LESS IS MORE

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

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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 5-year period. The primary exposure of interest was acid suppression therapy, classified by the most intense acid suppression therapy received (no acid suppression, histamine$_2$-receptor antagonist [H_2RA] 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 H_2RA 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) (H_2RA), 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.

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CLOSTRIDIUM DIFFICILE INfection poses a clear and escalating threat to public health. Incidence and severity of disease are increasing,[1,2] and costs total more than $1 billion in the United States annually.[3] Although other populations are at risk,[4] most cases remain both nosocomial and iatrogenic.[2] Prevention is therefore paramount, but preventive measures have generally focused on isolation of infected patients, hand hygiene, and antibiotic stewardship.[5]

Recently, attention has turned to the possible contribution of proton pump inhibitor (PPI) use to the acquisition of *C difficile*. This association is biologically plausible. More than 2 decades ago, Gurian et al[6] showed that more-acidic gastric juices were more effective than less-acidic gastric juices in killing *C difficile* and neutralizing its toxin. Mice receiving PPIs have similar susceptibility to *C difficile* infection as mice receiving antibiotics.[7] More recently, some,[8-11] but not all,[11-15] epidemiologic studies have suggested an association between *C difficile* infection and PPI use, both in the inpatient and outpatient setting. However, a recent review summarized the state of the literature regarding PPI and *C difficile* infection as remaining

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"controversial[1]"; another recent prominent *C difficile* review did not mention PPIs at all.[2]

Moreover, little work has addressed whether a dose-response effect exists between acid suppression and *C difficile* infection,[16] in spite of the fact that this is often viewed as one of the epidemiologic pillars of causal inference.[17-19] Therefore, we sought to examine the relationship be-

tween 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.[8] Only a first diagnosis of *C difficile* was included; subsequent admissions of patients with index *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 (H_2RA) therapy, daily PPI, and PPI more frequently than daily. We used these classifications because they result in stepwise increases in gastric acid suppression[20] 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[21]; more than 98% of daily PPIs were equivalent to 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.[13,22,23] Other antibiotics were classified as low risk. To classify patients' comorbidity status, we used the method of Elixhauser et al[24] for classification of specific comorbid conditions; we used the Charlson Comorbidity Index[25,26] to represent the cumulative burden of comorbid illness.

STATISTICAL METHODS

We performed unadjusted comparisons using the *t* test, the Mann-Whitney test, the χ^2 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 H_2RA 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.[27,28] 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/H_2RA; 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.

Table 1. Clinical and Demographic Characteristics Stratified by the Diagnosis of Nosocomial *Clostridium difficile*[a]

Characteristic	Admissions With *C Difficile* Infection (n=665)	Admissions Without *C Difficile* Infection (n=101 131)	*P* Value
Age, mean (SD), y	65.4 (16.9)	56.5 (19.9)	<.001
Female sex	49.2	59.0	<.001
Acid suppression			
No acid suppression	15.8	40.7	<.001
H_2RA	9.9	10.5	
Daily PPI	54.1	39.8	
>Daily PPI	20.2	9.0	
Antibiotics			
No antibiotics	12.2	43.1	<.001
Low-risk antibiotics	4.1	6.1	
High-risk antibiotics	83.8	50.8	
Comorbidities			
History of myocardial infarction	8.0	3.7	<.001
Heart failure	32.9	17.3	<.001
Peripheral vascular disorders	11.4	7.2	.003
Chronic pulmonary disease	19.2	15.9	.02
Diabetes uncomplicated	18.6	17.2	.34
Diabetes complicated	10.5	6.3	<.001
Hypertension	43.3	40.9	.20
Hypothyroidism	7.7	9.3	.15
Chronic renal failure	22.9	11.9	<.001
Liver disease	6.8	5.2	.07
Peptic ulcer disease	2.3	1.0	.001
HIV/AIDS	1.8	1.2	.20
Lymphoma	2.7	2.1	.31
Cancer	21.5	11.9	<.001
Metastatic cancer	6.2	6.3	.89
Rheumatoid arthritis/ collagen vascular disorders	3.2	2.5	.25
Coagulopathy	12.5	4.8	<.001
Weight loss	6.9	1.9	<.001
Fluid and electrolyte disorders	33.2	16.2	<.001
Blood loss anemia	1.5	2.3	.19
Deficiency anemia	16.4	14.1	.32
Alcohol abuse	4.2	3.6	.50
Drug abuse	1.5	2.8	.04
Charlson index (IQR), age not included	2 (1.0-4.0)	1.0 (0.0-3.0)	<.001
In-hospital mortality	8.9	2.4	<.001
Length of stay, median (IQR), d	15.0 (8.0-26.0)	5.0 (3.0-8.0)	<.001

Abbreviations: H_2RA, H_2 receptor antagonist; HIV, human immunodeficiency virus; IQR, interquartile range.
[a]Data are given as percentage of admissions unless otherwise indicated.

Nested Matched Case Control

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 5 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 1344 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 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

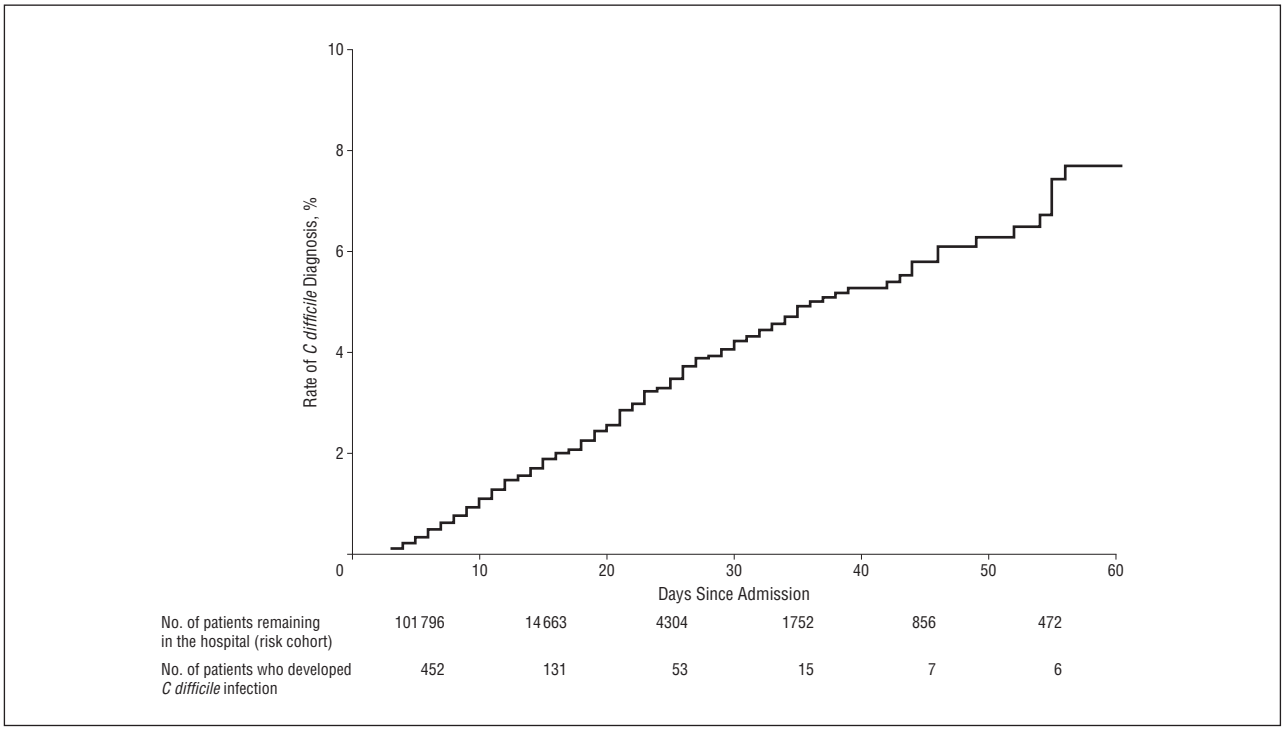

Figure 1. Kaplan-Meier rates of nosocomial *Clostridium difficile* infection during the hospitalization.

1.1% in patients who received high-risk antibiotics ($P<.001$). **Figure 2** shows the risk of *C 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 H_2RA 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 ($P=.64$, 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, H_2RA 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-

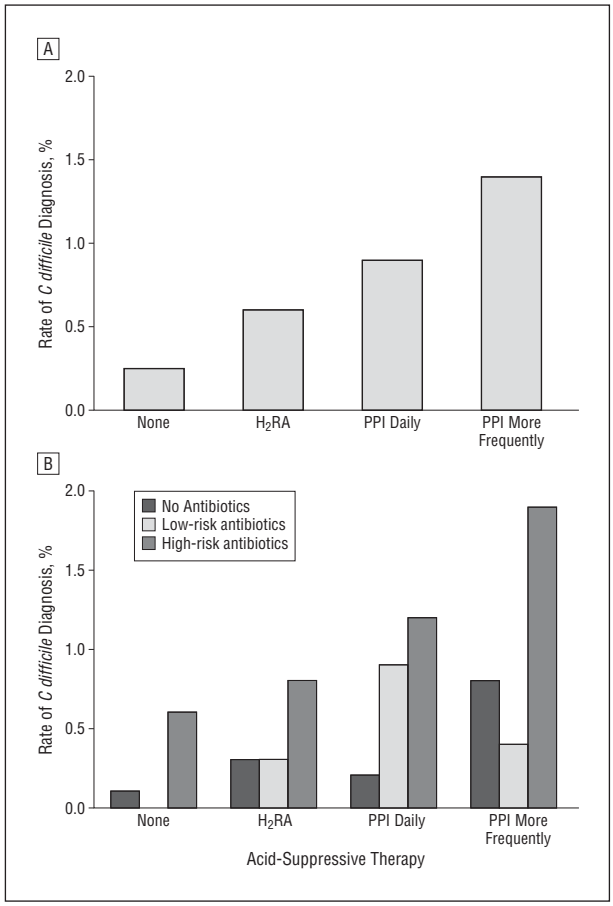

Figure 2. Rates of *Clostridium difficile* infection stratified by the type of antibiotics and acid-suppressive therapy. High-risk antibiotics included fluoroquinolones, cephalosporins, intravenous β-lactam/β-lactamase inhibitors, macrolides, clindamycin, and carbapenems.[13,22,23] All other antibiotics were classified as low risk. H_2RA indicates H_2-receptor antagonist; and PPI, proton pump inhibitor.

tween PPI use and *C difficile* infection, with findings on both sides of the issue,[8-15] we found none that addressed the question of dose-response effect (biological gradient). In fact, a recent editorial applied all of the commonly used causal criteria first laid out by Sir Austin Bradford Hill[17] to the question and found that "none of the studies published to date . . . have yet demonstrated a dose-response curve, whereby a stronger association between PPI exposure and the development of colitis was noted in individuals receiving higher doses of PPIs (biological gradient)."[16(p2315)] We therefore focused on a key element of the epidemiologic ascertainment of causality—biological gradient.[19] Our study provides clear evidence of just such a dose-response effect: more intense acid suppression is associated with increased risks of *C difficile* infection. In addition to addressing the issue of biological gradient, our results also provide further evidence in support of the temporality, consistency, and strength of the association.

Our study has several additional strengths. First, our cohort is large and includes all consecutive adults meeting inclusion criteria, limiting the likelihood of selection bias. Second, we ensured that acid suppression and antibiotic exposure occurred before development of *C difficile*, addressing the temporality criterion of Bradford Hill.[17] Third, we adjusted for the burden of comorbid disease, a criticism of some prior studies.[30,31] Fourth, we controlled for the likelihood of administration of more-intense acid suppression therapy using techniques commonly recommended in pharmacoepidemiology.[32] Finally, our results were resilient to the specific analytic technique applied, with remarkably similar estimates of the dose-response relationship.

Table 2. Multivariable Analysis for Factors Associated With Nosocomial *Clostridium difficile* Infection[a]

Factor	Odds Ratio (95% Confidence Interval)	*P* Value
Acid suppression		
No acid suppression therapy	1 [Reference]	
H_2RA only	1.53 (1.12-2.10)	.008
Daily PPI	1.74 (1.39-2.18)	<.001
PPI more frequently than daily	2.36 (1.79-3.11)	<.001
Age, per year	1.01 (1.01-1.01)	<.001
No antibiotics therapy	1 [Reference]	
Low-risk antibiotics	1.82 (1.17-2.82)	.008
High-risk antibiotics	3.37 (2.64-4.31)	<.001
Weight loss	2.29 (1.57-3.36)	<.001
Chronic heart failure	1.31 (1.06-1.62)	.01
Renal failure	1.57 (1.29-1.91)	<.001
Fluid and electrolyte disorders	1.49 (1.25-1.77)	<.001
Coagulation disorder	1.76 (1.30-2.40)	<.001
Malignancy	1.57 (1.29-1.91)	<.001

Abbreviations: H_2RA, H_2-receptor antagonist; PPI, proton pump inhibitor.
[a] General estimating equation model with diagnosis of nosocomial *C difficile* infection as a dependent variable, controlling simultaneously for variables listed as well as propensity score–based probability of receiving acid-suppressive therapy.

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' esti-

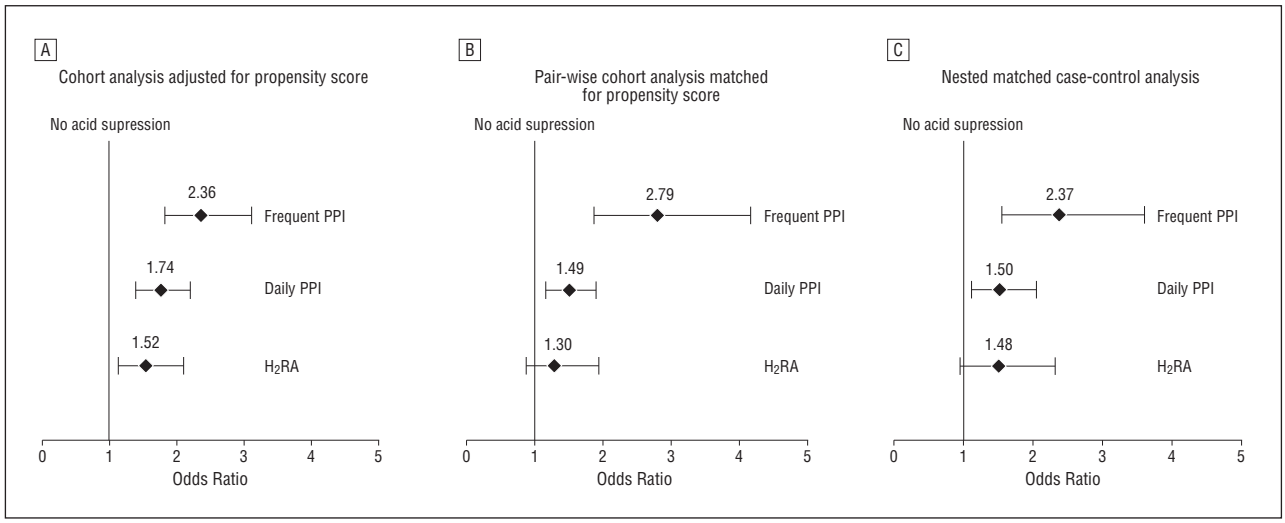

Figure 3. Multivariable models assessing the relationship of acid-suppressive therapy and nosocomial *Clostridium difficile* infection. A, Cohort analysis adjusted for propensity score. The generalized estimating equation (GEE) model included antibiotics, age, sex, length of hospital stay, and baseline comorbidity status. Results were adjusted for the propensity to receive more-intense acid-suppressive therapy. B, Pair-wise cohort analysis matched for propensity score. Three pairs of cohorts matched by propensity score were analyzed (no acid suppression/H_2RA only; no acid suppression/daily PPI; and no acid suppression/PPI more frequently than daily). Results were also adjusted for antibiotic therapy, age, sex, and baseline comorbidity status. C, Nested matched case-control analysis. 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 infection. Matching criteria included diagnosis related group, Charlson index with caliper of 1 point, age with caliper of 5 years, and propensity score. Conditional logistic regression with adjustment for comorbidities and sex was fitted. H_2RA indicates H_2-receptor antagonist; PPI, proton pump inhibitor. Error bars represent 95% confidence intervals.

mates.[33-35] Since there are about 32.7 million annual adult discharges in the United States annually,[36] the number of potentially attributable nosocomial *C 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 prescriptions are not strictly indicated.[33-35]

In conclusion, we found that the intensity of acid-suppressive therapy was strongly and independently associated with the development of nosocomial *C difficile* infection. Although determining causality is an extremely complex process,[18] it seems unlikely that a randomized controlled trial of acid suppressive therapy, with a primary outcome of nosocomial *C difficile* infection, will ever be conducted. Our study therefore adds new key information about the dose-response relationship between acid-suppressive medications and nosocomial *C difficile* infection. Given the importance of nosocomial *C difficile* infection to individual patient outcomes, hospitals, health systems, and physicians can take several reasonable, important steps even in the absence of randomized controlled trials. First, physicians should ensure that each patient receives the least-intense acid-suppressive therapy that is appropriate for his or her clinical condition. In particular, unless and until there is clear evidence that low-risk, noncritically ill patients receive benefit from stress ulcer prophylaxis,[37] we should strive to minimize exposure to acid-suppressive medications in this group. Many intensive care unit patients are also at low risk for clinically significant gastrointestinal tract bleeding,[38] and guidelines have not recommend prophylaxis for these patients.[39] Hospitals can also take an important step in this regard by re-examining any standing protocols for low-risk patients that include stress ulcer prophylaxis by default and by ensuring that prophylactic medications are not continued beyond discharge.[40-42] Finally, future interventional trials of acid-suppressive medications in inpatients should actively collect information about incident *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.

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