

Frequency and Predictors of Inappropriate Management of Recurrent Gout Attacks in a Longitudinal Study

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ABSTRACT. Objective. To evaluate the patterns and determinants of medication use during recurrent gout attacks.

Methods. We followed participants with documented gout in an online prospective case-crossover study. During an attack, subjects were asked if they had consulted a physician for the attack and what medications they were using. Definitely inappropriate therapy was defined as use of allopurinol or a uricosuric agent acutely without having used it as a prophylactic. Potentially inappropriate therapy was defined as use of analgesics alone, alternative remedies, or no medications. We estimated the risk of having ≥ 1 attack in 1 year using life table methods. We examined the relation of various risk factors to the risk of inappropriate therapy using Poisson regression.

Results. Among 232 participants (mean age 52 yrs, 81% male) with documented gout, the risk of having ≥ 1 attack in a year was 69%. One hundred ten participants consulted a physician for each attack, 49 did so for only some attacks, while 43 never consulted a physician for any attack. Fifty-three participants had definitely ($n = 10$) or potentially ($n = 43$) inappropriate therapy for their recurrent attacks. Physician consultation for an attack was associated with increased risk of inappropriate therapy (risk ratio, RR, 2.5, $p = 0.006$), whereas an increasing number of gout attacks was associated with lower risk of inappropriate therapy (RR 0.8, $p = 0.01$).

Conclusion. Given the high risk of recurrent attacks and the substantial number of persons whose attacks are not appropriately managed, further education about management of gout attacks for both patients and physicians may be warranted. (J Rheumatol 2006;33:104–9; First Release Nov 1, 2005)

Key Indexing Terms:

GOUT QUALITY ASSURANCE DRUG THERAPY INTERNET-BASED COHORT STUDY

Gout is a crystal-induced inflammatory arthritis, affecting up to 5.1 million people in the US in 1992¹. Recent studies have shown a rising incidence and prevalence of gout in the US^{2–4}. While the pathophysiology of gout is well understood and efficacious therapies are available, many patients with gout experience recurrent attacks⁵. These recurrent gout attacks can cause pain, joint damage, and functional limita-

tion⁶ and require specific therapy that differs from that aimed at normalizing serum urate levels. Inappropriate management of such attacks represents a missed opportunity given the possibility of effective treatment.

Management of gout consists of 3 stages: (1) treating the acute attack; (2) lowering excess stores of uric acid to prevent flares of gouty arthritis and to prevent tissue deposition of uric acid crystals; and (3) providing prophylaxis to prevent acute flares⁷. Inappropriate use of prophylactic therapy aimed at lowering urate levels such as allopurinol, or uricosuric agents (probenecid, sulfinpyrazone) to treat an attack may worsen or prolong the attack due to mobilization of urate in an already flaring joint^{8–11}. Further, lack of effective treatment of recurrent gout attacks can also prolong the course of these episodes. The use of analgesics alone to manage the symptoms does not address the synovial inflammation that occurs with such attacks^{12–14}. Some argue that for painful, disabling gout attacks, using no medication would be inappropriate and inhumane. Appropriate management of recurrent gout attacks depends on coexistent comorbidities and includes the use of at least one of nonsteroidal antiinflammatory drugs (NSAID), intravenous and oral colchicine, adrenocorticotrophic hormone (ACTH), and

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intraarticular, oral and parenteral corticosteroids, as appropriate^{7,15}.

Evaluating the management of recurrent gout attacks poses a challenge, particularly for those who self-manage their attacks without physician consultation. This information cannot be adequately determined in hospital- or clinic-based studies, or by physician surveys. Due to the acute onset of gout attacks, combined with their transitory nature, traditional epidemiologic methods are not well suited to study such research questions. The ideal approach is to recruit a cohort of subjects with intercritical gout and follow them over time. However, recruitment of a large number of people with gout can be difficult, and collecting data in real time regarding treatment of recurrent events can be cumbersome using interview or diary methods.

The Internet provides an efficient platform for conducting cohort studies. Studies have shown that the Internet allows researchers to recruit a large number of participants, collect information in real time, and encourage adherence, and provides for fast, convenient electronic followup, with participants entering their own data online^{16,17}. In the case of gout, this methodology also enables the timely capture of pertinent data for each recurrent attack.

We followed participants with documented gout in a prospective, Internet-based case-crossover study. Our objective was to estimate the risk of recurrent gout attacks, describe the frequency of physician consultation and inappropriate management for each recurrent attack, and to examine potential factors associated with inappropriate therapy.

MATERIALS AND METHODS

Study design. We conducted a prospective Internet-based case-crossover study of putative risk factors triggering recurrent gout attacks among participants with existing gout in the US. The case-crossover study uses each case as his/her own control and allows assessment of effects of triggers on acute flares¹⁸. Since this was a prospective study, we were able to analyze the data collected longitudinally with a cohort study design.

We constructed a website for this study (<https://dcc2.bumc.bu.edu/GOUT>) on an independent secure server within the Boston University School of Medicine domain. This website provided information about the study, invited applicants to participate, administered a screening questionnaire, linked eligible respondents to an online consent form, and administered additional questionnaires to assess risk factors and features of respondents' recurrent gout attacks.

Participant recruitment. We recruited participants over a 10-month period (February to December 2003) by means of an advertisement on Google[®] (www.google.com) linked to the search term "gout," which directed individuals to the study website. Upon entering the study website, subjects were invited to complete an online eligibility screening questionnaire. Eligible subjects consented online to participate in the study and to the release of their medical records pertaining to gout diagnosis and treatment in compliance with the Health Insurance Portability and Accountability Act (HIPAA) regulations, reported gout diagnosis by a physician, reported occurrence of a recurrent gout attack within the previous year, were age 18 years or older, and were residents of the US. This study was approved by the Institutional Review Board of Boston University Medical Center.

Participant and disease authentication. Participants were authenticated by

confirmation of a valid e-mail address that they provided (required for accessing the password-protected website questionnaires), and a valid US postal address for mailing medical records release, HIPAA authorization, and consent forms.

All subjects included in this study had a physician diagnosis of gout as determined by a study rheumatologist's review of medical records and/or physician checklist. Further we also assessed how many subjects fulfilled the American College of Rheumatology (ACR) Preliminary Criteria for gout¹⁹.

Data collection. Study instruments included a baseline sociodemographic questionnaire that included age, sex, home address, race and ethnicity, and number of years of education. We also collected information on history of gout, including duration of gout and medication used for gout prophylaxis, and other comorbidities. At the time of a recurrent attack, participants were asked to log on to the website and answer the gout attack questionnaire, which inquired about attack symptoms, whether or not a physician was consulted for the attack, and medication used to treat the recurrent attack. Specific attack symptoms queried included presence of maximal pain within 24 hours, redness of the affected joint, and location of the symptomatic joint(s) on a homunculus.

Analyses. We used life table methods to estimate cumulative incidence of having at least one and 2 recurrent gout attacks within a one-year followup period. In this analysis, we excluded participants whose first attack occurred within the first 10 days of study entry.

We assessed patterns of medication use and frequency of consulting a physician during recurrent gout attacks. We defined definitely inappropriate therapy for each recurrent gout attack as the use of allopurinol or a uricosuric agent (probenecid or sulfapyrazone) acutely in the absence of their use as a prophylactic^{9,10,15,20}. Prophylactic use of allopurinol and probenecid prior to the attack was determined from the baseline questionnaire, which asked about medications used to prevent gout attacks, and from the list of medications used in the 48-hour period immediately prior to the attack. Potentially inappropriate therapy for a recurrent gout attack was defined as the use of analgesics alone (narcotics/acetaminophen), alternative remedies, or no medications^{7,15,21,22}. Use of "no medication" was defined as the absence of the above plus absence of NSAID (including COX-2 inhibitors), corticosteroids, colchicine, and ACTH as treatment for their acute attack.

We examined risk factors for inappropriate therapy (i.e., either definitely or potentially inappropriate therapy) using Poisson regression. These risk factors included sociodemographic factors (age, sex, race, highest education level attained), self-reported comorbidities (renal disease, peptic ulcer disease, congestive heart failure), body mass index (BMI), duration of gout, consulting a physician for the attack, and the total number of recurrent attacks during the study. Because participants may have had more than one recurrent attack during the followup period, we adjusted for this correlation using generalized estimating equations. Only subjects who had at least one recurrent gout attack were included in this analysis. All analyses were performed using SAS 8.0 (SAS Institute Inc., Cary, NC, USA).

RESULTS

During the recruitment period (February to December, 2003), there were 57,627 "clicks" on the Google[®] advertisement. A total of 2857 subjects completed the eligibility screening questionnaire, and 2064 met the preliminary screening criteria. Of those, 772 consented electronically; all but 30 provided valid e-mail addresses. We obtained medical records or physician checklists for 248 subjects. Of those, 232 had a physician diagnosis of gout according to medical records review or physician checklist. Based on the information collected from the medical records, physician checklists, and patient questionnaires, 211 (91%) met the ACR Preliminary Criteria for gout¹⁹.

Participants were predominantly male (81%) and college-educated (59%), with a median disease duration of 4 years (Table 1). Ninety-one percent of these participants had first metatarsophalangeal (MTP) joint involvement, 51% had hyperuricemia, 35% had tophi, and 18% had crystal-proven gout. The average followup for subjects in this study was 268 days (standard deviation, SD: 178). During the followup, 202 participants had at least one attack (404 total attacks, 1–8 attacks/person). The median time to log on at time of attack was 2 days. The majority of participants in this study had between one and 3 attacks. The risk of having at least one recurrent gout attack over one year was 0.69 (95% confidence interval, CI: 0.59–0.78) and the risk of having at least 2 recurrent attacks over one year was 0.57 (95% CI 0.47–0.67).

The medications used to manage recurrent gout attacks among the participants, either alone or in combination, were as follows: NSAID (67%, including 5% COX-2 inhibitors), oral colchicine (35%), analgesics (23%), allopurinol (13%), no medication (9%), corticosteroids (9%), alternative remedies (2%), and probenecid (1%). Thirty-four percent of participants reported using allopurinol and 2% of participants reported using probenecid for gout prophylaxis prior to their

attacks. No participant reported using ACTH or sulfinpyrazone.

Fifty-three participants (26%) had definitely (10 participants) or potentially (43 participants) inappropriate therapy for some or all of their attacks. Of the different types of potentially or definitely inappropriate therapy used to manage a gout attack, “no medication” was the most commonly reported (60%) (Figure 1). Analgesics alone were used in 22% and alternative remedies were used in 2% of these attacks. Thirteen percent of these attacks were inappropriately managed with allopurinol acutely, while a small proportion of these attacks (3%) were managed with probenecid acutely, both occurring in the absence of prophylactic use of these medications.

One hundred ten (54%) participants always consulted a physician for each of their recurrent attacks, 49 (24%) did so sometimes, and 43 (21%) never consulted a physician for any attack. Among those who always consulted a physician, 7 participants (6%) had definitely inappropriate therapy: 5 attacks were treated with allopurinol acutely (in those who did not use it for prophylaxis), and 2 were managed with probenecid acutely (in those who did not use it for prophylaxis). Thirty participants (27%, 32 attacks) who always consulted a physician for each attack had potentially inappropriate therapy. Most (78%) were managed with no medications and 19% were managed with analgesics alone. Among the 43 participants who never consulted a physician for any attack, 3 subjects (7%) used analgesics alone for all of their recurrent gout attacks, and none of them used definitely inappropriate therapy.

The relation of each risk factor assessed to the risk of inappropriate therapy is presented in Table 2. An increasing number of recurrent gout attacks were associated with a decreased risk of inappropriate therapy. For each additional attack, the risk of having inappropriate therapy decreased by

Table 1. Characteristics of study participants with gout (n = 232).

Median age, yrs, range	53, 23–85
Male	81%
White	88%
College-educated	59%
Median BMI, kg/m ² , range	30.8, 17.8–53.5
Prevalence of self-reported comorbidities*	16%
Median duration of gout, yrs, range	4, 0–34
Median number of recurrent attacks during study followup, range	1, 1–8

BMI: body mass index. * Peptic ulcer disease, congestive heart failure, or renal disease.

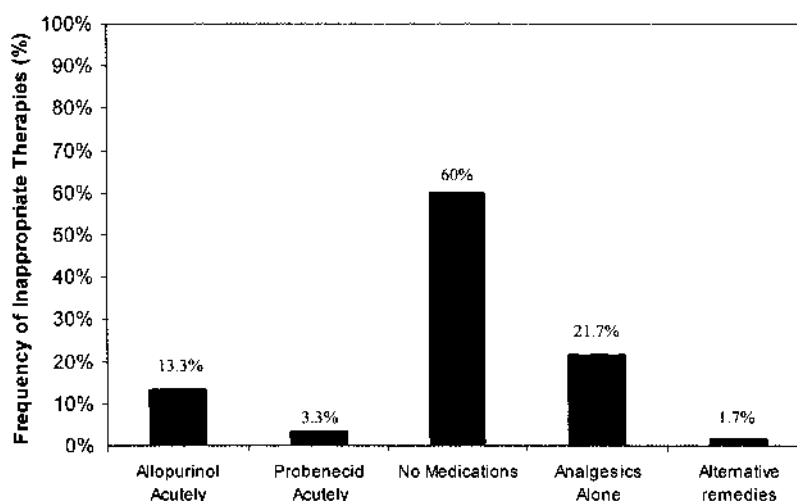


Figure 1. Prevalence of types of therapies among study participants with gout who had inappropriate therapy.

Table 2. Relative risk (RR) of taking inappropriate therapy during an attack of gout among study participants. Each predictor was adjusted for other covariates in the table.

Predictor	No. of Attacks	Attacks Inappropriately Managed, %	Adjusted RR [†] (95% CI)
No. of recurrent gout attacks during study followup	1–8/person	—	0.8 (0.7–0.9)
Consulted physician for a recurrent attack			
Yes (referent)	296	17.2	1.0
No	108	8.3	2.5 (1.3–4.7)
Duration of gout diagnosis prior to entering study			
≤ 1 yr	96	19.8	1.7 (0.95–3.1)
> 1 yr (referent)	308	13.3	1.0
Age, yrs			
< 60	291	14.8	1.1 (0.6–2.0)
≥ 60 (referent)	113	15.0	1.0
Sex			
Female (referent)	72	13.9	1.0
Male	332	15.1	0.9 (0.5–1.7)
BMI, kg/m ²			
≥ 25	30	16.7	0.8 (0.4–2.0)
> 25–30	139	14.4	0.9 (0.5–1.6)
> 30 (referent)	235	14.9	1.0
Education			
≤ High school	40	20.0	1.6 (0.8–3.2)
Some college	135	13.3	0.7 (0.4–1.3)
Completed college	94	11.7	0.7 (0.3–1.4)
Professional/graduate school (referent)	135	17.0	1.0
Race			
White	341	14.4	1.6 (0.8–2.9)
Non-White (referent)	63	17.5	1.0
Presence of self-reported comorbidities*			
Yes (referent)	60	21.7	1.0
No	344	13.7	1.5 (0.8–2.7)

* See Table 1 for comorbidities. [†] RR: relative risk of inappropriate therapy, with an increase in RR signifying an increase in risk of inappropriate therapy.

approximately 20%. Consulting a physician for a recurrent attack of gout was associated with a 2.5-fold increased risk of inappropriate therapy compared to attacks in which a physician was not consulted ($p = 0.006$). Participants with a shorter duration (≤ 1 year prior to study entry) of gout appeared to have an increased risk of inappropriate therapy compared to those with longer duration (> 1 year prior to study entry) (RR 1.7, $p = 0.07$). Further, those who had a shorter disease duration and consulted a physician for an attack had a higher risk of inappropriate therapy than those with longer disease duration who did not consult a physician (RR 3.9, $p = 0.004$). Other factors (e.g., age, sex, BMI, race, education, self-reported comorbidities) were not significantly associated with risk for inappropriate therapy.

DISCUSSION

We found that approximately one-quarter of gout patients had inappropriate management of their recurrent gout attacks. Participants with few attacks per year, those consulting physicians for recurrent attacks, and those with shorter disease duration were at increased risk for inappropriate therapy. These findings indicate that management of

gout remains a challenge, especially for participants who are newly diagnosed with gout or experience infrequent recurrent attacks.

In agreement with a previous study⁵, we found that the risk for recurrent attacks is high. Thus appropriate management of such attacks is clinically important. In our study, 26% of recurrent attacks were managed inappropriately. If we apply this estimate to the total number of recurrent attacks managed each year in the US, then the absolute number of gout patients receiving inappropriate therapy is significant. Further, the impact of inappropriate management of recurrent gout attacks with respect to quality of life, functional limitations, and work-related disability or absenteeism has not been well studied recently, particularly with reference to the changing epidemiology of the disease.

We found longer disease duration and more frequent attacks were associated with decreased risk of inappropriate therapy for recurrent gout attacks; however, the reason for this association is not clear. Participants with longer disease duration and with more frequent attacks may have gained greater experience in managing their own recurrent attacks and therefore may be less likely to consult a physician.

Surprisingly, we also found that physician consultation for an acute attack of gout was associated with increased risk of inappropriate therapy, particularly in those with shorter disease duration.

Although physician consultation during a recurrent gout attack was associated with increased risk of inappropriate therapy, this does not necessarily reflect poor physician decision-making. Participants may not follow or understand the physician's advice. This may apply to the use of allopurinol, which should only be used as a prophylactic, not as a treatment for an acute attack. Allopurinol requires a prescription and therefore participants who did not seek medical attention could only be at risk for using allopurinol or a uricosuric agent inappropriately if they had access to those medications by means other than a new prescription; for example, by having an old prescription at home. Of note, in our study, inappropriate use of allopurinol only occurred among participants who consulted a physician for those attacks. If physicians are indeed prescribing allopurinol in those cases, then physicians themselves may require reeducation regarding the management of recurrent gout attacks. While participants in early stages of disease, or those with infrequent attacks, may seek treatment in an acute care setting, where familiarity with the diagnosis and management of gout may be variable, we cannot comment on this possibility since we did not ascertain the specialty of the physicians consulted for recurrent attacks.

Prior studies focusing on medication errors have found that patients with contraindications to NSAID, allopurinol, or colchicine may inappropriately receive these medications, or receive inappropriate doses²³⁻²⁷. Because we did not collect information about drug doses, we may have misclassified subjects as having had appropriate therapy even though a suboptimal dose of an appropriate medication was used. The details of self-reported comorbidities were also not collected. Thus, we could not analyze the appropriateness of therapy or dosages with respect to the presence of comorbidities. However, in virtually all circumstances of an acute attack of gout, a short course of corticosteroids, intra-articular steroids, or ACTH are usually viable options, even in patients with various comorbidities. Additionally, "no medication" may not be an inappropriate option, especially if the attack was mild and transient, as can occur with so-called "petit gout" or if the symptoms are not related to gout attacks. However, 90% of the recurrent attacks in our study manifested typical signs and symptoms, such as a red and painful toe, with maximal pain attained within 24 hours. This indicates that the majority of participants experienced an attack suggestive of acute gout.

Several characteristics of our study are worth noting. First, we were able to recruit a large number of gout patients through the Internet from the entire US, with enrollment of participants from 43 US states and the District of Columbia. Second, all had a confirmed diagnosis of gout by medical

records or physician checklist. Third, the sex and age distributions of the participants are similar to those reported in previous studies of gout in which the male to female ratios are approximately 4 or 5 to 1, and mean age is in the fifties^{3,6,28}. Fourth, our study's participants were not recruited through physicians' offices or other medical points of care. They may therefore more accurately reflect the actual management of gout in the community and as a result, our estimates of the various management strategies for attacks are likely more accurate than clinic- or hospital-based studies. We were also conservative in our definition of inappropriate therapy, being careful to distinguish therapies that are truly inappropriate from those that may not be considered inappropriate under certain clinical circumstances.

Finally, given that a relatively large proportion of patients who experienced recurrent gout attacks are not seeking care from their physicians, using data generated from the clinic or hospital cannot adequately describe the pattern of medication use for recurrent gout attacks in all patients. By using the Internet, in addition to recruiting a large number of gout patients, participants were able to enter the data themselves in a timely manner (median time to log in after an attack was 2 days), thus minimizing recall bias and allowing capture of data not available in clinic or hospital records.

Our study has some limitations as well. First, the participants in our study were volunteers and therefore the findings may not be generalizable to the whole gout population. However, this should not bias the internal validity of our study. Nevertheless, participants in our study tended to be better educated than the general US population. It is conceivable that participants who are more educated could be less likely to use inappropriate therapy than those who are less educated. It is also possible that gout patients "surfing the web" may be ones that have the poorest disease control. However, lack of generalizability is also a concern for studies using patients from clinics or hospitals. In clinic- or hospital-based studies, participants are likely to have more comorbidities than the general gout population, complicating therapeutic decisions.

Secondly, we did not require a crystal-proven diagnosis of gout. While all our study participants had a physician diagnosis of gout and 91% met the ACR preliminary criteria for gout, only 18% of these cases had crystal-proven gout. However, the majority had a history of first MTP joint involvement and hyperuricemia, and one-third had a history of tophi. Further, all medical records pertaining to the gout diagnosis may not have been made available to us. Thus, the proportion of crystal-proven gout may have been underestimated. Nevertheless, it is possible that some of these subjects may have had pseudogout or other episodic acute arthritis that may have been misdiagnosed as gout.

In summary, we found that the risk of recurrent gout attacks is high. Although efficacious treatments for gout are widely known and available, inappropriate management of

recurrent gout attacks still occurs frequently, indicating that management of gout remains a challenge, particularly in the early stages of disease, and further education of patients and physicians may be warranted.

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