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Gout A Review of Epidemiology, Pathophysiology, Diagnosis and Management

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Abstract: *Gout is one of the oldest known diseases and the most common form of inflammatory arthritis. The established risk factors for gout include hyperuricemia, chronic renal disease, genetic, alcohol consumption, dietary factors, diuretic use, hypertension, obesity, and metabolic syndrome. Patients with gout have an increased risk of all-cause mortality, particularly from cardiovascular disease, cancer, and infectious diseases. Gout is also associated with several complications, such as nephrolithiasis. This literature review describes the global epidemiology and trends associated with gout, before providing an overview of its risk factors and complications.*

Keywords: *Gout*

I. INTRODUCTION

Historically termed the "disease of kings and king of diseases," gout represents one of the most prevalent etiologies of chronic inflammatory arthritis in the United States. It is pathophysiologically defined by the presence of monosodium urate (MSU) monohydrate crystals within joints and periarticular tissues. First described by Hippocrates in ancient Greece, gout is among the most extensively studied and clinically manageable rheumatic diseases.

Gout is biochemically characterized by the saturation of urate in the extracellular fluid, typically reflected by hyperuricemia, with plasma or serum urate concentrations exceeding 6.8 mg/dL (approximately 400 µmol/L); this level is the approximate limit of urate solubility in the blood. The clinical manifestations of gout may include:

- Acute gout flare (recurrent flares of inflammatory arthritis)
- Chronic gouty arthropathy
- Accumulation of urate crystals in the form of tophaceous deposits
- Uric acid nephrolithiasis
- Chronic nephropathy

Etiology

The etiology of gout is usually multifactorial, involving a combination of genetic predisposition, medical comorbidities, and dietary influences. In rare cases, a single-gene defect may underlie the development of gout, often in association with additional medical complications. Irrespective of the precipitating factors, the common pathogenic outcome is sustained hyperuricemia, which can manifest as clinical gout in susceptible individuals.

Genes Associated with Gout

The heritability of hyperuricemia is estimated at approximately 73%, and 40% to 50% of individuals with gout have a positive family history of the disease. Genetic factors associated with gout can be categorized into 4 major categories (see **Table.** Genes Associated With Gout).

Gene function	Gene name	Gene product	Location
Reabsorption of uric acid in renal tubule	*SLC22A11*	Organic anion transporter 4 (OAT4)	11q13.1
	SLC22A12	Urate transporter 1 (URAT1)	11q13.1
	SLC22A13	Organic anion transporter 10 (OAT10)	3p22.2

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	SLC2A9	Glucose transporter 9 (GLUT9)	4p16.1
Excretion of uric acid in renal tubule	*ABCG2*	ATP-binding cassette transporters G2 (ABCG2)	4q22.1
	ABCC4	Multidrug resistance protein 4 (MRP4)	13q32.1
	SLC22A6	Organic anion transporter 1 (OAT1)	11a12.3
	SLC22A8	Organic anion transporter 3 (OAT3)	11q12.3
	SLC17A1	Sodium-dependent phosphate transporter 17A1	6p22.2
	SLC17A3	Sodium-dependent phosphate transporter 17A3	6p22.2
	SLC17A4	Sodium-dependent phosphate transporter 17A4	6p22.2
	SLC2A12	Glucose transporter 12	6p23.2
Other	*PDZK1*	PDZ domain-containing 1 (scaffolding protein)	1q21.1
	GCKR	Glucokinase regulatory protein	2p23.2
	PKD2	Ion channels of transient receptor potential superfamily	4q22.1
	SLC16A9	Monocarboxylic acid transporter 9 (MCT9)	10q21.2
	CARML1	Myosin 1 connexin (CARMIL)	6p22.2
	SCGN	Seceragogin	6p22.2
	UMOD	Uromodulin	16p12.3
	ALDH2	Aldehyde dehydrogenase 2	12q24.12

Table 1. Genes Associated With Gout.

Risk Factors

The final step of purine metabolism is the conversion of hypoxanthine to xanthine, followed by the conversion of xanthine to uric acid by xanthine oxidase. This process is then completed by the transformation of uric acid to allantoin by uricase. Allantoin has a much higher solubility than uric acid. Humans, other primates, giraffes, and Dalmatians possess gene mutations that result in the absence of uricase production, a genetic mutation resulting in the inactivation of the uricase gene occurred about 25 million years ago. Simultaneously, there was an increase in URAT1 activity, responsible for uric acid excretion. About 20 million years ago, humans and other primates lost the ability to produce vitamin C, leading to the emergence of the antioxidant theory in which uric acid replaced ascorbic acid as the main antioxidant.

One unique aspect of this evolutionary process is the development of hyperuricemia in humans, making them the only known mammals to develop spontaneous gout. Hyperuricemia is the leading cause of gout, a condition characterized by the accumulation of uric acid crystals in joints, resulting in inflammation and pain. Research has shown that individuals with higher serum urate levels face an increased risk of developing gout and experiencing more frequent flare-ups over time. In a study involving over 2000 older adults with gout, those with serum urate levels exceeding 9 mg/dL were 3 times more likely to experience a flare over the next 12 months than those with levels below 6 mg/dL (see **Table.** Relationship Between Serum Uric Acid Concentration and Incident Gout).

Baseline serum urate	Incidence of gout at 3 years	Incidence of gout at 5 years	Incidence of gout at 10 years	Incidence of gout at 15 years
<6.0	0.21%	0.33%	0.79%	1.12%
6.0-6.9	0.37%	0.66%	1.98%	3.70%
7.0-7.9	0.92%	1.91%	6.37%	9.00%
8.0-8.9	4.00%	6.94%	11.32%	16.28%
9.0-9.9	8.31%	14.02%	24.18%	35.21%
≥10.0	10.00%	26.25%	40.00%	48.47%

Table 2. Relationship Between Serum Uric Acid Concentration and Incident Gout.

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Hyperuricemia, while a significant risk factor, does not singularly account for the development of gout (see **Table.** Risk Factors of Hyperuricemia and Gout); only a minority of individuals with elevated uric acid levels develop the condition. To assess the impact of diet on uric acid levels, examining the lower physiological uric acid range in species that do not produce uricase becomes essential. Dietary sources that can contribute to hyperuricemia and gout include the consumption of animal products such as seafood (eg, shrimp and lobster), organs (eg, liver and kidney), and red meat (eg, pork and beef). Additionally, beverages like alcohol, sweetened beverages, sodas, and those containing high-fructose corn syrup may also contribute to the onset of this disease.

Obstructive sleep apnea (OSA) is pathophysiologically linked to hyperuricemia through intermittent hypoxia, which increases purine nucleotide turnover and uric acid production, and through impaired renal uric acid excretion due to hypoxemia-induced renal dysfunction. Epidemiological studies show that OSA is associated with higher serum uric acid levels and an increased risk of hyperuricemia, independent of other risk factors. However, the association between OSA and clinically manifest gout is more modest and is substantially attenuated after adjusting for confounders such as body mass index and type 2 diabetes. Randomization studies suggest that OSA is causally associated with increased serum uric acid, but not independently with gout, after accounting for shared risk factors.

Epidemiological studies have reported a rising burden of gout, primarily attributed to lifestyle changes like increased protein consumption and a sedentary lifestyle. These shifts in habits highlight the complex relationship between modern lifestyle patterns and the prevalence of gout in contemporary society.

Additional factors linked to gout and hyperuricemia include older age, male sex, obesity, a purine-rich diet, alcohol, certain medications, comorbid diseases, and genetic predisposition (see **Table.** Causes of Hyperuricemia). Medications such as diuretics, low-dose aspirin, ethambutol, pyrazinamide, and cyclosporine have been identified as potential contributors to elevated uric acid levels and gout development.

Modifiable risk factors	**Nonmodifiable risk factors**
Hypertension	Age
Obesity	Genetic variants
Hyperlipidemia	Gender
Diabetes mellitus	Ethnicity
Cardiovascular disease	
Alcohol	
Medications altering urate balance	
Chronic kidney disease	
Dietary factors	

Table 3. Risk Factors of Hyperuricemia and Gout.

Clinical disorders leading to urate and/or purine overproduction	**Drug, diet, or toxin-induced urate and/or purine overproduction**	**Inherited enzyme defects leading to purine overproduction (rare monogenic disorders)**	**Causes of hyperuricemia due to decreased uric acid clearance**
Malignancies	Cytotoxic drugs	Glucose-6-phosphatase deficiency (glycogen storage disease, type I)	Diabetic or starvation ketoacidosis
Hemolytic disorders	Ethanol	Hypoxanthine-guanine phosphoribosyltransferase deficiency	Lactic acidosis

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Myeloproliferative disorders	Fructose (high fructose corn syrup)	Phosphoribosylpyrophosphate synthetase overactivity	Chronic renal insufficiency of any form
Lymphoproliferative disorders	Ethylamino-1,3,4-thiadiazole		Lead nephropathy (saturnine gout)
Tissue hypoxia	Vitamin B12 deficiency		Hyperparathyroidism
Down syndrome	Pancreatic extract		Sarcoidosis
Psoriasis	Excessive dietary purine ingestion		Chronic beryllium disease
Glycogen storage diseases (types III, V, VII)	4-amino-5-imidazole carboxamide riboside		Hypothyroidism
Obesity			Preeclampsia
Insulin Resistance syndrome			Effective volume depletion (eg, fluid losses and heart failure)

Table 4. Causes of Hyperuricemia.

Triggers:-

Any condition leading to changes in extracellular urate concentration has the potential to trigger a gout flare-up. These conditions include various factors such as stress (mainly due to medical illnesses like cardiovascular illnesses, recent surgical procedure, trauma, dehydration, or starvation), dietary choices (such as the consumption of high-purine foods like organ meats or seafood, as well as alcoholic beverages like beer, wine, and spirits), and drugs (including aspirin, diuretics, or even allopurinol).

Epidemiology

Epidemiological estimates depend on the definition of the disease. A definitive diagnosis of gout is accepted in the presence of monosodium urate monohydrate crystals in the joint fluid or the identification of tophus. However, given the impracticality of identifying gout through these criteria alone, various case definitions have been devised, including self-reports, the Rome criteria, the New York criteria, the American College of Rheumatology (ACR) criteria, and the 2015 ACR/European League Against Rheumatism (EULAR) criteria. The 2015 ACR/EULAR criteria have a sensitivity of 92% and specificity of 89%, surpassing the accuracy of all previous definitions and ensuring a more precise and reliable diagnosis of gout in epidemiological studies.

In men, serum urate levels typically range from 5 to 6 mg/dL and are usually attained during puberty, with a slight increase in levels due to age alone. Conversely, women exhibit lower serum urate concentrations, averaging 1.0 to 1.5 mg/dL, compared to men of corresponding ages, a difference likely influenced by renal uric acid clearance under the influence of estrogen. Following menopause, urate concentrations in women rise to levels comparable to those in adult men. The gender-based variation in urate concentration affects the clinical differences between women and men at the onset of gout.

The prevalence of gout can vary by age, sex, and country of origin. Generally, the prevalence of gout is 1% to 4%. Older age and male sex are 2 common risk factors recognized globally. In Western nations, the prevalence of gout is significantly higher in men (3%-6%) compared to women (1%-2%), with a notable 2- to 6-fold difference. The prevalence of gout rises with age but plateaus after 70 years (see **Table.** Prevalence by Age Range).

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Data from 2007 to 2008 revealed that around 3.9% of US adults received a gout diagnosis. Estimates regarding gout prevalence in the United States range from less than 3 million to over 8 million individuals. The latest estimates suggest a gout prevalence of over 3% among the adult population in the United States.

Additionally, data based on the National Health and Nutrition Examination Survey (NHANES) from 2007 to 2016 indicate a higher prevalence of gout in African-American individuals than in White individuals in the USA. Among females, gout prevalence is 3.5% in African Americans and 2.0% in White Americans, with an odds ratio (OR) of 1.81. Among males, the prevalence in African Americans is 7.0% and 5.4% in White Americans, with an OR of 1.26. Hyperuricemia was also more prevalent in African American females and males than their White counterparts, with ORs of 2.00 and 1.39, respectively.

Location/Age (years)	20-29	30-39	40-49	50-59	60-69	70-79	80-85	>85
USA	0.70	0.70	3.40	3.40	8.80	8.80	8.70	8.70
Australia	0.08	0.33	1.84	1.68	3.03	4.9	6.72	7.19
Sweden	0.06	0.27	0.80	1.54	2.83	4.89	6.61	7.38
South Korea	0.03	0.20	0.59	0.85	1.15	1.59	1.90	1.49

Table 5. Prevalence by Age Range.

The incidence rates of gout have displayed an upward trend over the past several decades, with a higher incidence observed in men than women and the incidence rising with age. A study conducted in Olmsted County, MN, from 1989 to 2009 revealed an increase in gout incidence and comorbidities over the 20 years. Similarly, in the United Kingdom, the prevalence of gout increased from 1.52% to 2.49% between 1997 and 2012.

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 contribute to MSU crystal formation.

Soluble inflammatory factors, cellular elements, and 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.

Uric Acid Physiology

Uric acid is the final product of purine metabolism in humans and higher primate species, resulting from a mutation that silences the gene encoding the enzyme uricase. Traditionally, it was believed that uric acid played a crucial role as a natural antioxidant in the human body, primarily responsible for eliminating reactive oxygen species. However, recent studies revealed that uric acid is not a significant factor in controlling oxidative stress. Instead, it is thought to be involved in immune surveillance and the regulation of blood pressure and intravascular volume.

Uric acid is a weak organic acid that predominantly exists in its ionized form, MSU, at pH 7.4. This form is less soluble due to the high sodium concentration. In acidic environments, such as urine, uric acid exists in its nonionized form, which is even less soluble within the physiological range. Consequently, uric acid crystals and stones can form in the urinary tract, distinguishing them from MSU associated with gout.

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Most urate in the body is produced endogenously in the liver, with a minor contribution from the small intestines. Renal excretion is pivotal in managing the body's urate pool under steady-state conditions since the glomerulus filters nearly all urate. In a hyperuricemic state, the urate pool expands.

In men, the normal urate range is 800 to 1000 mg; in women, it ranges from 500 to 1000 mg. Urate turnover ranges from 500 to 1000 mg daily. During male puberty, serum urate concentrations increase to reach the adult range, whereas urate levels remain low in females of reproductive age. This disparity is attributed to estrogen's influence on renal urate transporters, leading to reduced renal urate reabsorption and increased clearance in women. However, in menopausal and postmenopausal women, urate levels approach those of adult males and may be influenced by hormone replacement therapies.

The following distinguishes between causes of lower and higher urate levels:

Lowered urate pool	**Raised urate pool**
Intestinal excretion (ABCG2)	Renal tubular reabsorption
Glomerular filtration	Dietary purines, alcohol
Urate-lowering drugs	Metabolic disorders, insulin resistance
Weight reduction	Purine salvage pathways
Renal tubular secretion	ATP turnover

Hyperuricemia

Hyperuricemia plays a pivotal role in the development of gout as it facilitates the nucleation and growth of MSU crystals by reducing urate solubility. Several factors contribute to hyperuricemia in humans, including the genetic absence of uricase, the reabsorption of approximately 90% of filtered uric acid, and the limited solubility of MSU and urate in body fluids. An imbalance in the production and excretion of uric acid leads to elevated serum uric acid levels. When renal urate excretion is decreased, intestinal uricolysis increases to half of the total urate disposal, with the transporter ABCG2 playing a pivotal role. Serum urate concentrations exceeding 6.8 mg/dL become saturated and increase the risk of crystal deposition. Hyperuricemia affects 20% of adult white men in the US and is associated with several chronic disorders.

Hyperuricemia can occur as either primary (idiopathic) or secondary. Overproduction of uric acid is observed in several diseases, toxic states, and due to certain medications. Examples include acute leukemia, tumor lysis syndrome, and psoriasis.

Purine Metabolism

Purines consist of 9-carbon purine nuclei that form fused pyrimidine and imidazole rings. Purines perform essential functions in all living cells through purine-based nucleic acids, including adenine, guanine, and hypoxanthine. The contribution of dietary purines to the urate pool is significant. Removing purines from the diet of normal individuals for 10 days reduces urate levels by 25% and urinary uric acid excretion by 50%. However, implementing severely purine-restricted diets is impractical. Conversely, diets high in fructose, meat, alcohol, and fish are associated with an increased risk of hyperuricemia.

The endogenous pathway of purine production, known as de novo purine synthesis, involves the conversion of ribose-5-phosphate from 5-phosphoribosyl 1-pyrophosphate (PRPP) into nucleotide inosine monophosphate through 10 key steps. This energy-intensive process prompts energy conservation through the interconversion and salvage of purine nucleotides. Urate precursors of purine degradation are hypoxanthine and guanine, most of which are salvaged. Unused guanine is deaminated to become xanthine, while hypoxanthine is oxidized to xanthine by xanthine oxidase.

Xanthine oxidase is a flavoprotein containing molybdenum-pterin and iron sulfide clusters. It operates in 2 forms: as an oxidase, utilizing oxygen to convert hypoxanthine to xanthine and then to urate, and as a dehydrogenase, using

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nicotinamide adenine dinucleotide (NAD^+). Inhibiting xanthine oxidase is the primary target for lowering urate levels in patients with gout.

The primary regulatory steps in purine synthesis include:

The synthesis of PRPP in the PRPP synthetase pathway.

The utilization of PRPP in the first step of de novo purine synthesis.

The pathway is regulated through inhibition by purine nucleotide products of purine synthesis and activation by increased PRPP. This antagonistic control mechanism is disrupted in 2 rare X-linked disorders: deficiency of the salvage enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT) and overactivity of PRPP synthetase (PRS1). Conditions such as excessive adenosine triphosphate (ATP) depletion during tissue hypoxia or acute alcohol intoxication can lead to decreased concentrations of inhibitory nucleotides and excess urate production.

Advanced Gout

Tophi are deposits of MSU crystals associated with granulomatous inflammation. They are nests of crystals surrounded by a corona zone composed of differentiated macrophages and multinucleated giant cells encased within a fibrous layer. Proinflammatory cytokines like IL-1 and TNF-α are expressed within the corona. Aggregated NETs are also part of the tophus. The tophus is a dynamic, chronic inflammatory response to MSU crystal deposition that is complex and organized.

Tophi are primarily found in periarticular, articular, and subcutaneous areas, including cartilage, bone, joints, tendons, and skin, all of which are rich in proteoglycan. The tissue reaction to tophus is generally characterized by chronic inflammation, involving both adaptive and innate immunity. Few patients with tophaceous gout also present with chronic gouty arthritis (chronic synovitis). There is a close relationship between MSU crystal deposits and the development of cartilage and bone erosions.

Tophi contribute to joint damage and bone erosion in gout. At the bona and a tophus interface, MSU crystal deposits are surrounded by osteoclast-like cells.T-cells within the tophus express the receptor activator of nuclear factor κB ligand (RANKL), contributing to bony erosions. Additionally, urate crystals decrease the function, viability, and differentiation of osteoblasts and reduce osteoprotegerin expression. Hence, more osteoclasts and reduced osteoblasts are present at the bone-tophus interface.

The double-contoured ultrasound sign is observed in the superficial articular cartilage of patients with chronic gout and represents the presence of urate deposits. Urate crystals degrade cartilage matrix by inducing nitric oxide generation and the expression of matrix metalloprotease 3. Consequently, joints with persistent crystals experience ongoing progressive damage in the absence of acute flares.

Treatment / Management

Specific goals guide the treatment of gout. During acute flares, the primary objective is to alleviate inflammation and symptoms. In the long term, the goal shifts toward reducing serum urate levels to suppress flare-ups and regression of tophi.

General Principles of Therapy

Early on, introducing treatment for a gout flare leads to a more rapid resolution of symptoms.

The duration of gout flare therapy ranges from a few days to several weeks, depending on when treatment is initiated.

Anti-inflammatory gout flare prophylaxis should generally be continued during the early months (up to 6 months) of ULT.

For patients receiving urate-lowering therapy (ULT) at the time of a gout flare, the medication should be continued without interruption, as there is no benefit to temporary discontinuation.

The presence of tophi indicates the initiation of long-term ULT either during or following the resolution of a gout flare to reverse or prevent joint damage and chronic gouty arthritis.

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Acute Gout Flare

The management of acute flares of gouty arthritis aims to decrease inflammation and resulting pain. Treatment should commence within the first 24 hours of onset to reduce the severity and duration of the flare-up if possible. Nonpharmacological management, such as rest with topical application of ice packs can be combined with medications that reduce inflammation. First-line treatments for gout flares are nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, or systemic glucocorticoids. The length of treatment should be at least 7 to 10 days to prevent rebound flare-ups Early initiation of NSAIDs may lead to the resolution of the attack with a single dose.

NSAIDs

NSAIDs are most effective when therapy is initiated within 48 hours of the onset of gout symptoms. Indomethacin and naproxen are the more potent NSAIDs for gout, although many other commonly used NSAIDs exist. NSAID names and dosing are as follows:

Indomethacin 50 mg 3 times daily
Naproxen 500 mg twice daily
Naproxen 500 mg twice daily
Ibuprofen 800 mg 3 times daily
Diclofenac 50 mg 2 to 3 times daily
Celecoxib 200 mg twice daily

Typically, NSAID treatment for a gout flare lasts for 5 to 7 days. There is no significant preference for one NSAID over another, but high-dose, fast-acting NSAIDs such as naproxen or diclofenac are options. Indomethacin is not preferred due to its toxicity profile. NSAIDs are usually given in full doses for the first 3 days and then tapered according to the clinical improvement. COX-2 selective inhibitors, such as celecoxib, can be used to reduce adverse gastrointestinal effects.

Contraindications for the use of NSAIDs include active duodenal or gastric ulcer, cardiovascular disease (uncontrolled HTN or CHF), NSAID allergy, and CKD with creatinine clearance (CrCl) of less than 60 ml/minute per 1.73 square meters. Aspirin is not recommended for treating gout flares due to the paradoxical effects of salicylic acid on serum urate levels. This paradoxical effect results from uricosuria at higher doses and renal uric acid retention at lower doses (less than 2-3 g/day).

Oral Glucocorticoids

Glucocorticoids are recommended for gout patients with contraindications to NSAIDs and colchicine, and they are also preferred for patients with renal insufficiency. The initial dose for a gout flare is:

Prednisolone or prednisone 30 to 40 mg once daily or divided into twice-daily doses until resolution begins. Taper the dose over the next 5 to 10 days.

This has been proven to be at least comparable to NSAID efficacy. High starting doses of systemic steroids (>0.5 mg/kg body weight) are required for acute gout, especially in patients with a polyarticular presentation. A depot preparation for triamcinolone (60mg once) or methylprednisolone has been reported to be effective. However, the dose may need to be repeated at 48-hour intervals to achieve resolution of the flare. Glucocorticoids can be administered intra-articularly for a monoarticular gout flare-up or orally for polyarticular flare-ups. The efficacy of glucocorticoids is similar to or superior to that of other agents, and they have no greater risk of adverse effects in most patients.

In patients with an unclear diagnosis of an acute gout flare, arthrocentesis and synovial fluid analysis should be performed. Oral and intra-articular glucocorticoids should be avoided until the results are available. Initiation of other agents, such as NSAIDs or colchicine, should be considered. Frequent adverse effects of moderate-to-high-dose, short-term glucocorticoid use include hyperglycemia, fluid retention, increased blood pressure, and mood changes. Repeated and regular courses of glucocorticoids should be avoided to limit adverse effects.

In patients with concomitant or suspected infections, uncontrolled diabetes mellitus, prior glucocorticoid intolerance, and post-operative status, glucocorticoids may heighten the risk of impaired wound healing. Careful consideration of these factors is crucial when determining the appropriate course of treatment for patients with gout flares.

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Parenteral Glucocorticoids

Intravenous or intramuscular glucocorticoids are recommended for patients who are not candidates for intraarticular glucocorticoid injection or who are unable to take oral medications. A typical methylprednisolone dose is 20 mg intravenously twice daily, with a stepwise reduction and rapid transition to oral prednisone when improvement begins. Adrenocorticotropic hormone (ACTH) is also efficacious for treating gout flare, but limited availability and high cost restrict its use.

Colchicine

Colchicine, derived from the Colchicum autumnale plant and with a history spanning over 3500 years, has proven comparable in efficacy to other agents when taken within 24 hours of gout flare onset. In a randomized control trial, colchicine reduced pain by over 50% at 24 hours compared to a placebo. The lipophilic nature of colchicine makes it readily bioavailable for cellular uptake after oral administration. The primary target of colchicine is tubulin, and it is metabolized through hepatic elimination.

Colchicine acts by binding tightly to unpolymerised tubulin and forms a colchicine-tubulin complex that regulates microtubule and cytoskeletal function. This regulation extends to various cellular processes, including cell proliferation, gene expression, signal transduction, chemotaxis, and the secretion of granule contents by neutrophils. Furthermore, colchicine decreases neutrophil adhesion by suppressing the redistribution of E-selectin in the endothelial membrane.

Prophylaxis For Acute Gout

The subclinical joint inflammation in gout justifies colchicine prophylaxis, as acute gout flares are ULT's most common adverse effect. For prophylaxis, low-dose colchicine therapy is the first choice It is commenced 1 or 2 weeks before using urate-lowering drugs and continues for up to 6 months after normalizing uric acid levels or until the clinically visible tophi are resolved. Low-dose NSAIDs and low-dose corticosteroids can be used but carry more toxicity. The recommended colchicine dosage is 0.6 mg once or twice daily without renal or hepatobiliary compromise. In patients with renal impairment, the colchicine dose may be reduced to 0.3 mg daily or 0.6 mg every other day.

Interleukin-1 Inhibition

IL-1 antagonists have shown efficacy in refractory cases of gouty arthritis. Anakinra, a soluble IL1 receptor antagonist, is administered at 100 mg/day subcutaneously for 3 days or a single dose of IL-1 beta monoclonal antibody, canakinumab. The subcutaneous dose of 150 mg canakinumab was more effective than a single-dose intramuscular (IM) dose of triamcinolone acetonide, although the risk-benefit ratio is uncertain.

Urate lowering therapy (ULT)

Non-pharmacologic treatment

Gout is associated with several comorbidities, including obesity. In a study examining the association between obesity and gout, adults aged 40 to 75 years (n = 11,079) in NHANES 2007 to 2014 were categorized into 4 groups: stable obese, weight gain, weight loss, and those maintaining a normal BMI over time (reference group). Among those with stable obesity, the risk of gout was the highest, with an HR of 1.84 (95% CI 1.08-3.14). Patients who gained weight as adults also exhibited an increased risk of gout with HR of 1.65 (95% CI 1.19-2.29).

Diet can affect serum uric acid levels. Weight loss and dietary adjustments can reduce serum uric acid by 1 to 2 mg/dL. Foods high in purines, such as organ meats, shellfish, and beer, can elevate uric acid levels. Soft drinks containing high-fructose corn syrup are associated with an increased risk of gout; therefore, reducing their intake can help reduce serum uric acid. The DASH diet has been proven to lower serum uric acid compared to a standard Western diet, making it beneficial for gout management. Consuming at least 500 mg daily of vitamin C has also been shown to decrease serum uric acid levels and lower the risk of incident gout. Studies have shown that higher doses of vitamin C correspond to reduced risk of gout in men. Cherry consumption has also been linked to lowered serum uric acid levels and a decreased risk of recurrent gout attacks.

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Pharmacologic

The 2020 American College of Rheumatology Guideline for managing gout advises against initiating ULT after the first episode of acute gouty arthritis. ULT should not be initiated in patients with asymptomatic hyperuricemia. The guidelines provide specific criteria for initiating ULT, including the following:

Frequent or disabling gout flares (≥2 yearly) that are difficult to treat

Gout with chronic kidney disease (stage 3 or higher)

Tophus diagnosis on physical examination or imaging

Past urolithiasis

Chronic tophaceous gout

The decision to initiate ULT should be individualized. For instance, in a younger patient with their first gout attack with elevated serum uric acid levels, the likelihood of future gout attacks and progressive joint damage with tophi is higher, making it prudent to start ULT. Conversely, in an elderly patient with gout, multiple comorbidities, and taking multiple medications, the decision to treat may be more nuanced, and careful consideration should be given in this scenario. It is essential to note that the guidelines are to provide guidance but not dictate therapy.

ULT is started at a low dose to monitor the side effects and treatment response. Dose adjustments are made every 2 to 6 weeks to achieve serum urate levels of less than 6 mg/dL or 5 mg/dL in patients with tophi. The 2020 American College of Rheumatology Guideline conditionally recommends starting ULT during acute gout flares, with some evidence supporting its safety with medications such as allopurinol and febuxostat. However, initiating therapy during an acute attack might pose challenges regarding patient compliance, especially considering that patients experiencing acute flares are often hospitalized for the first time.

During the initiation of ULT, there is an increased risk of gout flare-ups. As a prophylactic measure, colchicine is recommended for 3 months after achieving the serum urate goal in patients without tophi or 6 months in those with tophi. This strategy helps to minimize the risk of flare-ups during this critical period.

ULT can be categorized into 3 classes based on their mechanisms:

Xanthine oxidase inhibitors (XOI)

XOIs work by inhibiting uric acid synthesis. This class includes allopurinol and febuxostat. Allopurinol is the recommended first-line pharmacological ULT in gout. Physicians should regularly monitor liver enzymes, renal function, and blood count. Adverse effects from allopurinol can range from skin rashes to life-threatening severe allopurinol hypersensitivity, especially in HLA-B*5801-positive patients.

Allopurinol

Allopurinol is converted to its active metabolite, oxypurinol, in the liver and has a half-life of approximately 24 hours. The initial allopurinol dose is 100 mg daily in patients with a CrCl greater than 60 mL/min and is titrated upward by 100 mg every 2 to 4 weeks. A daily dose of 300 mg of allopurinol reduces serum urate levels in 33% of the population. Allopurinol can be increased above 300 mg daily to achieve the target serum uric acid.

Allopurinol is taken once daily. Medications such as allopurinol and oxypurinol lower serum urate levels through a dual mechanism: inhibition of xanthine oxidase and interference with the purine salvage pathway by competing with phosphoribosylpyrophosphate, along with suppressive effects of their nucleotide metabolites on aminotransferase activity. Allopurinol also nonselectively inhibits pyrimidine metabolism. In patients with stage 3 or greater CKD, the starting dose of allopurinol should be 50 mg daily.

Adverse effects associated with allopurinol include the potential to trigger gout flares, pruritic and maculopapular rashes, leukopenia, thrombocytopenia, diarrhea, and severe cutaneous adverse reactions. Bone marrow suppression is uncommon but may occur at very high doses or in patients with CKD. Allopurinol can lead to a drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, a life-threatening reaction to allopurinol.

Allopurinol can enhance the cytolytic and immunosuppressive effects of azathioprine and 6-mercaptopurine (6-MP), as these drugs are partially metabolized by xanthine oxidase. Therefore, allopurinol should be avoided in

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patients undergoing treatment with these agents. Additionally, in patients on warfarin, their anticoagulation status must be carefully monitored when allopurinol is prescribed.

Febuxostat

Febuxostat is a selective XOI that occupies the access channel to the molybdenum-pterin active site of the enzyme. Renal elimination plays a minor role in the pharmacokinetics of febuxostat. FDA approval for febuxostat in treating patients with gout and hyperuricemia includes initial daily doses of 40 mg. If the urate levels do not normalize within 2 weeks, the dosage is increased to 80 mg daily. Studies have demonstrated the superior effectiveness of febuxostat over allopurinol (maximum dose of 300 mg daily). However, febuxostat may be more common with allopurinol than cardiovascular and hepatic abnormalities.

Allopurinol and febuxostat are similarly effective, although some data suggest that febuxostat may be more effective in patients with CKD. In a comparative noninferiority trial of allopurinol and febuxostat, where at least 33% of patients had stage 3 CKD, both drugs showed similar efficacy in managing flares and reducing serum uric acid levels to the target range.

XOIs have demonstrated various effects, particularly in population studies focusing on cardiovascular disease. The theory is that chronic hyperuricemia and MSU deposition result in chronic inflammation, thereby enhancing the progression of atherosclerosis. Notably, allopurinol has been associated with a modest reduction in all-cause mortality among patients with gout. A case-matched cohort study conducted in Taiwan revealed that patients with gout faced an increased risk of cardiovascular and all-cause mortality. However, ULT treatment was linked to a reduced risk of cardiovascular (HR 0.29, 95% CI 0.11-0.80) and all-cause mortality (HR 0.47, 95% CI 0.29-0.79). Allopurinol use was correlated with a lower risk of developing incident atrial fibrillation.

ULT may also slow the progression of CKD, and allopurinol is associated with a lower risk of incident renal disease in elderly patients compared to febuxostat.Literature suggests that ULT in gout patients might affect outcomes, including dementia, erectile dysfunction, and other comorbidities. While some controlled trials have explored the effect of allopurinol on the incidence rate of cardiovascular events, renal disease, and DM, these studies were performed in at-risk patients, not specifically in those with gout. Therefore, the relevance of these findings to patients with gout remains unclear.

Uricosuric Drugs

The uricosuric agents work by increasing renal urate clearance. Patients with low or normal urinary uric acid excretion in the presence of hyperuricemia are potential candidates for uricosuric therapy. Drugs in this class include probenecid and lesinurad (withdrawn from the US market). These agents inhibit URAT1 at the apical membrane of renal proximal tubular epithelial cells. However, they are ineffective as monotherapy in patients with low creatinine clearance (<30 mL/min) and contraindicated in patients with a history of nephrolithiasis.

The significant adverse effects of uricosuric drugs are the precipitation of a gout flare, uric acid urolithiasis, gastrointestinal intolerance, and rash. Uricosuric agents are not appropriate for patients with CKD and a creatinine clearance of less than 60 mL/min. Patients with tophi are best treated with XOIs or pegloticase.

Uricase Pegloticase (urate oxidase)

Uricase is present in nonprimates and lower primates. Pegloticase, a pegylated recombinant form of uricase, is a potent agent that rapidly reduces serum urate levels by directly degrading uric acid into highly soluble allantoin. Polyethylene glycol (PEG) molecules are attached to the recombinant porcine-baboon uricase in a process known as PEGylation.This process extends the PEG molecule's half-life to days or weeks, decreasing but not eliminating immunogenicity.

Pegloticase is reserved for patients with refractory gout, usually those with a high tophaceous burden. Patients must discontinue ULT while starting this medication because antibodies against pegloticase may develop. Pegloticase is administered as intravenous infusions every 2 weeks. Before each infusion, serum urate levels should be monitored to confirm urate-lowering efficacy. If the serum uric acid rises above 4 mg/dL, the infusions should be stopped, indicating that the patient is developing antibodies to pegloticase, which could lead to infusion reactions.

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Rasburicase, a nonpegylated recombinant uricase, has not received FDA approval for the treatment of gout. It prevents acute uric acid nephropathy due to tumor lysis syndrome in patients with high-risk leukemia and lymphoma.

Other Drugs With an Effect on Serum Uric Acid

Several drugs used to treat conditions such as hypertension, type 2 diabetes, and hyperlipidemia (HLD) can affect serum uric acid levels (see **Table.** Urate-Lowering Drugs and Mechanisms and **Table.** Urate-Increasing Drugs and Mechanisms).The sodium-glucose cotransporter-2 inhibitors (SGLT2i) are particularly noteworthy. Studies have demonstrated their effectiveness in lowering serum uric acid levels. In an investigation on the effect of empagliflozin therapy on heart failure, significant interactions were observed between empagliflozin treatment and baseline serum uric acid levels, affecting cardiovascular and all-cause mortality. Additionally, SGLT2 inhibitors have been shown to reduce the risk of developing incident gout and acute flares of gouty arthritis.

Drug class	Drug	Mechanism
Antihypertensive	Losartan CCBs	Increases excretion, decreases URAT1 Various
Anti-inflammatory Immunosuppressive	High-dose aspirin Leflunomide	Biphasic effect on resorption Increases excretion
Lipid-lowering	Statins Fenofibrate	Unknown Increases excretion
Metabolism modulator	SGLT2 inhibitors	Increases excretion, GLUT9
Sex hormone	Estrogen	Decreases resorption

Table 6. Urate-Lowering Drugs and Mechanisms .

Drug class	Drug	Mechanism
Diuretic	Loop diuretics	Decreases excretion, decreases MRP4 Increases resorption, increases URAT1
Other antihypertensive	Thiazide diuretics Beta-blockers	Decreases excretion, decreases MRP4 Increases resorption, increases URAT1 Unknown
Antituberculosis drug	Pyrazinamide Ethambutol	Increase resorption, increases URAT1 Decreased renal clearance
Anti-inflammatory Immunosuppressive	Low-dose aspirin Calcineurin inhibitors	Biphasic effect on reabsorption Decreases renal clearance
Metabolism modulator	Lactate Insulin	Increases resorption, increases URAT1 Increases resorption, increases URAT1
Sex hormone	Testosterone	Increases resorption, increases URAT1

Table 7. Urate-Increasing Drugs and Mechanisms .

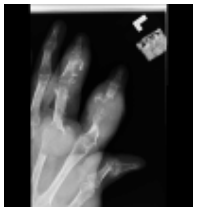

Figure Hand Radiograph, Gout Contributed by Scott Dulebohn, MD

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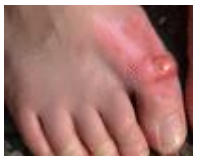

Figure Gout, [SATA] Contributed by Steve Bhmji, MS, MD, PhD

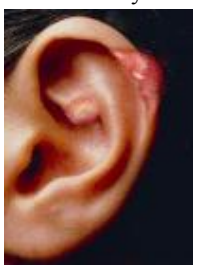

Figure Gout in the Ear Image courtesy S Bhimji MD

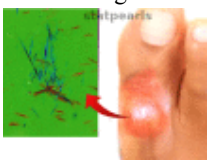

Figure Acute gout attack Image courtesy O.Chaigasame

Figure Gout Tophi Contributed by Dr. Shyam Verma, MBBS, DVD, FRCP, FAAD, Vadodara, India

Herbal Drug Used For Gout Disease:-

Sr. No	Herbal Drug (Botanical Name)	Common Name	Major Active Constituents	Mechanism of Action	Pharmacological Activity
1	Boswellia serrata	Shallaki	Boswellic acids	5-LOX inhibition, ↓ leukotrienes	Anti-inflammatory, anti-arthritic
2	Curcuma longa	Turmeric	Curcumin	COX-2 inhibition, ↓ TNF-α, IL-6	Anti-inflammatory, antioxidant
3	Zingiber officinale	Ginger	Gingerols, shogaols	Inhibits prostaglandins & leukotrienes	Anti-inflammatory, analgesic
4	Tinospora cordifolia	Guduchi	Tinosporin, glycosides	Immunomodulation, ↓ uric acid	Anti-gout, anti-inflammatory
5	Apium graveolens	Celery seed	Flavonoids, phthalides	Uricosuric effect (↑ uric acid excretion	Anti-gout, diuretic
6	Allium sativum	Garlics	Allicin, sulfur compounds	↓ uric acid synthesis, antioxidant	Anti-gout, hepatoprotective

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