

Proton Pump Inhibitor Use Elevates the Risk of Severe Clostridium Difficile Colitis

Fyeza Haider, Naeem Raza, Michael Komar, Omar Rahman, Jennifer Sartorius, H. Lester Kirchner

Fyeza Haider, Naeem Raza, Michael Komar, Department of Gastroenterology, Geisinger Medical Center, Danville, PA 17821, United States
Omar Rahman, Adult Intensive Care Unit, Department of Critical Care Medicine, Geisinger Medical Center, Danville, PA 17821, United States
Jennifer Sartorius, Center for Health Research, Geisinger Medical Center, Danville, PA 17821, United States

H. Lester Kirchner, Division of Medicine, Geisinger Medical Center, Danville, PA 17821, United States

Correspondence to: Naeem Raza, Department of Gastroenterology, Geisinger Medical Center, Danville, PA 17821, United States. nrazal@geisinger.edu

Telephone: +1-570-271-6405 Fax: +1-570-271-6852

Received: January 10, 2012 Revised: March 26, 2012

Accepted: April 3, 2012

Published online: May 21, 2012

ABSTRACT

AIM: Gastric acid suppression is identified as a risk factor for Clostridium difficile infection (CDI). Our objective was to determine if the use of proton pump Inhibitors (PPI) are associated with increased severity of CDI (severe CDI).

METHODS: Retrospective analysis of hospitalized patients with CDI at Geisinger Medical Center was performed. Hospital admissions with CDI over an 8 year period (Jan 2001 to Oct 2009) were assessed for proton pump inhibitor (PPI)/histamine 2 receptor antagonist (H2RA) use, antibiotic (ABX) use, and features of severe CDI defined as two or more of the following within 5 days of a positive stool test (of index CDI): WBC>15 K or <4 K/ μ L, bacteremia >10%, shock (SBP< 90 mmHg), subtotal/total colectomy after index CDI, organ dysfunction (acute respiratory failure, acute renal failure, altered mental status or serum lactate>2.5 mmol/L). Death (30-day death attributed to CDI) was also analyzed.

RESULTS: 627 patients with CDI were divided into four groups: those on neither PPI nor H2RA, those on purely PPI blockers, those on purely H2RA blockers, and on both PPI and H2RA. Patients on PPI or H2RA were more likely to be on antibiotics (ABX) antibiotics within 90 days of CDI index case or vasopressors. Among all patients, 40% developed severe CDI. Unadjusted odds ratio (OR) of developing severe CDI for PPI was 1.91 (95% CI: 1.36, 2.69, $p=0.0002$), and for H2RA the OR was 0.66 (95% CI: 0.41, 1.05, $p=0.0770$). After controlling for confounders the effect of PPI was significantly elevated (OR=1.60, 95% CI: 1.09, 2.351) whereas the effect of H2RA was protective (OR=0.50, 95% CI: 0.31, 0.83). There

was no statistically significant difference in 30-day mortality by medication group.

CONCLUSIONS: Results suggest PPI use could lead to an elevated risk of developing severe CDI, while H2RA was found to decrease the risk of severe CDI. This study suggests limiting the indiscriminate use of PPI in hospitalized patients.

© 2012 Thomson research. All rights reserved.

Key words: Proton pump Inhibitors; Clostridium difficile infection

Haider F, Raza N, Komar M, Rahman O, Sartorius J, Kirchner HL. Proton Pump Inhibitor Use Elevates the Risk of Severe Clostridium Difficile Colitis. *Journal of Gastroenterology and Hepatology Research* 2012; 1(4): 53-56 Available from: URL: <http://www.ghrnet.org/index./joghr/>

INTRODUCTION

Clostridium *difficile* infection (CDI) is one of the most frequently occurring nosocomial infections and in the past decade has been observed to be becoming more frequent, more severe, and more likely to relapse than previously described^[1].

The offending organism, a gram positive spore forming rod, releases toxins and in a susceptible colon resulting in inflammation, mucosal damage and pseudomembrane formation. The clinical spectrum of CDI can range from an asymptomatic carrier state to a more life threatening fulminant colitis with acute diarrhea, diffuse abdominal pain, marked leukocytosis, lactic acidosis, and toxic megacolon.

Besides certain well established risk factors associated with CDI including antibiotics, advanced age and prolonged hospitalization, gastric acid suppression has been implicated as a possible contributor. The two commonly used medications for gastric acid suppression are the proton pump inhibitors (PPIs) and histamine 2 receptor antagonists (H2RA). A number of studies have reported a higher risk of CDI secondary to concomitant use of gastric suppressants, more specifically PPIs as compared to H2RA^[2,3,4]. Janarthanan and colleagues in a recent meta analysis of 21 observational studies reported that PPI use was associated with an 80% greater risk of CDI compared with no history of PPI use^[5]. However, it is not clear whether gastric acid suppression has any role in severity of CDI.

MATERIALS AND METHODS

We performed a retrospective cohort study at Geisinger Medical Center, a tertiary care hospital, located in central PA. Hospitalized patients with CDI from January 1, 2001 to October 31, 2009 were identified. Data was obtained using electronic health records. The patients were included if they were >18 years of age and had a positive stool antigen or PCR for *C difficile*. This was defined as the index CDI. Patients less than 18 years of age, pregnant women and those with previous history of CDI, if indicated in the problem list prior to admission, were excluded.

Baseline characteristics were obtained on all patients including age, sex, co-morbidities, use of ABXs within 90 days of index CDI and the use of PPI/H2RA within 30 days of index CDI. Patients were defined as having severe CDI if they had 2 or more of the following criteria within 5 days of index CDI: (1) WBC > 15 or < 4 μ K/L or bands >10; (2) shock (defined as any SBP<90) with or without the use of vasopressors; (3) subtotal or total colectomy within 5 days of index CDI; and (4) multi-organ failure with either (a) respiratory failure requiring BiPAP or mechanical ventilation, (b) acute renal failure (rise in serum creatinine by 1.5 mg/dL from baseline), (c) altered mental status and/or (d) lactic acidosis (>2.5 mmol/L). The study was approved by the institutional review board of Geisinger Medical Center.

death, and multi-organ failure (identified by either: respiratory failure, acute renal failure (ICD-9 code or increase of >1.5 in creatinine from baseline to ever post-index), altered mental status, or lactic acidosis (>2.5). Logistic regression was used to estimate the associations of PPI and H2RA with development of severe CDI. Potential confounders were included in a multivariable model to estimate an unbiased relationship. Variables were considered in the model if they were related to both the outcome (severe CDI) and either of the medications. Results are presented as odds ratios (OR) and corresponding 95 percent confident intervals (95% CI). The analysis was performed using SAS v9.2 (SAS Institute Inc., Cary NC).

RESULTS

A total of 627 patients with index CDI were identified from January 1, 2001 to October 31, 2009. Baseline characteristics of the cohort and by PPI and H2RA usage are displayed in table 1. The median age was 69 years (inter-quartile range was 57 to 79 years).

There were 297 (47%) men and the cohort was mostly Caucasians (98%). Of the 627 patients with CDI, 61% were prescribed antibiotics within 90 days of index CDI. 358 patients did not receive PPI or H2RA within 30 days of index CDI; 172 received only PPI, 37 received

Table 1 Demographics.

	Overall (n = 627)	Neither (n = 358)	H2 only (n = 37)	PPI only (n = 172)	Both (n = 60)	P-value
	N (%)					
Male sex	297 (47.4%)	160 (44.6%)	20 (54.0%)	80 (46.8%)	7 (61.7%)	0.0815
White race	614 (97.9%)	350 (97.8%)	37 (100%)	169 (98.8%)	58 (96.7%)	0.5616
Antibiotic Use w/in 90 days	380 (60.6%)	145 (40.4%)	30 (81.1%)	147 (86.0%)	58 (96.7%)	<.0001
Vasopressor use w/in 5 days	31 (4.9%)	2 (<1%)	1 (2.7%)	20 (11.7%)	8 (13.3%)	<.0001
Cardiac disease	113 (18.0%)	78 (21.7%)	3 (8.1%)	24 (14.0%)	8 (13.3%)	0.0362
Pulmonary disease	80 (12.8%)	41 (11.4%)	4 (10.8%)	25 (14.6%)	10 (16.7%)	0.5603
Renal disease	46 (7.3%)	21 (5.8%)	0 (0%)	19 (11.1%)	6 (10.0%)	0.0321
Diabetes	100 (15.9%)	46 (12.8%)	4 (10.8%)	38 (22.2%)	12 (20.0%)	0.0278
Death w/in 6 months	199 (31.7%)	110 (30.6%)	9 (24.3%)	62 (36.3%)	18 (30.0%)	0.418
Developed severe CDI w/in 5 days of index	254 (40.5%)	132 (36.7%)	8 (21.6%)	87 (50.9%)	27 (45.0%)	0.0013
In-hospital death	58 (9.2%)	5 (9.8%)	2 (5.4%)	16 (9.4%)	5 (8.3%)	0.8446
Leukocytosis	418 (66.7%)	241 (67.1%)	22 (59.5%)	118 (69.0%)	37 (61.7%)	0.5733
Shock (hypotension)	198 (31.6%)	83 (23.1%)	9 (24.3%)	78 (45.6%)	28 (46.7%)	<.0001
Colectomy	11 (1.8%)	2 (<1%)	0 (0%)	7 (4.1%)	2 (3.3%)	0.0146
Multi-organ failure ¹	194 (30.9%)	113 (31.5%)	5 (13.5%)	59 (34.5%)	17 (28.3%)	0.0891
	Median (IQR)					
Age	69 (57-79)	68 (56-78)	67 (61-80)	72 (60-81)	66.5 (53.5-78.0)	0.0722
BMI (41% known)	27.8 (23.5-34.0)	27.8 (23.9-34.6)	26.5 (23.2-34.7)	27.8 (22.9-34.7)	28.4 (23.9-33.4)	0.9104
Length of hospital stay	10 (5-18)	9 (5-18)	14 (9-18)	8 (4-15)	15 (7-26.5)	0.0001

¹respiratory failure, acute renal failure, altered mental status, or lactic acidosis >2.5 mmol.

Statistical Analysis

Data are presented as mean and standard deviation, or median and inter-quartile range, for continuous variables, and as frequency and percentage for categorical variables. Baseline comparisons between the medication groups were made using the Kruskal-Wallis non-parametric and Pearson's Chi-square or Fisher's Exact tests, as appropriate. For purposes of describing the sample patients were assigned to one of four medication groups; neither PPI nor H2RA, PPI only, H2RA only, or both. The descriptive statistics are also shown stratified by severe CDI. Antibiotic use was coded within 90 days pre-index CDI. Severe CDI was coded as 2 or more of the following: leukocytosis (WBC>15 or <4 or bands>10), shock (SBP<90), subtotal or total colectomy, in-hospital

only H2RA, and 60 received both PPI and H2RA. Patients on PPI or combination of PPI and H2RA blockers were more likely than those on neither to also be on vasopressors within 5 days or antibiotics within 90 days of index CDI. Patients on PPI only were also more likely to have diabetes or renal disease. Gender, age, BMI, and race didn't really vary by medication usage group.

It can be seen in table 2 that those only on PPIs were more likely to develop severe CDI. It can also be seen that among the criteria used to define development of severe CDI, patients on PPI only were more likely to have shock (hypotension), a colectomy or multi-organ failure. Similar results were observed for those patients on both PPI and H2RA. In a logistic regression model that included indicators of

the medications of interest, it was found that use of PPI was associated with an increased odds of severe CDI (OR=1.91, 95% CI: 1.36, 2.69, $p=0.0002$) whereas H2RA was not found to be significantly associated (OR=0.66, 95% CI: 0.41, 1.05, $p=0.0770$). A test for the interaction between medications was non-significant ($p=0.3193$) implying that the effect of one medication was not dependent on the level of the other. After controlling for potential confounders including antibiotic use within 90 days, vasopressor use, pulmonary and renal co-morbidity and hospital length of stay, the effect of PPI, although somewhat attenuated, was significant (OR=1.60, 95% CI: 1.93, 2.35, $p=0.0156$). However, among patients that had received an H2RA the odds of developing severe CDI was reduced by approximately 50% (OR=0.50, 95% CI: 0.31, 0.83, $p=0.0071$).

Table 2 Characteristics of CDI Patients by CDI Status.

	Severe CDI (<i>n</i> = 254)	Non-Severe CDI (<i>n</i> = 373)	P-value
Male sex	119 (46.8%)	178 (47.7%)	0.8303
White race	251 (98.8%)	363 (97.6%)	0.2672
Antibiotic Use w/in 90 days	172 (67.7%)	208 (55.8%)	0.0026
Vasopressor use w/in 5 days	28 (11.0%)	3 (0.8%)	<0.0001
Cardiac disease	50 (19.7%)	63 (16.9%)	0.3714
Pulmonary disease	41 (16.1%)	39 (10.5%)	0.0362
Renal disease	28 (11.0%)	18 (4.8%)	0.0035
Diabetes	42 (16.5%)	58 (15.6%)	0.7407
Death w/in 6 months	125 (49.2%)	74 (19.8%)	<0.0001
Age	68 (57 - 80)	70 (57 - 78)	0.4738
BMI (41% known)	28.1 (23.7 - 35.6)	27.6 (23.5 - 33.6)	0.3208
Length of hospital stay	12 (6 - 22)	8 (4 - 16)	<0.0001

DISCUSSION

ICDI continues to be a serious nosocomial and community acquired infection with significant morbidity and mortality. For the health care system, it's a substantial expenditure estimated at more than 1.1 billion dollars per year in the United States^[6]. In 2005, the Centers for Disease Control and Prevention reported the emergence of the hypervirulent strain B1/NAP-/027, also known as the non-North American Pulse field type 1 and since then there has been a steady increase in the detection of this strain even low risk populations^[7]. Several methods have been implemented by health care systems to reduce the spread of this infection including strict hand washing, patient isolation and antibiotic stewardship.

The role of gastric acid suppression causing CDI is poorly understood. Dr. Gurian in 1982 demonstrated that, in vitro, a gastric pH of 2 to 4 rapidly killed Clostridium difficile but as the pH of gastrointestinal secretions increased, the bactericidal action was minimal^[8]. Jump and colleagues showed that the Clostridium difficile spores are able to survive longer because of a more sustained rise in gastric pH created by PPIs^[9]. However, more recently Nerandzic *et al.*, demonstrated that rather than gastric acid, an alteration in the conjugation of bile acids, results in germination of C diff spores in intestines^[10]. PPIs, by delaying gastric emptying and leading to conversion of bile salts to unconjugated form, possibly result in a higher germination of the vegetative spores of C diff. A higher incidence of small bowel bacterial overgrowth with chronic PPI use has also been postulated as a cause^[11]. There has also been recent suggestion of impaired leukocyte and immune response with use of

PPIs^[12,13].

The inpatient hospital mortality for fulminant CDI is around 35%. However it can be up to 57% in patients >70 years presenting with marked leukocytosis, shock requiring pressors and cardio-pulmonary failure^[14]. A recent study from the UK also reported a 30 day mortality of 58% especially in the older age group^[15]. Multi-system organ failure is an independent predictor of mortality and associated with a higher need for colectomy^[16]. Our data shows that more than a third of the patients who developed severe CDI received a PPI within 30 days of diagnosis. Although the total number of colectomies was just 9, out of these 7 were on a PPI. Hypotension was also more common in those who received PPIs. The risk was much lower if patient received an H2RA. We did not look at fever, the frequency of diarrhea and the presence or absence of pseudomembranes in our patients, which is a study limitation, as these are also markers of severe Clostridium difficile infection. However, not all patients are able to mount a fever and especially those who are immunosuppressed. With fulminant C difficile infection there can be significant ileus and often the frequency of stooling is not precisely charted. Pseudomembranes are significant but sigmoidoscopy or colonoscopy can be deferred in patients with CDI as stool studies have high sensitivity and specificity^[17]. The need for endoscopy usually arises when the clinical diagnosis is in question. We don't believe we could have missed or added additional patients by reviewing endoscopy data although it might be worthwhile in a more prospective study. The most important risk factor for the development of CDI is the use of antibiotics. With administration of antibiotics there is disruption of the natural microbial flora making the colon susceptible to toxin induced inflammation. Our study also shows that 57% of the patients got antibiotics within 90 days of CDI. Those who received antibiotics were more likely to be on acid suppression.

The question that arises is whether significant acid suppression makes the environment more susceptible to severe CDI? Our data suggests limiting use of acid suppression while on antibiotics and at least while admitted to the hospital. Some experts advocate implementation of a check list in the hospitalized setting to reduce the spread of CDI^[18]. We propose that acid suppression be incorporated into medication reconciliation process. Choudhry *et al* showed that in UK up to 63% of the hospitalized patients may not have an apparent indication for a PPI prescription at the time of discharge. This group also had a higher incidence of CDI^[19]. Moreover the risk of recurrence of CDI is also higher if PPIs are continued once a diagnosis of CDI is established^[20,21]. Patients are usually started on stress ulcer prophylaxis while in the ICU but as they move to a lower level of care, these medications may no longer be indicated.

Since the introduction of PPIs in the early 90s, there has been a steady increase in the use of these medications. According to a report in Nov 09 by the US news, 113.4 million prescriptions for PPIs are filled each year making this class of drugs the third commonly prescribed medication in the US. PPIs have no doubt revolutionized the treatment of peptic ulcer disease and gastroesophageal reflux, and gastroenterologists prescribe these medications more than any other. Until a head to head double blinded trial is done to confirm or exclude the role of acid suppression in CDI, it might be reasonable to ascribe to the theory of less is more, particularly PPI use in hospitalized patients.

REFERENCES

- Bartlett JG. Narrative review: the new epidemic of Clostridium difficile-associated enteric disease. *Ann Intern Med* 2006; **145**: 758-764

- 2 Dial S, Delaney JA, Barkun AN, Suissa S. Use of gastric acid-suppressive agents and the risk of community-acquired Clostridium difficile-associated disease. *JAMA* 2005; **294**: 2989-2995
- 3 Aseeri M, Schroeder T, Kramer J, Zackula R. Gastric acid suppression by proton pump inhibitors as a risk factor for clostridium difficile-associated diarrhea in hospitalized patients. *Am J Gastroenterol* 2008; **103**: 2308-2313
- 4 Cunningham R, Dial S. Is over-use of proton pump inhibitors fuelling the current epidemic of Clostridium difficile-associated diarrhoea? *J Hosp Infect* 2008; **70**: 1-6
- 5 Janarthanan S, Ditah I, Kutait A, et al. A meta-analysis of 16 observational studies on proton pump inhibitor use and risk of Clostridium difficile associated diarrhea. *ACG* 2010; Abstract 378.
- 6 Kyne L, Hamel MB, Polavaram R, Kelly CP. Health care costs and mortality associated with nosocomial diarrhea due to Clostridium difficile. *Clin Infect Dis* 2002; **34**: 346-353
- 7 Severe Clostridium difficile-associated disease in populations previously at low risk--four states, 2005. *MMWR Morb Mortal Wkly Rep* 2005; **54**: 1201-1205
- 8 Gurian L, Ward TT, Katon RM. Possible foodborne transmission in a case of pseudomembranous colitis due to Clostridium difficile: influence of gastrointestinal secretions on Clostridium difficile infection. *Gastroenterology* 1982; **83**: 465-469
- 9 Jump RL, Pultz MJ, Donskey CJ. Vegetative Clostridium difficile survives in room air on moist surfaces and in gastric contents with reduced acidity: a potential mechanism to explain the association between proton pump inhibitors and C. difficile-associated diarrhea? *Antimicrob Agents Chemother* 2007; **51**: 2883-2887
- 10 Nerandzic MM, Pultz MJ, Donskey CJ. Examination of potential mechanisms to explain the association between proton pump inhibitors and Clostridium difficile infection. *Antimicrob Agents Chemother* 2009; **53**: 4133-4137
- 11 Lombardo L, Foti M, Ruggia O, Chiecchio A. Increased incidence of small intestinal bacterial overgrowth during proton pump inhibitor therapy. *Clin Gastroenterol Hepatol* 2010; **8**: 504-508
- 12 Zedtwitz-Liebenstein K, Wenisch C, Patruta S, Parschalk B, Daxböck F, Graninger W. Omeprazole treatment diminishes intra- and extracellular neutrophil reactive oxygen production and bactericidal activity. *Crit Care Med* 2002; **30**: 1118-1122
- 13 Kuroda M, Yoshida N, Ichikawa H, Takagi T, Okuda T, Naito Y, Okanoue T, Yoshikawa T. Lansoprazole, a proton pump inhibitor, reduces the severity of indomethacin-induced rat enteritis. *Int J Mol Med* 2006; **17**: 89-93
- 14 Sailhamer EA, Carson K, Chang Y, Zacharias N, Spaniolas K, Tabbara M, Alam HB, DeMoya MA, Velmahos GC. Fulminant Clostridium difficile colitis: patterns of care and predictors of mortality. *Arch Surg* 2009; **144**: 433-440
- 15 McGowan AP, Lalayiannis LC, Sarma JB, Marshall B, Martin KE, Welfare MR. Thirty-day mortality of Clostridium difficile infection in a UK National Health Service Foundation Trust between 2002 and 2008. *J Hosp Infect* 2011; **77**: 11-15
- 16 Perera AD, Akbari RP, Cowher MS, Read TE, McCormick JT, Medich DS, Celebrezze JP Jr, Beck SJ, Fischer PE, Caushaj PF. Colectomy for fulminant Clostridium difficile colitis: predictors of mortality. *Am Surg* 2010; **76**: 418-421
- 17 Myhal ML, Laux DC, Cohen PS. Relative colonizing abilities of human fecal and K 12 strains of Escherichia coli in the large intestines of streptomycin-treated mice. *Eur J Clin Microbiol* 1982; **1**: 186-192
- 18 Abbett SK, Yokoe DS, Lipsitz SR, Bader AM, Berry WR, Tamplin EM, Gawande AA. Proposed checklist of hospital interventions to decrease the incidence of healthcare-associated Clostridium difficile infection. *Infect Control Hosp Epidemiol* 2009; **30**: 1062-1069
- 19 Choudhry MN, Soran H, Ziglam HM. Overuse and inappropriate prescribing of proton pump inhibitors in patients with Clostridium difficile-associated disease. *QJM* 2008; **101**: 445-448
- 20 Kim JW, Lee KL, Jeong JB, Kim BG, Shin S, Kim JS, Jung HC, Song IS. Proton pump inhibitors as a risk factor for recurrence of Clostridium-difficile-associated diarrhea. *World J Gastroenterol* 2010; **16**: 3573-3577
- 21 Linsky A, Gupta K, Lawler EV, Fonda JR, Hermos JA. Proton pump inhibitors and risk for recurrent Clostridium difficile infection. *Arch Intern Med* 2010; **170**: 772-778

Peer reviewers: Luis Rodrigo, Professor, Department of Gastroenterology, University Hospital Central of Asturias, c/ Celestino Villamil s. n.º, 33.006, Oviedo, Spain; Diego Sánchez Muñoz, Gastroenterologist, Usp Clínica Sagrado Corazón, C/ Rafael Salgado , 3, 41003 Sevilla, Spain.