International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar–Apr 2025, pp: 2043-2053 www.ijprajournal.com ISSN: 2456-4494

A Systemic Review on Clinical Manifestation pathogenesis and Tretment on Hyperurecemia

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Date of Submission: 15-04-2025 Date of Acceptance: 25-04-2025

ABSTRACT: Hyperuricemia is an elevated uric acid level in blood. Gout is a common systemic metabolic disease characterized by deposition of monosodium urate monohydrate crystals with resultant acute intense inflammation of the involved joint. The clinical spectrum ranges from asymptomatic hyperuricemia to intermittent acute episodes of gouty arthritis to chronic tophaceous gout and chronic gouty arthropathy. a common metabolic disorder associated with gout, kidney disease, hypertension, and cardiovascular complications. Despite its widespread prevalence, the exact mechanisms underlying its pathogenesis and optimal treatment strategies remain topics of ongoing research.MSU crystals in the synovial fluid using polarized light microscopy. Imaging modalities include conventional radiography, ultrasonography, conventional CT, Dual-Energy CT, Magnetic Resonance Imaging, nuclear scintigraphy, and positron emission tomography.Newer drugs in the pharmacological armamentarium are proving successful and supplement older ones. Other important points in its management include patient education, diet and life style changes, as well as cessation of hyperuricemic drugs.

KEYWORDS: Hyperuricemia, Gout, Uric Acid, Pathogenesis, Treatment, Xanthine Oxidase Inhibitors.

I. INTRODUCTION

1.1 Hyperuricemia

Figure 1: Hyperuricemia

Hyperuricemia is defined as an elevated serum uric acid level, usually greater than **6 mg/dL in women and 7 mg/dL in men**. Elevated serum uric acid is present in an estimated. Most people with this condition will not have obvious clinical manifestations, however, it is unclear what the long-term effects of hyperuricemia are on overall cardiovascular health, renal function, and overall morbidity.

Hyperuricemia results from increased uric acid production, decreased excretion, or a combination of both processes. Dietary purines are responsible for about one-third of the body's daily serum uric acid production; the rest is synthesized from endogenous sources.

Most people with hyperuricemia are asymptomatic (85% to 90%), but elevated uric acid levels in the blood or urine can lead to gout or nephrolithiasis. Hyperuricemia and hyperuricosuria have also been linked with other disorders such as metabolic syndrome, diabetes mellitus, cardiovascular disease, hypertension, atherosclerosis, obesity, and chronic renaldisease.

The association between elevated serum uric levels (SUA) and cardiovascular diseases (CVD) has long been documented in the epidemiological database. With the passage of time, short- and long-term studies have been conducted to strengthen this association.

Hyperuricemia (HU) to be an independent risk factor for CVD including major cardiovascular events (MACE) such as stroke and ischemic cardiac diseases.

Hyperuricemia is an elevated uric acid level in blood. Gout is a common systemic metabolic disease characterized by deposition of monosodium urate monohydrate crystals with resultant acute intense inflammation of the involved joint.

The clinical spectrum ranges from asymptomatic hyperuricemia to intermittent acute

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episodes of gouty arthritis to chronic tophaceous gout and chronic gouty arthropathy.

Prevalence: Overall prevalence of Hyperuricemia was 12.13%.

Sign and symptoms:
Hyperuricemia itself doesn't usually cause symptoms. Most people don't know they have it until their uric acid levels are high enough to cause gout or kidney stones.
Symptoms of a gout attack in one of your joints include:

- Intense pain.
- Discoloration or redness.
- Stiffness and Swelling.
- Tenderness, even to light touch (like your bedsheet covering it).
- Warmth, or a feeling like the joint is "on fire."

Symptoms of kidney stones include:

- Pain in your lower back or side.
- Nausea or vomiting caused by the pain.
- Blood in your pee.
- Pain while you're peeing.
- Being unable to pee.
- Feeling the need to pee more often.
- Pee that smells bad.
- looks cloudy.

1.2 INTRODUCTION OF GOUT

The term gout describes a disease spectrum including hyperuricemia, recurrent attacks of acute arthritis associated with monosodium urate crystals in leukocytes found in synovial fluid, deposits of monosodium urate crystals in tissues (tophi), interstitial renal disease, and uric acid nephrolithiasis.

Gout is a chronic inflammatory arthritis characterized by sudden, severe attacks of pain, swelling, redness, and tenderness in one or more joints, typically the big toe. It affects approximately 1-2% of the global population.

1.2 GOUT: Gout is a type of inflammatory arthritis that causes pain and swelling in your joints, usually as flares that last for a week or two, and then resolve. Gout flares often begin in your big toe or a lower limb.

Figure2: GOUT

In gout, mean serum urate concentration values are 6.8 mg/dl for men and 6.0 mg/dl for women.

MSU crystals can be deposited in all tissues mainly in and around the joints forming tophi. Gout is mainly diagnosed by identification of the pathognomonic MSU crystals by joint fluid aspiration or in tophi aspirate. Early presentation of gout is an acute joint inflammation that is quickly relieved by NSAIDs or colchicine. Renal stones and tophi are late presentations. Lowering SUA levels below deposition threshold either by dietary modification and using serum uric acid lowering drugs is the main goal in management of gout. This results in dissolution of MSU crystals preventing further attacks.

Stages of Gout:

1. **Asymptomatic Hyperuricemia:** Elevated uric acid levels without symptoms.
2. **Acute Gouty Arthritis:** Sudden onset of symptoms.
3. **Intercortical Gout:** Periods between acute attacks.
4. **Chronic Tophaceous Gout:** Persistent symptoms with tophi formation.
5. **Hyperuricemia:** elevated levels of uric acid in the blood.

Classification based on etiology:

Primary gout	Secondary gout
Idiopathic Rare enzyme deficiencies: Hypoxanthine-guanine phosphoribosyl transferase deficiency (HPRT) Phosphoribosyl pyrophosphate synthesises super-activity Ribose- 5-	**Increased uric acid production:** Lymphoproliferative/my eloproliferative Chronic haemolytic anaemias Secondary polycythaemia Severe exfoliative psoriasis Gaucher's disease Cytotoxic drugs Glucose

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phosphate AMP-deaminase deficiency	6 phosphate deficiency High purine diet overproduction **Reduced uric acid secretion:** Renal failure Hypertension Drugs (diuretics, aspirin, cyclosporin) Lead neuropathy Alcohol Down's syndrome Myxoedema Beryllium poisoning

Clinical features:

- The classical presentation is with an acute monoarthritic, which affects the MTP joint 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 onset, reaching maximum severity in 2–6 hours, worse in the early morning
- severe pain, often described as the 'worst pain ever'
- extreme tenderness, so the 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.
- During the attack, the joint shows signs of marked synovitis, swelling and erythema. 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. The main differential diagnosis is septic arthritis, cellulitis and reactive arthritis. Acute attacks may also manifest as bursitis, or tenosynovitis. Sometimes an acute attack will be followed by further attacks in other joints a few days later (cluster attacks),
- Patients with repeated attacks may progress to chronic gout, with chronic pain, joint damage, deformity and functional impairment. Patients with uncontrolled hyperuricaemia who suffer multiple attacks of acute gout may also progress to chronic gout.

EPIDEMIOLOGY

There is a direct correlation between the serum uric acid concentration and both the **incidence** and **prevalence** of **gout.** The incidence of gout varies from 20 to 35 per 100,000 persons, with an overall prevalence of 1.6 to 13.6 per thousand. **Prevalence increases** with age, especially in men. Men are affected by gout approximately 10 times more often than women. Although no genetic marker has been isolated for gout, the familial nature of gout strongly suggests an interaction between genetic and environmental factors.

Prevalence:

In Globally estimated 1-2% of the global population has gout (approximately 70-140 million people

In India, the prevalence rate of a particular condition (not specified) varies across different segments of the population. Overall, the prevalence rate stands at 1.36%. However, there is a significant urban-rural divide, with the prevalence rate being higher in urban areas at 2.44% compared to rural areas at 1.14%. Additionally, there is a notable gender disparity, with men having a higher prevalence rate of 2.15% compared to women at 1.03%.

Comorbidities:

Some people with gout may be more likely to have or develop other conditions or complications, especially with the heart and kidneys. Common conditions include:

- Hypertension (high blood pressure).
- Chronic kidney disease.
- Obesity.
- Diabetes.
- Nephrolithiasis (kidney stones).
- Cardiovascular Disease.

PATHOGENESIS:

Urate is the ionized form of uric acid present in the body. Uric acid is a weak acid with pH of 5.8. Urate crystals deposition in tissues starts to occur when serum uric acid level rises above the normal threshold. Pathological threshold of hyperuricemia is defined as 6.8 mg/Dl.

Some factors may affect the solubility of uric acid in the joint. These include synovial fluid pH, water concentration, electrolytes level, andother synovial components such as proteoglycans and collagen. SUA level in the body is determined by the balance between its production either from purine intake in diet or endogenous production by cellular turnover and its excretion by the kidneys and GIT. Increased production of UA is responsible for only 10% of cases of gout while the remaining 90% are caused by its renal under-excretion.

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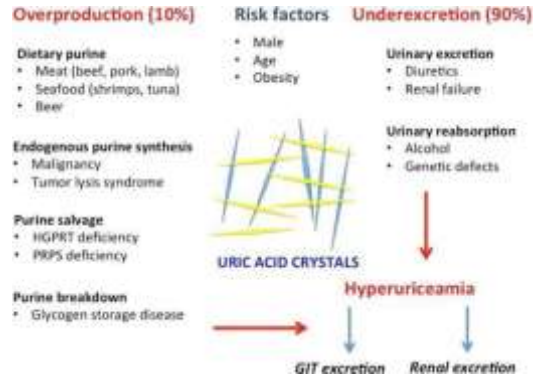

Figure 3: Pathogenesis

➢ **Triggering of inflammation by crystals**

The predilection of gout for the first metatarsophalangeal joint (MTP) has been hypothesized to represent the result of a number of factors. It is hypothesized that a small joint effusion forms during daytime activities, particularly activities that are more strenuous or traumatic to the joint (the first MTP is a frequent site of minor trauma and hence, osteoarthritis). At night (when most gout attacks occur) tissue oedema fluid (more abundant more distally in the lower extremity) is gradually reabsorbed into the circulation. The concentration of urate rises in the joint because urate is reabsorbed more slowly than water.

For a gout attack to occur, there must be deposition of MSU in the tissues and there must also be the triggering of inflammation. Crystals alone are not enough, as evidenced by the fact that tophi only occasionally become inflamed, and also that MSU crystals can often be found floating freely in synovial fluid from uninflamed joints. A number of factors have been discovered in recent years that control the inflammatory process, and there are several eloquent reviews.

Liberation of free crystals is one factor that can trigger the acute gout attack. Free crystals can be newly deposited, or may form through dissolution of tophi (as when instituting treatment with a hypouricemic agent) or may be dislodged from otherwise stable deposits by trauma.

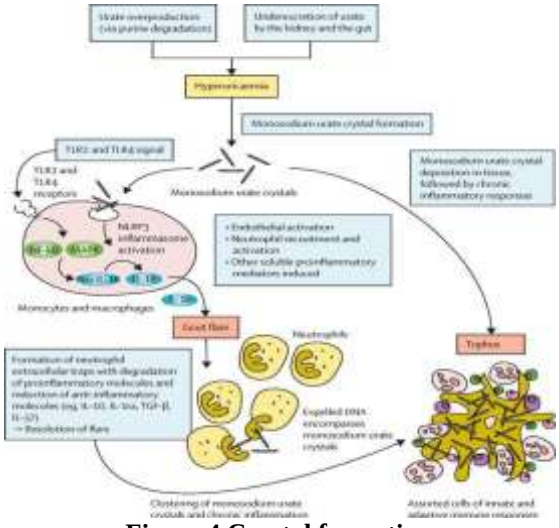

Figure 4 Crystal formation

PATHOPHYSIOLOGY:

Gout is an inflammatory arthritis triggered by the deposition of MSU crystals, the end product of human purine metabolism, in joints, soft tissues, and bones. This condition may manifest in many forms, including acute gout flare (acute arthritis), chronic gouty arthritis (chronic arthritis), tophaceous gout (formation of tophi), renal functional impairment, and urolithiasis.

The pathophysiology of gout involves a series of complex and interacting processes as follows:

- Various genetic and metabolic factors contribute to hyperuricemia in the bloodstream.
- Metabolic, physiologic, and other characteristics are responsible for MSU crystal formation.
- Soluble inflammatory factors, cellular elements, innate immune processes, along with the characteristics of MSU crystals, promote an acute inflammatory response.
- Immune mechanisms come into play to mediate the resolution of acute inflammation induced by MSU crystals.
- Chronic inflammatory processes coupled with the effects of immune cells and crystals on osteoblasts, chondrocytes, and osteoclasts contribute to cartilage attrition, bone erosion, joint injury, and the formation of tophi.

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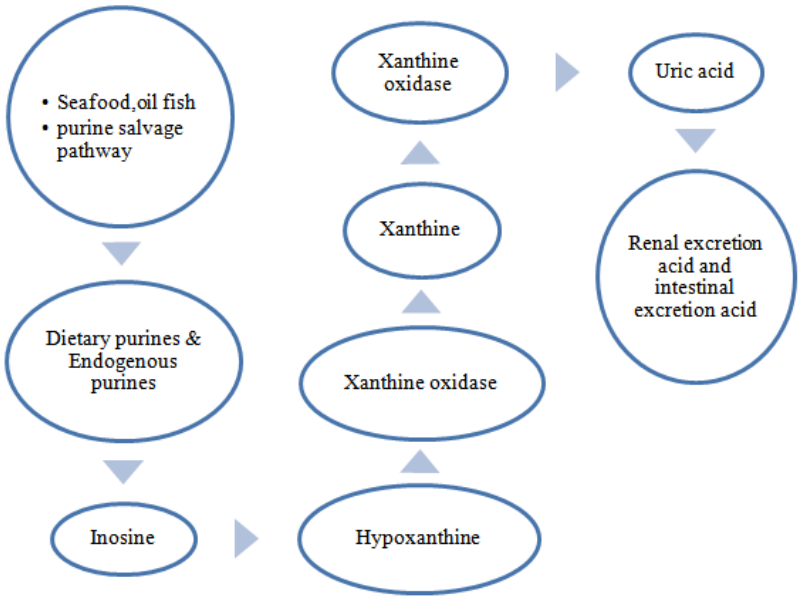

Figure 5 Pathway for uric acid production and elimination

Treatment of acute flares

Acute gout flares are characterized by rapid onset (hours) of severe pain, often at night. Early in the course of the disease acute attacks are usually monoarticular and, especially in men, localized to the foot and great toe. This understanding of the biology of acute flares helps guide current treatment, and the development of future therapies.

Management of acute flares requires treatment with one or more potent anti-inflammatory agents. Four categories are available: NSAIDs, colchicine, corticosteroids, and anti-IL-1β biologics, which are not United States (US) Food and Drug Administration (FDA)-approved. All are effective, and selection should be directed at minimizing individual risk.

SIGN AND SYMPTOMS:

1. **Sudden and severe joint pain**: Typically occurring in one joint, often the big toe, but can also affect other joints like ankles, knees, wrists, and fingers.
2. **Swollen and red joints**: Affected joints become swollen, red, and warm to the touch.
3. **Tender joints**: Joints are extremely sensitive to touch or pressure.
4. **Chronic gout**: Repeated attacks can lead to chronic gout, causing:

- Persistent joint pain and swelling
- Joint deformity
- Kidney stones
- Tophi (hard, uric acid deposits under the skin)

Other signs and symptoms may include:

- Fever
- Chills
- Fatigue
- Loss of appetite
- Redness and swelling in surrounding areas

Areas of the body that can be affected by gout include

- Tendon sheaths, membranes that surround tendons.
- Kidneys, because the high uric acid levels can lead to stones.

Gout is a disease that can move through several stages:

- Hyperuricemia, when you have elevated levels of urate in your blood over a long period of time and even crystals in the joint, but you do not have symptoms.
- Gout flares, when you have periodic attacks of intense pain and swelling in your joints.
- Interval or intercortical gout, which is the time between gout attacks when you do not have any symptoms.
- Tophi, a late stage of gout when crystals build up in the skin or other areas of the body. Depending on their location, tophi can permanently damage your joints and other internal organs such as the kidneys. Proper treatment can prevent the development of tophi.

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Cause of Gout

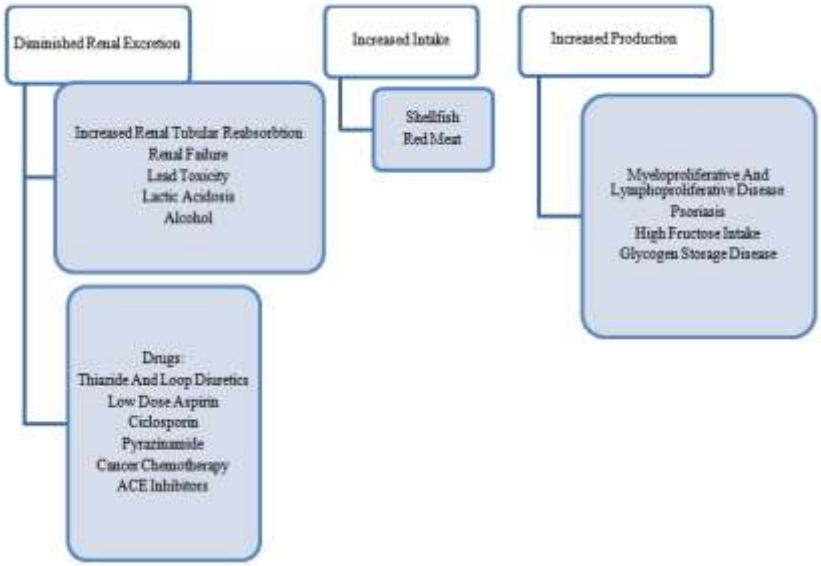

Figure 6 Causes of Gout

Gout happens when urate, a substance in your body, builds up and forms needle-shaped crystals in your joints. This leads to pain, swelling, redness, and changes in the movement and use of the affected joint. However, not everyone with high urate levels develops gout.

- high urate levels.
- family history of gout.
- menopause.
- Gout is developed with Increasing age.
- Drinking alcohol.
- Drinking sugar-sweetened beverages, such as soda.
- Having an unhealthy diet and eating foods that are rich in purines (usually from animal sources), a substance that breaks down into urate.
- Some health conditions may increase your risk of developing gout, such as:
- Overweight or obesity.

Complications

Complications of gout are diverse and may encompass various systemic issues, including the following:

1. Skeletal Complications

Tophi
Joint deformity
Osteoarthritis
Bone loss

2. Urological Complications

Urate nephropathy
Nephrolithiasis

3. Ocular Complications

Conjunctivitis
Uveitis
Scleritis

Laboratory investigation:

The serum uric acid and urine uric acid concentrations are the two most used tests to diagnose gout and assess the effectiveness of its treatment. The BUN and Serum creatinine also should be monitored as appropriate.

	Normal Range	**High**	**Low**
Serum uric acid concentrate on	4–8.5 mg/dL (237– 506 mmol/L) for males 2.7–7.3 mg/dL (161– 434 mmol/L) for females	Gouty arthritis Renal stones Uric acid nephropathy Renal dysfunction - >13mg/dl in men and 10 mg/dl Endocrine abnormalities	Inherited disorders
Urine uric acid	250–750 mg/24 hr (1.48–	Uric acid and Calcium oxalate	

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concentration	4.46 mmol/24 hr)	nephrolithiasis Renal calculi or uric acid nephropathy	Chronic kidney disease Falcon syndrome
Joint fluid aspiration SF leucocyte count	MSU crystals are needle shaped 2 to 20 mm long. 2000 to 100 000/mL	Chronic gout attack	
Renal function Serum creatinine	55–120 mmol/L or 0.6–1.35 mg/d	Muscular dystrophy reduced GFR Dehydration	low protein diet Liver damage
Blood urea nitrogen	2.9–7.1 mmol/L or 8– 20 mg	High protein diet upper GIT. Bleeding Medications Reduced renal blood flow CHF Impaired renal function	over hydration Liver damage
C-reactive protein	0.0.5mg/dl	Inflammation	
ESR	0–15 mm/hr for males; 0–20 mm/hr for females	Acute gout attack severity of inflammation	

Diagnosis:

- **Clinical diagnosis**

Asymptomatic hyperuricemia

Gout undergoes 4 stages during its course starting with asymptomatic hyperuricemia. In this stage, patients have no symptoms or signs and are usually accidentally discovered when measuring SUA (serum level greater than 7 mg/dL). However, some patients with hyperuricemia may develop an acute gouty attack.

Figure 7 Asymptomatic hyperuricemia

Acute gouty attack

Acute gouty attack is usually monoarthritic that peaks within hours to severely inflamed joint with cardinal signs of inflammation including redness, hotness, tenderness, swelling and loss of function. In large joints such as knees and ankles, skin signs are infrequent, but swelling and pain can be intense.

Intercortical period

When the acute attack settles down within hours to days following the introduction of colchicine or NSAIDs, patients enter into a remission phase. This period is characterized by the absence of symptoms. It may be interrupted suddenly by newer attacks if proper treatment for hyperuricemia has not been introduced. This quiescent stage can be prolonged after the first attack. Without proper treatment, however, attacks become more frequent and more severe.

Figure 8 Intercortical period

Chronic tophaceous gout

It happens in chronic untreated gout. It can be present around the joints in the ears, the subcutaneous tissue or the skin. It is a manifestation of chronicity and uncontrolled disease. Tophi may lead to joint destruction and deformity. Bony erosions may also occur as growing tophi extend to the bone. This can be easily done by taking a simple needle biopsy that will show MSU crystals characteristic of gout.

Figure 9 Chronic tophaceous gout

Clinical diagnosis of gout is widely used all over the world especially in developing countries where resources are limited. However, when clinical diagnosis has been compared to microscopic

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diagnosis of crystals, it appeared to have low sensitivity and specificity.

Formation of tophi is a late clinical manifestation of gout (figure 9), though it may develop early in the disease course.

Radiological diagnosis

The significance of imaging in gouty arthritis cannot be overemphasized. It is extremely important for diagnosis and follow-up in clinical practice. Also, its potential as an outcome measure in clinical trials is growing. Recently, developments in the field of technology are influencing the staging, and even the type of gout nomenclature.

Conventional Radiography (CR)

It is the most widely used method in clinical practice, however in early stages of the disease it is not very helpful. Radiographic changes may be missed for a minimum of 10 years after the first gouty attack. During the early stages of gout, radiographic images are usually normal or may show asymmetric soft tissue swelling near the affected joints, but subtle early lesions such as small erosions and tophi are difficult to detect. In chronic tophaceous gout, the main radiographic features are

Figure 10 Bone erosions

Bone erosions are characteristic. They are well circumscribed intraarticular or Jux articular lesions with overhanging margins. They result from the growth of tophi into the bone, hence are usually seen near tophi.

Figure 11 Monosodium urate crystals deposits

Periarticular osteopenia is usually absent and proliferating bone can be seen mostly as irregular spicules.

Calcified MSU deposits can penetrate in the bone; in severe cases, they should not be confused with bone infarcts or enchondromas. Radiography has low sensitivity (31%) however, its specificity is high (93%).

Synovial fluid

Synovial fluid varies from being totally anechoic to containing aggregates of variable echogenicity. Aggregates of MSU microcrystals can be detected as hyperechoic spots or bright stippled foci. They tend to float in the joint space sometimes giving a snow-storm appearance when applying gentle pressure on the skin surface.

Conventional CT (CCT)

CT is characterized by excellent resolution and high contrast hence it is the best technique for the assessment and characterization of crystal arthropathies. the specificity of CCT for the assessment of tophi exceeds that of US or MRI. CT of tophi has been confirmed microscopically by identifying MSU crystals. Tophi, soft tissue, intra-articular as well as intra-osseous ones appear as soft tissue masses with well described attenuation, making it easier to distinguish them from other soft tissue lesions.

Dual-Energy CT (DECT)

The introduction of this new imaging technique opened a new horizon. It allows the differentiation of deposits based on their different X-ray spectra. It applies the concept that the attenuation of tissues depends on their density, atomic number as well as the photon beam energy. DECT can offer a quick, non-invasive method to visualize MSU crystals, soft tissue changes, and early erosions at high-resolution, even before CR. DECT is highly accurate in detecting MSU crystals in joints, tendons, ligaments and soft tissues and can be used to identify subclinical gout with high specificity.

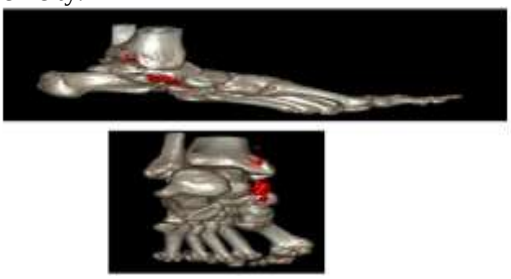

Figure 12: DECT

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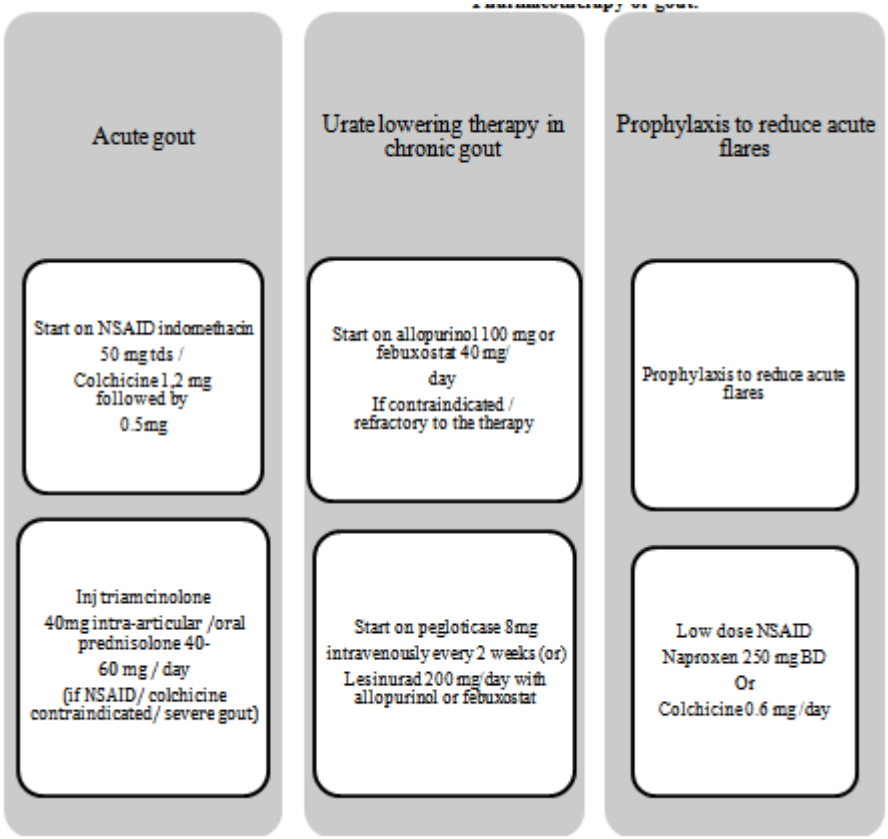
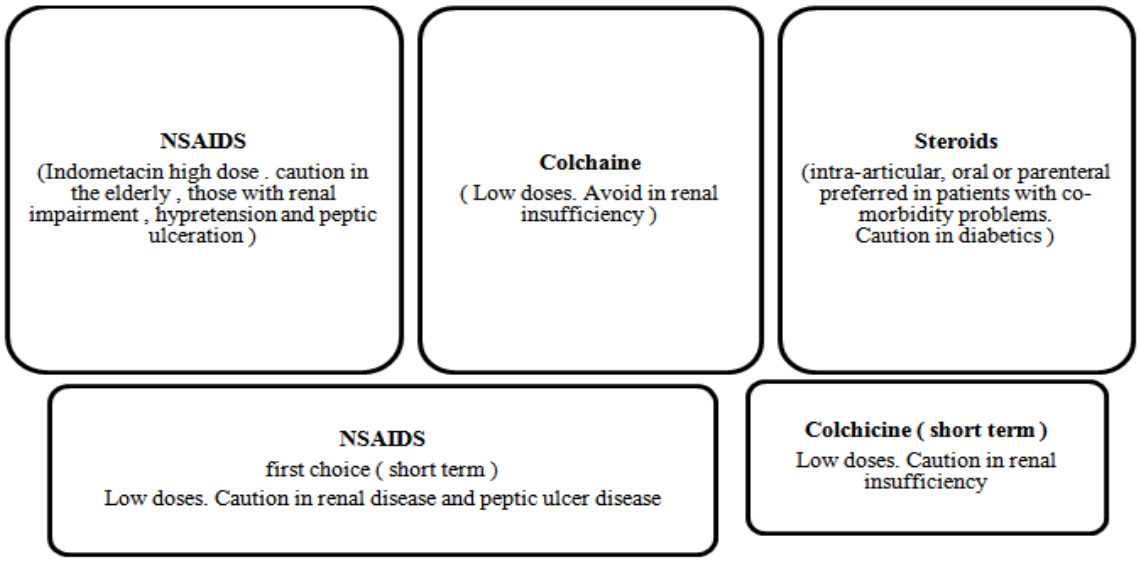
TRETMENT **Pharmacotherapy of gout:**



Asymptomatic hyperurecemia :
(Do not treat , check renal function , Advice on weight reduction , Advice on alcohol consumption reduction **)**

Acute attack of gouty arthritis



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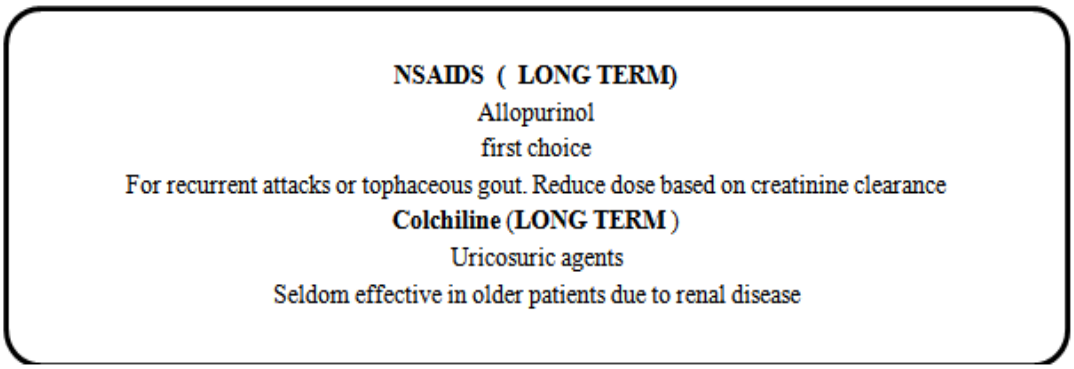

Figure 13 Algorithm for the management of gout

Treatment of established gout

Urate-lowering therapy

Xanthine oxidase inhibitors

ACR 2012 guidelines recommend a xanthine oxidase inhibitor, either allopurinol or febuxostat, as the initial ULT agent ; as discussed below, possible concerns about cardiac risk with febuxostat have led the FDA to recommend treatment with allopurinol first, and febuxostat only if allopurinol is not tolerated or inadequately effective. ACR guidelines published in June 2020 follow this recommendation. Xanthine oxidase inhibitors block the production of urate, and reduce hyperuricemia whether caused by metabolic urate overproduction, or GI or renal urate underexcretion (the latter accounting for approximately 90% of primary hyperuricemia). With prolonged use, appropriately-dosed xanthine oxidase inhibitors can prevent the deposition of urate and resolve crystals already deposited, including tophi. The rate of crystal dissolution is generally proportional to the degree of urate lowering achieved. Because xanthine oxidase inhibitors block the metabolism not only of purines, but also of purine-like drugs, they raise the concentration of azathioprine and its metabolite 6MP; co-administration with one of these agents can result in serious marrow suppression .

Allopurinol

Allopurinol remains as first-line agent for ULT due to its efficacy, availability, and low cost. It is a nonspecific competitive XOI that is later converted to oxprenolol for its renal excretion. Starting dose, as recommended by ACR guidelines, is usually 100 mg with slow-up titration of the dose every 2–4 weeks until target SU is achieved. Doses up to 800 mg/day are approved in the US, in comparison with up to 900 mg/day in Europe.

Despite the wide availability of allopurinol, target SU concentrations are not always achieved due to multiple factors, including failure to monitor SU, low adherence to medication, and inadequate. A study that randomized patients to fixed doses of 100 and 300 mg of daily allopurinol based on renal function, showed that only 39–41% achieved a target SU of 6 mg/dl Another trial that titrated allopurinol up to 300 daily mg showed that only 56% of patients reached a target SU of 6 mg/dl.

Febuxostat

Febuxostat is a nonpurine-specific XOI that is primarily metabolized in the liver. It is currently approved in the US at doses of 40–80 mg/day and up to 120mg/day in Europe. In a 52-week phase III trial that compared febuxostat 80 and 120 mg to allopurinol 300 mg in 762 patients with estimated glomerular filtration rate (eGFR) > 50 ml/min, 53%, 62%, and 21%, respectively, achieved a SU of 6 mg/dl. Another large phase III trial compared febuxostat 80, 120, and 240 mg to fixed doses of allopurinol, 300 and 100 mg based on renal function, in patients with normal and impaired renal function. Among patients with normal kidney function, the primary end point of SU less than 6 mg/dl was achieved in 48%, 65% and 69% of the 80, 120 and 240 mg of febuxostat compared to only 22% in the allopurinol arm. Results were similar in the groups with renal impairment. An important observation for all studies comparing febuxostat with allopurinol, and claiming a higher potency for febuxostat, is that allopurinol comparator doses are fixed and not titrated as recommended in most practice guidelines. This places allopurinol at a relative disadvantage, and should call for a word of caution about simplistic statements of comparative efficacy.

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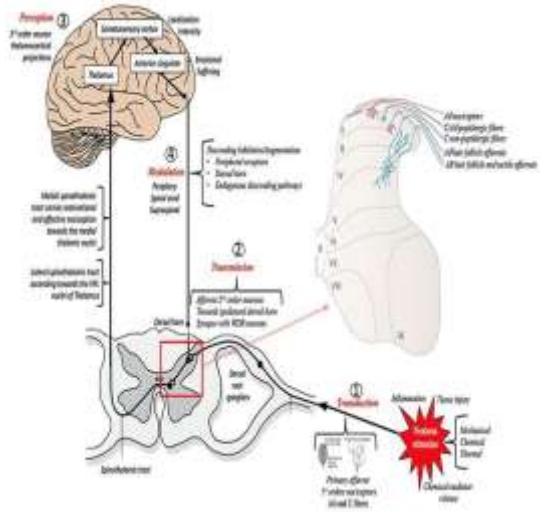
Probenecid

Probenecid acts by inhibiting URAT 1 and GLUT 9 transporters and is the prototypical uricosuric drug. In a small case series of 30 patients on probenecid monotherapy and 27 patients on probenecid and allopurinol, 33% and 37% reached a target SU of 6 mg/dl, respectively .Another trial of probenecid at a dose of 1000 mg twice a day added to allopurinol 300 mg daily resulted in 65% of patients reaching a target SU of 5 mg/dl .Probenecid is still reserved as an option for those who cannot tolerate allopurinol or cannot reach target SU on monotherapy with xanthine-oxidase inhibitors.

Although the efficacy of uricosurics is believed to be impaired with decreasing glomerular filtration rate (GFR), a recent study showed no difference in the percentage of patients achieving target SU when comparing patients with GFR below or above 50 ml/min/1.73m^2.Probenecid also has multiple significant drug interactions with commonly used drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), beta-lactams, and heparin, which limit its use.

Pain pathway:



Complex pain pathways: stimulation of nociceptive nerve endings from joints, muscles/tendons, and skin are transmitted from the periphery to the spinal cord to the cortex in a complex pathway involving transduction, transmission, and modulation of the pain signal.

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