

Clinical, Humanistic, and Economic Outcomes of Gout

Diana I. Brixner, RPh, PhD; and Mei-Jen Ho, PharmD

Abstract

Gout is a low prevalence disease not often considered by managed care organizations with regard to cost management. Understanding the development of the disease and its potential long-term, high-cost consequences can lead to appropriate treatment strategies and cost-management opportunities that can improve patient outcomes and potentially lower the overall cost of treatment of patients with gout in a managed care organization. The acute and chronic nature of the disease is best managed up front to avoid negative long-term effects. Adherence to medications can also impact the manifestation of the disease.

(Am J Manag Care. 2005;11:S459-S464)

Gout is a disease of relatively low prevalence in relation to the disease categories most often considered in managed care populations. Despite a relatively low prevalence, however, the impact of this disease on patients, health plans, and their employer clients can be substantial. As the disease progresses, clinical outcomes may be severe, with marked impairment of activities of daily living and ability to work. Management of this disease can be complex and long-term, leading to substantial direct costs to a health plan.

The purpose of this article is to provide a review of the prevalence of gout, how the disease presents to the healthcare provider, and management of the disease during its progression through acute and chronic phases. After a review of clinical outcomes, the humanistic impact of gout will be presented along with the direct and indirect costs associated with treating this disease. This information should assist health plans in overall management of the disease for their patients and clients.

Disease Background and Prevalence

Gout results from an inflammatory response caused by hyperuricemia and the resulting deposition of monosodium urate monohydrate crystals in the articular cartilage and synovial membrane. Patients experience acute attacks of arthritis in 1 or more of the extremities, and the majority of patients will have another attack within 2 years of the previous one.¹ Crystal deposition is also associated with urinary tract stones. Left untreated, patients may develop crystal aggregates, which can destroy cartilage and bone and lead to organ dysfunction, particularly renal impairment.²

Although age, body mass index (BMI), hypertension, cholesterol level, and alcohol intake are all associated with the development of gout, the incidence of the disease most closely correlates with elevated uric acid levels. In the Normative Aging Study, 2046 healthy and asymptomatic men were followed for 14.9 years and evaluated for serum urate (SU) levels and first episodes of gouty arthritis. The annual incidence of gouty arthritis was 4.9% for those with prior SU levels of ≥ 9.0 mg/dL compared with 0.5% among patients with urate levels between 7.0 and 8.9 mg/dL, and only 0.1% among those having urate levels >7.0 mg/dL. Also, those with urate levels of ≥ 9.0 mg/dL showed a cumulative incidence of gouty arthritis of 22% after 5 years.³

The National Arthritis Data Workgroup reviewed self-reported gout data and estimated the prevalence of gout to be about 8.4 cases per 1000 individuals, correlating to 2.1 million US patients with the disease. The incidence of gout increases with age and is 3.8 per 1000 individuals among those

aged 18 to 44 years, 16.8 per 1000 among those aged 45 to 64, and 29.0 per 1000 for those aged 65 and older (Table). Gout prevalence is higher in men than in women and higher in blacks than whites.¹

Left untreated, 75% of patients will develop severe and crippling tophaceous gout within 20 years of the initial attack of gouty arthritis.⁴ With adequate treatment, however, only 5% of patients will develop tophaceous gout during this time.⁵

Recent data show that the prevalence of gout and hyperuricemia in a managed care claims database increased by approximately 2 cases per 1000 patients during the 10-year period between 1990 and 1999, and this increase occurred primarily among those older than age 65.⁶

Delayed or erroneous diagnoses led to ineffective treatment and persistent joint pain in more than one quarter of gout patients in a hospital-based rheumatology practice. Erroneous diagnoses included cellulitis, phlebitis, septic arthritis, venous thrombosis, and osteomyelitis. A correct diagnosis can eliminate unnecessary medications and hasten pain relief.⁷

Despite this incidence of misdiagnoses, a British survey of general practitioners showed that 86.3% felt confident in their ability to manage gout without advice from a specialist. Nonetheless, 32.1% reported that they were likely to refer patients with gout to a rheumatologist.⁸

Table. Prevalence per 1000 Persons of Self-reported Gout in the United States by Age, Sex, and Race, 1992

Age, years	18-44	45-64	65
Sex (all races)			
Men	4.4	26.3	44.1
Women	0.3	8.1	18.2
Race			
Black	1.4	38.5	54.5
White	2.5	14.7	26.7

Source: Benson V, Marano MA. Current estimates from the National Health Interview Survey, 1992. *Vital Health Stat 10*. 1994;189:1-269.

Potential Causes and Associations

Gout has been associated with a spectrum of causes, including renal impairment, cardiovascular disease, weight change, diet, and substance use. The articular symptoms are often the first manifestation of a reversible metabolic or endocrine disorder.⁹ Renal impairment is observed in 10% to 15% of patients with gout and is manifested as urate and uric acid nephropathy or nephrolithiasis, potentially resulting in renal failure.⁹

Hyperuricemia and gout frequently coexist with cardiovascular disorders, and insulin resistance has been proposed as the pathogenic link explaining this association. Hypertension, diuretic use, and obesity are significantly more common among patients with gout than in the general population, and gout often accompanies other traditional coronary artery disease risk factors, such as diabetes and hyperlipidemia. Although gout has not been shown to be an independent risk factor for heart disease, it may be prudent to assess cardiovascular risk in these patients.^{10,11}

Researchers have found that weight gain and increased adiposity are strong risk factors for gout and that weight loss is protective against the disease. The relative risk of gout is 1.95 in men with a BMI of 25 to 29.9 kg/m², 2.33 for those with a BMI of 30 to 34.9 kg/m², and 2.97 for obese men with a BMI of > 35 kg/m² (P for trend <.001).¹⁰

Dietary restriction has been shown to reduce serum uric acid levels and the frequency of gouty attacks.¹² In contrast, a diet including increased amounts of purine-rich foods, meat, and alcoholic beverages is associated with increased gouty attacks. In one study, beer consumption showed the strongest independent association with increased gout incidence, spirit consumption showed a significant association, but wine consumption was not related to increased incidence.¹³ Other research suggests that consumption of vegetable protein may be protective against gout.¹⁴

Although adherence to dietary restrictions and reduced alcohol consumption are helpful, pharmacologic therapy remains the mainstay of gout treatment. Urate-lowering therapy is generally cost effective for any

patient with more than 2 gouty flares annually, and the choice of urate-lowering agent should be individualized to the patient. In addition, nonsteroidal anti-inflammatory drugs (NSAIDs) or other anti-inflammatory agents may be used to reduce symptoms and disability.

Clinical Outcomes

An acute gouty attack is the primary clinical manifestation. Attacks are usually monoarticular with inflammation of the first metatarsophalangeal joint. Although less common, gouty attacks may spread to other joints, including the instep, forefoot, ankle, knee, wrist, and fingers. Symptoms may be self-limiting if untreated, but 60% of patients have a second attack within 1 year, and 78% have a second attack within 2 years. Only 7% of patients do not experience a second gouty attack in a 10-year period.¹⁵ Chronic gouty arthritis with persistent pain and joint involvement occurs in <5% of patients with gout.¹⁶ Acute uric acid nephropathy may also occur.

After 10 to 20 years of inadequately treated gouty attacks, chronic tophaceous gout may develop.¹⁶ The percentage of patients with gout who develop tophaceous gout has decreased significantly, however, from 14% in 1949 to 11% in 1959, 8% in 1969, and 3% in 1972, according to a retrospective study.⁵ The authors attributed the decrease to enhanced diagnostic methods and the development of uricosuric drugs along with the increasing use of colchicine for gout between the 1960s and 1972. Tophi can cause joint deformity, damage surrounding soft tissue, and lead to joint destruction as well as chronic, persistent pain and nerve compression syndromes.¹⁷ In rare cases, tophaceous gout of the spine develops with back pain and fever that make it difficult to distinguish from epidural infection.¹⁸

Hyperuricemia control is superior to self-medication alone in improving the prognosis of chronic gout, decreasing comorbidity, and reducing mortality. In fact, self-medication alone may cause significant adverse effects, such as gastrointestinal (GI) complications from long-term use of NSAIDs.¹⁹ The overall incidence of upper GI bleeding and upper GI bleeding resulting in hospitaliza-

tion was 2.9 and 1.0 per 1000 indomethacin-exposed patients in one study.²⁰ Each incident exacerbated gout and decreased patient comfort.

Humanistic Outcomes

Patients with gout exhibit poorer social functioning than those with hypertension, angina, diabetes, or lower urinary tract symptoms, as measured by the quality-of-life Short Form-36. Men aged 55 to 64 years with gout scored worse in terms of physical functioning, general health perception, vitality, role limitations due to emotional problems, and mental health than those with other disease states.²¹ However, in another study, patients with gout scored lower, indicating better functioning, on the Health Assessment Questionnaire (0.44) compared with patients with rheumatoid arthritis (0.87) and polymyalgia rheumatica (0.68).²²

Treatment nonadherence contributes to decreased quality of life in patients with gout. A recent analysis of 9482 managed care enrollees with gout revealed that patients were adherent with allopurinol therapy for an average of 56% of the treatment period, but were nonadherent 44% of the time. Also, 65.9% of patients filled 1 allopurinol prescription and 10.4% discontinued use after the first prescription. Only 18% of patients were adherent throughout the study period, and 13.7% never achieved adherence with therapy.² Nonadherence with urate-lowering drugs allows the SU concentration to increase, and this eventually may lead to increased frequency of future gouty attacks.²³

Economic Outcomes

Gout is associated with significantly decreased productivity, a high economic burden, and a managed care burden. The annual direct burden of illness for new cases of acute gout among men in the United States is estimated at \$27.4 million. Data on gout in women are lacking, and they were not included in this estimate.²⁴ Exact indirect costs associated with gout are difficult to determine. However, gout accounted for 37 million days of restricted activity from 1979 to 1981 in the United States, with 9.2%

of all men with gout reporting limitations in performing major activities.²⁵

Patients with acute gouty arthritis attacks miss an average of 3 to 5 days of work annually, and it is likely that individual productivity losses are made up on return to work or at the worksite during the absence.²⁰ This loss can translate to thousands of dollars per employee per year to an employer for days paid with no labor in return.²⁶

Treatment by a specialist, although initially more expensive, is likely to reduce the direct and indirect costs of gout through reduced symptoms and hospitalizations. A retrospective study showed that patients with acute arthritis treated by rheumatologists fared better than those treated by another type of physician. Mean duration of symptoms was 3.5 days for rheumatologist-treated patients versus 6.6 days for the others; mean duration of hospitalization was 7.4 days compared with 14.7 days; and the mean cost of hospitalization was \$8755 versus \$14 750.²⁷

Improved adherence to urate-lowering and other medications may also reduce overall costs of gout and is critical in gout management, because adequate treatment can reduce the development of tophaceous gout by up to 70%.⁵

Adherence to maintenance colchicine therapy was strikingly low in one study, which showed 65% of patients adherent with taking the medication, 44% adherent with dosing, and 32% adherent with the timing of medication use. Adherence to urate-lowering agents was better, with 84% taking the medication, 74% using the correct dosing, and 54% timing medication use correctly.²² During the entire study period, patients missed doses on 15% of the days. The patients in this study said use of an electronic monitoring system that recorded each bottle opening increased their adherence.²² The findings of this study concur with retrospective managed care data showing that only 18% of allopurinol-treated patients were adherent during the 2-year study period.²

Currently, there are no studies that correlate urate-lowering drug adherence with outcomes, but nonadherence with hormone replacement therapy in one study led to significant increases in the number of emergency department visits.²⁸ Similarly, low

medication adherence in patients with gout can lead to recurrent gouty arthritis and chronic gouty arthropathy, resulting in additional healthcare visits in the long-term.

A decision-analysis model demonstrated that treatment with urate-lowering drugs is cost effective (based on 1993 Canadian dollars) in patients with 1 recurrent gouty arthritis flare per year and cost-saving in patients presenting with 2 attacks per year. The average cost-effectiveness ratio for patients using urate-lowering drugs is \$487 to \$983 compared with a cost of \$5070 to \$6571 for those not using these agents.²⁰

Because of the nature of gout, a disease-management program may be quite effective in a managed care population. Currently, there are very sparse data regarding such an approach, but the approach warrants consideration.

Results of a small community pilot advocacy program showed that patients with various treatable musculoskeletal disabilities, including rheumatoid arthritis, psoriatic arthritis, and tophaceous gout, had improved functioning with intervention. A total of 172 adults with confirmed disability were identified from a survey of 1805 households. Of these, 78 patients underwent functional assessments and 40 received only verbal and written recommendations for seeking treatment and services. The remaining 38 patients received intensive advocacy, including specific suggestions for treatment, followed by a letter and phone call to assist them in finding the recommended treatments or services. At follow-up, 47% of patients in the advocacy group versus 33% in the information-only group reported improved functioning; 16% in the advocacy group and 37% in the information group reported no change; and 37% versus 30%, respectively, reported worse functioning. However, the study was too small to demonstrate significance.²⁹

Fine-needle aspiration biopsy to identify tophaceous gout may allow earlier treatment, leading to reduced pain and disability. In addition, fine-needle aspiration biopsy can reduce the use of more costly radiographic and laboratory studies as well as rule out infection and other differential diagnoses.³⁰

Future Directions for Outcomes Research

This review of current research in the management of gout illustrates some important humanistic and economic concerns of gout. There are limited studies describing long-term health outcomes of treatment nonadherence. A thorough analysis of the progression of acute gout to chronic gout and then tophaceous gout, with the cost of treatment at each stage, would allow for a better understanding of the opportunities to improve patient outcomes and decrease costs. Although pharmacotherapies currently used for gout treatment are relatively inexpensive, gout is a lifelong condition that warrants continuous management to avoid painful and debilitating flares. Future research should examine underlying reasons for nonadherence and the long-term direct and indirect healthcare costs associated with recurrent flares.

Conclusion

Although gout is a low prevalence disease, the nature of its progression from acute to chronic stages provides opportunities for managed care to improve patient outcomes and decrease costs in this population. The progression of the disease can be slowed by improving early diagnosis and increasing medication adherence. Pharmacoeconomics research can assist in directing these strategies and outlining the potential outcome and economic benefits. Gout may also be well suited to disease-management approaches.

REFERENCES

1. **Lawrence RC, Helmick CG, Arnett FC, et al.** Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum.* 1998;41:778-799.
2. **Riedel AA, Nelson M, Joseph-Ridge N, Wallace K, MacDonald P, Becker M.** Compliance with allopurinol therapy among managed care enrollees with gout: a retrospective analysis of administrative claims. *J Rheumatol.* 2004;31:1575-1581.
3. **Campion EW, Glynn RJ, DeLabry IO.** Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study. *Am J Med.* 1987;82:421-426.
4. **Gutman AB.** The past four decades of progress in the knowledge of gout, with an assessment of the present status. *Arthritis Rheum.* 1973;16:431-445.
5. **O'Duffy JD, Hunder GG, Kelly PJ.** Decreasing prevalence of tophaceous gout. *Mayo Clin Proc.* 1975;50:227-228.
6. **Wallace KL, Riedel AA, Joseph-Ridge N, Wortmann R.** Increasing prevalence of gout and hyperuricemia over 10 years among older adults in a managed care population. *J Rheumatol.* 2004;31:1582-1587.
7. **Ho G Jr, Denuccio M.** Gout and pseudogout in hospitalized patients. *Arch Intern Med.* 1993;153:2787-2790.
8. **Roberts C, Adebajo AO, Long S.** Improving the quality of care of musculoskeletal conditions in primary care. *Rheumatology (Oxford).* 2002;41:503-508.
9. **Reginato AJ, Schumacher HR Jr.** Crystal-associated arthropathies. *Clin Geriatr Med.* 1988;4:295-322.
10. **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;165:742-748.
11. **Janssens HJ, van de Lisdonk EH, Bor H, van den Hoogen HJ, Janssen M.** Gout, just a nasty event or a cardiovascular signal? A study from primary care. *Fam Pract.* 2003;20:413-416.
12. **Dessein PH, Shipton EA, Stanwix AE, Joffe BI, Ramokgadi J.** 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;59:539-543.
13. **Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G.** Alcohol intake and risk of incident gout in men: a prospective study. *Lancet.* 2004;363:1277-1281.
14. **Choi HK, Curhan G.** Gout: epidemiology and lifestyle choices. *Curr Opin Rheumatol.* 2005;17:341-345.
15. **Harris MD, Siegel LB, Alloway JA.** Gout and hyperuricemia. *Am Fam Physician.* 1999;59:925-934.
16. **Agarwal AK.** Gout and pseudogout. *Prim Care.* 1993;20:839-855.
17. **Hawkins DW, Rahn DW.** Gout and hyperuricemia. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy: A Pathophysiologic Approach.* 3rd ed. Stamford, Conn: Appleton & Lange; 1997:1755-1761.
18. **Barrett K, Miller ML, Wilson JT.** Tophaceous gout of the spine mimicking epidural infection: case report and review of the literature. *Neurosurgery.* 2001;48:1170-1172.
19. **Darmawan J, Rasker JJ, Nuralim H.** The effect of control and self-medication of chronic gout in a developing country. Outcome after 10 years. *J Rheumatol.* 2003;30:2437-2443.
20. **Ferraz MB, O'Brien B.** A cost effectiveness analysis of urate lowering drugs in nontophaceous recurrent gouty arthritis. *J Rheumatol.* 1995;22:908-914.
21. **Welch G, Weinger K, Barry MJ.** Quality-of-life impact of lower urinary tract symptom severity: results from the Health Professionals Follow-up Study. *Urology.* 2002;59:245-250.
22. **de Klerk E, van der Heijde D, Landewe R, van der Tempel H, Urquhart J, van der Linden S.** Patient compliance in rheumatoid arthritis, polymyalgia rheumatica, and gout. *J Rheumatol.* 2003;30:44-54.
23. **Shoji A, Yamanaka H, Kamatani N.** A retrospective study of the relationship between serum urate level and recurrent attacks of gouty arthritis: evidence for reduction of recurrent gouty arthritis with antihyperuricemic therapy. *Arthritis Rheum.* 2004;51:321-325.
24. **Kim KY, Ralph Schumacher H, Hunsche E, Wertheimer AI, Kong SX.** A literature review of the epi-

REPORTS

demiology and treatment of acute gout. *Clin Ther.* 2003;25:1593-1617.

25. Roubenoff R. Gout and hyperuricemia. *Rheum Dis Clin North Am.* 1990;16:539-550.

26. Joish VN, Donaldson G, Stockdale W, et al. The economic impact of GERD and PUD: examination of direct and indirect costs using a large integrated employer claims database. *Curr Med Res Opin.* 2005;21:535-544.

27. Solomon DH, Bates DW, Panush RS, Katz JN. Costs, outcomes, and patient satisfaction by provider type for patients with rheumatic and musculoskeletal conditions: a critical review of the literature and proposed methodologic standards. *Ann Intern Med.* 1997;127:52-60.

28. Hurley JS, Frost EJ, Trinkaus KM, Buatti MC, Emmett KE. Relationship of compliance with hormone replacement therapy to short-term healthcare utilization in a managed care population. *Am J Manag Care.* 1998;4:1691-1698.

29. Liang MH, Phillips E, Scamman M. Design and evaluation of a pilot community program for musculoskeletal disability. *J Community Health.* 1981;6:257-266.

30. Nicol KK, Ward WG, Pike EJ, Geisinger KR, Cappellari JO, Kilpatrick SE. Fine-needle aspiration biopsy of gouty tophi: lessons in cost-effective patient management. *Diagn Cytopathol.* 1997;17:30-35.