

Gout: Update on Pathogenesis, Diagnosis, and Treatment

Dan A. Mandel, MD
Peter A. Simkin, MD

Division of Rheumatology
Department of Medicine
University of Washington

Because the manifestations of gout are due to inflammation caused by urate crystal deposition, therapy focuses on normalization of serum urate levels by xanthine oxidase inhibition and uricosurics, and on control of arthritis and inflammation with colchicine, NSAIDs, and corticosteroids. Recent studies investigating the pathogenesis of gout and its treatment have prompted several useful reviews.¹⁻¹³ This article focuses on the epidemiology, pathogenesis, diagnosis, and treatment of gout with an emphasis on new developments.

Epidemiology

Gout most commonly affects males above the age of 40. Using data from 1988-1994, the overall prevalence in the U.S. was estimated to be 5.1 million persons (3.4 million men and 1.7 million women).¹⁴ Although gout is more common in men, its prevalence in postmenopausal women approaches that in men.¹⁵

In the past, gout was considered a disease of the affluent. In the last two centuries, however, gout has been recognized increasingly in the general population. The annual prevalence of gout has increased from 4.8/1000 in 1969 to 9.4/1000 in 1996, based on NHIS data.¹⁶ Because the gene pool has not changed, this dramatic increase presumably reflects lifestyle changes.

Risk Factors

Risk factors for gout include age, gender, hyperuricemia, adiposity, and diet. Its prevalence increases with age, from 1.8/1000 in people under the age of 45 to 30.8/1000 in people over the age of 65 and was as high as 46.4/1000 in men over the age of 65, based on NHIS data from the 1996 survey.¹⁵ Elevated serum urate levels are also linked with increased risk (Table 1).¹⁷ Additionally, the risk for gout correlates with truncal obesity, as measured by body mass index and waist-to-hip ratios.¹⁸⁻²⁰

Various medications are known to cause hyperuricemia and are therefore risk factors for gout. Diuretics are the most common of these, and cyclosporine is probably the most severe. Low-dose aspirin can also be a factor, although the 81 mg/day

dosage for cardioprotection does not cause clinically meaningful problems.²¹

Associated Conditions

Hyperuricemia and gout have been linked to other disease states, including hypertension, metabolic syndrome, cardiac disease, stroke, and renal disease. As many as 76% of gout patients have metabolic syndrome (hypertension, insulin resistance, truncal obesity, and dyslipidemia).^{22,23} In rats, all elements of the metabolic syndrome were induced by fructose feeding and reversed by allopurinol therapy.²⁴ Fructose has long been recognized as a cause of hyperuricemia,²⁵⁻²⁷ and its presence in the American diet has risen markedly in recent decades.

Under usual circumstances, serum urate levels reflect the balance between filtration at the glomerulus and reabsorption and secretion in the proximal renal tubule. On a daily basis, roughly 10 grams of urate are filtered (more than seven times the normal total body pool), more than 9 grams are reabsorbed, and a much smaller but clinically important amount is secreted. The critical reabsorptive role is performed by URAT1,²⁸ while other transporters (UAT, OAT1, and OAT3) play smaller parts that are still being investigated. URAT1, in turn, may be controlled by a hepatic hormone that offers a potentially important new target for therapeutic intervention.²⁹

Through several mechanisms, urate ions may damage the kidneys. Rarely, and almost always in patients

Table 1. Annual incidence of first gout attack in men

Serum Urate (mg/dl)	Incidence %
<7.0	0.1
7.0-7.9	0.4
8.0-8.9	0.8
9.0-9.9	4.3
>10	7.0

with hyperacidic urine, uric acid stones form in the renal pelvis causing subsequent ureteral obstruction. More commonly, and especially in the tumor lysis syndrome, uric acid nephropathy develops when the filtered burden of uric acid overwhelms reabsorptive capacity and the tubules become obstructed by uric acid sludge. A third problem, gouty nephropathy, is ubiquitous in patients with long-term gout. It occurs when the same sodium urate crystals that cause gouty arthritis precipitate in the renal interstitium, causing chronic inflammation and nephron loss. Unfortunately, the formaldehyde used in tissue fixatives forms highly soluble complexes with urate, and these deposits are leached away during tissue fixation and often go unrecognized by pathologists.³⁰ Finally, urate ions in solution may damage the renal vascular endothelium and represent a critical factor in the pathogenesis of hypertension.^{31,32} Further work will be necessary to resolve the relative contributions of the interstitial crystals and the plasma urate ions in urate-induced renal injury.

A recent small study suggests that reduction of serum urate levels with allopurinol therapy may slow the progression of chronic renal disease, and an interventional study is currently in progress in patients with hypertension.³³

Pathogenesis of Gout

The pathogenesis of gout begins with crystallization of urate within the joint, bursa, or tendon sheath, which then leads to inflammation manifested as rapidly progressive pain, swelling, warmth, and tenderness.

Uric acid is a weak acid with pKa of 5.8; it is supersaturated at 6.8 mg/dl in saline at 37°C. Because peripheral joints are colder than central joints, the arthritis has an acral distribution. Osteoarthritic involvement (as in the bunion joints of the feet or Heberden's nodes in the hands) predisposes such joints to gout.^{34,35} Urate crystals persist in joints and in tophi during quiescent periods, but coating with serum proteins, especially apolipoproteins B and E, protects against acute inflammatory response.³⁶⁻³⁹

Episodes of acute gout usually resolve in one to two weeks, even without treatment. This self-limited course may reflect development of protein coating of the crystals during the course of an attack. As monocytes mature into macrophages, their function becomes more suppressive, via production of TGF- β , than proinflammatory, and this evolution may also contribute to the limited duration of acute gout.

Recently, several studies using in vitro assays and knockout mice have examined the role of the immune system in gouty inflammation. These studies suggest that inflammation occurs via pathways that depend on intracellular proteins of the innate immune response such as NALP-3, MyD88, the inflammasome, and also on the IL-1 receptor and IL-1 production.⁴⁰⁻⁴²

The tophus consists of a granuloma in a dynamic process of remodeling, composed of mono- and multinucleate macrophages surrounding a core of material containing urate crystals.^{43,44} The granulomatous response in bone and joints leads to erosions and bone destruction.

Diagnosis

The diagnosis of gout can be straightforward, as in recurrent cases of classic podagra, or less apparent when the condition mimics cellulitis or presents with polyarthritis. Although elevated serum urate levels increase the probability of gout, levels may be misleadingly low during an acute attack. Crystal confirmation of diagnosis via arthrocentesis excludes other crystal diseases such as calcium pyrophosphate crystal deposition disease (CPPD), for which urate reduction therapy would not be indicated, and makes infection less likely (although septic arthritis may occur in gouty joints). The sensitivity of crystal evaluation of synovial fluid, approximately 80%, can be increased by repeat microscopy of the same slide after 24 hours. Yuan et al.⁴⁵ found five samples that became crystal-positive (urate or CPPD) out of 23 suspected cases that initially tested negative.

Treatment

The treatment of gout has three main components: (1) therapy of the acute attack; (2) prophylaxis against flares; and (3) management of hyperuricemia. Treatment of the acute attack can be achieved with colchicine, non-steroidal anti-inflammatory drugs (NSAIDs), and/or steroids. A combination of these medications is often necessary. After an acute attack, it is best to wait for full resolution before initiating urate-lowering therapy. Suppressive therapy to prevent flares usually involves colchicine or NSAIDs.

An important factor in choosing therapeutic agents for an acute attack is the presence of comorbidities (see Table 2). The most common therapy for acute gout in the setting of acute or chronic renal or hepatic failure is steroids.

Table 2. Preferred treatment for acute gout in a patient with comorbidities

	IA steroid	Oral steroid	NSAID	Colchicine
Normal	+++	+	+++	++
Ulcer	++	–	–	+
Serum Cr >1.5	+++	++	–	+/-
Severe hypertension	+	–	–	+
Anticoagulation	+	++	–	++
Severe diabetes	+	–	+	+

IA=intra-articular

Note: +++ is preferred over ++ over +, – indicates agents which should be avoided, +/- indicates agents which may be used but with caution; if two comorbidities exist, then avoid agents with –

Acute Gout

Colchicine, the classic antidote for gouty arthritis, functions by blocking microtubule assembly. Microtubules are involved in the movement of intracellular organelles. Disruption of microtubules reduces phagocytosis; inhibits release of chemotactic factors; down-regulates TNF- α receptors, insulin, and B-adrenergic agonists; decreases adhesion and recruitment of polymorphonuclear lymphocytes to the area of inflammation; and also suppresses the NALP3 inflammasome induced by urate crystals.^{41,46} The fact that colchicine acts on multiple targets of the inflammatory response likely accounts for its high efficacy in treating acute gout. Like all other agents for gouty arthritis, colchicine is most effective if taken early in the acute attack and less effective later. Chronic use of colchicine rarely can cause myopathy, neuropathy, and bone marrow suppression.⁴⁷ However, due to the gastrointestinal toxicity of hourly colchicine regimens, NSAIDs have generally replaced colchicine for acute gout. Currently, colchicine is used at lower doses during acute gout, preferably at 3 mg on the first day, with lower doses thereafter.

NSAIDs, including COX-2 inhibitors, are generally thought to be the treatments of choice for acute gout in patients with normal kidneys and may be used for prophylaxis as well. Although indomethacin has historically been the NSAID of choice, several studies have shown no significant difference among NSAIDs, and

the choice of agent should be based on factors such as side-effect profile, cost, and adherence.⁴⁸⁻⁵¹ NSAIDs should be given at high doses initially but should not be used in patients with acute or chronic renal failure, bleeding, peptic ulcer disease, congestive heart failure, melena or hematochezia, or in those on anticoagulation or with thrombocytopenia. Selective COX-2 inhibitors provide a greater margin of safety than other NSAIDs in patients receiving anticoagulation therapy.

Glucocorticoids (steroids) are generally the treatments of choice for acute gout when colchicine or NSAIDs cannot be used, as in the setting of renal insufficiency. Administration may be intra-articular, oral, or intramuscular. Intra-articular glucocorticoid injection is preferable if only one or a few joints are involved or when there is a need to avoid systemic steroid therapy.

Hyperuricemia

Treatments for chronic gout are aimed at reducing serum urate levels to less than 6.0 mg/dl in order to dissolve existing crystals and prevent formation of new ones. Agents to achieve this goal include xanthine oxidase inhibitors (allopurinol and febuxostat), uricosuric drugs (probenecid), and pegylated uricase. Uricosuric agents should not be given to patients who are overproducers and overexcretors of uric acid because of the increased risk of renal stones.

Allopurinol, the established xanthine oxidase inhibitor, is a purine analog which inhibits conversion of hypoxanthine to xanthine and uric acid. Allopurinol is often started at 100 mg orally per day, and the daily dose is increased in 100 mg increments every 2 to 4 weeks until the target urate level of less than 6 mg/dl is reached. This approach is used in the belief, as yet unproved, that a gradual reduction of urate levels will minimize flares. It is crucial to understand that the ultimate dose is not necessarily 300 mg per day but rather the amount required to normalize serum urate. Thus, the appropriate daily dose may be as little as 100 mg or as much as 900 mg. Up to 5% of patients are unable to tolerate allopurinol due to adverse effects including rash, nausea, and bone marrow suppression.⁵² A rare but serious side effect of allopurinol is an acute hypersensitivity reaction, which may include fever, toxic epidermal necrolysis, hepatitis, eosinophilia, and renal failure.⁵³

Allopurinol may be used in patients with renal insufficiency by starting at a dose of 50 mg per day and

increasing in increments of 50 mg every month until the same target urate level of <6 mg/dl is reached. Doses >300 mg per day can be given if necessary. In an important pharmacokinetic study, Hande et al.⁵⁴ found that plasma levels of oxipurinol (the effective metabolite of allopurinol) are inversely proportional to the GFR. This means that patients with renal insufficiency generally require lower doses to attain adequate inhibition of xanthine oxidase. Each patient's dose, however, should still be that amount required to control that patient's serum urate level. Arbitrary GFR-based dose reductions often lead to inadequate control and have not been found to reduce hypersensitivity problems.^{55,56}

Mild rashes are common, and a desensitization protocol may permit resumption of allopurinol.⁵⁷ If severe rash occurs, however, allopurinol should be discontinued. In a study by Hung et al.⁵⁸ 100% of Han Chinese patients with severe cutaneous adverse reactions to allopurinol had HLA-B*5801 allele, while only 20% of controls without severe cutaneous adverse reactions had this allele. If this HLA subtype is found to be predictive in other populations as well, HLA-B*5801 may represent a useful marker in patients with mild to moderate rash to help determine whether allopurinol must be permanently discontinued.

Febuxostat is a potent, new, selective xanthine oxidase inhibitor which is in Phase III trials for use in gout.⁵⁹ Its mechanism is quite similar to that of allopurinol, but because this agent is not a purine analog, it may not have cross-reactions in patients with allopurinol hypersensitivity. Additionally, because febuxostat is primarily metabolized by the liver, it may be a preferable alternative for patients with renal insufficiency. In clinical trials, the most frequently encountered adverse effects of febuxostat were an elevation in liver enzymes, rash, diarrhea, and headache. Febuxostat is awaiting FDA approval pending review of additional safety data.

Probenecid is the only potent uricosuric agent available in the U.S. Its mechanism of action is inhibition of the URAT1 transporter involved in the reabsorption of uric acid. Probenecid is most useful in patients with mild gout and normal renal function. Probenecid is ineffective in patients with renal insufficiency and is contraindicated in patients with renal stones of any kind. The drug is given twice daily at breakfast and dinner, not at bedtime, in order to ensure that peaks of uricosuria coincide with peaks in urine pH and flow, thus lessening the risk of urinary stones.

Uricase, an enzyme that oxidizes urate to highly soluble allantoin, is present in all mammals other than the great apes and humans. These species therefore have urate levels higher than those of other mammals and are vulnerable to gout. Rasburicase, a recombinant uricase derived from *Aspergillus flavus*, is available for human use. However, this expensive protein is immunogenic and carries a significant risk of anaphylaxis. For this reason, its preferred usage is as a brief single course aimed at reducing the acute urate burden from purine release in the tumor lysis syndrome. To reduce the problem of immunogenicity and to extend the biological half-life of the enzyme, polyethylene glycol groups have been added to porcine uricase to create PEG-uricase.^{60,61} PEG-uricase has shown significant promise and is currently in Phase III trials for refractory or tophaceous gout.

Prophylaxis Against Gouty Flares

All agents that control hyperuricemia convey an increased risk of gouty flares as existing deposits of urate crystals are mobilized and dissolved. Apparently, the dissolving crystals lose the protein coating that keeps them relatively inert, and the risk of flares persists until even the smallest microdeposits have been cleared.

Colchicine, the usual choice for prevention of acute gouty flares, was studied in a controlled trial of allopurinol-treated patients by Borstad et al.⁶² Acute flares occurred in 14% of patients in the colchicine group versus 63% in the placebo group. Comparable efficacy was shown by Becker and colleagues in the FACT trial.⁵⁹ These investigators found a marked increase in flares when colchicine was stopped (by protocol) after the first eight weeks of therapy in both the allopurinol- and the febuxostat-treated groups. Therefore, we routinely employ colchicine 0.6 mg to 1.2 mg per day until all likelihood of persisting deposits is gone (usually six months or more). In cases of renal or hepatic insufficiency, the risk of toxicity, especially myoneuropathy, is increased, and the drug must be used with caution. When daily NSAIDs are needed for concomitant osteoarthritis, additional colchicine is usually unnecessary.

Compliance Issues

Compliance with chronic therapy of gout has generally been poor, possibly because acute gouty arthritis is self-limiting without risk for mortality, and the progressive potential of the disease is unrecognized by

either the patient or the physician. During the chronic phase, urate-lowering therapy offers no immediate symptomatic benefit. Tophus mobilization may take months to years to achieve, and initial treatment may cause flares. In a recent study by Serawate et al.,⁶³ the median length of therapy with allopurinol was only three months out of a one-year period, 83% of patients did not have serum urate levels measured within 180 days, and patients with gout flares were less likely to be compliant with allopurinol. Methods to improve compliance include an explanation of the role of urate reduction therapy in achieving control, an understanding that urate reduction therapy may lead to an initial increase in flares but that these will subside and ultimately cease over time, prophylactic therapy with colchicine or NSAIDs to decrease the likelihood of flare, and a contingency plan for breakthroughs that occur despite ongoing prophylaxis.

Therapeutic Options on the Horizon

The future brings the possibility of new xanthine oxidase inhibitors, novel uricase preparations, and perhaps more powerful uricosurics which may provide consistent control of hyperuricemia. As the mechanism of inflammation is further elucidated, additional targeted interventions, including biologic agents, may provide better control of the classic arthritis. Ultimately, however, the key to control will continue to lie in convincing the patient of the likely progression of disease without faithful adherence to an effective program.

Dan A. Mandel, MD
Senior Fellow in Rheumatology
Peter A. Simkin, MD
Professor Emeritus of Medicine
Division of Rheumatology
Department of Medicine
University of Washington
Seattle, Washington

References

- Nuki G. Treatment of crystal arthropathy – history and advances. *Rheum Dis Clin North Am* 2006;32:333-57.
- Nuki G, Simkin PA. A concise history of gout and hyperuricemia and their treatment. *Arthritis Res Ther* 2006;8 suppl 1:S1.
- Lee SJ, Terkeltaub RA, Kavanaugh A. Recent developments in diet and gout. *Curr Opin Rheumatol* 2006;18:193-8.
- Becker MA, Jolly M. Hyperuricemia and associated diseases. *Rheum Dis Clin North Am* 2006;32:275-93.
- Dalbeth N, Haskard DO. Mechanisms of inflammation in gout. *Rheumatology* 2005;44:1090-6.
- Cronstein BN, Terkeltaub R. The inflammatory process of gout and its treatment. *Arthritis Res Ther* 2006;8 Suppl 1:S3.
- Mount DB, Kwon CY, Zandi-Nejad K. Renal urate transport. *Rheum Dis Clin North Am* 2006;32:313-31.
- Liote F, Ea HK. Gout: update on some pathogenic and clinical aspects. *Rheum Dis Clin North Am* 2006;32:295-311.
- Joseph-Ridge N, Cazzetta S, MacDonald P. Clinical trials in crystal arthropathy. *Rheum Dis Clin North Am* 2006;32:359-82.
- Schumacher HR Jr, Chen LX. Newer therapeutic approaches: gout. *Rheum Dis Clin North Am* 2006;32:235-44.
- Terkeltaub R, Bushinsky DA, Becker MA. Recent developments in our understanding of the renal basis of hyperuricemia and the development of novel antihyperuricemic therapeutics. *Arthritis Res Ther* 2006;8 Suppl 1:S4.
- Zhang W, Doherty M, Pascual E, et al. EULAR evidenced based recommendations for gout. Part I: Diagnosis: Report of a task force of the Standing Committee For International Clinical Studies Including Therapeutics (ESCSIT). *Ann Rheum Dis* 2006;65:1301-11.
- Zhang W, Doherty M, Bardin T, et al. EULAR evidenced based recommendations for gout. Part II: Management: Report of a task force of the EULAR Standing Committee For International Clinical Studies Including Therapeutics (ESCSIT). *Ann Rheum Dis* 2006;65:1312-24.
- Kramer HM, Curhan G. The association between gout and nephrolithiasis: the National Health and Nutrition Examination Survey III, 1988-1994. *Am J Kidney Dis* 2002;40:37-42.
- Centers for Disease Control and Prevention, National Center for Health Statistics. Vital and health statistics: current estimates from the National Health Interview Survey, 1996. Series 10, #200 (pages 81-3). Atlanta: Dept. of Health and Human Services (US). Available at www.cdc.gov/nchs/data/series/sr_10/10_200_1.pdf. Accessed September 14, 2006.
- Choi H. Epidemiology of crystal arthropathy. *Rheum Dis Clin North Am* 2006;32:255-73.
- Campion EW, Glynn RJ, DeLabry LO. Asymptomatic hyperuricemia. Risks and consequences in the normative aging study. *Am J Med* 1987;82:421-6.
- Roubenoff R, Klag MJ, Mead LA, et al. Incidence and risk factors for gout in white men. *JAMA* 1991;266:3004-7.
- Abbott RD, Brand FN, Kannel WB, Castelli WP. Gout and coronary heart disease: the Framingham Study. *J Clin Epidemiol* 1988;41:237-42.
- Choi HK, Atkinson K, Karlson EW, Curhan G. Obesity, weight change, hypertension, diuretic use, and risk of gout in men: the health professionals follow-up study. *Arch Intern Med* 2005;165:742-8.
- Schlesinger N, Schumacher HR Jr. Update on gout. *Arthritis Rheum* 2002;47(5):563-5.
- Fam A. Gout, diet, and the insulin resistance syndrome. *J Rheumatol* 2002;29(7):1350-5.
- Dessein PH, Shipton EA, Stanwix AE, et al. Beneficial effects of weight loss associated with moderate calorie/carbohydrate restriction, and increased proportional intake of protein and unsaturated fat on serum urate and lipoprotein levels in gout: a pilot study. *Ann Rheum Dis* 2000;59:539-43.
- Nakagawa T, Hu H, Zharikov S, et al. A causal role for uric acid in fructose-induced metabolic syndrome. *Am J Physiol Renal Physiol* 2006;290:F625-31.
- Fox IH, Kelley WN. Studies on the mechanism of fructose-induced hyperuricemia in man. *Metabolism* 1972;21:713-21.
- Raivio KO, Becker A, Meyer LJ, et al. Stimulation of human purine synthesis de novo by fructose infusion. *Metabolism* 1975;24(7):861-9.
- Perheentupa J, Raivio K. Fructose-induced hyperuricaemia. *Lancet* 1967;2(7515):528-31.
- Enomoto A, Kimura H, Chairoungdua A, et al. Molecular identification of a renal urate anion exchanger that regulates blood urate levels. *Nature* 2002;417(6887):447-52.
- Simkin PA. The Dalmatian defect: a hepatic endocrinopathy of urate transport. *Arthritis Rheum* 2005;52(8):2257-62.
- Simkin PA, Bassett JE, Lee QP. Not water, but formalin, dissolves urate crystals in tophaceous tissue samples. *J Rheumatol* 1994;21(12):2320-1.
- Feig DI, Johnson RJ. Hyperuricemia in childhood primary hypertension. *Hypertension* 2003;42:247-52.
- Feig DI, Rodriguez-Iturbe B, Nakagawa T,

- Johnson RJ. Nephron number, uric acid, and renal microvascular disease in the pathogenesis of essential hypertension. *Hypertension* 2006; 48:25-6.
33. Siu YP, Leung KT, Tong MK, Kwan TH. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. *Am J Kidney Dis* 2006;47(1):51-9.
34. Simkin PA. The pathogenesis of podagra. *Ann Intern Med* 1977;86(2):230-3.
35. Simkin PA, Campbell PM, Larson EB. Gout in Heberden's nodes. *Arthritis Rheum* 1983;26(1):94-7.
36. Terkeltaub R, Curtiss LK, Tenner AJ, Ginsberg MH. Lipoproteins containing apoprotein B are a major regulator of neutrophil responses to monosodium urate crystals. *J Clin Invest* 1984; 73(6):1719-30.
37. Perl-Treves D, Addadi L. A structural approach to pathological crystallizations. Gout: the possible role of albumin in sodium urate crystallization. *Proc R Soc Lond B Biol Sci* 1988;235 (1279):145-59.
38. Terkeltaub RA, Dyer CA, Martin J, Curtiss LK. Apolipoprotein (apo) E inhibits the capacity of monosodium urate crystals to stimulate neutrophils. Characterization of intraarticular apo E and demonstration of apo E binding to urate crystals in vivo. *J Clin Invest* 1991;87:20-6.
39. Terkeltaub R, Smeltzer D, Curtiss LK, Ginsberg MH. Low density lipoprotein inhibits the physical interaction of phlogistic crystals and inflammatory cells. *Arthritis Rheum* 1986;29: 363-70.
40. Liu-Bryan R, Scott P, Sydlaske A, et al. Innate immunity conferred by toll-like receptors 2 and 4 and myeloid differentiation factor 88 expression is pivotal to monosodium urate monohydrate crystal-induced inflammation. *Arthritis Rheum* 2005;52(9):2936-46.
41. Martinon F, Petrilli V, Mayor A, et al. Gout-associated uric acid crystals activate the NALP3 inflammasome. *Nature* 2006;440(7081):237-41.
42. Chen CJ, Shi Y, Hearn A, et al. MyD88-dependent IL-1 receptor signaling is essential for gouty inflammation stimulated by monosodium urate crystals. *J Clin Invest* 2006;116(8):2262-71.
43. Palmer DG, Highton J, Hessian PA. Development of the gout tophus. An hypothesis. *Am J Clin Pathol* 1989;91:190-5.
44. Schweyer S, Hemmerlein B, Radzun HJ, Fayyazi A. Continuous recruitment, co-expression of tumour necrosis factor-alpha and matrix metalloproteinases, and apoptosis of macrophages in gout tophi. *Virchows Arch* 2000; 437:534-9.
45. Yuan S, Bien C, Wener MH, et al. Repeat examination of synovial fluid for crystals: is it useful? *Clin Chem* 2003;49(9):1562-3.
46. Spilberg I, Mandell B, Mehta J, et al. Mechanism of action of colchicine in acute urate crystal-induced arthritis. *J Clin Invest* 1979;64:775-80.
47. Lai IC, Cheng CY, Chen HH, et al. Colchicine myoneuropathy in chronic renal failure patients with gout. *Nephrology* 2006;11:147-50.
48. Smyth CJ, Percy JS. Comparison of indomethacin and phenylbutazone in acute gout. *Ann Rheum Dis* 1973;32:351-3.
49. Schweitz MC, Nashel DJ, Alepa FP. Ibuprofen in the treatment of acute gouty arthritis. *JAMA* 1978;239:34-5.
50. Karachalios GN, Donas G. Sulindac in the treatment of acute gout arthritis. *Int J Tissue React* 1982;4:297-9.
51. Altman RD, Honig S, Levin JM, Lightfoot RW. Ketoprofen versus indomethacin in patients with acute gouty arthritis: a multicenter, double blind comparative study. *J Rheumatol* 1988;15: 1422-6.
52. Schlesinger N. Management of acute and chronic gouty arthritis: present state-of-the-art. *Drugs* 2004;64:2399-416.
53. Singer JZ, Wallace SL. The allopurinol hypersensitivity syndrome. Unnecessary morbidity and mortality. *Arthritis Rheum* 1986;29:82-7.
54. Hande KR, Noone RM, Stone WJ. Severe allopurinol toxicity. Description and guidelines for prevention in patients with renal insufficiency. *Am J Med* 1984;76(1):47-56.
55. Vazquez-Mellado J, Morales EM, Pacheco-Tena C, et al. Relation between adverse events associated with allopurinol and renal function in patients with gout. *Ann Rheum Dis* 2001;60 (10):981-3.
56. Dalbeth N, Kumar S, Stamp L, Gow P. Dose adjustment of allopurinol according to creatinine clearance does not provide adequate control of hyperuricemia in patients with gout. *J Rheumatol* 2006;33(8):1646-50.
57. Fam AG, Dunne SM, Iazzetta J. Efficacy and safety of desensitization to allopurinol following cutaneous reactions. *Arthritis Rheum* 2001; 44(1):231-8.
58. Hung SI, Chung WH, Liou LB, et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. *Proc Natl Acad Sci USA* 2005;102(11): 4134-9.
59. Becker MA, Schumacher HR Jr, Wortmann RL, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med* 2005;353:2450-61.
60. FDA Office of Orphan Products Development. Pegylated recombinant mammalian uricase (PEG-uricase) as treatment for refractory gout. www.clinicaltrials.gov/ct/show/NCT00111657. Accessed September 14, 2006.
61. Ganson NJ, Kelly SJ, Scarlett E, et al. Control of hyperuricemia in subjects with refractory gout, and induction of antibody against poly(ethylene glycol) (PEG), in a phase I trial of subcutaneous PEGylated urate oxidase. *Arthritis Res Ther* 2005;8(1):R12.
62. Borstad GC, Bryant LR, Abel MP, et al. Colchicine for prophylaxis of acute flares when initiating allopurinol for chronic gouty arthritis. *J Rheumatol* 2004;31:2429-32.
63. Sarawate CA, Brewer KK, Yang W, et al. Gout medication treatment patterns and adherence to standards of care from a managed care perspective. *Mayo Clin Proc* 2006;81:925-34.