

- In the United States, the prevalence of gout is increasing. The prevalence of gout in US adults is 3.9 (8.3 million). This represents a 1.2% increase in prevalence compared to 1988 to 1994.

- Obese persons are twice as likely to have gout as non-obese

- Gout affects **men** about 3 more times than women.

INTRODUCTION

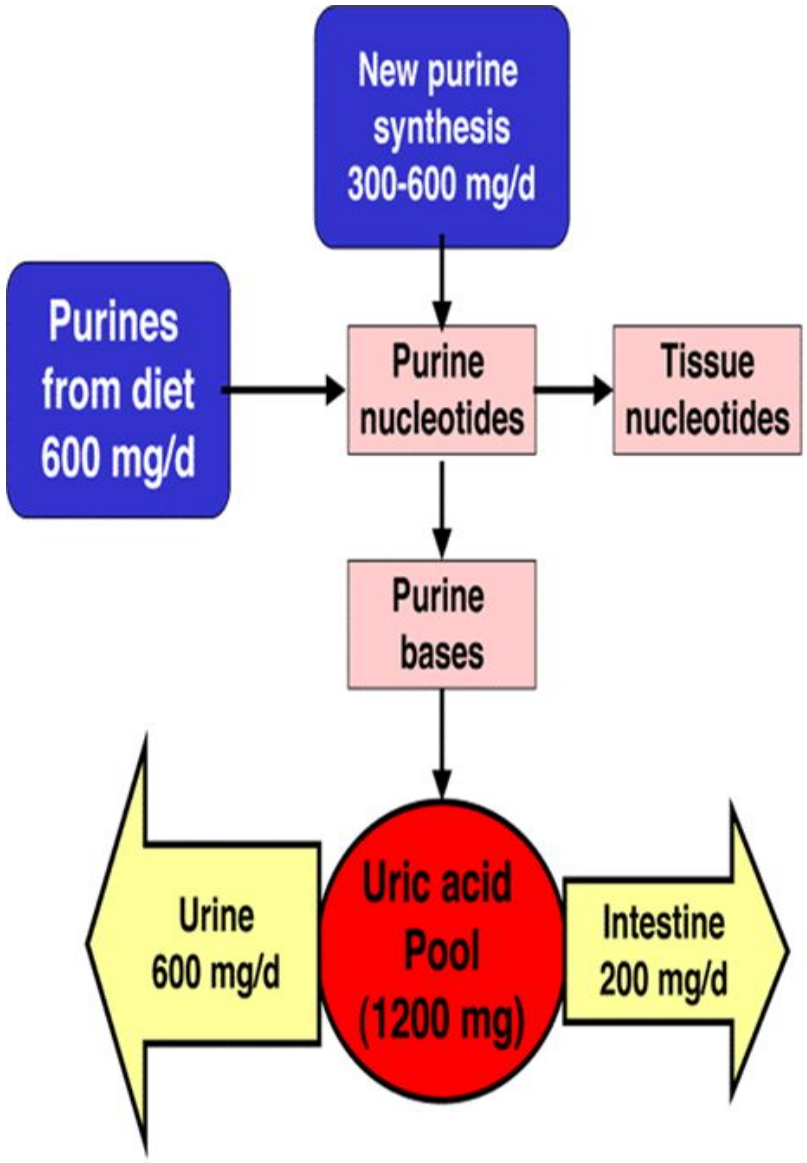
- The incidence of gout increases with **age**, peaking at 30 to 50 years of age.

- Gout in men younger than 30 years of age or in premenopausal women indicate an **inherited** enzyme defect or the presence of renal disease (genetic but still under investigation).

- No studies are available in **Egypt**, but the incidence is expected to be warning.

Pathophysiology

- uric acid is the end product of the degradation of purines (a waste product). The **average human excrete about 600 to 800 mg of uric acid each day**
- Gout occurs exclusively in humans in whom a **miscible pool of uric acid exists**. **Under normal conditions, the amount of accumulated uric acid is about 1,200 mg in men and about 600 mg in women**.
- The purines from which uric acid is produced originate from three sources: **dietary purine, conversion of tissue nucleic acid to purine nucleotides, and de novo synthesis of purine bases.**



OVERPRODUCTION OF URIC ACID

- This excess uric acid accumulation may result from either overproduction or underexcretion.
- Two Abnormalities in the enzyme systems that regulate purine metabolism may result in overproduction of uric acid (de Nevo synthesis).
- The first is an **increase in the activity of phosphoribosyl pyrophosphate (PRPP) synthase**, and the second is a **deficiency of hypoxanthine-guanine phosphoribosyl transferase (HGPRT).**
- **Uric acid also increase in hypertensive patients (low renal blood flow)**

OVERPRODUCTION OF URIC ACID

- Uric acid may also be overproduced as a consequence of increased breakdown of tissue nucleic acids, as with myeloproliferative and lymphoproliferative disorders

Condition associated with hyperuricemia	
Diabetic ketoacidosis	obesity
Myeloproliferative disordrs	Renal dysfunction
Lactic acidosis	Thyroid disorder
starvation	Parathyroid disorder
Hemolytic anemia	psoriasis

- Dietary purines play an unimportant role in the generation of hyperuricemia in the absence of some derangement in purine metabolism or elimination.

UNDEREXCRETION OF URIC ACID

- The vast majority of patients (80% to 90%) with gout have a relative decrease in the renal excretion of uric acid.
- Some conditions are asscociated with a decrease in the uric acid elimination as in diabetic ketoacidosis, .

- Drugs that decrease renal clearance of uric acid include diuretics (thiazides), niacin, nicotinic acid, **salicylates (less than 2 g/day) (bimodal effects),** ethanol, pyrazinamide, levodopa, ethambutol, cyclosporine, and cytotoxic drugs (methotraxate).

Differential test for identifying under exceretion

- Hyperuricemic Individuals who excrete more than 600 mg per 24 hours after being on a purine-free diet for 3 to 5 days are considered overproducers.
- Hyperuricemic individuals who excrete less than 600 mg of uric acid per 24 hours on a purine-free diet are defined as underexcretors of uric acid.

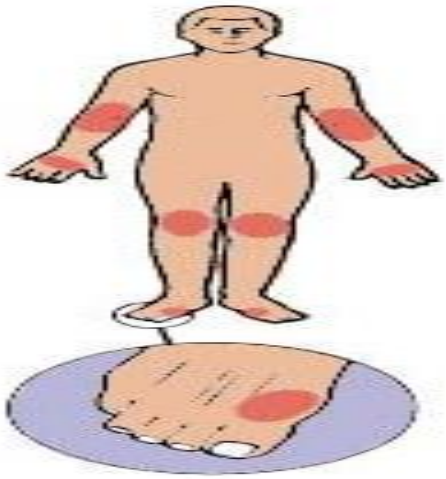
Pathophysiology

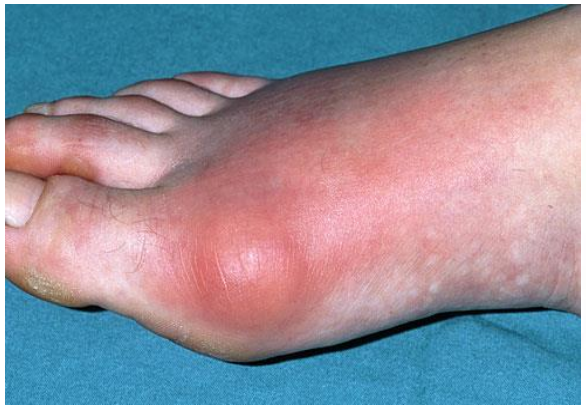
- Deposition of urate crystals in synovial fluid results in an inflammatory process involving chemical mediators **(interleukin 1 mainly)** that cause vasodilation, increased vascular permeability, and chemotactic activity for **polymorphonuclear leukocytes**.

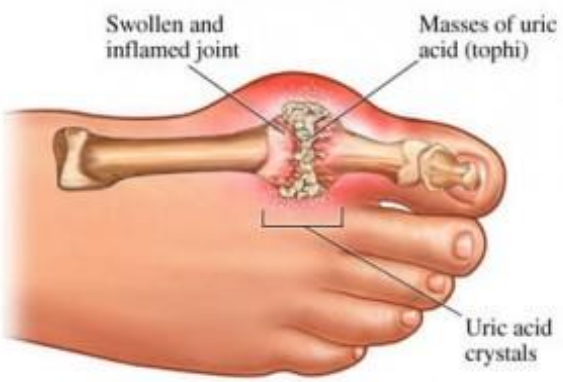
- The resulted inflammatory reaction is associated **with intense joint pain, erythema, warmth, and swelling.**

Manifestation

- Acute attacks of gouty arthritis are characterized by **rapid onset** of joint pain, swelling, inflammation, and redness.
- The attack typically is **mono articular at first**, most often affecting the first metatarsophalangeal joint (great toe known as ***podagra***) and then, ankles, heels, knees, wrists, fingers, and elbows.







Manifestation

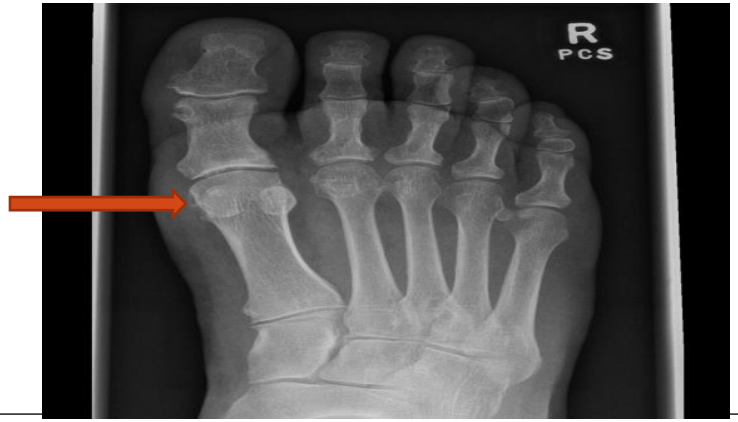
- Attacks commonly begin **at night**, with the patient awakening from sleep with excruciating pain often in the early hours of the morning.
- **Fever and leukocytosis may occur**.
- The inflamed skin over the joint is often **red, shiny and dry**.
- Untreated attacks may last from **3 to 14** days before spontaneous recovery.
- Attacks precipitated by **Stress, alcohol ingestion, regional infection, trauma, surgery, and certain drugs.**

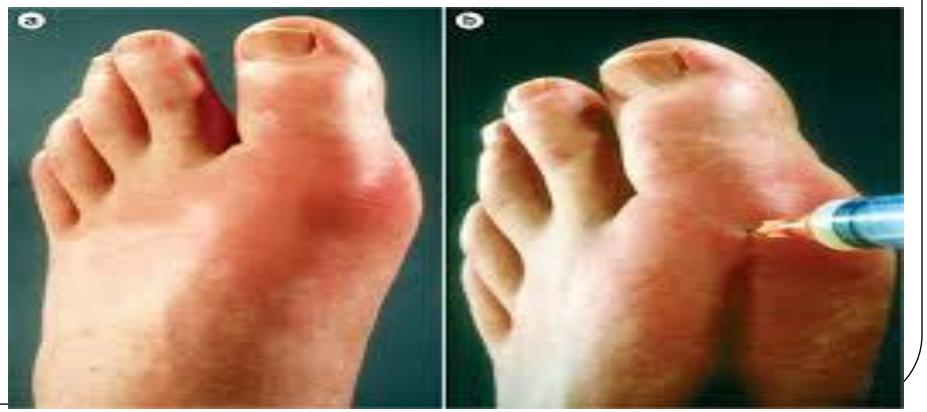
Diagnostic Principles for Gout

1-For typical presentations of gout (such as **recurrent podagra** with **hyperuricemia**), a clinical diagnosis alone is reasonably accurate

2-Demonstration of mono sodium urate (MSU) crystals with leucocyte in synovial fluid aspirates permits a definitive diagnosis of gout

3-Although radiographs may be useful for differential diagnosis and may show typical features in chronic gout, they are not useful in confirming the diagnosis of early or acute gout





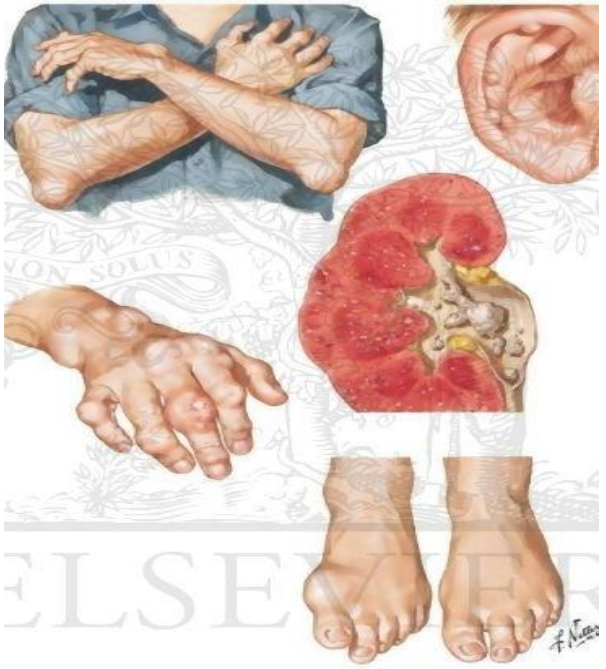
TOPHACEOUS GOUT

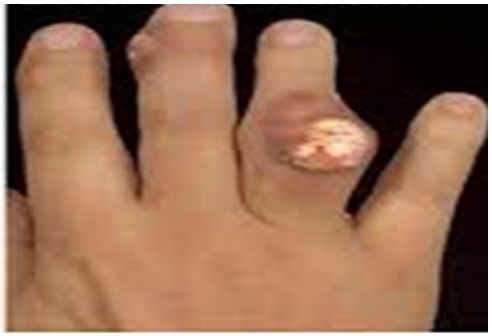
- Tophi (urate deposits) are uncommon in the general population of gouty subjects and are a late complication of hyperuricemia.

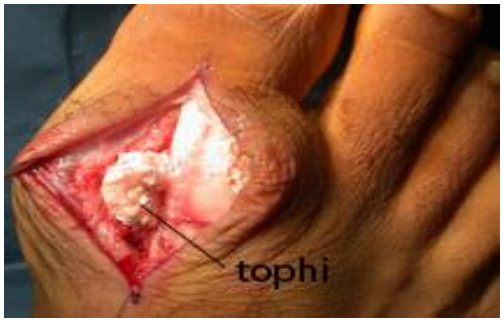
- The most common sites of tophaceous deposits in patients with recurrent acute gouty arthritis are **the base of the great toe, elbow, helix of the ear, knees, wrists, and hands.**

- Tophi causes **deformities, damage surrounding soft tissue, cause joint destruction and pain, and even lead to nerve compression**

- **Treated by surgical removal added to uric acid control.**







URIC ACID NEPHROLITHIASIS

- Nephrolithiasis (Kidney stones) **20 %** of patients with gout.
- The frequency of urolithiasis depends on **serum uric acid concentrations**, **acidity of the urine (urinary pH of <6.0)"precipitate uric acid"**, and **urinary uric acid concentration**. Normal urine PH is **4.5-8.**
- Other factors for uric acid nephrolithiasis include excessive urinary excretion of uric acid (renal excretion of uric acid exceeds 1100 mg/day).

treated with adequate hydration (2 to 3 L/day), and a daytime urine alkalinizing agent, 60 to 80 mEq/day (60 to 80 mmol/L) of potassium bicarbonate or potassium citrate.

GOUTY NEPHROPATHY

- There are two types of gouty nephropathy: acute uric acid nephropathy and chronic urate nephropathy.

- In acute uric acid nephropathy, acute renal failure occurs as a result of blockage of urine flow secondary to **massive precipitation** of uric acid crystals in the collecting ducts and ureters.

- Chronic urate nephropathy is caused by the long-term deposition of urate crystals in the renal parenchyma.

- A decrease in the kidneys' ability to concentrate urine. **Proteinuria, Hypertension and nephrosclerosis** are common associated findings.

Treatment desired outcome

- terminate the acute attack
- Maintain uric acid level below 6 mg/dl (not the primary end point)
- prevent recurrent attacks of gouty arthritis
- prevent complications associated with chronic deposition of urate crystals in tissues.

The treatment involve :

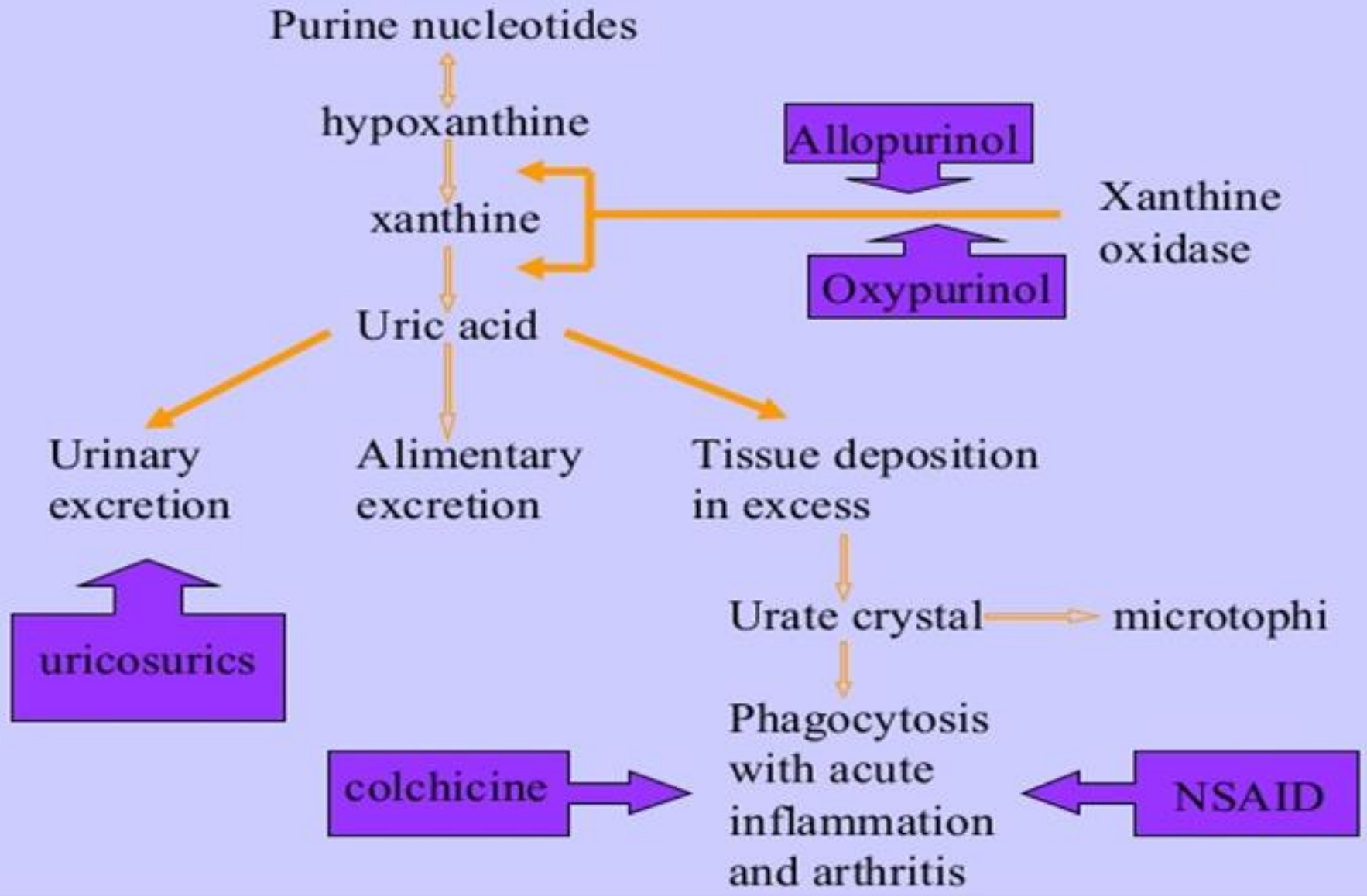
1. Treatment of acute gouty attacks
2. Prevent of chronic attacks (prophylaxis)

Non-pharmacologic Therapies

- reduce their dietary intake of foods high in purines (e.g., organ meats, beans, etc).
- increase fluid intake and decrease salt consumption.
- Decrease weight if obese
- Joint rest for 1 to 2 days should be encouraged
- local application of ice is highly recommended. Joint exercise and application of heat to the affected area should be avoided, as they can worsen the condition.

- Decrease tea and coffee intake
- Decrease alcohol intake
- Avoid stress
- Avoid drugs that precipitate attack specially diuretics

Drug Therapies for Gout



Non-steroidal Antiinflammatory Drugs

Non-steroidal antiinflammatory drugs are the mainstay of therapy for acute attacks of gouty arthritis because of their excellent efficacy and minimal toxicity with short-term use.

Indomethacin is the NSAID of choice for acute gout flares

Indomethacin, naproxen, and sulindac have been approved by FDA for gout. **Aspirin is contraindicated**.

Therapy should be initiated with **maximum dosages** at the onset of symptoms and **continued for 24 hours** after complete resolution of an acute attack, then **tapered quickly over 2 to 3 days.**

Resolution of an acute attack for most patients generally occurs within **5 to 8 days after initiating therapy**.

NSAIDs	
Etodolac	300 mg twice daily
Fenoprofen	300–600 mg three times per day to four times per day
Ibuprofen	800 mg four times per day
Indomethacin[a]	25–50 mg four times per day initially for 3 days, then taper to twice daily for 4–7 days
Ketoprofen	75 mg four times per day
Naproxen[a]	500 mg twice daily initially for 3 days, then 250–500 mg daily for 4–7 days
Piroxicam	20 mg daily or divided twice daily
Sulindac[a]	200 mg twice daily for 7–10 days

- the GI system (gastritis, bleeding, and perforation "**may be given with PPI")**, kidneys (renal papillary necrosis), and cardiovascular system (sodium and fluid retention, increased blood pressure).

- Caution should be exercised when using NSAIDs in individuals with a history of peptic ulcer disease, congestive heart failure, **uncontrolled** hypertension, renal insufficiency, or if receiving **anticoagulants concurrently**.

NSAIDS


Naprofen
500 mg tablets


Sulide
100 mg
Sulide
Sulide
Sulide


30
CAPSULES
INDOCID
INDOMETHACIN
25 MG
CAUTION : to be dispensed only by
or on the prescription of a physician
Manufactured by :
KAHIRA PHARM. & CHEM. IND.CO.
CAIRO - EGYPT
INDOCID
25 mg


liometacen®
Chiesi

Colchicine (new guidelines changes)

- Colchicine is an **antimitotic drug** that is highly effective at relieving acute attacks of gout but has the **lowest benefit/toxicity ratio**.

- Although it is a highly effective therapy, oral colchicine can cause **dose-dependent** gastrointestinal adverse effects, including **nausea, vomiting, and diarrhea**, in **50% to 80%** of patients and non-gastrointestinal adverse effects include **neutropenia and neuromyopathy.**

- When begun within the first 36 hours of an acute attack, colchicine produces a response in two-thirds of patients within hours of administration **(rapid onset)**. If the initiation of colchicine is delayed, the probability of success diminished. So, use colchicine only if started within 36 hours of attack onset

Colchicine

- Colchicine should be reserved for patients with intolerance or contraindications to NSAID use, or in whom ineffective relief with NSAIDs is obtained.

- Colchicine is available in only oral given **1 mg** initially, followed by **0.6 mg 1 hour later**

- Low-dose colchicine is highly effective at relieving acute attacks of gout; dose titration leads to more adverse effects but does not improve efficacy.

Colchicine

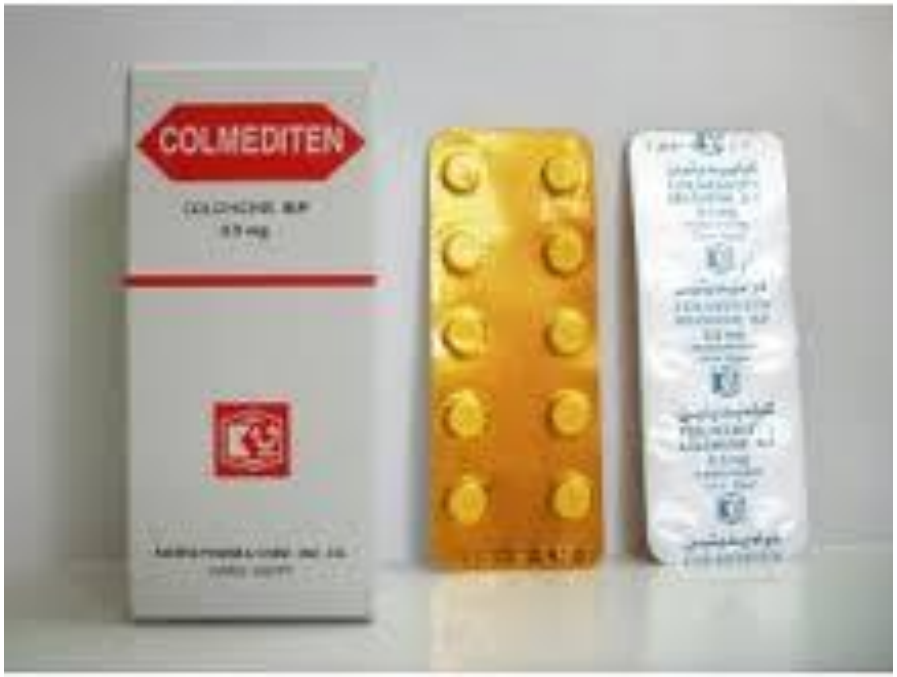
- Colchicine should not be used concurrently with **macrolide antibiotics** (especially clarithromycin) because reduced **biliary excretion** may lead to increased plasma colchicine levels and agranulocytosis.

- IV colchicine is **not recommended (withdrawn)** because it is associated with fatal adverse effects (e.g., bone marrow suppression, disseminated intravascular coagulation, hepatocellular toxicity, and renal failure).

- Dose adjustment recommended when used with selected

CYP3A4 and P-glycoprotein Inhibitors (polypharmacy)

Colchicine



Colchicine combination (common)

- Usually as sachets (effervescent) contain colchicine in addition to:
- Piperazine and Na bicarbonate (solubilize urate crystal by alkalinize urine)
- Khelin, and atropine sulfate (antispasmodic)
- Ex: **Urosolvine, Urivin**,

NB:

- Potassium sodium hydrogen citrate(Uralyt-U) action is based on the fact that it can stabilize the pH of urine within the correct pH range of 6.2 to 6.8.

Colchicine combination (common)

Corticosteroids

- Corticosteroids may be used to treat acute attacks of gouty arthritis for patients with a contra-indication or who are unresponsive to NSAID or colchicine therapy.

- They can be used either systemically or by intraarticular injection.

- Oral corticosteroids may be administered in doses of 30 to 60 mg for **3 to 5 days**.

- Because **rebound attacks** may occur upon steroid withdrawal, the dose should be **tapered gradually in 5 mg decrements spread over 10 to 14 days and then discontinued**.

Corticosteroids

- A single **intramuscular injection** of a long-acting corticosteroid, such as methylprednisolone, can be used as an alternative to the oral route if patients are **unable to take oral therapy.**

- **Intraarticular administration** of triamcinolone acetonide in a dose of 20 to 40 mg may be useful in treating acute gout limited to one or two joints.

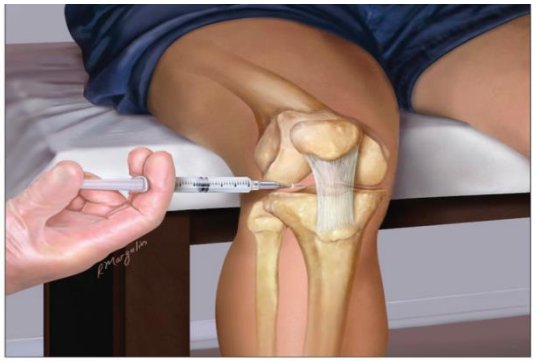
- Adrenocorticotropic hormone (ACTH) gel, 40 to 80 USP units, may be given **intramuscularly** every 6 to 8 hours for 2 to 3 days and then discontinued. reserved for patients with contraindications to corticosteroids.

Corticosteroids

- Corticosteroids should be used with caution in patients with **diabetes** as they can increase blood sugar.

- In addition, patients with a history of **gastrointestinal problems, bleeding disorders, cardiovascular disease, and psychiatric disorders** should be monitored closely.

- **Long-term corticosteroid use show risk for osteoporosis, hypothalamic– pituitary axis suppression, cataracts.**



Adverse effects

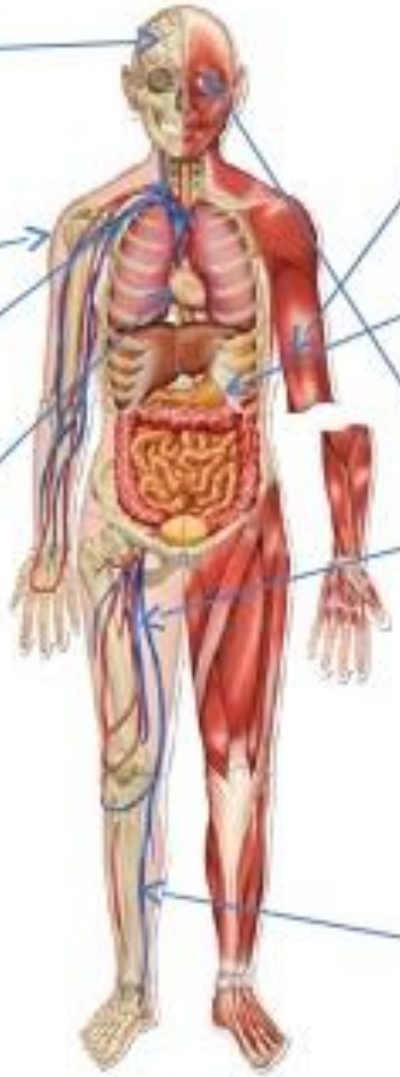
- Occur with prolonged use of high doses
- Cushing's disease

Psychiatric
- Sleep disturbance/activation
- Mood disturbance
- Psychosis

Skin/soft tissue
- Cushingoid appearance
- Abdominal striae
- Acne
- Hirsutism
- Oedema

Neurologic
- Neuropathy
- Pseudomotor cerebri

Cardiovascular
- Hypertension



MSK
- Osteoporosis
- Asceptic necrosis of bone
- Myopathy

Endocrine
- Diabetes mellitus
- Adrenal cortex suppression

Immunologic
- Lymphocytopenia
- Immunosuppression
- False-negative skin test

Opthalmic
- Cataract
- Narrow-angle glaucoma

Developmental
- Growth retardation

Interleukin-1 inhibitors

- Urate crystals elicit an inflammatory response that triggers the production of interleukin-1 (IL-1). This finding has led to the investigational use of IL-1 inhibitors in the treatment of acute gout.

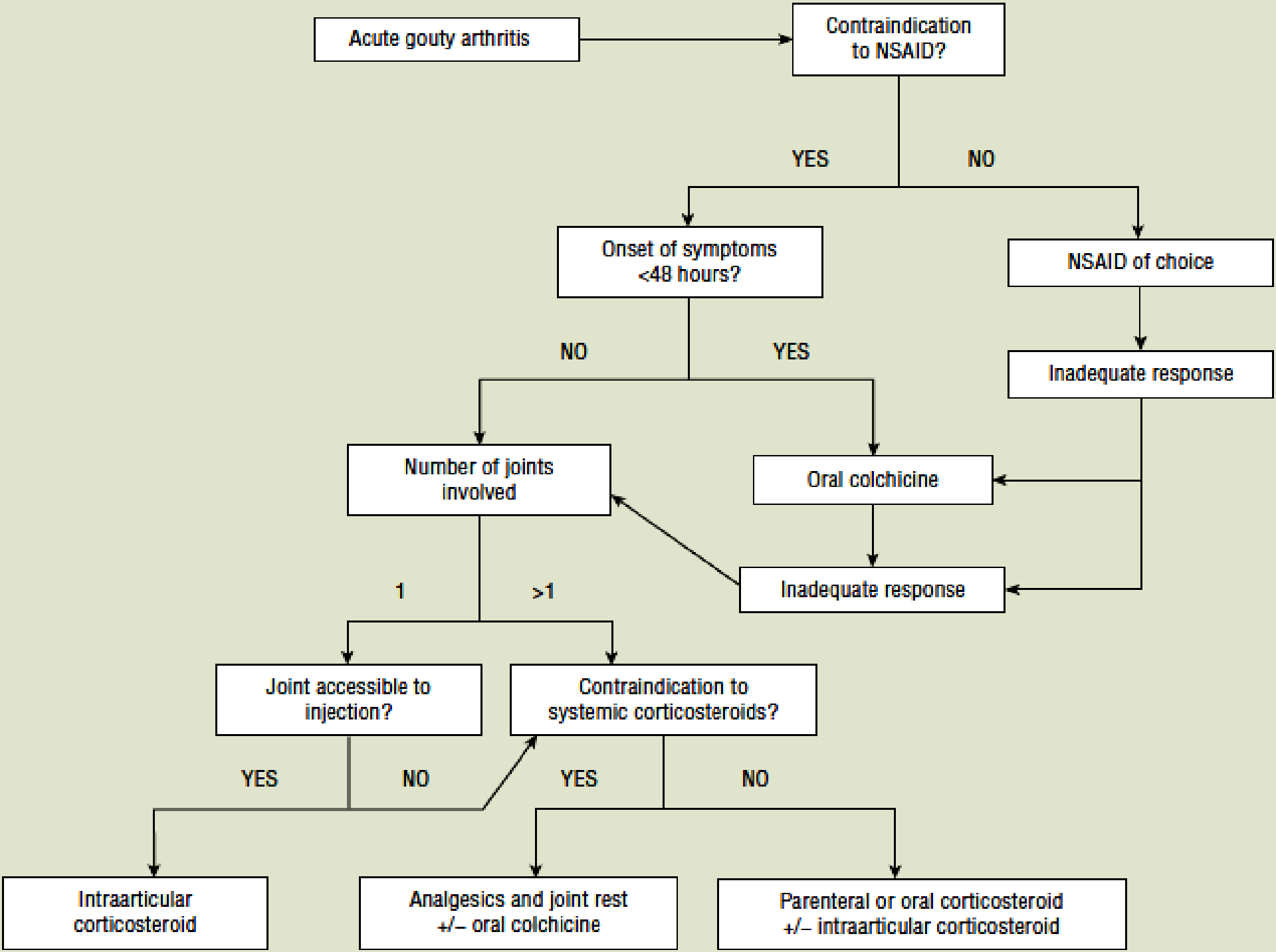
- Interleukin-1 inhibitors **Reserve use for refractory cases**

Anakinra 100 mg SC daily for 3 days

Canakinumab Single dose 150 mg SC

- Effect: Resolution of pain and Avoidance of gout attacks when used for prophylaxis

- Caution: **Neutrophil count** (prior to initiation, monthly for the first 3 months of therapy) and safety for use in acute gout and gout prophylaxis during initiation of urate-lowering therapy has not yet been established; **not FDA approved** for use in gout


Acute gouty arthritis
Contraindication to NSAID?
YES
NO
Onset of symptoms <48 hours?
NSAID of choice
NO
YES
Inadequate response
Number of joints involved
Oral colchicine
1
>1
Inadequate response
Joint accessible to injection?
Contraindication to systemic corticosteroids?
YES
NO
YES
NO
Intraarticular corticosteroid
Analgesics and joint rest +/– oral colchicine
Parenteral or oral corticosteroid +/– intraarticular corticosteroid

PROPHYLACTIC THERAPY

- WHEN TO INSTITUTE?
- If the patient had a severe attack of gouty arthritis with two or more episode yearly
- A complicated course of uric acid nephrolithiasis, or chronic kidney disease, the presence of one or more tophus
- A substantially elevated serum uric acid level (>10 mg/dL), or A 24-hour urinary excretion of uric acid of more than 1,000 mg

PROPHYLACTIC THERAPY

prophylactic treatment should be instituted immediately after resolution of the acute episode.

Pharmacoeconomics data:

Prophylactic therapy is **cost-effective** for patients with frequent attacks of gouty arthritis (i.e., two or more attacks per year)

- Discontinuation of prophylaxis may be attempted if the serum urate concentration remains normal and the patient is symptom-free with no complication for **1 year**.

PROPHYLACTIC THERAPY

- Recent guidelines include **uric acid-lowering therapy** with **anti-inflammatory prophylaxis during initiation of urate-lowering therapy**

- Reduction of the serum urate concentration can be accomplished pharmacologically by:
  - **Decreasing the synthesis of uric acid (xanthine oxidase inhibitors)**
  - **Increasing the renal excretion of uric acid (uricosurics).**

- The therapeutic objective is to achieve no gouty attacks and maintain a serum uric acid concentration <6 mg/dL.

Anti-inflammatory Prophylaxis During Initiation of Urate-Lowering Therapy

- Low-dose colchicine, NSAID, or corticosteroid therapy should be administered **during the first 3 to 6 months of urate-lowering therapy** to minimize the risk of acute gout attacks that may occur during this initiation period.

- 1-NSAIDs **Lowest effective dosage**
- 2-Oral colchicine 0.6 mg daily 0.6 mg once or twice daily
- 3-Prednisone or prednisolone ≤10 mg daily
- 4-Second-line therapy (Interleukin-1 inhibitors)

Rilonacept 320 mg loading dose followed by 160 mg weekly (SC) Studied for 16-weekduration

Canakinumab Single SC dose (50 mg to 300 mg) or four times weekly SC dosing (50 mg —50 mg— 25 mg—25 mg)

Xanthine Oxidase Inhibitor

- Allopurinol and its major metabolite, **oxypurinol**, are xanthine oxidase inhibitors and impair the conversion of hypoxanthine to xanthine and xanthine to uric acid.

- Xanthine oxidase inhibitors are efficacious for the prophylaxis of recurrent gout attacks in **both underexcreters and overproducers of uric acid**.

- Because of the long half-life of its metabolite, allopurinol can be given **once daily orally**

Xanthine Oxidase Inhibitor

- It is typically initiated at a dose of 100 mg/day, and titrated by **100 mg/day at 2-5 weeks** intervals to achieve a serum uric acid level of 6 mg/dL or less.

- Serum uric acid levels can be checked approximately 2-5 weeks after initiating or modifying the dose of allopurinol. Typical doses of 100 to 300 mg/ day are used.

- The dose of allopurinol should be reduced in patients with **renal insufficiency** (**200 mg/day** for creatinine clearance of 60 mL/min, and **100 mg/day** for creatinine clearance of 30 mL/min).

Xanthine Oxidase Inhibitor

- The major side effects of allopurinol are skin rash, urticaria, **leukopenia**, GI problems, headache, and increased frequency of acute gouty attacks with the initiation of therapy (avoided now).

- An allopurinol **hypersensitivity** syndrome characterized by fever, eosinophilia, dermatitis, vasculitis, and renal and hepatic dysfunction occurs but rarely

Febuxostate (Adenuric)

- It inhibits xanthine oxidase, thus reducing production of uric acid in the body can be **used for both overproduction and under excretion cases.**
- Febuxostat is more effective than standard doses of allopurinol, but not more effective than higher doses.
- The adverse effects associated with febuxostat therapy include nausea, diarrhea, arthralgia, headache, **increased hepatic serum enzyme levels and may kidney toxicity**.
- Febuxostat is a non-purine-selective inhibitor of xanthine oxidase. It works by non-competitive blocking

Uricosuric Drugs (new guidelines)

- **Recent guideline by American College of Rheumatology (ACR)**

- uricosuric therapy, is recommended as an **alternative first-line therapy in patients with a contraindication or intolerance to xanthine oxidase inhibitor therapy**.

- **In refractory cases**, **combination therapy** including a xanthine oxidase inhibitor plus an agent with uricosuric properties (probenecid, losartan, or fenofibrate) is suggested.

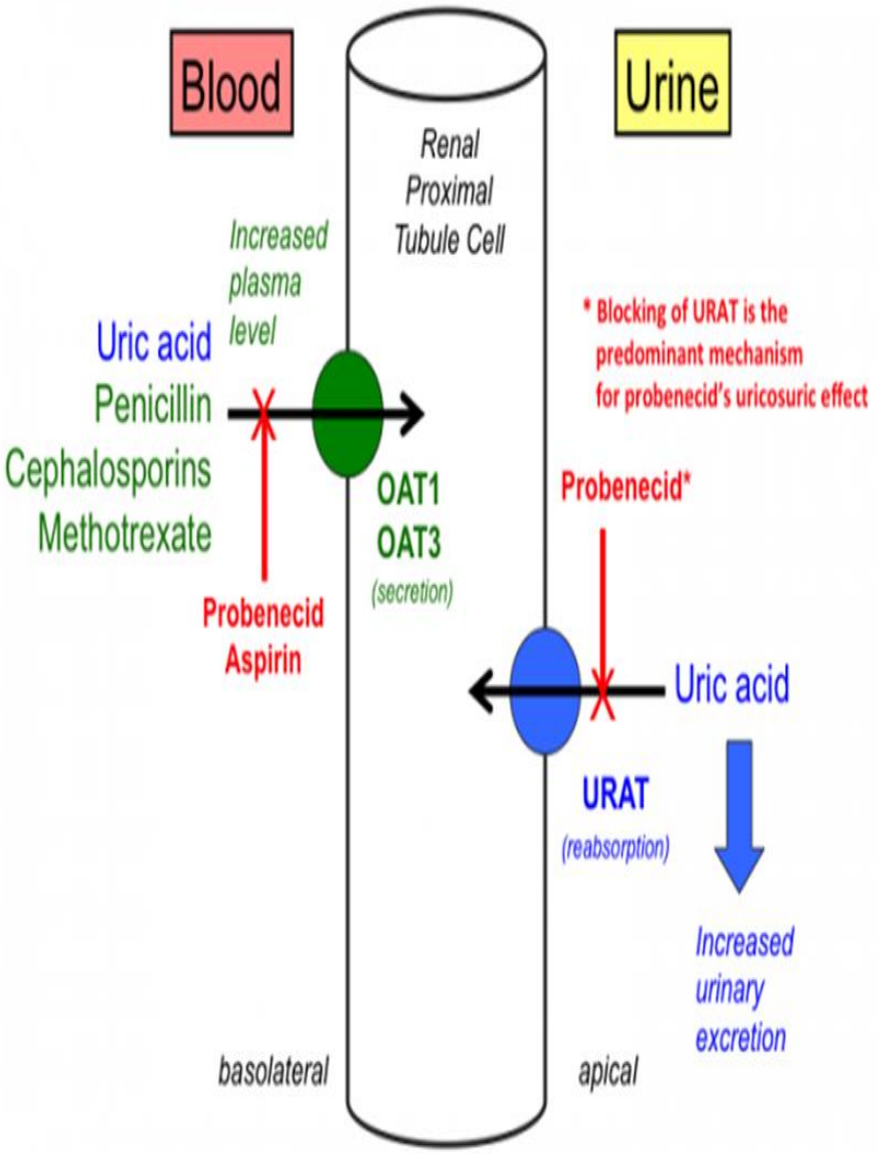
- Finally, in severe cases in which the patient cannot tolerate or is not responding to other therapies, **pegloticase i**s recommended.

Uricosuric Drugs

- Uricosuric drugs increase the renal clearance of uric acid by inhibiting postsecretory renal tubular reabsorption of uric acid.

- This include probenecid (sulfinpyrazone not used now "history").

- Probenecid is given initially at a dose of **250 mg twice a day for 1 to 2 weeks** and **then 500 mg twice a day for 2** weeks.



Uricosuric Drugs

- Thereafter the daily dose is **increased by 500-mg increments every 1 to 2 weeks** until satisfactory control is achieved or a **maximum dose of 2 g** is reached.

- The major adverse effects associated with uricosuric therapy are gastrointestinal irritation, rash and **hypersensitivity, precipitation of acute gouty arthritis at initiation therapy (avoided now), and stone formation**.

- **Maintenance of adequate urine flow and alkalinization of the urine** with sodium bicarbonate during the first several days of uricosuric therapy further diminish the possibility of uric acid stone formation.

Propencid Drugs drug interactions

- A disadvantage of uricosurics is that **salicylates** may interfere with this mechanism and result in treatment failure.

- Probenecid can inhibit the tubular secretion of other organic acids; thus, increased plasma concentrations of **penicillins, cephalosporins, sulfonamides, and indomethacin can occur**.

- Uricosuric drugs are **contraindicated** in patients who are **allergic** to them and in patients with **impaired renal function** (a creatinine clearance <50 mL/min), a history of **renal calculi**. For such patients, allopurinol should be used.

Pegloticase (uricase)

- Pegloticase is a **pegylated recombinant uricase** that works to reduce serum uric acid by **converting uric acid to allantoin**, a water-soluble and easily excreted substance.

- In two 6-month randomized controlled trials, biweekly pegloticase therapy demonstrated efficacy in reducing serum uric acid and resolving tophi in patients with severe gout and hyperuricemia (uric acid ≥8 mg/dL **who failed or had a contraindication to allopurinol therapy**.

- The ideal duration of pegloticase therapy is currently unknown (weakness point)

Pegloticase

- pegloticase has several drawbacks that limit widespread use.

-route of administration. The biweekly IV infusions of pegloticase must be given over no less than 2 hours, a potential inconvenience to many patients.

-Furthermore, given potential infusion-related **allergic reactions**, patients must be treated with antihistamines and corticosteroids before therapy.

-very expensive (Pharmacoeconomics view)

- **Reserved for patients with gout refractory to conventional therapies Can be used in both urate overproduction and urate underexcretion**

Fenofibrate and losartan

- **Fenofibrate** can also be prescribed for patients with gout. a secondary benefit by increasing the clearance of hypoxanthine and xanthine, leading to a reduction in serum urate concentrations. fenofibrate does not appear to not cause an acute gout flare when initiated and is well tolerated overall.

- **Losartan**, an angiotensin II receptor antagonist, has also demonstrated benefit in reducing serum urate concentrations independent of angiotensin receptor antagonism.

- The ACR guidelines support the use of fenofibrate or losartan in combination with a xanthine oxidase inhibitor in patients with refractory disease

EVALUATION OF THERAPEUTIC OUTCOMES

- Repeat serum uric acid measurements are generally not necessary except during **the dose titration phase** of allopurinol to achieve a goal serum urate less than 6 mg/dL. acute gout can occur in the presence of normal serum uric acid concentrations.

- Patients with acute gout should be **monitored for symptomatic relief of joint pain as well as potential adverse effects and drug interactions related to drug therapy**.

- Patients receiving **hypouricemic medications** should have baseline assessment of **renal function, hepatic enzymes, complete blood count, and electrolytes (uric acid level)**. The tests should be rechecked **every 6 months** in patients receiving long-term prophylaxis.

Patient education about gout

Concepts:

- -*Gout* is a type of arthritis that is caused by uric acid crystals getting caught in the spaces between the joints of the feet, the hands and some larger joints. The tissue around the joints becomes inflamed, and this inflammation triggers the sensitive nerve endings at the joint, causing extreme pain.
- -*Uric acid* is a waste product from the body and if the body cannot cope with the load of uric acid, and this causes a build-up in body.
- -The main symptom is severe pain, usually in the hands or feet, especially at the base of the big toe. Sometimes gout can strike in other joints, such as the elbow or the knee.
- Almost any person can get gout. However, it far more common in men, especially between the ages of 30 and 60.
- It is one of the oldest disorders known to humans specially with rich people.
  -It is associated with obesity and high blood pressure.
- -Some drugs, particularly diuretics (fluid tablets), injury, surgery or starvation (tissue degradation) can bring on gout.
  -Gout is a curable disease, but if it is untreated it can cause kidney disease, including kidney stones.
- -The earlier the attack is treated the better.
  -Aspirin is not recommended for the pain of gout.
  -Bed rest is important. Some relief can be obtained by applying a hot compress or ice to the affected joint.
- -If gout keeps returning, it will be necessary to go onto tablets that may have to be taken for a lifetime in order to prevent more acute attacks.

Recommendation:

- restrict intake of food high in purines, especially organ meats (liver, brain, kidneys, sweetbread), shellfish and tinned fish (sardines, anchovies, herrings)
- reduce your intake of alcohol
- eat a normal, well-balanced diet
- drink plenty of water
- maintain a normal weight,
- wear comfortable shoes
- get regular exercise
- do not take your worries to bed
- do not overexpose yourself to cold

Avoid

Meat & Meat Products

Fish

All Sugars

Dairy

Grains

Grain Products

Chocolate

Coffee & Tea

Fruit Juice & Soda

All Alcohol

Recommend

Vegetables!

Non-sweet Citrus

Some Fruits

Sprouts

Fresh Vegetable Juice

THANK YOU