

# THE PATHOGENESIS AND TREATMENT OF GOUT

Daniel Silberstein

## ABSTRACT

In the past, the etiology of gout was simplistically believed to be based in the generous indulgence of rich foods and alcohol. However, research has revealed that gout has complex environmental and genetic origins. Specifically, researchers have begun to focus attention on the molecular basis of gout and its related features. These features include hyperuricemia, the stages of gout, and the decreased solubility of uric acid. Furthermore, with epidemiologic evidence indicating that the prevalence of gout is consistently rising, it is imperative that medical providers understand the research-based guidelines for treatment. This includes what medications to administer, monitoring for drug-induced adverse effects, and modifying the treatment plan in elderly or unresponsive patients. Medical providers must also be aware of the importance of diet as a contributing factor to gout and which foods increase or decrease the risk of gout. This review will, therefore, attempt to present the current understanding of the pathophysiology of gout and guidelines for treatment and dietary modifications.

Because gout is a disease related to metabolic dysfunction and produces arthritic symptoms, the information presented in this review was extracted from textbooks and journals chiefly relating to biochemistry, rheumatology, and pharmacology. The results of the research conducted revealed that there are three features that are genetically induced that independently contribute to the onset of gout: phosphoribosyl pyrophosphate (PRPP) synthetase hyperactivity, partial deficiency of hypoxanthine-guanine phosphoribosyltransferase (HGPRT), and hyperactivity of the uric acid transporter in the renal tubule. In addition, diets rich in meat and seafood and devoid of dairy products substantially increase the risk of developing gout. Finally, research has indicated that the preferred treatment plan for gout includes using NSAIDs to alleviate the pain and inflammation of an acute gout attack, using colchicine for prophylactic therapy, and using either uricosurics or xanthine oxidase inhibitors for the long-term management of uric acid levels. Based on the results presented, medical providers will be better informed of methods to treat gout by knowing how to skillfully manage drug therapy, thereby reducing dangerous adverse effects and improving patient adherence to the drug regimen. In addition, by understanding the role of diet in the onset of gout, providers will better be able to advise patients on what foods to include or limit in their diet. From a research perspective, the elucidation of the pathophysiology of gout can lead to the development of even more effective therapeutic options.

## INTRODUCTION

The number of patients who have developed gout has increased to approximately three to five million people in the United States (Smith, 2009), making gout a serious health concern. In the past, gout was portrayed as a demonic affliction, a punishment for immorality and excessive indulgence in food and alcohol; gout was, therefore, known as “the disease of kings (Smith, 2009).” Researchers, however, have established that the development of gout depends on the complex interplay of genetic and environmental influences. Gout is a syndrome chiefly defined by hyperuricemia, a term that describes levels of uric acid that exceed the solubility limit of the blood. Men and postmenopausal women are considered hyperuricemic if the serum uric acid level surpasses 7.0 mg/dl. Premenopausal women are considered hyperuricemic if the serum uric acid level surpasses 6.0 mg/dl. This higher threshold for premenopausal women is due to the increased clearance of uric acid by estrogen (Helms, et. al. 2006). After the concentration of uric acid surpasses its saturation point, crystallization of uric acid occurs in

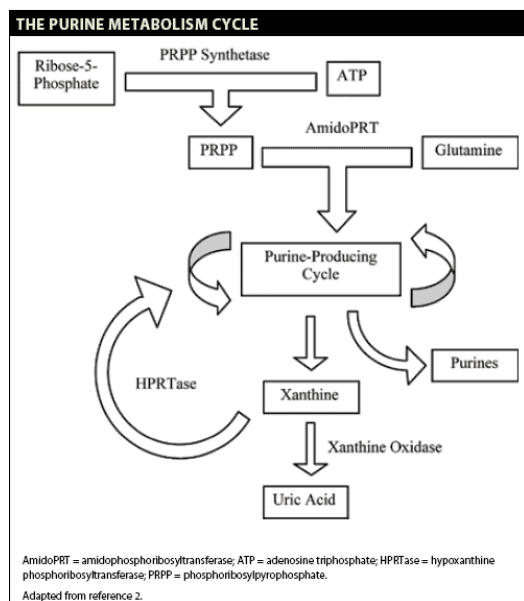
the joints and tissues, triggering debilitating attacks involving pain and inflammation. Furthermore, gout is classified into two forms. Primary gout is caused by the inheritance of genetic defects that result in either the overproduction or the underexcretion of uric acid. In contrast, secondary gout is caused by other syndromes that cause secondary hyperuricemia (Wyngaarden, et. al. 1992). Regardless of the classification, in treating gout, medical providers seek to alleviate the inflammation and lower serum uric acid levels by pharmacologic intervention and nutritional adjustments. This paper will, therefore, explore the pathogenesis and treatment of gout by investigating the underlying biochemical dysfunction, by analyzing the effects of hyperuricemia, and by advancing pharmacologic and nutritional treatment options.

## METHODS

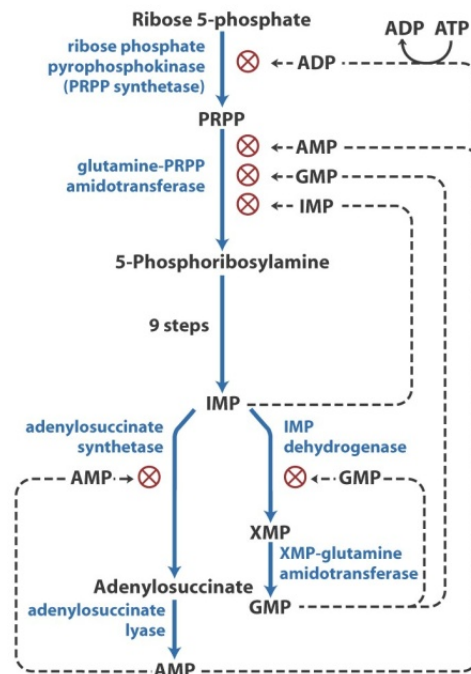
Since gout is a disease that can be caused by a genetically induced change in metabolism, the author selected and extracted information from medical biochemistry texts and journals to elucidate the metabolic pathways related to the onset of gout and to clarify mechanisms of pathogenesis. Moreover, articles from journals relating to rheumatology were consulted when addressing the symptomatology of gout and the detrimental effects that gout causes to the integrity of the joints. Finally, pharmacology texts and journals were accessed to synthesize a general treatment approach for patients with gout.

## DISCUSSION

Hyperuricemia is intimately related to the dysregulation of the purine metabolic cycle. As Figure 1 illustrates, the purine metabolic cycle can be divided into three distinct metabolic pathways: purine biosynthesis, purine catabolism, and the purine salvage pathway.



**Figure 1:** A depiction of the three components of the purine metabolic cycle (Prescott, et. al. 2011a).



**Figure 2:** A survey of the purine biosynthetic pathway and its regulation by feedback inhibition (Nelson, Cox, 2005).

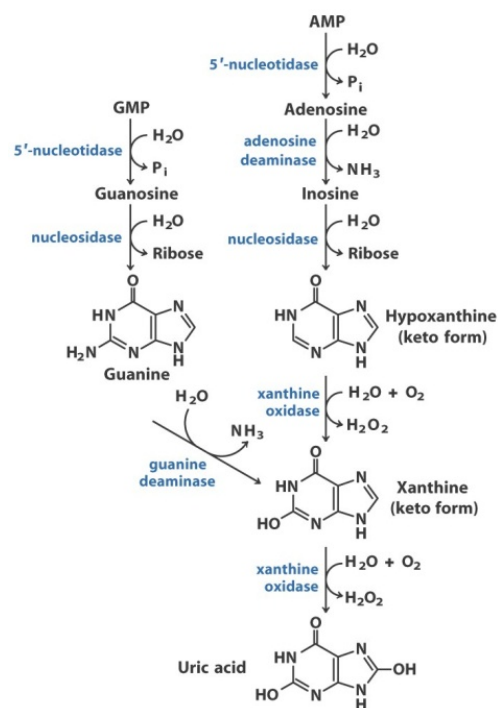
Although purine biosynthesis is a complex series of reactions, Figure 2 depicts the two key steps that determine the operation of the pathway. The first step is the catalytic conversion of ribose-5-phosphate and ATP into phosphoribosyl pyrophosphate (PRPP) by phosphoribosyl pyrophosphate synthetase (PRPP synthetase). In the second step, glutamine-PRPP amidotransferase, the rate limiting step of the pathway, then adds glutamine to the PRPP to produce 5-phosphoribosylamine. Moreover, PRPP is not only a substrate but is also the positive allosteric modulator of glutamine-PRPP amidotransferase. The subsequent steps involve further chemical modifications to produce the characteristic purine bicyclic ring structure, and these steps culminate in the production of the purines, adenylate monophosphate (AMP) and guanylate monophosphate (GMP) (Nelson, Cox, 2005).

In addition, Figure 2 displays the two prominent feedback regulation mechanisms to ensure excess production of AMP and GMP does not occur. Firstly, the AMP and GMP end products are phosphorylated to ADP and GDP, which act as negative allosteric modulators, reducing the flux through the pathway when end products accumulate by reducing the catalytic activity of PRPP Synthetase. Secondly, AMP and GMP allosterically inhibit glutamine-PRPP amidotransferase (Nelson, Cox, 2005).

Purine catabolism also plays an important role in regulating the concentration of purines. Cells normally maintain a steady concentration of the purines, adenine and guanine, by ensuring that the biosynthesis of purines is balanced by purine catabolism. As Figure 3 shows, purine catabolism is a series of metabolic reactions that aid in degrading AMP and GMP into uric acid when cellular requirements for these purines are met. Through a series of enzymatic conversions, GMP is chemically modified to xanthine by xanthine oxidase. AMP is also converted to xanthine, but through the intermediate hypoxanthine. Xanthine oxidase then oxidizes the xanthine from both paths into uric acid (Sheriff, 2004).

The Purine Salvage Pathway ensures the recycling of excess guanine and hypoxanthine significantly contributing to AMP and GMP biosynthesis. This reaction is catalyzed by hypoxanthine-guanine phosphoribosyltransferase (HPRT). This enzyme attaches the hypoxanthine to PRPP to synthesize inosine monophosphate (IMP), which is further converted to AMP or GMP. The enzyme also attaches guanine to PRPP to synthesize GMP (Horton, et. al. 2002).

The source of purine biosynthesis dysregulation is a genetically acquired defect that results in structural variations of PRPP synthetase that endow this enzyme with unusual catalytic or regulatory properties. Point mutations in the X linked gene known as PRPS1 lead to the translation of a PRPP synthetase that exhibits hyperactivity (Becker, et. al. 1996). The mutation can either adversely alter the structural integrity of the catalytic site of PRPP synthetase, resulting in an abnormally accelerated rate of catalysis, or target the regulatory site of PRPP synthetase, desensitizing the enzyme to the allosteric inhibitors GDP and ADP (Ronco, Rodeghiero, 2005). Enzymatic resistance to inhibition has been



**Figure 3:** The steps of the purine catabolic pathway (Nelson, Cox, 2005).

demonstrated experimentally by comparing the catalytic activity of the mutant PRPP synthetase to the catalytic activity of the normal enzyme.

As table 1 illustrates, the PRPP synthetase of Propositus (O.G.), who has inherited the mutant, is weakly responsive to inhibition by GDP and ADP in both the low and high protein media, displaying more than a two-fold increase in activity as compared to the enzyme of the control subjects (Zoref, et. al. 1975). In addition, overactive PRPP synthetase is hypersensitive to its allosteric activator, inorganic phosphate ( $P_i$ ), even at low concentrations (ibid). PRPP synthetase superactivity results in the overproduction of PRPP, the positive allosteric modulator and substrate for glutamine-PRPP amidotransferase, which promotes purine biosynthesis.

Despite the loss of PRPP synthetase regulation, why does the feedback mechanism fail to inhibit glutamine-PRPP amidotransferase if this enzyme has structural and catalytic integrity? Kinetically, it has been demonstrated that glutamine-PRPP amidotransferase activity is sigmoidal in the presence of its inhibitors (Zoref, et. al. 1975). Enzymes that possess a sigmoidal character exhibit large changes in catalytic activity in response to small changes in substrate concentration (Nelson, Cox, 2005). Therefore, an overproduction of PRPP can result in a substantial increase in catalysis even in the presence of enzymatic inhibitors. The consequence is excessive purine production beyond cellular needs with the unneeded purines sent to be degraded to uric acid, resulting in hyperuricemia.

The source of purine salvage pathway dysregulation is a genetically induced partial deficiency of HPRT that results in three prominent changes in metabolism that promote hyperuricemia. Firstly, since the concentration of HPRT has been reduced, the need for PRPP will decline and as a result, PRPP will accumulate. Increased levels of PRPP will allosterically activate purine biosynthesis by stimulating glutamine-PRPP amidotransferase. Secondly, the inability to recycle the guanine and hypoxanthine released during metabolic turnover will drive significant quantities of purines into catabolic pathways that will produce large quantities of uric acid. Thirdly, since salvage pathways generate AMP and GMP, the reduced flux through the salvage pathway will result in decreased concentrations of AMP and GMP. The lower levels of AMP and GMP will no longer be able to allosterically reduce the activity of glutamine-PRPP amidotransferase, further promoting excessive purine biosynthesis (Puri, 2011).

In contrast to purine biosynthesis and purine salvage metabolism, dysregulation of purine catabolism has not been implicated as a contributor to hyperuricemia. The purine catabolic pathway simply directs excess purines into uric acid. Although examination of the xanthine oxidase from the liver of patients with gout revealed an increased capacity to process purines, this observation seems to be a response to the elevated purine concentration rather than an independent inherited enzymatic defect (Wyngaarden, et. al. 1992).

Hyperuricemia is also related to renal underexcretion of uric acid. The regulation of the serum uric acid levels by the kidneys depends chiefly upon glomerular filtration and tubular reabsorption.

**Table 1:** The degree of PRPP synthetase responsiveness to inhibition by ADP and GDP in control subjects as compared to the Propositus (Zoref, et. al. 1975).

		Activity of PRPP synthetase‡		
Inhibitor	Concentration	Control subjects	Propositus O. G.	Mother D. G.
<i>mM</i>		<i>nmol/h/tube</i>		
Low protein concentration				
—	—	0.416	0.436	
ADP	0.05	0.087	0.213	
	0.10	0.036	0.143	
GDP	0.05	0.133	0.213	
	0.10	0.095	0.205	
High protein concentration				
—	—	8.3	9.9	10.0
ADP	0.05	0.645	2.58	2.61
	0.10	0.408	0.84	0.98
GDP	0.05	1.30	5.79	6.02
	0.10	1.18	3.42	4.20

Secretion, however, plays a minor role in uric acid homeostasis (Schrier, 2007). Filtration is the process by which substances under high pressure in the glomerular capillaries are released through the capillary fenestrations and are captured by the glomerular capsule. Reabsorption then occurs as the filtrate flows from the capsule into the proximal convoluted tubule where substances are transported from the filtrate into the blood. (Tortora, Derrickson, 2006). The urate transporter 1 (URAT-1) has been recently identified as the organic anion protein transporter that is responsible for orchestrating the reabsorption of uric acid. The URAT-1 is located in the apical membrane of the cells that line the proximal convoluted tubule and is coded by a gene known as SLC22A12 (Hediger, et. al. 2005). The role that URAT-1 plays was confirmed by analyzing patients that possessed mutations in SLC22A12 gene that rendered the expressed URAT-1 nonfunctional. The kidneys of these patients were unable to reabsorb urate from the filtrate, resulting in hypouricemia and hyperuricosuria. This patient analysis illustrates that URAT-1 is the principal mediator of urate reabsorption, and in its absence, the filtered urate is excreted in the urine (Klippel, 2008). Furthermore, URAT-1 has been recognized by researchers as playing a significant role in the development of hyperuricemia. Research conducted on the German Caucasian population strongly suggests that underexcretion of uric acid is associated with genetic variations of the N terminus of the URAT-1 gene (Graessler, et. al. 2006). The genetic polymorphisms induce URAT-1 hyperactivity, promoting excessive uric acid reabsorption with a subsequent elevation of serum uric acid (Prescott, et. al. 2011a).

In contrast to primary gout, the classification of secondary gout is warranted when an independent syndrome results in secondary hyperuricemia. Tumor lysis syndrome (TLS) is an example of this phenomenon. Patients that are diagnosed with acute leukemia, a malignancy characterized by a heightened sensitivity to chemotherapy and a high rate of cellular division, have greater risk for developing TLS. Two to three days after the administration of chemotherapy treatment, large numbers of leukemic cells may burst, releasing enormous quantities of DNA and RNA into circulation. The free nucleotides derived from the degradation of the DNA and RNA are then directed into the purine catabolic pathway, significantly elevating the serum uric acid level. The patient, therefore, will experience the clinical features of gout (Del Toro, et. al. 2005).

All the signs and symptoms of gout can be traced back to the decreased solubility and subsequent crystallization of uric acid (Bhagavan, 2002). Therefore, although hyperuricemia is a predisposing factor for uric acid crystallization, factors that affect uric acid solubility play significant roles in determining the onset, location and severity of uric acid deposits. The elements that influence uric acid solubility include: the local biochemical environment, temperature, and pH.

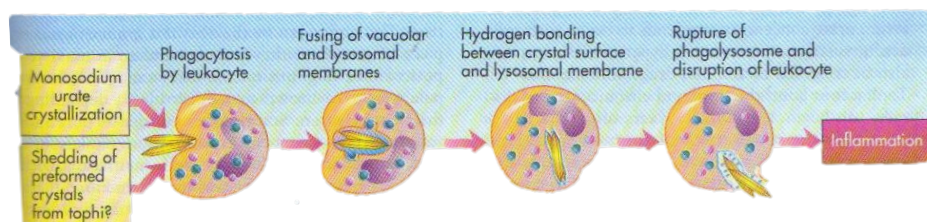
The local biochemical environment strongly determines the solubility of uric acid. A reduced concentration of albumin, which binds to uric acid, and the occurrence of trauma may stimulate crystal formation (McCance, Huether, 1998). Furthermore, an elevated local ion concentration, the presence of a large proportion of compounds that promote crystal growth, and a relatively small concentration of compounds that hinder crystallization elevate the risk of developing gout. The variable presence of these factors in the human population helps to explain why many patients with hyperuricemia are asymptomatic. A similar explanation can be offered to explain the symptomatology of gout in patients with a serum uric acid level less than 7.0 mg/dl (Oloff, 1994).

The solubility of uric acid is a function of temperature, with the saturating concentration of uric acid rising with an increasing temperature. For example, at 37°C with a pH of 7 the solubility of uric acid is 6.8 mg/dl. Under identical conditions, but at a lower temperature of 30°C, only 4.5 mg/dl of uric acid is soluble. The dependency of solubility on temperature explains the tendency of gout to manifest itself chiefly in the extremities like the knee or ankle which have temperatures of 32°C and 29°C respectively (Wyngaarden, et. al. 1992).

The solubility of uric acid is a function of pH. Uric acid is a weak organic acid with a physiologically relevant  $pK_{a1}$  of 5.5. The  $pK_{a1}$  value describes the tendency for uric acid to release a proton. A medium that has a pH above the  $pK_{a1}$  of uric acid will promote ionization of uric acid and cause an increase in the urate anion concentration. Since urate is a charged species, it has an increased solubility in water. In a medium with a pH below 5.5, a large percentage of uric acid remains protonated and exists as a neutral species, thereby displaying poor solubility in water. For example, after adding uric acid to a medium with a pH of 7.0, the urate ion was the predominate species and displayed a solubility of 200 mg/dl. In contrast, after adding uric acid to a medium with a pH of 5.0, uric acid was the predominate species with a measured solubility of only 15 mg/dl. This has significant implications in patients who have hyperuricemia. Hyperuricemic patients excrete higher concentrations of uric acid and if the patients' urine is acidic, the uric acid may crystallize forming renal calculi (Dipiro, et. al. 1997).

In the absence of medical intervention, a hyperuricemic patient can gradually develop increasingly severe symptoms that culminate in joint deterioration and potential immobility. The course of gout can be segmented into four distinct stages. The first stage is the asymptomatic stage. The patient presents with elevated serum uric acid but does not experience any symptoms of gout. Approximately twenty-percent of the patients in the asymptomatic stage will progress to the next stage known as the acute gouty arthritis stage where the manifestation of gout takes the form of painful and debilitating arthritis. The extremities are chiefly affected during this stage with, for example, 90% of patients eventually experiencing an arthritic attack involving the metatarsophalangeal joint (Oloff, 1994). Depending on the severity of the attack, the duration of the symptoms can range from several hours to several weeks. The characteristic symptoms of swelling, redness, and pain are a result of the leukocyte mediated inflammatory reaction in response to uric acid crystallization in the joints. The cellular sequence that initiates the inflammatory response is described in Figure 4. Figure 4 depicts a neutrophil engulfing uric acid crystals by enclosing the crystals in a membrane vesicle. The vesicle then fuses with a lysosome, forming a phagolysosome. The crystals, however, puncture the phagolysosome and cause the release of hydrolytic enzymes into the cytoplasm. The release of enzymes that promote cellular degradation causes a loss of membrane integrity, which results in the discharge of the cytoplasmic contents of the neutrophil into the synovial fluid of the joint. The discharge attracts mast cells, macrophages, and lymphocytes that gather at the site releasing pro-inflammatory chemicals, such as leukotriene B4 and interleukin1. Moreover, the antibody Immunoglobulin G binds to the uric acid crystals inducing increased neutrophil phagocytic activity (McCance, Huether, 1998).

With the termination of the symptoms, the patient enters the intercritical stage. This stage is defined as the time interval between acute gouty arthritic attacks. Although the patient experiences



**Figure 4:** A linear portrayal of how neutrophils trigger an inflammatory response that results in painful acute gout attacks (McCance, Huether, 1998).

symptomatic relief of the arthritic symptoms, an analysis of the synovial fluid would reveal uric acid crystals. Moreover, the concentration of uric acid continues to rise during this stage, potentially promoting a regression to the second stage. For example, it has been found that approximately 62% of patients revert to the second stage and suffer another arthritic attack; with each recurrence, the severity and the duration of the attacks escalate. Approximately five to twenty- five percent of patients with



gout will advance to the fourth stage known as the chronic tophaceous gout stage. During this stage, uric acid exerts deleterious effects on the structural integrity of the cartilage and bone, resulting in joint degeneration and hampered patient mobility. In addition, uric acid also accumulates subcutaneously, forming localized areas of uric acid deposition known as tophi (Oloff, 1994).

Because untreated gout can progress and cause irreversible joint damage and painful arthritis, it is essential that a treatment plan be formulated. However, since research has shown that many patients with asymptomatic hyperuricemia never develop the more severe stages of gout (Koda-Kimble, et. al. 2005), medical providers initiate treatment when the patient experiences recurrent gouty arthritic attacks or renal complications. Table 2 lists the optimum dosage, dose schedule, and potential adverse side effects for a number of pharmaceutical agents that are used in the course of treating a patient who is diagnosed with gout. Medical providers utilize pharmacological intervention to address three principal aims. Firstly, if the patient is currently experiencing an acute gout attack, it is imperative that the inflammation and pain is controlled. Secondly, it is vital that future attacks are limited or prevented. Thirdly, the patient's serum uric acid must be reduced and maintained at a level less than 6.0mg/dl (Helms, et. al. 2006).

**Table 2:** A survey of the pharmaceutical agents that are used to treat gout, with the optimum dosage, dose schedule, and potential adverse effects provided (Prescott, et. al. 2011b).

Therapeutic Agent	Typical Regimen	Side Effects/Comments
NSAIDs	Lowest effective dose	<ul style="list-style-type: none"><li>• Avoid in patients with peptic ulcer disease, active bleeding</li><li>• May cause gastritis, liver dysfunction, fluid retention, hypertension</li><li>• Use with caution in patients with congestive heart failure</li></ul>
Colchicine (Colcrys)	0.6-1.2 mg a day	<ul style="list-style-type: none"><li>• Diarrhea, peripheral neuropathy, rhabdomyolysis</li></ul>
Xanthine Oxidase Inhibitors		
Allopurinol (Zyloprim)	50-300 mg a day	<ul style="list-style-type: none"><li>• Allopurinol can be used in urate overproduction and urate underexcretion</li><li>• Common class side effects: rash, gastric irritation, and acute gout attacks</li><li>• Rash is less common with febuxostat than with allopurinol</li></ul>
Febuxostat (Uloric)	40-80 mg a day (target serum urate <6 mg/dL)	
Uricosurics		
Probenecid (Benemid)	250 mg twice a day, titrated up to 500-2000 mg a day (target serum urate <6 mg/dL)	<ul style="list-style-type: none"><li>• Avoid in patients with history of urolithiasis and impaired renal function</li><li>• Probenecid can affect the excretion of many drugs</li><li>• Sulfinpyrazone has fewer side effects than probenecid</li><li>• Class side effects: gout flares, gastrointestinal irritation, rash</li></ul>
Sulfinpyrazone (Anturane)	50 mg twice daily, titrated to 100-400 mg a day (target serum urate <6 mg/dL)	

Nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine are used to alleviate and control the intense inflammation and incapacitating pain that is characteristic of acute gout flares. Upon the

initiation of an acute gout flare, colchicine is administered in doses of 0.6 mg every one to two hours for a maximum of ten doses in a twelve-hour time period or until the patient experiences relief. Furthermore, the therapeutic effects of colchicine are only achieved if it is administered less than 48 hours after the start of symptoms. The adverse effects of colchicine, which include vomiting and diarrhea, limit its usage. Medical providers are, therefore, prescribing NSAIDs more frequently because of limited side effects and equivalent effectiveness as compared to colchicine (Fiebach, et. al. 2007). The most popular NSAID prescribed is indomethacin. For optimal effectiveness, Indomethacin should be initially administered within one to two days of the start of the gout flare at 75 mg. After the administration of the initial dose, the dosage is adjusted to 50 mg every six hours for the following two days, and is then modified to 50 mg every eight hours for the fourth day of treatment (Dipiro, et. al. 1997).

Though immediate treatment with anti-inflammatory drugs offers considerable relief to patients who are afflicted with acute gout flares, there are certain characteristics that promote susceptibility to future attacks. There are three features that aid in the identification of a patient that requires prophylaxis against a potentially impending attack: a serum uric acid level that surpasses 10.0 mg/dl, a history of renal calculi, and persistent gout flares. Prophylactic therapy is terminated when the serum uric acid levels decline to below 7.0 mg/dl and when the patient has not experienced recurrent flares for a period of a year (Dipiro, 1997). Though NSAIDs are the optimum choice for combatting acute gout attacks, chronic use of NSAIDs during prophylactic therapy is associated with more severe adverse effects as compared to colchicine. Therefore, medical providers prefer a low dosage of 0.6 mg of colchicine administered twice a day for the long term prevention of recurrent gout attacks (Fiebach, et. al. 2007).

Long term management of serum uric acid levels is indispensable for precluding future acute gout attacks and detrimental effects to the skeletal system. Serum uric acid levels that are less than 6.0 mg/dl result in substantial improvements in patients with recurrent gout flares (Helms, et. al. 2006). There are two classes of drugs that are commonly used to reduce serum uric acid levels: Uricosuric drugs, which enhance renal excretion of uric acid, and xanthine oxidase inhibitors, which decrease the production of uric acid.

Probenecid and sulfinpyrazone are the two uricosuric agents that are frequently prescribed to enhance uric acid excretion. These drugs, therefore, should be preferentially prescribed to patients that have demonstrated uric acid underexcretion in a twenty-four hour urine collection test; if the urine contains less than 800 mg of uric acid when the patient is on a regular western diet, it strongly suggests that the patient is an underexcreter (Prescott, et. al. 2011a). Although sulfinpyrazone is more effective as a uricosuric agent as compared to probenecid, sulfinpyrazone possesses additional antiplatelet biological activity. Uricosuric drugs promote renal excretion of uric acid by interfering with the proximal tubular reabsorption of uric acid (West, 2002). These drugs are weak organic acids that competitively inhibit URAT-1, the protein transporter responsible for mediating the selective passage of uric acid from the filtrate into the blood. Inhibition of this transporter prevents excessive tubular reabsorption of urate from the filtrate, resulting in a reduction of serum uric acid with a simultaneous elevation of uric acid in the urine (Klippel, 2008; West, 2002). These changes have been observed in patients given doses of 1-2 mg of Probenecid; the urinary uric acid excretion level in these patients increased between four to six fold (Helms, et. al. 2006).

The dosage of probenecid and sulfinpyrazone is low upon initiation of drug therapy to prevent an abrupt elevation in the quantity of uric acid excreted. For example, the dosage of probenecid is 250 mg twice a day for the first week and is subsequently increased to 500 mg twice a day (Koda-Kimble, et. al. 2005). Similarly, the dosage of sulfinpyrazone is started at 50 mg twice a day for four days, with the dose subsequently increased to 100 mg twice a day. Thereafter, the dose is increased by 100 mg every



week until the maximum dose of 800 mg is reached. This precautionary measure is necessary to lessen the possibility of developing uric acid nephrolithiasis or kidney stones in patients that have a low urinary pH; a low pH promotes protonation of urate, raising the concentration of poorly soluble uric acid in the urine (Dipiro, 1997).

There are other methods of further reducing the risk of nephrolithiasis. Patients are advised to increase their fluid intake by drinking 2.0 L per day to ensure that their urine becomes more dilute, reducing the concentration of uric acid. In addition, sodium bicarbonate dosed at one gram three times a day can be used to alkalinize their urine, effecting the ionization of uric acid to the more soluble urate anion. Furthermore, since a diminished renal clearance results in a decrease in the volume of the filtrate and a consequent increase in uric acid concentration, patients with a creatinine clearance lower than 50 ml/min should avoid using uricosurics (Helms, et. al. 2006). Therefore, patients with a history of uric acid nephrolithiasis, or patients who have renal insufficiency characterized by a glomerular filtration rate that is less than 60ml/dl, or patients above 60 years old who have experienced the inevitable renal impairment that accompanies aging should not be administered uricosuric drugs (Panda, 2002). The adverse side effects of uricosurics include gastrointestinal upset, rash, headaches, and allergic reactions (West, 2002).

The xanthine oxidase inhibitors, allopurinol and the newly designed febuxostat, on the other hand, are commonly prescribed to reduce uric acid biosynthesis. These drugs, therefore, should be preferentially prescribed to patients who have demonstrated uric acid overproduction by excreting more than 800mg of uric acid in a twenty-four hour urine collection test (Koda-Kimble, et. al. 2005). Therefore, xanthine oxidase inhibitors are warranted in a situation where uric acid overproduction is a result of enzymatic deficiency or hyperactivity (Panda, 2002). However, xanthine oxidase inhibitors would also be effective in underexcreters, reducing the load of uric acid the kidney has to process (Koda-Kimble, et. al. 2005). To reduce the possibility of triggering an acute attack by dramatically altering the serum uric acid concentration, allopurinol is dosed gradually; a daily dose of 100 mg is administered and the dose is steadily raised during a three-week period until the dose reaches 300 mg daily (Seth, Seth, 2009). In addition, the magnitude and frequency of the dose must reflect the creatinine clearance, an indicator of renal function. A patient with a reduced creatinine clearance will be administered a decreased dose of allopurinol (Seyffart, 1991). In contrast, the dosage of febuxostat remains unaltered regardless of renal efficiency, with doses of either 80 mg daily or 120 mg daily available depending on the severity of the gout symptoms (Seth, Seth, 2009).

The effectiveness of Allopurinol as compared to Febuxostat was tested in the Febuxostat Allopurinol Controlled trial (FACT). This randomized, double blind trial attempted to evaluate what percentage of patients taking either allopurinol or febuxostat would achieve a uric acid level below 6.0mg/dl, called the endpoint. When patients were administered 80 mg and 120 mg of febuxostat, 53 percent and 62 percent of patients achieved the endpoint, respectively. In contrast, only 21 percent of the patients achieved the endpoint when administered allopurinol. This result suggests that febuxostat is more effective than Allopurinol. Moreover, both drugs produced approximately the same number of adverse effects (Becker, et. al. 2005). The adverse effects of allopurinol include the development of rashes and allopurinol hypersensitivity syndrome, a potentially fatal syndrome that is characterized by fever, cutaneous rash, and multi-organ injury (Lee, et. al. 2008). The side effects of febuxostat include liver and gastric complications as well as headaches (Bridgeforth, cherf, 2011).

Allopurinol inhibits the inordinate production of uric acid by interfering with both purine biosynthesis and catabolism. Since allopurinol is structurally similar to the purine hypoxanthine, hypoxanthine-guanine phosphoribosyl transferase (HGPT) catalyzes the attachment of PRPP to allopurinol to produce allopurinol ribonucleotide. The impact of this reaction is twofold. Firstly, the

production of allopurinol ribonucleotide consumes PRPP, the allosteric stimulator and substrate of the rate limiting step of purine biosynthesis. Secondly, the allopurinol ribonucleotide operates as a negative allosteric effector to glutamine-PRPP amidotransferase, further strengthening the inhibition of purine synthesis (Bhagavan, 2002). In addition, allopurinol functions as a xanthine oxidase inhibitor, inhibiting the final two steps that are responsible for synthesizing uric acid. Allopurinol is converted into alloxanthine in the active site of xanthine oxidase, and it acts as a competitive inhibitor, resulting in an increase in the more soluble endogenous substrates xanthine and hypoxanthine (Finkel, et. al. 2009). The consequence of allopurinol's effects is to decrease excessive purine biosynthesis and reduce the production of uric acid. Febuxostat administration achieves its hypouricemic effect by exclusively targeting xanthine oxidase for inhibition and, in contrast to allopurinol, does not interfere in purine biosynthesis. The selectivity of febuxostat can be attributed to its non-purine structure, preventing catalysis by HGPT (Seth, Seth, 2009).

**Table 3:** A listing of different food categories patients with gout should consume in limited quantities because of their elevated purine content (Prescott, et. al. 2011b).

Category	Foods
Non-Poultry Meats	Beef
	Pork
	Lamb
	Sausage
	Bologna
	Bacon
	Hot dogs
Poultry	Hamburgers
	Chicken
	Turkey
Fish	Chicken liver
	Tuna
Other Seafood	Dark fish
	Shrimp
	Lobster
Plant-Based Foods	Scallops
	Peas
	Beans
	Lentils
	Spinach
	Mushrooms
Alcoholic Beverages	Oatmeal
	Cauliflower
	Beer
	Spirits
	Wine

Although drug therapy is effective in the management of gout, the patient needs to dramatically modify dietary habits to ensure a low and stable uric acid level. Table 3 lists six categories of foods that have been shown to have elevated purine content. An increase in ingested purines will increase the production of uric acid. Therefore, it is essential for the patient to recognize foods that are high in purine content and those foods that promote a decrease in serum uric acid. A study carried out by the Third National Health and Nutrition Examination Survey, which was conducted on 14,363 subjects, sought to evaluate how different food categories influence the serum uric acid level. The study found a link between the daily consumption of milk and reduced serum uric acid levels. The importance of

expanding one's diet to include the daily consumption of dairy products was further strengthened by the discovery of an association between a diet devoid of dairy products and an elevated serum uric acid level (Choi, et. al. 2005). Furthermore, Choi et al organized a study to assess the relationship between a person's dietary practices and the onset of gout. It was found that compared to the participants who consumed 0.5 daily servings of meat, participants who consumed 2.5 daily serving had a 41 percent increased risk of developing gout. Seafood consumption was also shown to significantly increase the risk of developing gout. As compared to the participants who consumed 0.04 daily servings of seafood, participants who consumed 0.8 daily servings had a 51 percent elevated risk of developing gout (Choi, et. al. 2004). The results of the above-mentioned studies emphasize how diet can be a significant contributing factor to the onset of gout. Therefore, patients need to modify their dietary practices in order to ensure maximum reduction and stabilization of serum uric acid levels.

## CONCLUSION

Though it can be a potentially debilitating and painful metabolic disease, gout is not as disabling as it was in the past. With a deeper understanding of the purine metabolic cycle and the identification of the URAT-1 transporter in the renal tubules, researchers have made headways into clarifying the pathogenesis of gout. These advances will likely lead to even more effective therapeutic solutions. However, the current treatment regimen generally includes the use of NSAIDs to control the acute gout attacks, the use of colchicine for prophylactic therapy, and the use of either uricosurics or xanthine oxidase inhibitors for the long-term management of uric acid levels. The patient must also make lifestyle changes by limiting the intake of purine-rich foods. If the patient is committed to a new dietary regimen and is compliant with drug therapy, gout will be a chronic but manageable disease.

## REFERENCES

- Becker MA, Schumacher HR Jr, Wortmann RL.(2005) Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med.*; 353(23):2450-61. doi: 10.1056/NEJMoa050373.
- Becker, MA, Taylor W, Smith PR, Ahmed M.(1996) Overexpression of the Normal Phosphoribosylpyrophosphate Synthetase 1 Isoform Underlies Catalytic Superactivity of Human Phosphoribosylpyrophosphate Synthetase *J. Biol. Chem.*; 271: 19894-19899. doi:10.1074/jbc.271.33.19894.
- Bhagavan N. (2002) *Medical Biochemistry*. San Diego, CA: Harcourt Academic Press.
- Bridgeforth GM, Cherf J. (2011) *Lippincott's Primary Care Musculoskeletal Radiology*. Philadelphia, PA: Lippincott Williams & Wilkins.
- Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. (2004) Purine-rich foods, dairy and protein intake, and the risk of gout in men. *N Engl J Med.*;350(11):1093-1103.
- Choi HK, Liu S, Curhan G. (2005) Intake of purine-rich foods, protein, and dairy products and relationship to serum levels of uric acid: The Third National Health and Nutrition Examination Survey. *Arthritis Rheum.* (1):283-9. doi: 10.1002/art.20761.
- Del Toro G, Morris E, Cairo MS. (2005) Tumor lysis syndrome: pathophysiology, definition, and alternative treatment approaches. *Clin Adv Hematol Oncol.* Jan;3(1):54-61. Available at: [http://www.clinicaladvances.com/article\\_pdfs/ho-article-200501-deltoro.pdf](http://www.clinicaladvances.com/article_pdfs/ho-article-200501-deltoro.pdf). Accessed May 14, 2012.
- Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. (1997) *Pharmacotherapy: A Pathophysiologic Approach*. New York: McGraw-Hill.

- Fiebach NH, Kern DE, Thomas PA, Ziegelstein RC, eds. (2007) *Principles of Ambulatory Medicine*. Philadelphia, PA: Lippincott Williams & Wilkins.
- Finkel R, Cubeddu LX, Clark MA. (2009) *Pharmacology*. Philadelphia, PA: Lippincott Williams & Wilkins.
- [Graessler J](#), [Graessler A](#), [Unger S](#), et. al. (2006) Association of the human urate transporter 1 with reduced renal uric acid excretion and hyperuricemia in a German Caucasian population. *Arthritis Rheum.* Jan; 54(1):292-300. <http://dx.doi.org/10.1002/art.21499> .
- Hediger MA, Johnson RJ, Miyazaki H, Endou H. (2005) Molecular physiology of urate transport. *Physiology*. April 20;(2) 125-133; doi:10.1152/physiol.00039.2004.
- Helms RA, Quan DJ, Herfindal ET, Gourley DR, eds.(2006) *Textbook of Therapeutics: Drug and Disease Management*. Philadelphia, PA: Lippincott Williams & Wilkins.
- Horton HR, Moran LA, Ochs RS, Rawn JD, Scrimgeour KG.(2002) *Principles of Biochemistry*. NJ: Prentice-Hall, Inc.
- Klippel J. *Primer on the Rheumatic Diseases*. (2008) New York, NY: Springer Science and Business Media.
- Koda-Kimble MA, Young LY, Kradjan WA, Guglielmo BJ, Alldredge BK, Corelli RL. (2005) *Applied Therapeutics: The Clinical Use of Drugs*. Philadelphia, PA: Lippincott Williams & Wilkins.
- Lee HY, Ariyasinghe JT, Thirumoorthy T. (2008) Allopurinol hypersensitivity syndrome: a preventable severe cutaneous adverse reaction? *Singapore Med J*. May; 49(5):384-7. Available at: <http://smj.sma.org.sg/4905/4905a3.pdf>. Accessed April 30, 2012.
- McCance KL, Heuther SE. (1998) *Pathophysiology: The Biologic Basis for Disease in Adults and Children*. ST. Lois, MO: Mosby.
- Nelson DL, Cox MM. *Lehninger Principles of Biochemistry*. (2005) New York, NY: Freeman and Company.
- Oloff LM. (1994) *Musculoskeletal Disorders of the Lower Extremities*. Philadelphia, PA: W. B. Saunders Company.
- Panda U, eds. (2002) *Current Medical Diagnosis and Treatment*. New Delhi, India: Jaypee.
- Prescott J, Page M, Ayyala S. (2011) The Contemporary Management of Gout: Identification and Diagnosis of Gout (Case 1). *Pharmacy Times*. April. Available at: <https://secure.pharmacytimes.com/lessons/201104-02.asp>. Accessed April 30, 2012 (a).
- Prescott J, Page M, Ayyala S. (2011) The Contemporary Management of Gout: Active Treatment of Gout (Case 2). *Pharmacy Times*. April. Available at: <https://secure.pharmacytimes.com/lessons/201104-02.asp>. Accessed April 30, 2012 (b).
- Puri D. (2011) *Textbook of Medical Biochemistry*. India: Elsevier.
- Ronco C, Rodeghiero, eds. (2005) *Hyperuricemic Syndromes: Pathophysiology and Therapy*. Basel (Switzerland): Karger.
- Schrier R. (2007) *Diseases of the Kidney and Urinary Tract*. Philadelphia, PA: Lippincott Williams & Wilkins.
- Seth SD, Seth V. (2009) *Textbook of Pharmacology*. India: Elsevier.
- Seyffart G. (1991) *Drug Dosage in Renal Insufficiency*. AA Dordrecht, Netherlands: Kluwer Academic Publishers.
- Sheriff DS. 2004 *Medical Biochemistry*. New Delhi, India: Jaypee Brothers medical Publishers.
- Smith RG. The Diagnosis and Treatment of Gout. *US Pharm*. 2009; 34 (5): 40-47. Available at: [http://www.uspharmacist.com/content/c/13430/?t=men's\\_health,pain\\_management](http://www.uspharmacist.com/content/c/13430/?t=men's_health,pain_management). May 19, 2009. Accessed April 30, 2012.

- Tortora GJ, Derrickson B. (2006) *Principles of Anatomy and Physiology*. Hoboken, NJ: John Wiley and Sons, Inc.
- West S. *Rheumatology Secrets*. 2002 Philadelphia, PA: Hanley and Belfus.
- Wyngaarden JB, Smith LH, Bennett JC, eds. (1992) *Cecil Textbook of Medicine*. Philadelphia, PA: W. B. Saunders Company.
- Zoref E, De Vries A, Sperling O. (1975) Mutant feedback-resistant phosphoribosylpyrophosphate synthetase associated with purine overproduction and gout. Phosphoribosylpyrophosphate and purine metabolism in cultured fibroblasts. *J Clin Invest*. November; 56(5): 1093–1099. doi: 10.1172/JCI108183.