Iatrogenic Gastric Acid Suppression and the Risk of Nosocomial Clostridium difficile Infection

Michael D. Howell, MD, MPH; Victor Novack, MD, PhD; Philip Grgurich, PharmD; Diane Soulliard, PharmD; Lena Novack, PhD; Michael Pencina, PhD; Daniel Talmor, MD, MPH

**Background:** The incidence and severity of Clostridium difficile infections are increasing. Acid-suppressive therapy has been suggested as a risk factor for C difficile, but this remains controversial.

**Methods:** We conducted a pharmacoepidemiologic cohort study, performing a secondary analysis of data collected prospectively on 101,796 discharges from a tertiary care medical center during a 3-year period. The primary exposure of interest was acid suppression therapy, classified by the most intense acid suppression therapy received (no acid suppression, histamine2-receptor antagonist [H2RA], therapy, daily proton pump inhibitor [PPI], and PPI more frequently than daily).

**Results:** As the level of acid suppression increased, the risk of nosocomial C difficile infection increased, from 0.3% (95% confidence interval [CI], 0.21%-0.31%) in patients not receiving acid suppressive therapy to 0.6% (95% CI, 0.49%-0.79%) in those receiving H2RA therapy, to 0.9% (95% CI, 0.80%-0.98%) in those receiving daily PPI treatment, and to 1.4% (1.15%-1.71%) in those receiving more frequent PPI therapy. After adjustment for comorbid conditions, age, antibiotics, and propensity score-based likelihood of receipt of acid-suppression therapy, the association persisted, increasing from an odds ratio of 1 (no acid suppression [reference]) to 1.53 (95% CI, 1.12-2.10) (H2RA), to 1.74 (95% CI, 1.39-2.18) (daily PPI), and to 2.36 (95% CI, 1.79-3.11) (more frequent PPI). Similar estimates were found with a matched cohort analysis and with nested case-control techniques.

**Conclusions:** Increasing levels of pharmacologic acid suppression are associated with increased risks of nosocomial C difficile infection. This evidence of a dose-response effect provides further support for the potentially causal nature of iatrogenic acid suppression in the development of nosocomial C difficile infection.

Arch Intern Med. 2010;170(9):784-790

Author Affiliations: Silverman Institute for Healthcare Quality and Safety (Dr Howell) and the Departments of Medicine (Dr Howell), Pharmacy (Dr Soulliard), and Anesthesia, Critical Care, and Pain Medicine (Dr Talmor), Beth Israel Deaconess Medical Center, Boston, Massachusetts; Departments of Medicine (Dr Howell) and Anesthesia, Critical Care, and Pain Medicine (Dr Talmor), Harvard Medical School, Boston; the Harvard Clinical Research Institute, Boston (Drs V. Novack, L. Novack, and Pencina); and the Department of Pharmacy, Froedtert Hospital, Milwaukee, Wisconsin (Dr Grgurich).
between increasing levels of pharmacologic acid suppression and nosocomial acquisition of *C. difficile* in a large pharmacoepidemiologic cohort.

### METHODS

#### SETTING AND DESIGN

This was a pharmacoepidemiologic cohort study, in which we performed a secondary analysis of data prospectively collected for other reasons on patients discharged between January 1, 2004, and January 31, 2008, at the Beth Israel Deaconess Medical Center, a large, urban, tertiary care center in Boston, Massachusetts. The hospital’s institutional review board approved the study with a waiver of informed consent.

#### DATA SOURCES

Data were obtained from electronic medical databases created as part of usual care. These databases contain information from each admission, such as demographics, discharge diagnosis codes, medication orders, microbiologic results, length of stay, and inpatient mortality.

#### PATIENTS AND DEFINITIONS

All patients who were at least 18 years old and had a length of stay of 3 or more days were included. The outcome of interest, nosocomial *C. difficile* infection, was defined as a newly positive *C. difficile* toxin assay result on or after the third hospital day, a definition used by others. Only a first diagnosis of *C. difficile* was included; subsequent admissions of patients with in-depth *C. difficile* infection were excluded.

The primary exposure of interest was receipt of acid suppression therapy. Exposure was classified by the most intense acid suppression therapy received before a positive *C. difficile* test result or hospital discharge, whichever was earlier. The 4 a priori acid suppression groups were no acid suppression therapy, histamine-2-receptor antagonist (H2RA) therapy, daily PPI, and PPI more frequently than daily. We used these classifications because they result in stepwise increases in gastric acid suppression and because they represent common clinical therapeutic approaches. Because of formulary selections in our hospital, clinical dosing of PPIs closely parallels the defined daily dose.

We collected other potentially important predictors of *C. difficile* infection. We assessed antibiotics received during the hospitalization before a diagnosis of *C. difficile* infection or discharge, categorizing patients as having received no antibiotics, low-risk antibiotics, or high-risk antibiotics. High-risk antibiotics were identified based on the medical literature and included fluoroquinolones, cephalosporins, intravenous β-lactam/β-lactamase inhibitors, macrolides, clindamycin, and carbapenems. Other antibiotics were classified as low risk.

To classify patients’ comorbidity status, we used the method of Elixhauser et al. for classification of specific comorbid conditions; we used the Charlson Comorbidity Index to represent the cumulative burden of comorbid illness.

#### STATISTICAL METHODS

We performed unadjusted comparisons using the t test, the Mann-Whitney test, the χ² test, or the Fisher exact test, as appropriate. We used the Kaplan-Meier method to assess time to the *C. difficile* diagnosis. Statistical analyses were performed with SAS software, version 9.1 (SAS Institute Inc, Cary, North Carolina) and SPSS, version 16.0.1 (SPSS Inc, Chicago, Illinois).

### PROPENSITY SCORE

Patients for whom physicians prescribe acid-suppressive medications are likely to differ systematically from those who do not receive the medications, resulting in potential selection bias. Thus, in addition to multivariable adjustment for comorbidities, we applied a propensity score adjustment technique. Since the method for propensity score construction for multilevel variables is less well established, as a first step we created a binary propensity score to reflect the probability of receiving the strongest level of acid suppression (PPI more often than daily) compared with no acid suppression therapy. The propensity score was derived from a logistic generalized estimating equation (GEE) model, which included 19 clinical and demographic variables. We then applied the propensity score equation to the rest of the study cohort (the H2RA only and daily PPI groups). Finally, we verified that the mean propensity scores of the 4 exposure groups were correctly ordered (ie, that there was a linear increase from the lowest level of acid-suppressive therapy to the highest). The propensity score was then included in the final logistic GEE regression model, with *C. difficile* infection as the dependent variable.

Because each patient could have been admitted to the hospital more than once during the study period, we used a GEE model to address patient-level clustering, with a dependent variable of nosocomial *C. difficile* infection. To avoid model overfitting, forward stepwise selection was used to identify potentially significant predictors (P < .10) for retention in the model. Model discrimination was assessed using the area under the receiver operating characteristics curve; model fit was tested using the Hosmer-Lemeshow statistic (calculated under the assumption of independent correlation structure of the model). The model included exposure to acid suppression, exposure to prior antibiotics, age, sex, comorbid illness, propensity score, and log-transformed length of stay as an offset variable. Since acquiring *C. difficile* infection results in a longer length of stay, for *C. difficile−*positive patients, length of stay was substituted with time to the diagnosis.

### ADDITIONAL ANALYTIC APPROACHES

Because true findings should be resilient to the analytic technique applied, we also analyzed the relationship between acid suppression and *C. difficile* infection using 2 additional approaches.

#### Cohort Propensity Score Matching

We defined patients with no acid suppression therapy as a reference group. Then all other patients (those with varying acid suppression therapy levels) were matched 1:1 with the reference cohort using a propensity score with caliper of 0.10. A nearest-neighbor–matching algorithm with a “greedy” heuristic (one that always implements the best immediate or local solution) was applied. In greedy nearest-neighbor matching, a patient from the treatment cohort was randomly selected, and matching was attempted with the “nearest” patient from the reference group. This process was repeated until matches had been attempted for all patients in each acid suppression group. Each matched pair was unique, and data for unmatched patients were not used in subsequent analyses. By this approach, we created 3 matched cohorts: no acid suppression/H2RA; no acid suppression/daily PPI; and no acid suppression/PPI more frequently than daily. We applied a logistic GEE regression in each of the matched cohort pairs.

©2010 American Medical Association. All rights reserved.
Patients with C difficile infection were matched at a 1:2 ratio by a nearest-neighbor–matching algorithm with a “greedy” heuristic to patients without C difficile infection on the basis of their diagnosis related group, Charlson index with caliper of 1 point, age with caliper of 3 years, and propensity score with caliper of 0.10.27,28 Only cases with 2 controls matched were included in the analysis. Only the first admission for each patient was included. Multivariable conditional logistic regression analysis was then performed with inclusion of 4 groups of acid suppression therapy and adjustment for sex and number of comorbidities.

Lastly, because some hospital services are often believed to be very low risk for C difficile infection, we performed a sensitivity analysis that excluded patients admitted to the obstetrics and psychiatric services.

### RESULTS

The study period included 174,224 admissions and 1,344 cases of toxin-positive C difficile infection. Of these admissions, 72,428 did not meet inclusion criteria: 72,013 had a length of stay less than 3 days, 447 involved patients who were younger than 18 years, and 177 involved patients who had been diagnosed as having C difficile during prior admissions. Some patients had more than 1 exclusion criterion. Thus, 101,796 admissions were eligible for analysis. Nosocomial C difficile infection occurred in 665 cases (0.7% of admissions). Patients with nosocomial C difficile infection were older, more likely to be male, and more likely to have comorbid conditions such as congestive heart failure, renal failure, and cancer. Exposure to antibiotics was strongly associated with development of C difficile, and nosocomial C difficile infection was associated with higher mortality rates (Table 1). Length of stay was strongly associated with the rate of nosocomial C difficile infection (Figure 1): patients hospitalized for less than 7 days had a lower rate of C difficile infection than patients with longer stays (0.4% vs 1.1%; P < .001).

### PROPENSITY SCORE

The final propensity score included 19 variables that differentiated between the probability of receiving maximal acid suppression therapy and no acid suppression: age, sex, history of heart failure, chronic lung disease, diabetes mellitus, hypothyroidism, neurologic disorders, chronic liver diseases, gastric ulcer, malignancy, connective tissue diseases, coagulation disorders, AIDS/human immunodeficiency virus, chronic renal failure, obesity, history of weight loss, anemia, alcohol abuse, and history of blood loss. Applying the propensity score formula to all 4 acid suppression exposure groups, from lowest to highest, yielded mean propensity scores of 0.15, 0.19, 0.26, and 0.32. Simple regression demonstrated a strong linear trend based on propensity score analysis, further underscoring the adequacy of our approach.

### RISK OF NOSOCOMIAL C DIFFICILE INFECTION

In unadjusted analyses, increasing levels of acid-suppressive therapy were associated with increasing rates of nosocomial C difficile infection. As the level of acid suppression increased, the risk of developing nosocomial C difficile infection increased, from 0.3% (95% confidence interval [CI], 0.21%-0.31%) to 0.6% (95% CI, 0.49%-0.79%), to 0.9% (0.80%-0.98%), to 1.4% (1.15%-1.71%). Antibiotic therapy strongly predicted C difficile infection: 0.2% in patients who did not receive antibiotics, 0.4% in patients treated with low-risk antibiotics, and...
1.1% in patients who received high-risk antibiotics \( (P < .001) \). **Figure 2** shows the risk of *Clostridium difficile* infection, simultaneously stratified by acid suppression therapy and antibiotics.

After adjustment for comorbid conditions, age, receipt of antibiotics, and propensity score–based likelihood of receipt of acid suppression therapy, the association persisted. In our main analysis, which adjusted for propensity score as a continuous variable, we found that as the level of acid suppression increased, the adjusted odds of developing *C difficile* infection also increased, from an odds ratio (OR) of 1 (reference) to 1.53 (95% CI, 1.12-2.10) for H2RA only, to 1.74 (95% CI, 1.39-2.18) for daily PPI, and to 2.36 (95% CI, 1.79-3.11) for PPI more frequently than daily (Table 2). Because the incidence of *C difficile* infection in our unexposed cohort is low (0.25%), adjusted ORs are close approximations of adjusted relative risks.29

In addition, receipt of prior antibiotics, age, and comorbid conditions were important risk factors for nosocomial *C difficile*. Low-risk antibiotics were associated with a near doubling of the odds of *C difficile* infection, and high-risk antibiotics with a more than 3-fold increase in the odds of disease. The model had good discrimination (area under the receiver operating characteristics curve, 0.77 [95% CI, 0.76-0.79]) and good calibration \( (P = .64, \text{ Hosmer-Lemeshow test}) \).

To ascertain whether our results might be an artifact of the analytic method chosen, we used additional analytic approaches to verify our findings. In our main analysis, we used the entire cohort and adjusted for propensity to receive high-level acid suppression, treating this as a continuous variable. In our first additional approach, we conducted a cohort analysis matched by propensity score. In our second additional approach, we conducted a nested, matched case-control analysis. The results of these different approaches yielded results very similar to the main analysis (Figure 3).

We performed a sensitivity analysis, excluding patients admitted to the psychiatric and obstetrics services, which have low risks of nosocomial *C difficile* infection. The *C difficile* infection rate in the remaining cohort of 80 906 admissions was 0.8%. Multivariable GEE analysis demonstrated that the association between acid suppression and *C difficile* persisted. Compared with no acid suppression, H2RA treatment was associated with an OR of 1.29 (95% CI, 0.94-1.67); daily PPI, with an OR of 1.47 (95% CI, 1.18-1.84); and PPI more frequently than daily, with an OR of 1.98 (95% CI, 1.51-2.59).

**COMMENT**

This study demonstrates that increasing levels of pharmacologic acid suppression are independently associated with an increased risk of nosocomial *C difficile* infection. The strength of the association is both clinically and statistically meaningful. Compared with no acid suppression, receipt of a daily PPI was associated with a more than 70% increase in the odds of developing *C difficile*; patients who received more frequent PPIs had a more than doubling of risk.

We attempted to design a study that would contribute meaningfully to the debate about whether acid suppression contributes causally to nosocomial *C difficile* infection or is simply a confounder. Although a substantial number of studies have assessed the relationship be-
Antibiotics were classified as low risk. H2RA indicates H2-receptor antagonists, inhibitors, macrolides, clindamycin, and carbapenems.13,22,23 All other antibiotics were classified as high risk. C. difficile infection was a relatively rare event, such a trial would be very problematic. In addition, because the acquisition of C. difficile infection is a relatively rare event, such a trial would be very large and therefore costly. Second, there may be residual confounding. We attempted to control for selection bias using careful application of propensity score-based techniques and further adjusted for significant confounders, but unmeasured variables may still cause residual confounding. Effect estimates, as expected, moved closer to the null as we adjusted for covariates, but the magnitude of effect still remains plausibly large. Third, we were unable to collect information about use of acidsuppressive medications or antibiotics before admission, which could be an important effect modifier.

These results may have important public health implications. Our results suggest that, compared with no acid suppression, we should expect at least 1 additional case of nosocomial C. difficile infection for every 533 patients who receive a daily PPI, after controlling for other risk factors. Fourth, we controlled for the likelihood of administration of more-intense acid suppression therapy using techniques commonly recommended in pharmacoepidemiology. Finally, our results were resilient to the specific analytic technique applied, with remarkably similar estimates of the dose-response relationship.

Our study also has several key limitations. First, it remains an observational study. A randomized design would provide greater confidence in our findings. However, conducting a randomized controlled trial to assess whether a therapy causes C. difficile infection would ethically be problematic. In addition, because the acquisition of C. difficile is a relatively rare event, such a trial would be very large and therefore costly. Second, there may be residual confounding. We attempted to control for selection bias using careful application of propensity score-based techniques and further adjusted for significant confounders, but unmeasured variables may still cause residual confounding. Effect estimates, as expected, moved closer to the null as we adjusted for covariates, but the magnitude of effect still remains plausibly large. Third, we were unable to collect information about use of acid-suppressive medications or antibiotics before admission, which could be an important effect modifier.

These results may have important public health implications. Our results suggest that, compared with no acid suppression, we should expect at least 1 additional case of nosocomial C. difficile infection for every 533 patients who receive a daily PPI, after controlling for other risk factors. This is based on a nosocomial C. difficile infection incidence of 0.3% in patients receiving no acid suppression and an adjusted increase of 70% in odds of disease in patients receiving daily PPIs. Although this seems like a relatively large number-needed-to-harm, the magnitude of exposure is large. We found that 60% of patients received acid-suppressive therapy, similar to others’ estimations.
mates.\textsuperscript{33–35} Since there are about 32.7 million annual adult discharges in the United States annually,\textsuperscript{36} the number of potentially attributable nosocomial \textit{Clostridium difficile} cases in the United States numbers in the tens of thousands per year. This is particularly important, since prior work has found that more than two-thirds of inpatient acid-suppressive pre-

Finally, future interventional trials of acid-suppressive medications in inpatients should actively collect information about incident \textit{C. difficile} infection and other adverse events. Researchers can also further help reduce uncertainty in this field by using risk-benefit analysis to create tools that help select patients in whom stress ulcer prophylaxis may be clearly beneficial or clearly harmful.

Accepted for Publication: February 10, 2010.

Correspondence: Michael D. Howell, MD, MPH, Critical Care Quality, Silverman Institute for Healthcare Quality and Safety, Beth Israel Deaconess Medical Center, 330 Brookline Ave, Boston, MA 02215 (mhowell@bidmc .harvard.edu).

Author Contributions: Study concept and design: Howell, V. Novack, L. Novack, and Pencina, and Talmor. Acquisition of data: Howell. Analysis and interpretation of data: Howell, Novack, Pencina, Soulliard, and Talmor. Drafting of the manuscript: Howell, Novack, Soulliard, and Talmor. Critical revision of the manuscript for important intellectual content: Howell, Novack, Soulliard, and Talmor. Administrative, technical, and material support: Grgrurich, Soulliard, and Talmor. Study supervision: Howell.

Financial Disclosure: None reported.

REFERENCES

4. Centers for Disease Control and Prevention (CDC). \textit{Severe Clostridium difficile–


23. Winston DJ, Lazarus HM, Beveridge RA, et al. Randomized, double-blind, mul-