Comprehensive Medical Management of Gout

Annil Mahajan, Vishal R Tandon*, Shagun Mahajan**

Abstract
Recent advances in understanding and medical treatment of gout have helped to reduce morbidity and mortality in patients suffering from this disease. A comprehensive care including identification and treatment of co-morbid conditions is equally important in management of gout. Aggressive treatment of acute attack of gout and judicious treatment of symptomatic chronic hyperuricemia with lifestyle & dietary management and education of patients is of utmost importance. Present understanding of pathophysiology of gout has given a lead to identify a range of targets for pharmacotherapy and thus holds future promises for the development of new drugs and biologic agents for reversing refractory hyperuricemia and gout.

Key Words
Hyperuricemia, Gout, Uric Acid Metabolism, Acute Attack, Chronic Gout, Arthritis

Introduction
Gout is a disorder of uric acid metabolism and represents a heterogeneous group of diseases that include\(^{(1)}\), an elevated serum urate concentration (hyperuricemia); recurrent attacks of acute arthritis in which monosodium urate monohydrate crystals are seen in synovial fluid leukocytes; aggregates of sodium urate monohydrate crystals (tophi) are deposited chiefly in and around joints which sometimes leads to deformity and crippling; renal disease involving glomerular, tublar, interstitial tissue and blood vessels as well as uric acid nephrolithiasis. Hyperuricemia refers to an elevated level of urate in the blood greater than 7mg/dl in males and >6.5mg/dl in females.

Epidemiology
Epidemiologic investigations suggest that gout frequency is on the rise worldwide \(^{(2)}\). The incidence of gout varies in population with an overall prevalence of less than 1 to 15.3%. The prevalence increases substantially with age and increasing serum urate levels. For values greater than 9mg/dl the cumulative incidence of gout reaches 22% after 5 years \(^{(1)}\). Gout affects more than 1% of adults in the western countries \(^{(3)}\). Male: female ratio ranging from 7:1 to 9:1 \(^{(4)}\). In ages younger than 65, men have 4 times higher prevalence than women (4:1 ratio), but in the older age groups (> 65), the gender gap narrows to 1 woman to every 3 men with gout and/or hyperuricemia (3:1 ratio) \(^{(5)}\). The Bhigwan COPCORD survey demonstrated low prevalence of Gout (0.12%) in rural India \(^{(6)}\). In another Indian study gout prevalence of 2% was recorded \(^{(7)}\). One of our own study from Jammu recorded 241.6/1000 prevalence of rheumatic disease and only two case of gout were reported \(^{(8)}\).Hyperuricemia is fairly common, with a prevalence ranging from 2.3 to 41.4% in various populations. The prevalence for men is 13.6 cases per 1000 men, and the prevalence for women is 6.4 cases per 1000 women. This difference is largely a manifestation of age of onset because estrogenic hormones have a mild uricosuric effect; therefore, gout is unusual in premenopausal women.\(^{(1)}\)

Pathogenesis of Gout \(^{(9}, (10), (11)}\)
A weak organic acid with a \(pK_a\) of 5.75, uric acid is the final product of human purine metabolism. At the
physiologic pH of 7.4 in extracellular fluid, the concentration of urate ion is approximately 50-fold that of the less soluble un-ionized uric acid. Because of the high concentration of sodium in extracellular fluid, urate is largely present as MSU. As urate concentrations increasingly exceed 6.8 mg/dl, the risk for urate crystal formation and precipitation increases. The amount of urate in the body depends on the balance between dietary intake, synthesis and rate of excretion. Hyperuricemia results from urate overproduction (10%), under excretion (90%) or often a combination of two. Gout is mediated by super saturation and crystallization of uric acid with in the joints ultimately, the formation of tophi.

**Monosodium urate crystal- induced gouty inflammation** [1, 11,12,13,14]

Urate crystals are almost always present in acute gouty arthritis. Urate crystals and microtophi are present in the synovial membranes 2 days after the onset of a first attack of acute gout. The crystals of the synovium are often in a superficial location near the joint space. Therefore, crystals may flake off the synovial membrane into synovial fluid, triggering an inflammatory attack phagocytized by polymorphonuclear or synovial cells. Superstauration of serum or synovial fluid with monosodium urate is a necessary, but not sufficient, precondition for the development of acute gouty arthritis. In addition, acute gouty arthritis may develop at a time when serum urate levels are well below saturation. Factors that may regulate the deposition of urate in human tissue include lower intra-articular temperature, gamma globins, type I collagen, proteoglycans, change in pH, reduced binding of urate to plasma protein, trauma, aging, connective tissue turnover and level of articular dehydration. Futhermore these factors may explain the predilection of gout in the first metatarsal phalangeal joint (a peripheral joint with lower temperature) and osteoarthritic joints (degenerative joint with nucleating debris) and the nocturnal onset of pain (because of intra-articular dehydration). Interactions of MSU crystals with the components of the innate immune system trigger acute gouty inflammation as well as mechanisms that are involved in the resolution of this inflammation. (Fig-1 & Table-2)

**Classification of Gout**

**Primary Gout**: These are the cases that appear to be innate, neither secondary to another acquired disorder nor the result of a subordinate manifestation of an inborn error that leads initially to a major disease unlike gout; although some cases have a genetic basis, other do not.

**Secondary Gout**: These are the cases that develop in the course of another disease or as a consequence of drug use. **Idiopathic**: These are the cases in which précis classification cannot be assigned.

**Clinical Features** [1, 15, 16]

In the complete development of its natural history gout passes through four stages.

**Asymptomatic Hyperuricemia**: is a situation in which the serum urate level is high but gout as manifested by arthritic symptoms, tophi or uric acid nephrolithiasis has not yet appeared.

**Acute Gouty Arthritis**: Acute monoarticular arthritis is the initial presentation of gout in 90% of patients. The attacks begin abruptly and reach maximum intensity in 8-12 hours. The joints are red, hot, and exquisitely tender. If, untreated, the first attacks resolve spontaneously in less than 2 weeks. Gout can initially present as a polyarticular arthritis in 10% of patients (elderly women, particularly women with renal insufficiency and taking a thiazide diuretic). (Fig.2)

<table>
<thead>
<tr>
<th>Table.1 Factors / Events Which may Trigger an Acute Attack of Gout [1]</th>
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<tbody>
<tr>
<td>• Alcohol ingestion</td>
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<td>• Dietary excess of purine</td>
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<tr>
<td>• Hemorrhage</td>
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<tr>
<td>• Acute medical illness</td>
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<td>• Infections</td>
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<td>• Exercise</td>
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<tr>
<td>• Trauma</td>
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<tr>
<td>• Surgery</td>
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<td>• Drugs: closporine, Furosemide, ethambutol, aspirin (Low dose), Pyrazinamide, thiazides, nicotinic acids etc</td>
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**Definitive diagnosis** is best established by aspiration of joint and identification of urate crystal [1]. The triad of acute monoarticular arthritis, hyperuricemia and dramatic response to colchicines. Presence of 6 of the below mentioned 12 clinical, laboratory and radiographic criteria proposed by ACR & European league [15]. (Table-3)

**Intercritical gout**: The term has been applied to the period between gouty attacks.
**Fig 1. Induction of Acute Gout** [1, 11,12,13,14]

Monocytes secrete proinflammatory cytokines such as TNF-α, IL-1, IL-6 and IL-8. These cytokines can activate vascular endothelial cell expression of E-selectin, ICAM-1 and VCAM-1 and thereby stimulate both recruitment of neutrophils to the site of crystal deposition and amplification of inflammatory response.

Neutrophils are attracted to synovial fluid by crystal induced chemotactic factors C5a, leukotrine B4 and IL-1.

The interaction between the crystal and the lysosomal membrane leads to generation of free radicals and protease release.

Polypeptides like C1q, C1r, C1s, fibronectin, fibrinogen, IgG, lysosomal enzymes, apolipoproteins and TGF-β have been identified to mediate inflammatory response.

Other mediators released from polymorphonuclear leukocytes appear to have important role in inflammatory response include LTB4, kinins, collagenase, kallikrein, prostaglandin E2, 6-keto-PGF-1 and IL-1.

Phagocytosis of crystal by endothelial cells results in superoxide oxygen free radicals generation contributing to inflammatory cascade.

TNF-α and IL-1 can induce chondrocytes to release IL-8 and mono chemo attractant protein-1 contributes to amplification of inflammatory response.

Mast cell activation and release of Histamine contributes to swelling, edema and redness.

**Table 2. Resolution of Acute Gout** [1, 11,12,13,14]

- The acute attack continues as long as neutrophils are present and is terminated and is terminated with their disappearance through apoptosis.
- TNF-α has a proapoptotic effects on neutrophils.
- IgG may get displaced from joint space with help of apolipoprotein B.
- Increased heat of inflammation may increase urate solubility, decreasing the tendency of new crystal formation.
- Some ingested crystal may be destroyed by leukocyte myeloperoxidase.
- ACTH hormone released as an alarm to acute attack may suppress the inflammatory response.
- Differentiation of monocytes to mature macrophage may play very significant role.
- Superoxide anions may change the properties of crystal & release of TGF—β release (anti-inflammatory cytokine) from mature macrophage.
Table 3. Joint ACR & European league Criteria for the Classification of Acute Gouty Arthritis [15]

<table>
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<tr>
<th>Criteria</th>
<th>Description</th>
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<td>More than one attack of arthritis</td>
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<td>Maximum inflammation in one day</td>
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<tr>
<td>Monoarticular arthritis</td>
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<td>Joint redness</td>
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<td>First metatarsophalangeal joint involvement</td>
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<td>Unilateral attack involving tarsal joint</td>
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<tr>
<td>Suspected tophus</td>
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<td>Hyperuricemia</td>
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<td>Asymmetric swelling within joint (radiograph)</td>
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<tr>
<td>Subcortical cyst without erosion (radiograph)</td>
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<td>Negative culture of joint fluid for microorganism</td>
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Chronic tophaceous Gout: Eventually the patient may enter a phase of chronic polyarticular gout with no pain free intercritical periods. The attacks become more polyarticular. Although more joints may become involved, inflammation in a given joint may become less intense. More proximal and upper-extremity joints become involved. Attacks occur more frequently and last longer. Tophi are collections of uric acid crystals in the soft tissues. They occur in more than half of untreated patients. While the classic location is along the helix of the ear, they can be found in multiple locations, including the fingers, toes, in the olecranon bursae, and along the olecranon, where they can resemble rheumatoid nodules [1].

Co morbid Conditions [1,17,18,19]

Patients with gout have a 1000-fold increased incidence of renal stones and therefore may have a history of renal colic. Patients with gout also are prone to develop urate nephropathy. Hyperuricemia patients have a higher incidence of hypertension, diabetes, and other risk factors for renal insufficiency. Hyperuricemia is associated with deleterious effects on endothelial dysfunction, oxidative metabolism, platelet adhesiveness, hemorheology, and aggregation. Obesity and chronic kidney failure are conditions with multifactorial inheritance that are associated with gout. Patients with gout often are clustered with the insulin resistance syndrome known as metabolic syndrome or syndrome X: diabetes, hypertension, hypertriglyceridemia, and low high-density lipoproteins [18]. Few studies have suggested hyperuricemia to be an independent risk factor for atherosclerosis and cardiovascular disease related mortality. However, on the contrary other reports deny it to be an independent risk factor [1,19]. Hyperuricemia is associated with increased cerebrovascular disease [18].

Treatmen of Gout

The therapeutic aims in gout are as follows: Treating acute arthritic attack promptly; To prevent recurrence of acute gouty arthritis; Lowering urate levels; To prevent or reverse complications of the disease resulting from deposition of sodium urate or uric acid crystal in joint, kidney, or other sites; To prevent or reverse co-morbid conditions like obesity, hypertension and triglyceridemia and renal complications.

Treatment of Acute Gouty Arthritis [1,10,13, 21,22,23,24]

The chief objective of therapy in acute gout is rapid, safe resolution of pain and functional debility. Drug that affect serum urate level including anti-hyperuricemic agents should not be changed (either started or stopped) during an acute attack of gout.

Nonsteroidal anti-inflammatory drugs [1,10,13, 21,22,23,24]

NSAIDs are preferred in patients with uncomplicated gout. Indomethacin is the traditional choice. Start with the highest dose for 2-3 days and taper down over approximately 2 weeks. An initial dose of 50 to 75 mg followed by 50 mg every 6 to 8 hours with maximum of 200 mg in the first 24 hours has been recommended. Oral naproxen, ibuprofen, sulindac, piroxicam, ketoprofen as well as intramuscular ketorolac are also effective. Avoid NSAIDs in patients who have a history of peptic ulcer disease or GI bleeding, patients with renal
Synovial fluid aspiration - crystal identification.
Finding intracellular urate crystals - polarizing light microscopy
During acute attacks, the synovial fluid is inflammatory - (WBC count).

Serum uric acid
- Five to eight percent of the population has elevated serum uric acid levels (>7 mg/dL), but only 5-20% of patients with hyperuricemia develop gout.
- As many as 10% of patients with gout have normal serum uric acid levels at the time of their attack.

Uric acid in 24-hour urine sample
- If patients excrete more than 800 mg of uric acid in 24 hours on a regular diet, they are overexcretors and thus overproducers of uric acid.
- Patients who excrete more than 1100 mg in 24 hours should have renal function monitored closely because of the risk of stones and urate nephropathy.

Blood chemistry
- Blood sugar, liver function tests, lipids profile to establish co-morbid conditions

Urinalysis: Patients with gout have a high incidence of renal stones

Table 4. Lab Studies

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Insufficiency and abnormal hepatic functions. Although COX-2 inhibitors have reduced incidence of gastrointestinal adverse events but may have significant renal and cardiovascular toxicities. [25]

Narcotic analgesics [1]: Opiates are widely used clinically as adjuncts for analgesia in the early treatment of acute gout.

Glucocorticoids [1,10,13, 21,22,23,24]

Intraarticular injection of a depot corticosteroid for gout affecting one or two large joints are useful. Prednisone 40-60mg daily for 3 days than decreased by 10-15 mg per day every day until discontinuation or methylprednisolone 100-150mg per day for 1-2 days or intramuscular triamcinolone acetonide 60mg can be used. However there use should be avoided if joint sepsis not excluded and in subjects with hyperglycemia. In a controlled trial, corticotrophin (25 USP units I.M/IV once) induced more rapid relief of symptoms with fewer side effects than indomethacin in patients with acute gout. It has been used effectively, especially in attacks in patients following surgery. Corticotropin appears to be effective within hours for monoarticular and polyarticular gout. However, this agent is not universally available. Primary treatment of acute gout with systemic corticosteroids or corticotropin can be associated with rebound arthritis flares. Therefore, concomitant treatment with adjunctive low-dose colchicine has been advocated.

Colchicine [1,10,13, 21,22,23,24]

Generally, colchicine is preferred for patients in whom the diagnosis of gout is not confirmed. It is most effective during the first 12-24 hours of an attack, but its effectiveness declines with the duration of inflammation. To treat an acute attack colchicine is given orally at 0.5-0.6 mg every hour until the patient has relief, has adverse GI effects, or takes 6 mg (ten 0.6-mg tabs). Colchicine is effective in inhibiting E-selectin mediated adhesiveness for neutrophils and thereby inhibits its expression, random motility, chemotaxis, PLA2 activation and IL-1 expression as well as chemotactic factors CCF and LTB4. It also inhibits endothelial cell ICAM-1 expression, mast cell, histamine release and down regulates TNF- alpha receptors on macrophages and endothelial cells. Colchicine causes adverse GI effects, particularly bloody diarrhea and vomiting, in 80% of patients. Colchicine also should be avoided in patients with hepatic dysfunction, biliary obstruction, or an inability to tolerate diarrhea. IV colchicine therapy is rarely necessary and is banned in some countries due to a 2% fatality rate. Granulocytopenia is a prime complication of IV colchicine. The WBC count should be measured before infusion. Other complications include disseminated intravascular coagulopathy, renal failure, hepatocellular toxicity, seizures, and shock.

Long-Term or Prophylactic Therapy [1,10,13, 21,22,23,24]

Lowering uric acid with either allopurinol or probenecid can precipitate attacks of gout. When used prophylactically, colchicine can reduce such flares by 85%. NSAIDs and colchicine are frequently used as prophylaxis against recurrent acute gout, since such episodes are common during the initiation of uric acid-lowering treatment, although data supporting the use of NSAIDs for prophylaxis against gout are sparse. A standard practice is to use low-dose oral colchicine (0.6 mg orally twice a day in patients with intact renal function) for the first six months of antihyperuricemic therapy. Long-term use of colchicine can lead to a muscle weakness associated with elevated levels of creatine kinase due to a drug-induced
neuromyopathy, particularly in patients with renal insufficiency. In patients who cannot take colchicine, NSAIDs can be used for prophylaxis, such as indomethacin at 25 mg bid.

**Approaches to Lowering Uric Acid Levels** [1,10,13, 21,22,23,24]

**Treatment of Asymptomatic Hyperuricemia** [1]

The presence of hyperuricemia is rarely an indication for specific antihyperuricemic drug therapy because. Renal function is not adversely affected by elevated serum urate concentrations. Correction of hyperuricemia has no apparent effect on renal function or the development of heart disease. Thus it seems wise to not treat asymptomatic hyperuricemia till symptom develops. Rare exceptions include individuals with known hereditary cause of uric acid over production or patients at risk for acute uric acid nephropathy. However it is strongly recommended that causes of hyperuricemia be determined and co morbid conditions are addressed.

**Symptomatic Hyperuricemia**

Life long therapy with anti-hyperuricemic therapy is indicated in following situation occurs ie >2 or 3 acute attacks; Renal stones; Tophaceous gout or Chronic gouty arthritis with bony erosions.

**Antihyperuricemic Therapy** [1,10,13, 21,22,23,24]

In general, the aim of antihyperuricemic therapy is to reduce the serum urate levels to 6.0mg/dl or less, well below the concentration at which monosodium urate saturates extracellular fluid. Elimination of hyperuricemia with antihyperuricemic drugs can prevent as well as reverse urate deposition. In general, the lower the serum urate level achieved, faster is the reduction of tophaceous deposits. In many cases, patients who have a first attack of gout should undergo therapy with agents that lower uric acid. Some rheumatologists advocate waiting for the second attack to begin therapy to lower uric acid levels because not all patients have a second attack. Antihyperuricemic therapy should be started a few weeks after the attack has resolved and with the institution of colchicine to prevent another attack.

**Allopurinol** [1,10,13, 21,22,23,24]

Allopurinol 300 mg/day is the most commonly used antihyperuricemic agent and is the only xanthine oxidase inhibitor. Advantages of allopurinol are, once-daily dosing regimen and urate-lowering efficacy regardless of the cause of hyperuricemia, can be used to treat both urate overproduction and renal urate under excretion, can also be efficacious in patients with renal insufficiency. Sudden increases or decreases in serum urate concentration can trigger acute gouty attacks. Approximately 3-10% of patients taking allopurinol develop dyspepsia, headache, diarrhea, or pruritic maculopapular rash. More infrequently, patients can develop allopurinol hypersensitivity, which has a mortality rate of 20-30%. Features of allopurinol hypersensitivity include fever, toxic epidermal necrolysis, bone marrow suppression, eosinophilia, leukocytosis, renal failure, hepatic failure, and vasculitis. Corticosteroids often are used to treat allopurinol hypersensitivity.

**Uricosuric Agents** [1,10,13, 21,22,23,24]

Urate is reabsorbed by renal tubular brush border anion transporter, the reabsorption of urate can be inhibited when uricosuric drugs are present in the lumen and compete with urate for the transporter in higher doses. Probenecid and sulfinpyrazone are the most widely used uricosuric agents

**Candidates for uricosuric drugs**

Who is younger than 60 years of age and normal renal function (creatinine clearance greater than 80ml/min) . Uric acid excretion of less than 800 mg/24 hours on a general diet. No history of renal calculi

**Probenecid** [1,10,13, 21,22,23,24]

Can reduce serum urate levels by enhancing the renal excretion of uric acid. Fewer significant adverse effects than allopurinol especially life threatening hypersensitivity reaction. Probenecid can be used in the majority of middle-aged, otherwise healthy men with gout. Indications for the use of allopurinol instead of probenecid include renal insufficiency (GFR <50 mL/min), renal stones, use of aspirin (blocks the effect of probenecid), overproduction of uric acid, and unresponsiveness to probenecid. Maintenance dose ranges from 500 mg to 3 g per day and is administered on twice daily or thrice daily schedule. Precipitation of gout, urolithiasis, and impairment of renal function are common side effects.

**Sulfinpyrazone** [1,10,13, 21,22,23,24]

Sulfinpyrazone is an alternative uricosuric agent that has antiplatelet activity but is seldom used because of the added risk of bone marrow suppression .It is a congener of phenylbutazone. Starting dose, 50 mg orally twice daily; gradually increased to 100-400 mg daily. Precipitation of gout, urolithiasis, and impairment of renal function are common side effects.

**Dietary management of hyperuricemia**

The association between alcohol consumption and risk of gout varies substantially according to type of alcoholic beverage: beer confers a larger risk than spirits, whereas moderate wine drinking does not increase the risk [25,26]. Hence it must be avoided. Diets like butter, red meat, pasta sweets, white rice, potatoes, white bread, wine beer, liquor, fish poultry and sea food etc have been shown to increase the risk of gout, whereas a higher level of
consumption of dairy products is associated with a decreased risk. Moderate intake of purine-rich vegetables or protein is not associated with an increased risk of gout. [27] Those who consume milk 1 or more times per day have a lower serum uric acid level. [28,29]

Recent advances in treatment

Recently, the Food and Drug Administration (FDA) approved recombinant Aspergillus flavus uricase (Rasburicase) for the prevention of tumor lysis syndrome. Recombinant uricase therapy profoundly lowers serum urate levels. Unlike currently available urate-lowering therapies, uricase can promote accelerated tophus dissolution in a therapeutic course limited to 3 months in duration. However, it is highly immunogenic and may cause anaphylaxis, can trigger hemolysis and methemoglobinemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. It can successfully alleviated hyperuricaemia in 98% of patients and prevent complications in 99.6% of those who were at risk. In a stratified, randomised trial, rasburicase has been shown more effective than allopurinol. [30,31,32]

Oxipurinol is the active metabolite of the only commercially available xanthine oxidase inhibitor, allopurinol. Patients with allopurinol hypersensitivity can often tolerate oxypurinol, which is a metabolite of allopurinol [33].

Febuxostat is an orally administered selective inhibitor of xanthine oxidase that is not a purine analog. It inhibits both the oxidized and reduced forms of xanthine oxidase. It is a potential alternative to allopurinol for patients with gout. It is orally administered and metabolized mainly in the liver. In contrast, allopurinol and its metabolites are excreted primarily by the kidney. Therefore, febuxostat can be administered in patients with renal insufficiency, with no dosage adjustment. Febuxostat result in sustained and superior (to allopurinol) urate-lowering efficacy. Its efficacy and side-effect profile otherwise appears similar to that of allopurinol [34,35,36].

Benzbromarone is an effective uricosuric agent that may eventually become available. However, it can cause fulminant hepatotoxicity. [1]

Anti-tumour Necrosis Factor as a new therapeutic option: The activation of monocytes and macrophages releases TNF into the synovial fluid. Increased concentrations of TNF are detectable in joints of gouty arthritis. On this hypothesis, the use of etanercept (25 mg subcutaneously twice weekly) produced a noticeable decrease in all the pathological clinical and laboratory findings of severe gouty arthritis refractory to anti-inflammatory drugs. [37] However, criticizing the above treatment, Reinders et al. [38] suggested that for a case of severe tophaceous gout, when an expensive treatment is indicated, rasburicase should be considered as a potentially very effective treatment before using costly anti-TNF therapy.

Treatment of Co morbid conditions

The angiotensin receptor blocker like losartan and the triglyceride-lowering agent micronized fenofibrate have moderately potent uricosuric effects. They should therefore be considered in patients with gout who also require treatment for hypertension and hypertriglyceridemia. [39] A combination of fenofibrate and losartan can have additive urate lowering effect. [40] In contrast to losartan drugs from same family like candesartan and irbesartan do not lower uric acid. [41] Amlodipine also has been shown to be uricosuric drug and can be another choice. [42]

Higher adiposity and weight gain are strong risk factors for gout in men, while weight loss is protective. [43] The amelioration of insulin resistance by either a low-energy diet or troglitazone decrease the serum UA level in overweight hypertensive patients. [44] Metformin therapy also has been suggested safe in patients of gout to treat diabetes and insulin resistance as it can also lower uric acid and attenuate the articular syndrome. [45]

Management of gout after organ transplantation requires care full consideration. Colchicine and NSAIDs may be inappropriate. Intrarticular glucocorticoids injections may be most helpful. Uricosuric agents can be used safely but their usefulness declines if renal function decreases during dialysis.
is poor.\textsuperscript{(1)} Colchicine-induced toxicity has been observed when the drug was used for acute treatment, as well as for chronic prophylaxis of gout in patients with CKD\textsuperscript{[46]} due to its reduced clearance. Allopurinol doses thus should be lower in patients with renal insufficiency. Similarly, nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with CKD should be avoided. However, glucocorticoids (local injections or systemic therapy) are often used to treat acute attacks. Corticocotropin (Acthar), anti-tumor necrosis factor agents, and interleukin 1 antagonists are effective but expensive. Febuxostat (Uloric), like allopurinol, is a xanthine oxidase inhibitor, but the elimination of the active drug is not by the kidney. Thus, should be preferred. \textsuperscript{(46)}

\textbf{Conclusion}

Recent advances in understanding and medical treatment of gout have helped to reduce morbidity and mortality in patients suffering from this disease.

\textbf{References}