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ORIGINAL CONTRIBUTIONS

Colon/Small Bowel

Gastric Acid Suppression by Proton Pump Inhibitors as a Risk Factor for *Clostridium difficile*-Associated Diarrhea in Hospitalized Patients

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BACKGROUND: Evidence for the association between *Clostridium difficile* (*C. difficile*) and the use of proton pump inhibitor (PPI) is unclear. This study investigated the relationship between *Clostridium difficile*-associated diarrhea (CDAD) and exposure to acid suppressive therapy in hospitalized adult patients while controlling for the most common predisposing risk factors.

METHODS: A retrospective case-control study was conducted at a local hospital of all hospitalized patients between October 1, 2005 and September 30, 2006 who developed CDAD during hospitalization. Subjects were determined to have CDAD if there was a positive *C. difficile* toxin and clinical correlation of diarrhea at the time of diagnosis. Subjects were pair-matched to controls on the following factors: admission date, antibiotic exposure, gender, age groups, patient location (medical or surgical unit), and room type at time of admission. Seven risk factors were assessed for association with onset of CDAD: exposure to PPIs or H_2-blockers, renal failure, diabetes mellitus, immunosuppression, malignancy, and gastrointestinal disease.

RESULTS: Ninety-four cases were successfully matched to controls. Cases were more likely than controls to receive acid suppressive therapy during hospitalization, 72 (76.6%) *versus* 40 (42.6%), respectively, $P = 0.030$. In a multivariate exact conditional logistic regression analysis, CDAD was associated with use of PPI (odds ratio [OR] = 3.6, 95% confidence interval [CI] = 1.7–8.3; $P < 0.001$), and with renal failure (OR = 5.7, CI = 1.3–39.1; $P = 0.02$).

CONCLUSION: This study showed elevated risk of developing CDAD in hospitalized patients with acid suppressive therapy, especially when PPIs were used.

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INTRODUCTION

Clostridium difficile (C. difficile) is a Gram-positive anaerobic spore-forming bacterium that is responsible for the most common cause of hospital-acquired diarrhea in developed countries with an incidence of 0.1–2% (1, 2). Toxin production from this pathogen is believed to be the main risk factor for nosocomial diarrhea (3). The incidence of *Clostridium difficile*-associated diarrhea (CDAD) is increasing and is associated with significant mortality, morbidity, increased length of hospital stay, and health-care costs (3–7). A prospective observational study by Kyne *et al*. found the development of CDAD in hospitalized patients is associated with increased length of hospital stay (by 3.6 days), resulting in additional health-care costs of more than $3,600 per patient (7). The clinical manifestation of CDAD ranges from asymptomatic carrier state to life-threatening conditions including toxic megacolon, colonic perforation, and death (8).

The most common risk factor for developing CDAD identified in the literature is the use of antimicrobial agents, particularly multiple treatment courses and/or broad-spectrum agents including clindamycin, cephalosporins, and quinolones (9–13). Other CDAD risk factors have been described and include advanced age, severe underlying illness, hospitalization, exposure to cytotoxic chemotherapy, and immunosuppressive treatment (2, 12, 14, 15).

Recent literature suggests the possibility of an association between the use of proton pump inhibitors (PPIs) and *C. difficile* infection in hospitalized patients, although results appear to be conflicting (16–24). A potential mechanism for this phenomenon is inhibition of gastric acidity resulting in the loss of a defense mechanism against ingested spores and bacteria. Having higher gastric pH than normal facilitates the survival of *C. difficile* spores and their toxins while in the vegetative state by affecting leukocyte function (16, 25). Moreover, recent data suggest that PPI prescribing has increased over the last few years, and PPIs are now among the most widely prescribed class of medications in the United States (26, 27). In many cases, PPIs are continued during subsequent hospital admissions without evaluating the necessity

of continuing such therapy, a factor that may have contributed to the increased occurrence of CDAD (26). The objective of this study was to investigate whether the use of gastric acid suppressive agents was associated with an increased risk of CDAD development in our hospital.

METHODS

After receiving approval from the local Institutional Review Board (IRB) in December 2006, a retrospective case-control analysis of patients admitted to Wesley Medical Center (WMC) was performed by utilizing patients who developed CDAD during hospitalization. WMC is a tertiary care teaching facility with a total of 760 licensed beds and 104 bassinets. Consecutive subjects selected had a positive *C. difficile* toxin between October 1, 2005 and September 30, 2006.

Cases included subjects who were identified as *C. difficile* toxin positive by Premier Toxin A and B enzyme immunoassay (Meridian Bioscience, Inc., Cincinnati, OH), had a new onset of two or more loose bowel movements per day after admission, were in the hospital for at least 3 days, and were at least 18 yr of age. Exclusion criteria for subjects in the case group included age less than 18 yr, history of CDAD in the previous 3 months, or immediate diagnosis of CDAD at the time of admission. A separate report was generated for the control group to identify subjects who were at least 18 yr of age, were in the hospital for at least 3 days, and did not have a positive *C. difficile* toxin. Subjects who experienced diarrhea during hospitalization were excluded from the control group to eliminate any suspicion of *C. difficile* infection that may have existed without confirmatory testing.

Each subject in the case group was matched to a subject in the control group in a 1:1 ratio based on the following factors: (a) date of hospital admission ($\pm$7 days); (b) antibiotic use (type, number, and duration); (c) gender; (d) age groups ($<$50, 50–60, 61–70, $>$70 yr old); (e) patient location at the time of admission (medical units or surgical units); (f) room type at the time of admission (private or semi-private). The first four factors were previously associated with an increased risk of *C. difficile* diarrhea in hospitalized patients from other studies (10–12). The patient's location and room type at the time of admission were other factors that were matched; these are considered to be important environmental factors as *C. difficile* spores may be transmitted from patients to patients by the hands of health-care workers and can survive and stay on hospital surfaces for months (28). CDAD was continuously monitored and no outbreak was identified during the study timeframe in our hospital.

Since antibiotic exposure is considered to be the most common risk factor for CDAD, antibiotic exposure was broken down into three classifications (antibiotic number, antibiotic type, and antibiotic duration) for matching purposes:

1. Number of antibiotics used by subjects during hospitalization and before the development of CDAD was comprised of four groups: no antibiotic exposure, one antibiotic, two antibiotics, and three or more antibiotics. Published data have indicated a single dose of an antibiotic can alter normal colonic microflora (29). Therefore, any antibiotic administered was taken into account, including single doses.
2. Type of antibiotic administered during hospitalization and before CDAD development was classified into three different groups. The first group included those patients who were not exposed to antibiotics while hospitalized; the second group of patients had been exposed to high-risk antibiotics defined as receiving one or more of the following antibiotics: clindamycin, cephalosporins or quinolones. The third group included patients who received antibiotics classified outside of the high-risk group.
3. Length of antibiotic use in days was categorized as: none, 1–3 days, greater than 3 days.

Exposure to gastric acid suppression (PPIs or H_2-blockers) was considered if one of the following conditions occurred: (a) Exposure occurred before admission based on the admission medication history and was continued during the hospital stay and before CDAD development. (b) Exposure occurred at least 3 days before development of CDAD as an inpatient.

The primary outcome of this study was to determine the relative risk of CDAD associated with PPIs use in hospitalized patients. Secondary outcomes measured the relative risk of other factors associated with CDAD in previous studies, including H_2-blockers and comorbid conditions including: (a) diabetes mellitus (DM); (b) renal failure (RF); (c) malignancy; (d) immunosuppression; and (e) gastrointestinal diseases (ulcerative colitis, Crohn's disease, or inflammatory bowel syndrome) (Appendix).

Sample Size and Statistical Analysis

To determine the sample size, a power analysis for dichotomous variables was conducted in *PS* version 2.1.31, following Dupont (31). Previous results from two studies, Dial *et al*. (16), and Yearsley *et al*. (17), were used to simulate sample sizes required for potential number of controls to be matched with cases. Two types of ratios were explored: levels of control to case matching ratios (1:1, 2:1, 3:1, 4:1, and 10:1) and odds ratios (1.5, 2.0, 2.5, 3.0, and 3.5). To determine appropriate ratios for the study, we assessed CDAD frequency in hospitalized patients, then followed Dial *et al*. (16) for 1:1 matching with an odds ratio of 3.0. Power analysis results for a 2-sided test with $\alpha = 0.05$ showed that approximately 90 participants per group were required to achieve 80% power to detect a significant difference between groups, for pair-matched case to controls when the odds ratio was 3.0.

To measure the association between CDAD in hospitalized patients and the primary and secondary factors, we conducted McNemar's test for matched pair data along with univariate and multivariate conditional logistic regression analysis (following Garson) (32) with SPSS, version 14 (SPSS Inc., Chicago, IL). Multivariate exact conditional logistic regression was conducted with LogXact 7 (Cytel Inc., Cambridge,

MA). LogXact 7 is statistical software for regression procedures featuring exact methods, which is specifically formulated to handle small samples and sparse data. For the logistic model, this software offers unconditional maximum likelihood inference, conditional maximum likelihood inference, and conditional exact inference. Since data were sparse, especially for comorbid conditions, we used the conditional exact approach to confirm results. This approach is based on generating the exact permutation distribution of the sufficient statistics for the parameters of interest and conditioning on the observed values of the sufficient statistics for all the remaining parameters (33, 34).

RESULTS

One hundred seventy-eight subjects were identified from the microbiology records as C. *difficile* toxin positive in the study timeframe. Of these subjects, 84 were excluded for various reasons (Table 1). After excluding those patients from the initial report, 94 subjects who met the definition of the case group were matched to controls based on the matching criteria reported in methods.

The study included 188 subjects, with 94 cases and 94 controls. Table 2 summarizes patients' characteristics and assesses the proportions within matching factors per group: antibiotic use, gender, age in groups, patient location at the time of diagnosis, and room type. As expected, there were no statistically significant differences between group proportions, although three incomplete matches occurred for patient location and room type. Note the majority of cases were exposed to antibiotics, female (56%), more than 70 yr old (44%), located in a medical unit (78%), and were in private rooms (73%).

Results from McNemar's test for association between gastric acid suppression therapy and CDAD were significant, $P = 0.030$: exposure was more likely in cases compared to controls, 72 (76.6%) *versus* 40 (42.6%), respectively. Table 3 displays discordant pairs for potential risk factors of CDAD and summarizes univariate associations; both PPI and renal failure were significant, $P < 0.001$ and 0.035, respectively.

Table 1. Subjects with *C. difficile* Toxin Positive Who Were Excluded From the Study

Reasons for Exclusion	Number of Subjects
Were not hospitalized	21
Less than 18 yr old	10
Had a diagnosis of CDAD within the previous 3 months	11
Did not have diarrhea with *C. difficile* toxin positive	2
Admitted with diarrhea resulting in an immediate diagnosis of CDAD	40
Total	84

Table 2. Distribution of Matching Factors for CDAD Case-Control Pairs

Factor	Case (%) N = 94	Control (%) N = 94	*P* Value*
Antibiotic Type			
No antibiotic exposure	4 (4.3)	4 (4.3)	NS
Not a high-risk antibiotic	10 (10.6)	10 (10.6)	NS
High-risk antibiotic	80 (85.1)	80 (85.1)	NS
Antibiotic Number			
One antibiotic	22 (23.4)	22 (23.4)	NS
Two antibiotics	25 (26.6)	25 (26.6)	NS
Three or more antibiotics	43 (45.7)	43 (45.7)	NS
Antibiotic Duration			
1–3 days	31 (33.3)	31 (33.3)	NS
Greater than 3 days	59 (62.7)	59 (62.7)	NS
Gender			
Male	41 (43.6)	41 (43.6)	NS
Female	53 (56.4)	53 (56.4)	NS
Age Group			
Less than 50 yr	21 (22.3)	21 (22.3)	NS
50–60 yr	18 (19.1)	18 (19.1)	NS
61–70 yr	14 (14.9)	14 (14.9)	NS
More than 70 yr	41 (43.6)	41 (43.6)	NS
Patient Location			
Surgical unit	20 (21.3)	23 (24.5)	0.761
Medical unit	74 (78.7)	71 (75.5)	0.868
Room Type			
Private room	69 (73.4)	67 (71.3)	0.932
Semi-private room	25 (26.6)	27 (28.7)	0.890

*Binomial test based on Z approximation.
NS = no significant differences between group proportions.

Matched odds ratios were calculated for risk factors with single variable conditional logistic regression (Table 4**)**. The odds of CDAD increased in both PPI and H_2-blocker: threefold among cases exposed to PPIs compared to controls who were not (OR 3.08, 95% CI 1.61–5.91) and more than twofold for H_2-blockers (OR 2.14. 95% CI 0.87–5.26). Also, the odds of CDAD were increased fourfold among patients with renal failure (OR 4.00, 95% CI 1.13–14.18), although the sample sizes were small (cases 14, controls 5).

Table 3. Potential Risk Factors for CDAD Case-Control Pairs

		Control Group (N = 94)		
Case Group (N = 94)		Yes	No	*P* Value*
PPI	Yes	24	37	
	No	12	21	<0.001
H_2-blocker	Yes	2	15	
	No	7	70	0.134
Renal failure	Yes	2	12	
	No	3	77	0.035
Diabetes mellitus	Yes	13	15	
	No	18	48	0.728
Immunosuppression	Yes	7	21	
	No	13	53	0.229
Malignancy	Yes	1	10	
	No	7	76	0.629
Gastrointestinal disease	Yes	0	4	
	No	1	89	0.375

*McNemar test; exact significance (2-sided) using Binomial distribution.

Table 4. Potential Risk Factors for CDAD Case-Control Pairs (Univariate Analysis)

Variable	Cases (%) N = 94	Controls (%) N = 94	OR Matched*	95% CI
PPI	61 (62.9)	36 (37.1)	3.08	1.61–5.91
H_2-blocker	17 (65.4)	9 (34.6)	2.14	0.87–5.26
Renal failure	14 (73.7)	5 (26.3)	4.00	1.13–14.18
Diabetes mellitus	28 (47.5)	31 (52.5)	0.83	0.42–1.65
Immunosuppression	28 (58.3)	20 (41.7)	1.62	0.81–3.23
Malignancy	11 (57.9)	8 (42.1)	1.43	0.54–3.75
Gastrointestinal disease	4 (80.0)	1 (20.0)	4.00	0.45–35.79

Based on single variable conditional logistic regression analysis.
*Matched on: date, gender, age group, antibiotic exposure, patient location, and room type.

To determine which risk factors were significant predictors of CDAD, exploratory multivariate conditional logistic regression (*e.g.*, Cox Regression for matched pair data stratified by patient) was conducted in SPSS. Results from forward stepwise, Likelihood Ratio process, indicated that PPI, H_2-blocker, and renal failure were potentially important determinants of CDAD, –2 Likelihood = 105.9, $\chi^2 = 21.5$, $P < 0.0001$. Because data were sparse for these three risk factors, multivariate exact conditional logistic regression was conducted in LogXact. Results indicated hospitalized patients exposed to PPIs were 3.6 times more likely to develop CDAD. In addition, patients with prior diagnosis of renal failure were 5.7 times more likely to develop CDAD (Table 5).

DISCUSSION

Using the results from this hospital-based study, we found inpatients who received gastric acid suppression therapy were more likely to develop CDAD than inpatients that did not. Specifically, the odds of CDAD diagnosis significantly increased with PPI usage when controlling for the following factors: date of hospital admission, antibiotic use, gender, age, patient location, and room type. Our data indicated that inpatients receiving PPIs were 3.6 times more likely to develop CDAD, while inpatients previously diagnosed with renal failure are nearly 6 times more likely to develop CDAD. Although the sample size was small for the renal failure group, our evidence was strengthened by conducting exact conditional logistic regression.

We were unable to confirm an association between exposure to H_2-blockers and onset of CDAD. This agent was ordered less frequently than PPI during the study time frame; therefore, further investigation with H_2-blockers may be merited. Similarly, comorbid conditions of diabetes mellitus, immunosuppression, malignancy, and gastrointestinal disease did not show significant associations to CDAD. Sample sizes may have accounted for the lack of findings, especially in the group with gastrointestinal disease (4 cases with CDAD compared to only 1 control).

Table 5. Risk Factors for CDAD (Multivariate Analysis)

Variable	Odds Ratio	95% CI	*P* Value
PPI	3.6	1.73–8.26	<0.001
H_2-blocker	2.5	0.90–7.96	0.082
Renal failure	5.7	1.26–39.08	0.016

Based on multivariate exact conditional logistic regression.

The association of CDAD with gastric acid suppression has become increasingly evident over the last few years reflecting the high usage of these agents in hospitalized patients (35, 36). In many cases, patients receiving these agents do not have an appropriate indication for maintaining gastric acid suppression during hospitalization (36). Recent data suggest that gastric acid suppression is overused in hospitalized patients, and nearly 50% of hospitalized patients have inappropriate indications to be receiving therapy (35, 36).

The strength of this study exists in the matching process. By matching date of hospital admission, age, antibiotic exposure, gender, patient location, and room type, the most common risk factors identified in the literature to be associated with CDAD in hospitalized patients have been controlled. Minimal studies have taken environmental factors into considerations for infection control purposes and to control for any potential influence on the occurrence of CDAD. In addition, previously published data have been criticized for not controlling environmental factors (20). Therefore, we decided to control patient location and room type in this study to reduce these factors' contribution to the outcome. After controlling for these environmental factors, we found the majority of patients who developed CDAD were located on medical floors and were staying in private rooms. We expected to see the opposite results with patient room type, as those patients who share rooms with others may be more prone to this type of pathogen, but the possible reason that might explain this finding is most of our patients stay in private rooms, including all the intensive care unit (ICU) patients. The matching process of this study was very precise in terms of eliminating the confounding variables that may be associated with CDAD development. This may explain the results of our study, as we have reported higher odds ratio of PPI use with CDAD than other studies in the literature (17–20, 24).

Several studies recently published have urged all prescribers ordering PPIs to review the indication for use, evaluate the necessity of this treatment for every patient, and if there is no clear-cut indication for maintaining gastric acid suppression (such as active peptic ulcer or stress ulcer prophylaxis [SUP] for high-risk patients), then this treatment should be considered for discontinuation (35–37). From the baseline characteristics after matching, we were able to confirm the effect of age and antibiotic exposure as important risk factors for CDAD development in hospitalized patients. The proportion of patients who received high-risk antibiotics during their hospital stay was high (85% in the case group) and elderly (>70 yr old) patients represented 43.6% of the CDAD cases.

This study was retrospective and has all the limitations associated with this type of study. We were unable to identify

the length of PPI treatment for outpatients and the correlation with subsequent CDAD in the hospital. The matching process of case to control subjects for antibiotic exposure was done by antibiotic grouping, as it was difficult to match every antibiotic used in the case group to identical antibiotics for each patient in the control group. Moreover, the study did not control for duration of hospitalization between the case and control groups as it was difficult to match for so many factors and perhaps not find enough patients to be recruited in this study. Longer duration of hospitalization acts as marker for severity of illness and probably is a risk factor for CDAD development in hospitalized patients although it is not clearly stated in the CDAD literature. Finally, case-control studies are usually criticized due to selection bias that may occur when choosing the control subjects. We overcame this problem by randomly assigning a control subject to a subject in the case group when more than one control subject matched on all factors.

In conclusion, this hospital-based case-control study showed elevated risk of developing CDAD in hospitalized patients with acid suppressive therapy, especially when PPIs were used. In addition, renally impaired patients had a significant association with CDAD, a finding that may warrant further investigation.

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STUDY HIGHLIGHTS

What Is Current Knowledge

- *Clostridium difficile* (*C. difficile*) is the most common cause of nosocomial diarrhea.
- *Clostridium difficile*-associated diarrhea (CDAD) in hospitalized patients is associated with increased length of hospital stay and health-care costs.
- Evidence for the association between CDAD and the use of proton pump inhibitors (PPIs) is unclear.

What Is New Here

- Case-controlled study matched for the most common factors predisposing hospitalized patients to CDAD.
- Environmental factors were controlled between case and control subjects.
- Results of this study reported higher odds ratio of CDAD with PPI use than other studies published in the literature.

APPENDIX: DEFINITION OF OUTCOME MEASURES

Outcome	Definition
Diabetes mellitus (DM)	Subjects diagnosed with either type 1 or 2 DM using hypoglycemic agents (insulin or oral) to control blood sugar.
Renal failure (RF)	Subjects with glomerular filtration rate (GFR) <15 mL/min/1.73 m^2 or on dialysis per K/DOQI clinical practice guidelines or CrCl $<$ 15 mL/min calculated by using Cockcroft-Gault Formula (30).
Malignancy	Subjects who have active cancer and are on chemotherapy.
Immunosuppression	Post-transplant patients receiving immunosuppressant drug therapy; immunosuppressed patients such as those with HIV or AIDS, or with rheumatoid arthritis, or lupus receiving immunosuppressant drug therapy; corticosteroid use in doses $\geq$10 mg/day of prednisone or equivalent on admission or during hospitalization before CDAD development.
Gastrointestinal diseases	Subjects who have ulcerative colitis, Crohn's disease, or inflammatory bowel syndrome.

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CONFLICT OF INTEREST

Guarantor of the article: Mohammed Aseeri, B.Sc., Pharm.D.

Specific author contributions: Mohammed Aseeri was principal investigator, responsible for study design, institutional review board approval (IRB), data collection, data entry, and writing the manuscript. Todd Schroeder was responsible for assisting with study design, IRB approval, and writing the manuscript. Joan Kramer was responsible for assisting with study design, IRB approval, data entry, and manuscript writing. Rosalee Zackula was responsible for statistical analysis and involved in manuscript writing.

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