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ORIGINAL ARTICLE

Proton Pump Inhibitors and the Risk for Hospital-Acquired *Clostridium difficile* Infection

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Abstract

Objective: To examine the relationship between proton pump inhibitor (PPI) usage and nosocomial *Clostridium difficile* infection (CDI) and determine the duration of therapy at which CDI risk increases.

Patients and Methods: This retrospective case-control study included consecutive adult patients in whom nosocomial CDI developed after hospitalization for 3 or more days at one of 2 affiliated hospitals between June 1, 2010, and October 31, 2011. These patients were matched to patients hospitalized within 6 months who did not have CDI development in a 1:2 ratio using age, sex, and antibiotic usage. Potential risk factors for CDI, including PPI use and duration, were evaluated. Multivariate analysis was performed to control for confounding variables and identify risk factors.

Results: A total of 201 patients were evaluated, 67 with CDI and 134 matched controls. Patients in whom CDI developed were more likely to have received a PPI (76% vs 39%; $P<.001$) and had a longer duration of PPI therapy (median [range], 5 [0-20] days vs 0 [0-11] days; $P<.001$) than those who did not have CDI development. After controlling for prior hospital admission, intensive care unit admission, admission from a skilled nursing facility, immunosuppression, number of antibiotics received, PPI duration, and time to event via multivariate analysis, PPI duration was found to be a risk factor for CDI (odds ratio, 1.14; 95% CI, 1.02-1.27; $P=.018$). The probability for CDI was higher when PPI use exceeded 2 days in patients without a prior hospital admission and 1 day in patients with a prior admission.

Conclusion: The duration of PPI therapy is significantly associated with CDI. Clinicians should strongly consider restricting PPI use given the short exposure time associated with this increased risk.

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Clostridium difficile is the leading cause of nosocomial infectious diarrhea, and its prevalence has increased substantially over the past 20 years.[1,2] Recent data from the Healthcare Cost and Utilization Project revealed 336,600 hospital stays associated with *C difficile* infection (CDI) in 2009 compared with 133,200 in 1999, a 3-fold increase in its occurrence.[3] Hospital-acquired CDI is associated with considerable morbidity and mortality and is estimated to contribute an added $13,675 per occurrence to hospital costs.[4,5] Thus, prevention of CDI has become an important goal in the acute care setting.[6]

Several interventions have been proposed to control the spread of CDI in the inpatient setting,[7] including improved hand hygiene, isolation of infected patients, enhanced room sanitation, and antimicrobial stewardship. Recently, acid-suppressive agents such as proton pump inhibitors (PPIs) and histamine 2 receptor antagonists (H2RAs) have been identified as potential risk factors for CDI. In fact, one report noted an increased risk for nosocomial CDI with increasing levels of pharmacological acid suppression defined by agent (H2RA vs PPI) and frequency of administration (daily vs other).[8] It was therefore recommended that clinicians use the least intensive acid-suppressive therapy and only when it is truly indicated. Nevertheless, the administration of acid-suppressive agents for stress ulcer prophylaxis (SUP) is widely utilized even in patients at low risk for clinically important gastrointestinal bleeding. In fact, approximately 50% to 60% of patients outside the intensive care unit (ICU) setting receive medications for SUP.[9-12] Furthermore, PPIs have become the predominant agent of choice despite the lack of randomized studies illustrating superiority over H2RAs.[13,14]

As institutions aim to reduce inappropriate medication usage and avoid untoward adverse drug events, the relationship between PPIs and CDI must be further explored. Although

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intensive acid suppression appears to be associated with CDI, most patients receive a standard daily dose of PPI as part of an SUP regimen. The level of risk specifically associated with the inpatient duration of PPI therapy has not been evaluated. We sought to examine the relationship between PPI usage and hospital-acquired CDI and determine if there is a specific duration of PPI use at which CDI becomes more prominent.

PATIENTS AND METHODS

Study Population

This study was conducted at 2 affiliated community hospitals. Institutional review board approval was obtained before study initiation. Consecutive adult patients in whom hospital-acquired CDI developed between June 1, 2010, and October 31, 2011, were retrospectively identified using an institutional database within the Department of Infection Control. *Hospital-acquired CDI* was defined as CDI acquired within the hospital at least 48 hours after admission.[6] Patients were included if they were 18 years of age or older and had a hospital length of stay of at least 72 hours. Patients were excluded if they had community-acquired CDI or a history of CDI within the preceding 90 days. These patients were matched in a 1:2 ratio to patients admitted within 6 months who did not have CDI development using the criteria of age (±5 years), sex, and the use of antibiotics. To identify controls, all patients without CDI who were admitted during the study period were reviewed for inclusion/exclusion criteria. Those who met inclusion and exclusion criteria were sorted on the basis of sex, age, and date of admission. Patients who were potential matches using the aforementioned criteria were then reviewed for antibiotic therapy. Receipt of one or more doses of any systemic antimicrobial agent was coded as "yes."

All patients meeting inclusion criteria and successfully matched were reviewed for demographic characteristics, medication history, comorbidities, and other potential confounding variables for CDI. These variables included PPI utilization (agent, dose, and duration), alternative acid-suppressive therapy (ie, H2RA), location (ICU vs non-ICU), hospital admission within the preceding 30 days, diabetes, malignancy (active cancer and/or receiving chemotherapy), renal failure, gastrointestinal disease (eg, ulcerative colitis, Crohn disease), immunosuppression (receipt of immunosuppressant drug therapy for posttransplant patients, lupus, rheumatoid arthritis, human immunodeficiency virus/AIDS, or receipt of greater than 10 mg prednisone equivalence), number of antibiotics received, antibiotic duration, and receipt of a high-risk antibiotic. Antibiotics considered as high risk for CDI were clindamycin, cephalosporins, fluoroquinolones, and carbapenems. Data collection stopped either when the diagnosis of CDI was confirmed (via a positive laboratory assay result) or the patient was discharged from the hospital.

Statistical Analyses

To determine the relationship between PPIs and CDI, patients were stratified into 2 groups on the basis of the presence or absence of CDI. Confounding variables were compared between groups using univariate statistics. To further examine the relationship of PPIs and antibiotics with CDI, subgroups were formed on the basis of the duration of PPI therapy, and the number of antibiotics received and the incidence of CDI was reported.

Data are presented as mean ± SD, median (range), or number (percentage). To compare continuous data, the Student *t* test was used if data were normally distributed, and the Mann-Whitney *U* test was used for data that were skewed. To analyze dichotomous variables, the Pearson χ^2 test or Fisher exact test was used as appropriate. Variables identified through univariate analysis with a value of $P<.10$ were considered for inclusion in a multivariate analysis. Conditional logistic regression modeling with a backward stepwise elimination procedure was performed with variables having a value of $P<.05$ retained as independent risk factors for CDI. To determine the duration of PPI use that was most strongly associated with CDI, classification and regression tree analysis was performed using the risk factors identified through multivariate testing. $P<.05$ was considered statistically significant. SPSS, version 19.0 (SPSS Inc), was used for all analyses.

RESULTS

A total of 201 patients were evaluated, 67 with CDI and 134 matched controls; the median (range) study duration for the entire study population was 7 (3-43) days (Table 1). The number

TABLE 1. Demographic Characteristics of the Study Population and Confounding Variables Associated With CDI[a,b]

Variable	Total population (N=201)	Patients without CDI (n=134)	Patients with CDI (n=67)	*P* value[c]
Age (y)	71±22	72±25	70±14	.65
Male sex	75 (37)	50 (37)	25 (37)	>.99
Admitted from skilled nursing facility	25 (12)	9 (7)	16 (24)	.001
Hospital admission within the previous 30 d	47 (23)	19 (14)	28 (42)	<.001
ICU admission	53 (26)	26 (19)	27 (40)	.002
Diabetes	67 (33)	47 (35)	20 (30)	.46
Cancer	14 (7)	9 (7)	5 (7)	.85
Acute kidney injury	4 (2)	3 (2)	1 (1)	>.99
Chronic kidney disease	32 (16)	22 (16)	10 (15)	.79
Ulcerative colitis/Crohn disease	4 (2)	1 (1)	3 (4)	.11
Immunosuppression	5 (2)	1 (1)	4 (6)	.04
PPI use in hospital	103 (51)	52 (39)	51 (76)	<.001
Duration of PPI therapy (d)	1 (0-20)	0 (0-11)	5 (0-20)	<.001
Standard PPI dosing regimen[d]	88/103 (85)	46/52 (88)	42/51 (82)	.38
PPI exposure in previous 30 d	64 (32)	29 (22)	35 (52)	<.001
H2RA use in hospital	45 (22)	30 (22)	15 (22)	>.99
H2RA duration (d)	0 (0-15)	0 (0-15)	0 (0-13)	>.99
Antibiotic duration (d)	5 (1-20)	4 (1-15)	6 (1-20)	<.001
High-risk ABX	167/195 (86)	112/130 (86)	55/65 (85)	.77
ABX exposure in previous 30 d	59 (29)	28 (21)	31 (46)	<.001
Total number of antibiotics given	2 (1-7)	2 (1-6)	3 (1-7)	<.001
Study duration (d)	7 (3-43)	6 (4-16)	8 (3-43)	<.001

[a]ABX = antibiotic therapy; CDI = *Clostridium difficile* infection; H2RA = histamine 2 receptor antagonist; ICU = intensive care unit; PPI = proton pump inhibitor.
[b]Data are presented as mean ± SD, median (range), or No. (percentage) of patients.
[c]*P* value comparing patients with and without CDI.
[d]Standard PPI dosing regimen refers to the common dose listed in tertiary references.

of patients evaluated at the 2 hospitals was 153 (76%) and 48 (24%). The average difference in admission dates between the cases and matched controls was 37±36 days. Of the 201 patients evaluated, 103 (51%) received a PPI, most commonly pantoprazole (in 86 of 103 patients [83%]). Eighty-eight of the 103 patients (85%) received typical dosage regimens listed in tertiary references (ie, pantoprazole, 40 mg/d; lansoprazole, 30 mg/d; omeprazole, 40 mg/d; esomeprazole, 40 mg/d). Five patients received intermittent doses (administered twice daily) that were higher than typical dosage regimens, 2 received a continuous infusion, and 8 received lower than typical doses. A total of 195 patients (97%) received an antibiotic, 167 (86%) of whom received a high-risk antibiotic.

Proton pump inhibitor use was higher in patients in whom CDI developed (51 of 67 [76%]) compared with patients who did not have CDI (52 of 134 [39%]; *P*<.001). Univariate analysis identified several possible confounding variables associated with CDI, including in-hospital PPI use and duration of PPI therapy (median [range], 5 [0-20] days vs 0 [0-11] days for those with and without CDI, respectively; *P*<.001) (Table 1). The matrix illustrating the incidence of CDI stratified by duration of PPI and total number of antibiotics received is displayed in Figure 1. The incidence of CDI increased significantly as PPI duration increased within each group for total number of antibiotics received (0 to 1, 2 to 3, 4 or more). However, no significant difference in CDI was noted as total number of antibiotics increased within each group for PPI duration.

On inclusion of potential compounding variables (prior hospitalization within 30 days of the current admission, ICU admission, admission from a skilled nursing facility, immunosuppression, total number of antibiotics received, and duration of PPI therapy) into a multivariate analysis and controlling for study duration (ie, time to event or discharge), duration of PPI therapy was retained as a risk factor for CDI (odds ratio [OR], 1.14; 95% CI, 1.02-1.27; *P*=.018) (Table 2). Using these risk factors

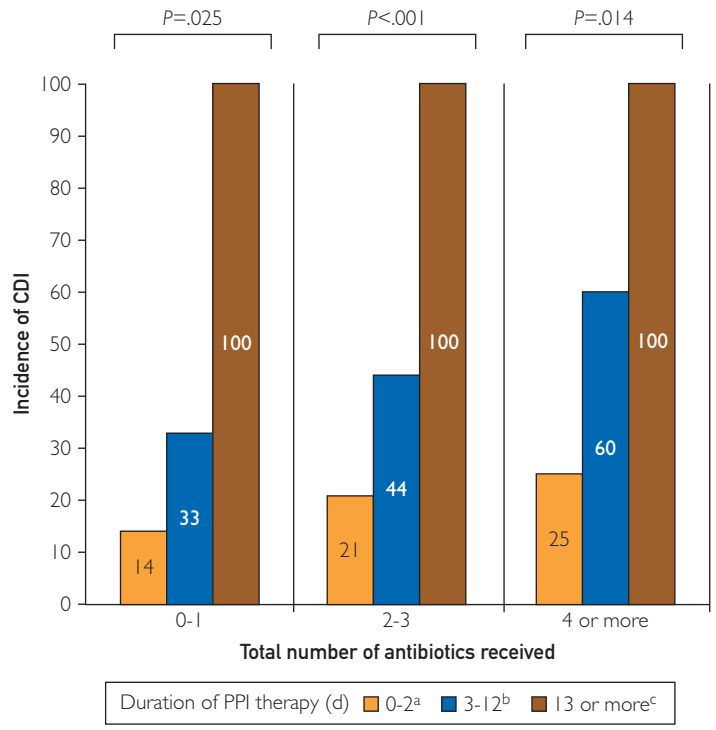

FIGURE 1. Incidence of *Clostridium difficile* infection (CDI) characterized by duration of proton pump inhibitor (PPI) usage and total number of antibiotics received. *P* values above each bar represent comparisons of duration of PPI therapy within each group for total number of antibiotics received. For comparisons between total number of antibiotics received within each group for duration of PPI therapy: [a]*P*=.579 for comparison of total number of antibiotics received within the cohort of patients receiving 0 to 2 days of PPI therapy; [b]*P*=.317 for comparison of total number of antibiotics received within the cohort of patients receiving 3 to 12 days of PPI therapy; [c]*P*>.99 for comparison of total number of antibiotics received within the cohort of patients receiving 13 or more days of PPI therapy.

in a classification and regression tree analysis, PPI use for more than 2 days and more than 12 days were identified as thresholds at which the acquisition of CDI increased for those patients without a prior hospital admission (Figure 2). For patients with a prior hospital admission, PPI use for greater than 1 day was identified as the threshold at which CDI increased.

TABLE 2. Multivariate Analysis of Risk Factors for *Clostridium difficile* Infection, Adjusted for Study Duration

Variable	Odds ratio (95% CI)	*P* value
Admitted from a skilled nursing facility	4.23 (1.51-11.86)	.006
Hospital admission within the previous 30 d	5.35 (2.32-12.35)	<.001
Intensive care unit admission	2.29 (0.99-5.32)	.054
Immunosuppression	15.48 (1.41-170.35)	.025
Duration of proton pump inhibitor use	1.14 (1.02-1.27)	.018

DISCUSSION

Acid-suppressive agents, particularly PPIs, are commonly prescribed for the prevention of stress-induced clinically important bleeding in hospitalized patients despite the lack of evidence supporting their need in low-risk patients. In fact, up to 60% of patients receive acid-suppressive agents for SUP in a non-ICU setting in which the risk for clinically important bleeding is less than 0.2%.[9,10,12,15] The rationale for the widespread use of these agents is unclear, but the perception of a safe adverse effect profile has been proposed.[16]

This study revealed that PPIs are independent predictors for the development of CDI, a finding that challenges prior justification for indiscriminant use of acid-suppressive therapy. Hospital-acquired CDI is associated with a 3-fold increase in mortality and attributable costs that approach $14,000 per occurrence.[4,5] Furthermore, we have identified duration of therapy as an important variable contributing to CDI, with a higher incidence occurring when PPI use exceeded 2 days and 12 days. For patients with a recent hospital admission, that threshold is likely lower. These findings add to the existing literature that has suggested a link between PPIs and CDI but did not stratify risk on the basis of duration of therapy. It also provides a window of opportunity for clinicians to intervene and reduce unnecessary PPI use before adverse drug events become more common.

Other studies have investigated the role of PPI therapy as a risk factor for development of CDI in inpatient settings.[8,17-19] One study identified age (OR, 1.02; 95% CI, 1.00-1.04), antibiotic use (OR, 5.25; 95% CI, 2.15-12.82), and PPI use (OR, 2.64; 95% CI, 1.71-4.09) as independent risk factors for health care–associated CDI.[19] The timing and duration of PPI use in that study was unknown because all medication use was characterized on the basis of use within 8 weeks before or during hospitalization. A second study noted an increased risk for nosocomial CDI as the intensity of acid suppression increased.[8] Specifically, the ORs reported were 1.53 (95% CI, 1.12-2.1) for H2RA therapy, 1.74 (95% CI, 1.39-2.18) for daily PPI therapy, and 2.36 (95% CI, 1.79-3.11) for more frequent PPI administration vs no acid suppression. Because most patients who received PPIs in our study were given daily doses as recommended in common tertiary references, we were unable

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to detect differences in risk based on dose. Given the dose-response relationship that exists between gastric pH and PPIs and the proposed mechanism for the acquisition of CDI, it is likely that both dose and duration contribute to the development of CDI.

The association between antibiotic use and CDI has been well described, and the increased risk with concomitant PPI therapy has been reported. In one meta-analysis, the OR (95% CI) for CDI with antibiotics was 1.97 (1.29-3.01) and that for PPI use (alone) was 1.82 (1.5-2.21). When the combined use of PPIs and antibiotics was considered, the OR (95% CI) was 3.44 (2.43-4.87).[20] Furthermore, the number needed to harm for the administration of a PPI to a hospitalized patient receiving antibiotics was 28. In a second study, the incidence of CDI was approximately twice that reported in patients receiving a high-risk antibiotic and daily PPI therapy vs those who received a high-risk antibiotic and no PPI.[8] In our study, most patients (97%) received antibiotics, and most of the antibiotics administered were considered high risk. Interestingly, results from our univariate analysis identified the total number of antibiotics received as a potential predictor for CDI, but this finding was not significant through multivariate modeling. Furthermore, an increase in CDI was not observed when the total number of antibiotics increased in subgroups stratified by duration of PPI use (0 to 2, 3 to 12, and 13 or more days). In contrast, when subgroups were formed according to the total number of antibiotics received (0 to 1, 2 to 3, 4 or more), a significant increase in CDI was detected as PPI use became more prolonged. This finding suggests that PPI use may be a driving factor behind the acquisition of CDI and emphasizes the increased potential for patient morbidity independent of antibiotic use.

Our study revealed that the risk for CDI increases after 2 days of PPI therapy and potentially sooner in patients with a previous hospital admission. Because many patients receive unwarranted acid-suppressive therapy and PPIs have become the most common agent prescribed, it is necessary for clinicians to reevaluate their practices. The perception that PPIs do not cause harm is false and should no longer be used to justify the widespread use of these agents, especially in the absence of high-quality clinical trials illustrating their superiority to H2RAs for SUP. Until randomized controlled trials document PPI superiority, we propose that a moratorium be placed on their use for SUP and that clinicians strongly consider the necessity for initiating PPI therapy for other indications. Clinical pharmacists and quality-improvement specialists (who routinely track adherence to core measures) should assure that acid-suppressive agents are used appropriately (ie, that SUP is provided only to high-risk patients) and that PPI use for that indication is discouraged. We encourage the use of therapeutic interchange programs and institutional guidelines, which have been reported to improve both clinical and economic outcomes.[21-24]

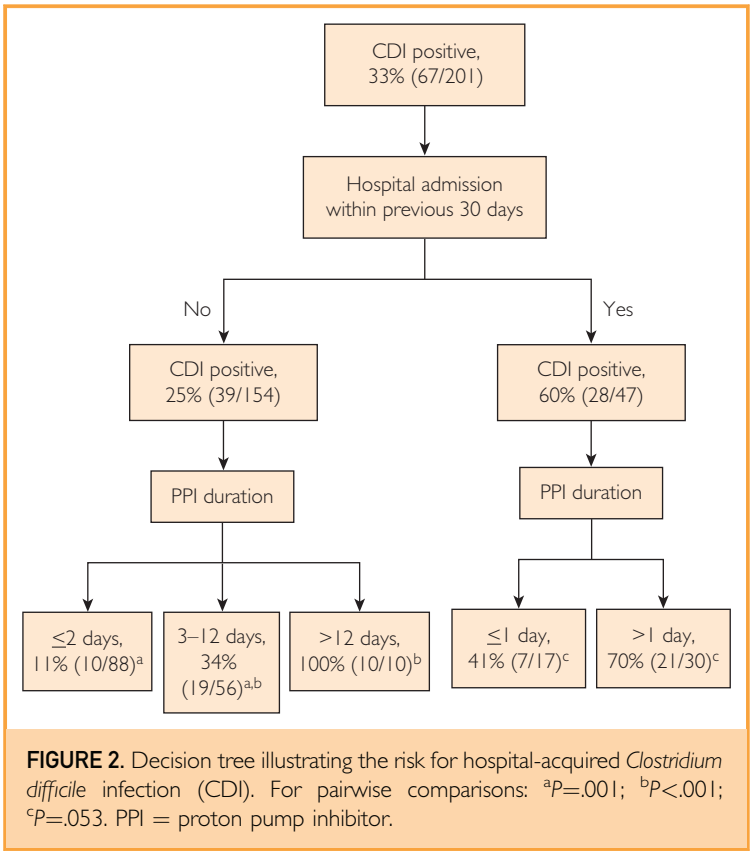

FIGURE 2. Decision tree illustrating the risk for hospital-acquired *Clostridium difficile* infection (CDI). For pairwise comparisons: [a]*P*=.001; [b]*P*<.001; [c]*P*=.053. PPI = proton pump inhibitor.

Our study has some limitations, the first of which is the case-control design and sample size. Although a randomized, placebo-controlled trial is the best design to examine the relationship of PPI and CDI, it is unlikely that one will ever be performed given the low incidence of hospital-acquired CDI (<1%). A second limitation is the differences between the patients who had CDI and those who did not. Although we matched our control group using 4 specific criteria, several

differences were identified that may impact the resulting statistics; thus, it is possible that the severity of illness was greater in the patients with CDI. We did attempt to control for these factors via multivariate analysis. A third limitation is the possibility of confounding variables that were not examined in our study. Although confounding variables were chosen after an exhaustive search of the literature, the potential for oversight and exclusion does exist.

CONCLUSION

Proton pump inhibitor use may contribute considerably to the development of hospital-acquired CDI. There are 3 tiers for risk characterized by the duration of PPI therapy: (1) PPI use for 2 days or less, (2) PPI use for 3 to 12 days, and (3) PPI use for 13 days or more. This initial threshold at which risk increases may occur sooner for patients who had a prior hospitalization within 30 days of the current admission. Hospitals should implement measures to restrict PPI use to appropriate indications given the unlikelihood that indiscriminant prescribing will be identified and addressed before patients are put at an increased risk for development of CDI.

Abbreviations and Acronyms: **CDI** = *Clostridium difficile* infection; **H2RA** = histamine 2 receptor antagonist; **ICU** = intensive care unit; **OR** = odds ratio; **PPI** = proton pump inhibitor; **SUP** = stress ulcer prophylaxis

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