Hospitalization Increases the Risk of Acute Arthritic Flares in Gout: A Population-based Study over 2 Decades

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ABSTRACT. ***Objective.*** To assess in-hospital gout flares in patients with gout.

Methods. Hospitalizations were evaluated for gout flares in a cohort of Olmsted County, Minnesota, residents with incident gout in 1989–1992 or 2009–2010.

Results. There were 429 patients followed up to 5 years. Of these, 169 patients experienced 454 hospitalizations. Hospitalization rates increased without reaching statistical significance from 1989–1992 to 2009–2010 [rate ratio (RR) 1.19, 95% CI 0.98–1.45]. The gout flare rate increased significantly during hospitalization (RR 10.2, 95% CI 6.8–14.5). In-hospital gout flare increased the average hospital stay by 1.8 days ($p < 0.001$).

Conclusion. Hospitalization increased the risk of gout flares 10-fold. In-hospital gout flares were associated with longer hospitalization. (First Release July 1 2018; J Rheumatol 2018;45:1188–91; doi:10.3899/jrheum.171320)

Key Indexing Terms:
GOUT HYPERURICEMIA HOSPITALIZATION HEALTHCARE USE

Gout is the most common inflammatory arthritis in the United States. The prevalence of gout and its burden on healthcare costs has increased over recent decades[1–5]. Gout is associated with several comorbidities but independently predicts increased health resource use, including hospitalization[6,7].

It is unclear how the increased risk for hospitalization among patients with gout may affect the risk of arthritic flares or length of hospital stay. A previous study suggested a significantly increased risk of a gout attack during hospitalization in patients with established gout[8]. Factors such as temporary discontinuation of gout medications and fluid shifts may influence urate hemostasis and risk of gout flare during hospitalization.

Our study aimed to examine factors associated with gout flare during hospitalization, whether hospital admission increased the risk of gout flares, and whether hospitalization rates for patients with gout have changed over time.

MATERIALS AND METHODS

Patients. Patients with incident gout in the Olmsted County, Minnesota, population were identified using the resources of the Rochester Epidemiology Project (REP)[9]. The REP enables the complete collection of all inpatient and outpatient medical records, and virtually complete ascertainment of all clinically recognized cases of gout. Using the REP, adult (aged ≥ 18 yrs) Olmsted County residents with a potential diagnosis of gout were retrieved using diagnostic codes (International Classification of Diseases Version 9, code 274.x) during 2 different periods (January 1, 1989–December 31, 1992, and January 1, 2009– December 31, 2010)[9]. Case definition was met when 1 of 3 proposed gout criteria was fulfilled[10,11,12]. All potential cases were manually reviewed to ascertain fulfillment of criteria as previously described[13]. All patients were followed from the date of gout diagnosis to the earliest of the following: 5 years after gout diagnosis, death, or migration from Olmsted County. This study was approved by the Institutional Review Boards of the Mayo Clinic (#12-007239) and the Olmsted Medical Center (#018-OMC-15). Informed consent was waived for this minimal-risk study.

All hospitalizations for patients with a diagnosis of gout were reviewed. Data collection included admission and discharge dates, primary reason for admission, comorbidities, body mass index (BMI), and kidney function at time of admission. Medication use was recorded for diuretics, statins, urate-lowering therapy (ULT), and antiinflammatory medications (nonsteroidal antiinflammatory drugs, colchicine, and glucocorticoids), as was in-hospital use of intravenous fluids, diuretics, and intravenous contrast.

In-hospital flare of gouty arthritis was defined as a new-onset inflammatory arthritis during hospitalization attributed to gout by the treatment providers and not attributed to an alternative cause. Only 1 flare per hospitalization was considered. Outpatient flares were defined similarly.

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Statistical analysis. Descriptive statistics (means, percentages, etc.) were used to summarize data. Person-year (PY) methods were used to calculate the rate of flares of gouty arthritis during hospitalizations and outside the hospital. The rate of inpatient flares was calculated by dividing the number of hospitalizations with flare by the total number of days in hospital to obtain the rate of flares per 100 inpatient PY. Generalized estimating equation regression models with binary outcomes and random effects (accounting for multiple hospitalizations per subject) were used to explore risk factors of in-hospital gout flares and to compare log-transformed in-hospital length of stay with and without gout flare. Cumulative incidence methods adjusting for the competing risk of death were used to estimate the percentage of patients with a hospitalization after gout diagnosis. Analyses were performed using SAS version 9.4 (SAS Institute) and R 3.1.1 (R Foundation for Statistical Computing).

RESULTS

A total of 429 patients with incident gout were identified (158 patients in 1989–1992 and 271 patients in 2009–2010). The demographic characteristics at gout diagnosis were similar between the 2 cohorts, including mean age (59.3 yrs in 1989–1992 vs 60.0 yrs in 2009–2010), and male predominance (73% in 1989–1992 vs 72% in 2009–2010; Table 1). BMI increased over the study period (mean 28.6 kg/m^2 in 1989–1992 vs 32.0 kg/m^2 in 2009–2010). Kidney disease also increased (11% in the early period vs 32% in the late period). The median length of followup was 5.0 years in the early period and 4.7 years in the late period, with only 17% of the early period and 11% of the late period with < 4 years of followup.

There were 454 hospitalizations in the 2 cohorts during the 5-year followup. By 5 years after gout diagnosis, at least 1 hospitalization occurred for 39.1% of patients in the early cohort and 43.1% of patients in the later cohort ($p = 0.56$, Figure 1). Accounting for multiple hospitalizations per patient, the overall rate of hospitalizations increased marginally from a rate of 2.26 per 10 PY (95% CI 1.91–2.65) in the early cohort to 2.69 per 10 PY (95% CI 2.40–3.01) in the later cohort [rate ratio (RR) 1.19, 95% CI 0.98–1.45].

Cardiovascular disease was the most common reason for admission in both periods (23% in the 1989–1992 cohort and 28% in the 2009–2010 cohort). Other reasons for admissions in the 1989–1992 and 2009–2010 cohorts, respectively, included infection (7% and 28%), gastrointestinal diseases (11% and 19%), pulmonary disease (4% and 6%), renal disease (3% and 6%), trauma (5% and 8%), and other reasons (65% and 37%).

Table 1. Characteristics at diagnosis of Olmsted County, Minnesota, residents with incident gout, 1989–1992 and 2009–2010. Values in table are n (%) or mean ± SD.

Characteristics	1989–1992, n = 158	2009–2010, n = 271
Age at diagnosis, yrs	59.3 ± 17.9	60.0 ± 17.0
Sex, male	116 (73)	196 (72)
Length of followup, yrs	4.1 (1.6)	4.2 (1.2)
Serum uric acid level, mg/dl	8.0 (1.8)	8.2 (2.0)
Body mass index, kg/m^2	28.6 ± 5.3	32.0 ± 6.8
Kidney disease	18 (11)	86 (32)

Gout flare occurred in 28 of these 454 hospitalizations; 23 patients had a gout flare during hospitalization, because individual patients could have multiple hospitalizations with gout flares. The relative risk of a gout flare during hospitalization was 10.2 (95% CI 6.8–14.5), with a rate of 85 flares per 100 inpatient PY compared to 8.5 per 100 PY of outpatient followup (554 outpatient flares during 1784 PY of followup). In addition, the rate of in-hospital flares increased marginally over time (6.3 per 10 PY in 1989–1992 vs 11.7 per 10 PY in 2009–2010; RR 1.85, 95% CI 0.89–4.00).

Variables evaluated as possible predictors of inpatient gout flares included discontinuation of ULT, recent start of ULT within 3 months prior to the hospitalization, diuretic use, intravenous fluids, and intensive care unit stay during the hospitalization, as well as sex, age, and number of prior outpatient flares. Several variables including recent start of ULT were associated with increased risk of gout flare but did not reach statistical significance (Table 2).

Hospitalizations complicated by gout flares were associated with an average length of stay 1.8 days longer than hospitalizations without gout flares ($p < 0.001$ adjusted for age, sex, and cohort). Unadjusted median lengths of stay were 3 days [interquartile range (IQR) 2–6] for hospitalizations without flare and 6 days (IQR 2–11.5) for hospitalizations with flare.

DISCUSSION

Our study adds to the evidence that hospitalization is associated with an increased risk of acute gout attacks in patients with preexisting gout. The risk of acute arthritic flare during hospitalization was 10-fold higher in patients with preexisting gout.

A study reported a 4-fold increased risk for hospitalization occurring in a 2-day risk window prior to an acute gout attack[14]. Methodological differences may account for the higher estimate in our study. This study was population-based and recorded precisely the hospitalization length, enabling accurate calculation of in- versus out-of-hospital events per PY of followup. In-hospital gout flares were associated with significantly longer hospital stays[8].

Factors that may increase the risk of gout flares during hospitalization include volume depletion, acidosis, fluid shifts, discontinuation of gout medications, diuretic use, and obesity[15,16,17,18]. Similar to a previous report, there were no statistically significant associations between these and other factors with gout flares[14]. This may be due to the limited power in both studies.

There was a marginally increased rate of hospitalization for patients diagnosed with gout in 2009–2010 compared with those diagnosed in 1989–1992. This finding is in contrast to secular trends of overall decreasing hospitalization rates in the United States[19]. This could be partly explained by the increased comorbidities among patients with gout[13].

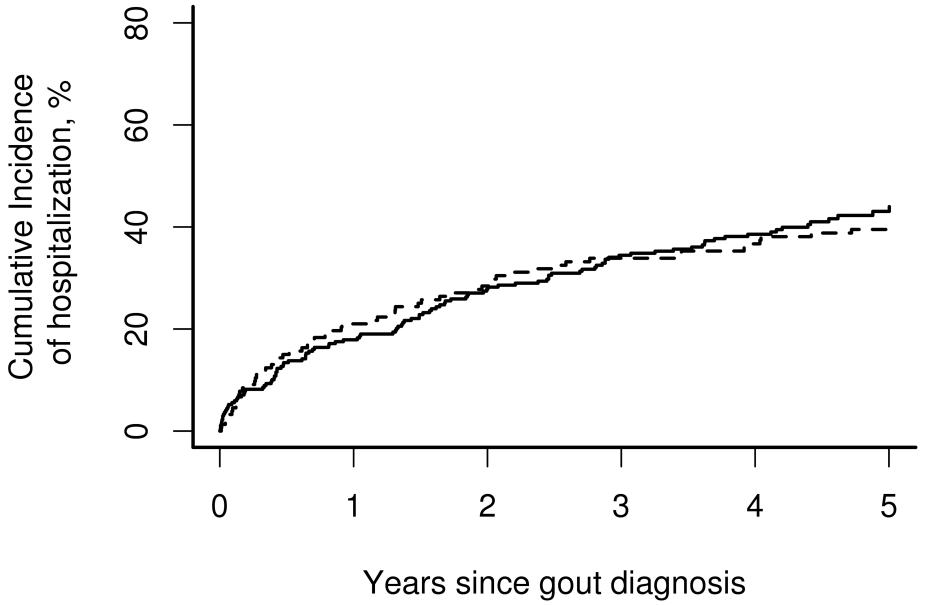

Figure 1. Cumulative incidence of first hospitalization following a diagnosis of gout in 1989–1992 (dashed line) and 2009–2010 (solid line).

Table 2. Potential predictors of in-hospital gout flares. Values are n (%) or mean ± SD unless otherwise specified.

Predictors	Value*	OR (95% CI)
Diagnosis year 2009–2010 (vs 1989–1992)	306 (56)	1.47 (0.65–3.35)
Age at gout diagnosis, yrs, per 10-yr increase	59.7 ± 17.3	1.15 (0.86–1.55)
Male sex	312 (73)	1.08 (0.46–2.56)
Time since most recent flare prior to hospitalization, per 1-year increase	3.4 ± 4.0	0.87 (0.74–1.02)
No. flares prior to hospitalization	2.7 ± 2.2	1.04 (0.88–1.23)
> 1 joint affected at gout diagnosis	861 (12)	1.75 (0.60–5.06)
Joint other than 1st MTP affected at gout diagnosis	253 (36)	1.31 (0.57–3.03)
Had ULT at hospital admission	211 (30)	0.36 (0.11–1.01)
Started ULT within 3 months prior to hospitalization	27 (8)	2.82 (0.71–11.25)
ULT discontinued at/during hospitalization	18 (4)	0.86 (0.11–6.83)
ICU stay during hospitalization	61 (13)	1.24 (0.45–3.42)
Taking diuretics during hospitalization	248 (55)	1.46 (0.64–3.30)
Kidney disease	325 (46)	0.91 (0.40–2.06)
Serum uric acid level at gout diagnosis, mg/dl	8.7 ± 1.9	1.40 (1.11–1.77)
BMI at hospital admission, kg/m^2	29.2 ± 7.8	0.99 (0.94–1.05)
Obesity at hospital admission, BMI ≥ 30 kg/m^2	244 (37)	0.80 (0.33–1.96)
Obesity at hospital admission, BMI ≥ 35 kg/m^2	120 (18)	1.43 (0.52–3.90)
Morbid obesity at hospital admission, BMI ≥ 40 kg/m^2	63 (10)	1.97 (0.61–6.39)

*Values based on no. hospitalizations, not no. unique patients. ULT: urate-lowering therapy; MTP: metatarsophalangeal joint; ICU: intensive care unit; BMI: body mass index.

The methodological strengths of our study include the population-based approach, eliminating the selection bias that may affect studies based on convenience samples and data registries without confirmation of diagnosis or reason for hospitalization[7,9,14]. Comprehensive data on hospitalizations were available. Criteria defining gout diagnosis were applied to all patients, thus limiting problems associated with a code or physician diagnosis-based case definition[9].

The limitations of our study are those inherent to its retrospective design. Flares in the outpatient setting may be underascertained if patients did not make a clinic visit or report the event to the provider. The validity of retrospective ascertainment of inpatient flares is unknown. The majority of the Olmsted County population is of Northern European descent, therefore it may not be possible to generalize the findings to more diverse populations[4,8,9,20]. The study was completed

prior to the publication of the updated 2015 American College of Rheumatology classification criteria for gout; it is unclear how, if at all, these might affect the study results[20].

Hospitalization is strongly associated with acute flares in patients with preexisting gout. The significantly prolonged hospitalization in patients who experience gout flare after admission warrant further studies to identify strategies to mitigate this risk and possibly reduce attendant costs.

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