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The Effect of Proton Pump Inhibitors on the Prevalence of *Clostridium difficile* Infection

By

Abir Kundu
MPH

Department of Biostatistics and Bioinformatics

_____Professor Paul Weiss_____
Committee Chair

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Abir Kundu

B.A.
University of Chicago
2008

Thesis Committee Chair: Professor Paul Weiss

An abstract of
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The Effect of Proton Pump Inhibitors on the Prevalence of *Clostridium difficile* Infection

By Abir Kundu

Clostridium difficile infection is an increasing problem in hospitals across the United States. Proton pump inhibitors (PPIs) have been implicated in many studies as a possible risk factor for *Clostridium difficile* infections. This study examines the prevalence of Clostridium *difficile* infections amongst the veteran population at the VA Hospital in New Haven, CT and whether the use of PPIs increases the chance for infection. The study was a retrospective cohort study with all unique admissions between fiscal years 2003 and 2007 being considered. Variables of interest in the study include: PPI use, age, race, hospital location, fluoroquinolone use, gender, length of stay, and intravenous vancomycin use. Odds ratios and corresponding confidence intervals were calculated in order to provide a measure of comparison. P-values were calculated from a logistic regression model that included all variables of interest. A final predictive model was created using backwards selection. What the study determined was PPI usage did not increase the chance of acquiring *Clostridium difficile* infection ($p=0.2752$). However, the study subject's length of stay in the hospital ($p<0.0001$) and fluoroquinolone use (OR: 2.29, 95% CI: 1.44-3.65) were found to be the most statistically significant factors in predicting the chance of a patient acquiring *Clostridium difficile* infection during the duration of the study period. In conclusion, the study suggests that there is no correlation between proton pump inhibitor use and the acquiring of a *Clostridium difficile* infection. However, the longer a patient resides in the hospital setting, the higher the chance that the patient will develop a *Clostridium difficile* infection. Also, the use of antibiotics such as fluoroquinolones increases the odds of developing the *Clostridium difficile* infection as well. Further studies should be conducted in order to determine what other consistent risk factors there are for *Clostridium difficile* infections.

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Chapter I

INTRODUCTION

Clostridium difficile is an obligate anaerobic, terminal spore-forming rod, Gram-positive bacterium. It causes diarrhea, as well as other diseases, in patients where antibiotic treatment may have cleaned out competing intestinal flora. *Clostridium difficile* was first noticed in 1935 as an element of the intestinal flora of newborn babies. However, the part that *C. difficile* plays in human disease was not realized until the 1970s when the bacteria was identified as the main culprit in the cause of pseudomembranous colitis. It is the most common cause of nosocomial diarrhea, which leads to significant morbidity, mortality, and increased cost of healthcare delivery. Nosocomial diarrhea is diarrhea resulting from an infection resulting from treatment at a hospital that occurs 48 hours after hospital admission or 30 days after hospital discharge. It is estimated that per case of *Clostridium difficile* associated disease (CDAD), there is an additional cost between $3,700 and $7,234 as well as an extra 3.6 days longer in the hospital, and CDADs have cost the US an estimated $1.1 billion [1].

Healthcare associated *Clostridium difficile* associated disease (HA-CDAD) is a rising problem in hospitals across the country. Healthcare associated CDAD is defined as patients diagnosed with CDAD after 48 hours of hospital admission or 30 days after hospital discharge. There are risk factors that are considered to contribute to the development of healthcare associated CDAD. One such factor would be a patient's inability to develop anti-toxin A antibodies. This is important because those patients who are asymptomatic *C. difficile* carriers are far less likely to develop CDAD. Age and co-morbidities are surrogate markers for exposure and lack of anti-toxin A antibodies.

Minor procedures such as enemas, NG tubes, and the use of motility altering drugs also increase the likelihood of developing a CDI. Major gastrointestinal surgery has been shown to increase the chance of developing a CDI markedly [1]. Also, an overall increased incidence density of CDI amongst patients in a hospital increases the likelihood, especially as the length of hospital stay (LOS) increases.

However, it is still unclear whether or not exposure to proton pump inhibitor medications (PPI) increases the risk for *Clostridium difficile* infections in the hospital setting. PPIs are a common form of acid suppressive therapy for gastroesophageal reflux and stress ulcer prophylaxis in critically ill patients. PPIs provide more potent suppression of gastric acid production than other therapies. Also, exposure to proton pump inhibitors has been previously implicated in other bacterial causes of gastroenteritis such as salmonella and campylobacter. It has also been linked with being a risk factor for community acquired and ventilator associated pneumonia [3]. Also, because PPIs decrease gastric acidity, it has been surmised that PPIs allow for an increased number of vegetative *C. difficile* cells to pass into intestines [2]. Therefore, this study hypothesizes that exposure to proton pump inhibitors during acute care hospitalization is an independent risk factor associated with healthcare associated CDI amongst Veteran patients in the VA healthcare system. By demonstrating whether or not proton pump inhibitors are a risk factor in acquiring healthcare associated CDI amongst Veteran patients in the VA healthcare system, it can be concluded as to whether or not patients on proton pump inhibitors are more at risk than patients who are not on the inhibitors.

In the context of the study conducted, *Clostridium difficile* associated disease is defined as a patient who has confirmed infection of *C. difficile* and is symptomatic at the

time of testing. Additionally, healthcare associated CDAD are confirmed cases of CDAD found at the Veterans' Affair Hospital in West Haven, Connecticut with healthcare referring to any treatment occurring at the VA Hospital.

Chapter II

REVIEW OF THE LITERATURE

Background

Clostridium difficile is acknowledged as the most common cause of nosocomial diarrhea in adults and is a growing problem in the healthcare field. While it has been documented that *Clostridium difficile* diarrhea accounts for 20% of all antibiotic-associated diarrhea it has been found in up to 30% of asymptomatic hospitalized patients. Infection by the organism can now be associated with substantial morbidity and mortality [1].

It has been noted in several studies that the development of the disease is strongly linked with antibiotic use. Clindamycin, ampicilin, amoxicillin, and cephalosporins are amongst the antibiotics closely related to *Clostridium difficile* infection. Antibiotics are associated with the development of *Clostridium difficile* in over 96% of patients who develop the disease. However, there are other risk factors that could contribute to the development of disease. Such factors include advanced age, underlying diseases, length of hospitalization, and the use of proton pump inhibitors [1].

Pathogenicity

As previously mentioned, antibiotics have a strong correlation to the development of *Clostridium difficile*. The antibiotics alter the microflora within the gut in such a way that any subsequent exposure to *Clostridium difficile* leads to colonization. Once

Clostridium difficile colonizes the host, most patients become asymptomatic carriers as the bacterium does not cause disease unless it is a toxigenic strain. Within those toxigenic strains, there are two types of toxins, toxin A and toxin B. Toxin A causes the excretion of inflammatory fluids from the colonic epithelium. Toxin B, however, causes cell death through the disruption of the actin cytoskeletal components of the colonocyte.

In those patients afflicted with the toxic *Clostridium difficile* strain, symptoms usually present 4-9 days after the antibiotic treatment course begins, but can present at any time up to 8 weeks after treatment begins. The most common symptoms include loose bowel movements, abdominal discomfort or pain, fever along with leukocytosis. However, one should take note that diarrhea may be absent in 20% of patients with *Clostridium difficile* infection, and should not discount it during a differential as a cause if diarrhea is not a presenting symptom [4].

Diagnosis

Diagnostic laboratory tests must be conducted in order to confirm *Clostridium difficile* infection. The cytotoxin assay is considered the gold standard and detects after 24 to 48 hours the presence of toxin B in the stool. Though it takes a day or two to obtain the results, the test is both sensitive (94%-100%) and specific (99%). Enzyme-linked immunosorbent assay (ELISA) will detect both toxin A and B and yields results within 2-6 hours. The ELISA is extremely specific (99%), but is lacking in sensitivity (70-90%), thus there are false-negatives. While there are other methods of detecting *Clostridium difficile*, the other tests are not nearly sensitive of specific enough to warrant further discussion [4].

Prevention

Many studies have been conducted in order to determine the better methods in decreasing and preventing *Clostridium difficile* infection amongst hospital patients. A controlled and reduced use of antibiotics is usually suggested to decrease the chances of *Clostridium difficile* colonization in hospital patients. This controlled and reduced use includes using one antibiotic less while simultaneously introducing similar antibiotics in lower doses into the regimen to decrease the chances of developing an antibiotic resistant strain of *Clostridium difficile* [5]. Also, the use of a 1:10 solution of hypochlorite bleach when wiping and sterilizing hospital equipment has been demonstrated to be somewhat effective in decreasing the rates of *Clostridium difficile* infections within the hospital setting [6]. An educational program implemented in the hospital setting for both physicians and other hospital employees has also been shown to decrease the rate of CDIs within the hospital setting. Ideally, a combination of all three therapies would most likely decrease the rate of CDIs even more [7].

Proton Pump Inhibitors

So far, research into the effect of gastric acid in preventing *Clostridium difficile* infection has been limited as well as the research looking into the potential effect of gastric antisecretory drugs on acquiring *Clostridium difficile* infections. The most prevalent of the gastric antisecretory drugs currently in use are proton pump inhibitors (PPIs). While PPI use has been correlated with other infectious gastroenteritis, such as salmonella and campylobacter infection, very little is known about the effect that the

proton pump inhibitors have on *Clostridium difficile*. The prescription of PPIs has increased by 129% from 1998 to 2003. Often the use of PPIs is conducted during hospital admissions and stays [8]. Kyne et al provided a method for hospitalized patients who are receiving antibiotics to be stratified according their risk for nosocomial *C. difficile* diarrhea. The authors conclude that the patients most at risk would benefit from cautious prescription of antibiotics and closer monitoring to provide attention to infection control. The purpose of the study was to determine the diagnostic accuracy of the Horn's index in identifying patients with a high probability of having nosocomial *C. difficile* diarrhea as a direct result for antibiotic treatments. This was a prospective cohort study (n=252) of patients who were admitted to the hospital and were receiving antibiotics. To determine the risk factors for *C. difficile* diarrhea, a retrospective study with a different patient group (n=300) was conducted. When the patients for the study were admitted, they were rated by clinicians using a modified Horn's index (1=mild, 2=moderate, 3=severe, and 4=extremely severe), and only patients who had expected lengths of stay longer than two days were considered. *C. difficile* was diagnosed through positive stool tests, and only patients with diarrhea as well as positive stool tests were considered to be cases. The data was analyzed with multivariable logistic regression in order to determine the odds ratio for *C. difficile* diarrhea associated with increasing levels of disease severity [9], which is similar to the methods employed in the current study. A strength of the study is that it carefully identifies the risk factors. However, the study does have some weaknesses in the methodology. For one, it seems that using the Horn's index is a bit arbitrary when trying to determine the degree of severity

Cunningham et al's study was among the first studies to examine the effect of proton pump inhibitors as a risk factor in being infected by *C. difficile*. The authors discovered that the use of PPIs within the preceding eight weeks to hospital admission was linked with an increased risk of *C. difficile* associated diarrhea (odds ratio 2.5, 95% CI 1.5-4.2). This led to their conclusion that the reduction of unnecessary PPI use is ideal to decrease the incidence of *C. difficile* infection. This was a retrospective case-control study (n=170 analyzed) with patients taken from inpatients of the Plymouth Hospitals NHS Trust in 1999. Cases were identified and confirmed from laboratory and infection control team records. Controls were matched by age within five years, sex, month of admission, admitting consultant, and PiMS diagnostic code. The data was analyzed using the McNemar test with only data for complete pairs of responses being analyzed. Each risk factor was considered separately on a case-wise basis. Additionally, all data were analyzed through a one to one pairing and stepwise binary logistic regression using SAS for PPI, antibiotic and cytotoxic use, as well as sex and age [8]. A strength of the study is that all of the cases are from a single year, thus limiting possible confounders that may occur over multiple years. A weakness of the study is that the cases and controls were matched within five years of each other, which lends to the possibility of cases that are older than their respective controls naturally having more diminished health than their controls.

Dial et al conducted a study in 2004 which examined the effects of patients who were being treated with proton pump inhibitors and their respective risk of diarrhea caused by *Clostridium difficile* infection. In the cohort study, the authors discovered that *Clostridium difficile* infection induced diarrhea was significantly associated with the use

of proton pump inhibitors (adjusted odds ratio 2.1 with 95% CI 1.2-3.5), as was receipt of three or more antibiotics (OR 2.1, 95% CI 1.3-3.4) and admission to a medical ward (OR 4.1, 95% CI 1.5-11.9). The case-control study determined that *Clostridium difficile* diarrhea was significantly associated with females (OR 2.1, 95% CI 1.1-4.0), before renal failure (OR 4.3, 95% CI 1.4-5.2), and the use of proton pump inhibitors (OR 2.7, 95% CI 1.4-5.2). The subjects of the cohort study were identified from a pharmacy database for patients who received antibiotics over a nine month study period which began August 2002. Patients in this group who had also received PPI treatment were compared to those who had not received any acid suppressive therapy. Lab tests were conducted to verify and confirm *Clostridium difficile* infection. To look into the possibility that the PPIs were a possible confounder, a case-control study was conducted at a second hospital. Here cases were defined as patients positive for *Clostridium difficile* toxin and who had a history of diarrhea (n=94). The control subjects were chosen and matched to the cases by ward, age within five years, and class of antibiotics (n=94). One of the biggest strengths of this study is that it did a second study to look more closely at a possible confounder that was also their main factor they were looking at. A weakness in the study again is the age difference which could mean unequal health statuses [10].

In 2005, Dial et al published another study that expanded on their previous publication from 2004. The purpose of the study was to examine whether or not gastric acid-suppressive agents is associated with an increased risk of *Clostridium difficile* infection in the community outside of a hospital setting. They identified patients who were not hospitalized for one year prior to their infection. The authors reach the conclusion that *Clostridium difficile* associated disease with the use of proton pump

inhibitors shows a rate ratio of 2.9 (95% CI of 2.4-3.4). The study was conducted using two population-based case-control studies using the United Kingdom General Practice Research Database. The first study identified 1,672 case of *Clostridium difficile* between 1994 and 2004, and the second study was a subset of the initial cases from the first study which met the definition of community acquired. What the study discovered was that the incidence of *C. difficile* in patients using proton pump inhibitors had an adjusted rate ratio of 2.9 (95% CI 2.4-3.4) [11].

Dial et al published a third study. This study examined whether there was more of an increased risk amongst patients on patients taking PPIs and antibiotics compared to those patients who were taking just PPIs. The group performed a case-control study using the same database from their study published in 2005. The cases were those patients with CDI as well as receiving oral vancomycin therapy and were matched to control subjects. Neither cases nor controls were admitted to the hospital or on oral vancomycin one year previous to their CDI diagnosis. What Dial et al discovered was that exposure to PPIs in the 90 days prior to index case resulted in an increased risk of CDI (OR 3.5; CI 2.3-5.2), and those patients who were on oral vancomycin therapy and PPIs at most 90 days prior to the index case demonstrated a significant risk for CDI (OR 8.2; 95% CI 6.1-11.0). What the group concluded was that PPI use was associated with an increased risk for CDI when cases also were prescribed oral vancomycin therapy [12].

In 2007, Dubberke et al conducted a retrospective study at a hospital in St. Louis, MO. Their goal was to determine the possible risk factors that could contribute to the endemic levels of CDAD. Their study included 36,086 patients who were admitted to Barnes-Jewish Hospital between January 1, 2003 and December 31, 2003, and used

multivariable pooled logistic regression models to evaluate the independent risk factors. Of the study patients, 382 were positive for CDAD. What they discovered was that increasing age, admission in the previous 60 days, hypoalbuminemia, leukemia and/or lymphoma, mechanical ventilation, and receipt of antimotility drugs, histamine-2 blockers, proton pump inhibitors, intravenous vancomycin, fluoroquinolones, and first-, third-, or fourth-generation cephalosporins were significant risk factors. However, it was also discovered that receipt of metronidazole had a protective effect against CDAD (odds ratio 0.5, 95% CI 0.3-0.6) [3].

Chapter III

METHODS

The study was conducted as a retrospective cohort study at the Veterans' Affair Hospital in New Haven, CT with all unique admissions between fiscal years 2003 and 2007 being considered. In order for a study subject to be designated as a case of *Clostridium difficile* infection, the patient had to meet the case definition. *Clostridium difficile* infection was defined as having unexplained diarrhea, abdominal discomfort, fever with a temperature of greater than 38.3°C or leukocytosis (>12k) with a lab test positive for *Clostridium difficile* or pseudomembranous colitis shown on endoscopy. Before May 2005, *Clostridium difficile* was tested for using the cytotoxin assay, and after May 2005 it was tested for using EIA (Enzyme-linked Immunosorbent Assay) for toxins A and B (Immunocard Toxin A & B, Meridian Biosciences, Cincinnati, OH) with 92% sensitivity and 95% specificity [4]. Also, patients must have been hospitalized for at least 48 hours to be considered for the study. The final aspect of the inclusion criteria was that the patient had no previous history of *Clostridium difficile* infections. Patients were excluded if they had previous histories of *Clostridium difficile* infections or had hospitalizations 28 days prior to the hospital study period. The period of exposure of *Clostridium difficile* was defined as the period from admission to the day prior to *Clostridium difficile* infection onset.

Selected patient information was chosen as variables of interest for examination based on previous literature and data availability. Much of the literature reviewed had patient length of stay and antibiotic use as common variables and were included in the current study. The data was collected from three different record sets. Patient

information related to demographics, acute care dates, and locations of care were taken from patient movement files within the VA electronic medical records. Pharmacy records that yielded information related to what sorts of acid inhibitors, antibiotics, steroids, or NSAIDs (nonsteroidal anti-inflammatory drugs) the patient was taking were also taken from the VA electronic medical record. The final piece of information extracted from the VA electronic medical record was the patient lab *Clostridium difficile* test results. Infection Control records were examined to find patients who were positive for *Clostridium difficile* infections. Medical records were reviewed in order to identify the inclusion or exclusion criteria. The last piece of information taken from the patients' medical record was whether they had undergone surgery, mechanical ventilation, and needed an NG tube (nasograstric tube).

The general study population was examined for patient admission by fiscal year. The population's mean age was also determined. Subject mortality rate (SMR), the number of deaths per 100 hospital admissions, and 95% confidence intervals (CIs) were calculated by race, gender, hospital location, age, proton pump inhibitor use, *Clostridium difficile* infection (cases), fluoroquinolone usage, and intravenous vancomycin. The subject mortality rate was calculated by dividing the total number of subject deaths corresponding to a binary value of 1 for the variable in question divided by the total number of subjects corresponding to a binary value of 1 for the same variable. This can be calculated with the equation

$$SMR_{variable} = \frac{deceased_{variable}}{total_{variable}} \times 100$$

The confidence intervals were calculated assuming that the data followed a normal distribution using the equations

$$lower\ limit = X - [1.96 \times \left(\frac{x}{\sqrt{N}}\right)]$$

$$upper\ limit = X + [1.96 \times \left(\frac{x}{\sqrt{N}}\right)]$$

where X is equal to the sample mean, x is equal to the sample standard deviation, and N being equal to the number of subjects in the study population.

For the logistic regression analysis to determine the best model to predict whether a study subject was a confirmed case of *Clostridium difficile* infection, variables analyzed include length of stay, age, race (white, black, other), whether or not the subject spent time in the intensive care unit, whether the subject was located in the hospital wards only or the intensive care unit, whether the patient was on proton pump inhibitors or fluoroquinolones, and the fiscal year for patient admission to properly account for the differences in *Clostridium difficile* infection detection techniques over the fiscal years in question. In order to determine which variables should be included in the model to predict if a subject would develop *Clostridium difficile* infection, backwards selection was conducted in SAS 9.2. This type of model selection begins by including all of the variables of interest that is put into the model. Then F statistics for each variable are calculated, and the variable which has the largest p-value which is greater than the α value that is designated (α=0.1 for the study) is removed from the model. This process is continued until the only variables that remain are those whose F-statistic's p-values are less than the designated cutoff value for α. For this study, because the variable denoting

whether or not a subject in the study was on proton pump inhibitors or not is of interest, the variable was forced into the final predictive model regardless of its F-statistic p-value. To test for interaction between proton pump inhibitors and other variables, interaction terms were created and put into the final model as well in order to test for significance.

2x2 contingency tables were created in order to calculate the odds ratios and their corresponding confidence intervals using the frequency procedure and tables command with SAS 9.2. The odds ratio allows us to estimate the relative risk assuming that the probability of a positive response is small. A 2x2 contingency table allows us to calculate the odds ratio using the formula

$$OR = \frac{n_{11}/n_{12}}{n_{21}/n_{22}} = \frac{n_{11}n_{22}}{n_{12}n_{21}}$$

where the 2x2 contingency table looks as follows:

n_{11}	n_{12}
n_{21}	n_{22}

The 95% confidence intervals were also calculated using SAS 9.2. The program, using the proc freq command, calculates the following equations, which are based on an algorithm from Thomas and Gart in 1971, iteratively in order to find the confidence limits:

$$Lower\ Limit = \sum_{i=n_{11}}^{n_{-1}} \binom{n_{1\cdot}}{i}\binom{n_{2\cdot}}{n_{\cdot 1}-i}\varphi_1^i \Big/ \sum_{i=0}^{n_{-1}} \binom{n_{1\cdot}}{i}\binom{n_{2\cdot}}{n_{\cdot 1}-i}\varphi_1^i = \alpha/2$$

$$Upper\ Limit = \sum_{i=0}^{n_{11}} \binom{n_{1\cdot}}{i}\binom{n_{2\cdot}}{n_{\cdot 1}-i}\varphi_2^i \Big/ \sum_{i=0}^{n_{-1}} \binom{n_{1\cdot}}{i}\binom{n_{2\cdot}}{n_{\cdot 1}-i}\varphi_2^i = \alpha/2$$

An odds ratio of greater than 1 implies that there is a higher chance of eliciting a positive response in row 1 compared to the possible response in row 2, whereas values less than 1 suggest that the chance of a positive response would be higher in row 2 than in row 1.

Further analyses were conducted on a sub-population to determine if there is an association of drug exposure and a specific outcome to any other variables. To test any such association, patients who were confirmed cases of *Clostridium difficile* infection and were also on proton pump inhibitors were examined to see if there were any variables that were successful at predicting whether or not a subject was both a case and on proton pump inhibitors. The purpose of this closer examination is to determine whether or not there is any variable in the study that is associated with both proton pump inhibitor use and being a confirmed case of *Clostridium difficile* infection.

It is acknowledged that there may be possible confounders in the study. To control for any such potential confounders a stratified analysis will be conducted. The crude odds ratio will be calculated without the stratification of the data after which the adjusted odds ratio will be calculated once the stratification is conducted. The crude odds ratio and adjusted odds ratio will be compared to one another. If the crude odds ratio is equal to the unadjusted odds ratio, then it can be said that the variable in question is not a confounder. If there is a difference, then confounding is occurring. It is understood that the odds ratios may not differ very much, so only if the crude odds ratio differs from the

adjusted odds ratio by 10% or more will the variable in question be considered a true confounder to the study [13].

There are potential limitations to the study. One is a risk of bias due to the misclassification of a subject as a positive case of *Clostridium difficile* infection. The reason for this is that *Clostridium difficile* test is neither 100% sensitive nor 100% specific. In order to best compensate for this limitation, the *Clostridium difficile* test that is used for the study is the current gold standard and the case definition used is the one acknowledged as the typical case definition. Also, another limitation of the study is that it is predominantly older white males, suggesting that our study may be yield results biased towards Caucasian males who are on proton pump inhibitors. This would perhaps lead to the presumption that Caucasian males are more likely to use proton pump inhibitors than other races.

Chapter IV

RESULTS

Between fiscal years 2003 and 2007, the Veterans' Affairs hospital in West Haven, CT recorded 5,773 unique patient admissions who met the inclusion criteria. Between fiscal years 2003-2007, patient admissions were as following: 1,244 patients, 1,107 patients, 1,290 patients, 1,005 patients, and 1,127 patients respectively for each of the fiscal years in question (Table 1). Within the study population, the average age for the subjects was 72.6 years old. Also, the study subjects had an average length of stay after admission in the VA hospital of 33 days. There were 785 deaths out of 5,773 (13.6%) unique patient admissions in the hospital between fiscal years 2003 and 2007. This yielded a mortality rate of 13.7 deaths per 100 hospital admissions (95% CI: 12.8-14.6) (Table 2). The average age for patients who passed away within the hospital was 77.4 years of age while those patients who survived the duration of their hospital stay was 71.8 years of age. 1,963 cases of *Clostridium difficile* infection were confirmed between fiscal years 2003 and 2007. This suggested that 34 cases of *Clostridium difficile* infection were discovered per 100 hospital admissions during that time period (95% CI: 33.1-34.9) (Table 3). Of the 1,963 patients that developed *Clostridium difficile* infections, 19.5% (n=383) died in the hospital. The odds of a case dying are 2.05 times higher than the odds of a subject without *Clostridium difficile* infection dying (95% CI: 1.09-3.79). This suggests that *Clostridium difficile* infection alone doubles the chances of a patient passing away.

4.1 Modeling

In order to develop a model which would predict whether a subject was a case or not, variables were input into a model, and then backwards selection was conducted with a slstay=0.1 to see which variables were left after the procedure. Since our primary interest is to look into the effects of proton pump inhibitors, the variable was forced into the model. Other variables which remained were length of stay ($p<0.0001$), Caucasian race ($p=0.0916$), and the use of fluoroquinolones ($p=0.0047$). Thus, the final model is:

$$\log\frac{P(Case)}{1-P(Case)} = \beta_0 + \beta_1(Proton\ Pump\ Inhibitor\ Use) + \beta_2(Length\ of\ Stay) + \beta_3(Race = Caucasian) + \beta_4(Fluoroquinolones\ Use)$$

4.2 Gender

Gender was seen as a potential confounder, so the results were stratified. The mortality rate was not significantly different between the sexes. Female patients had a mortality rate of 12.9 deaths per 100 hospital admissions (95% CI: 12.4-13.3), while men had a slightly higher mortality rate of 13.6 deaths per 100 hospital admissions (95% CI: 13.0-14.2) (Table 2). The rate of *Clostridium difficile* infection was almost the same between male and female patients. Males exhibited a rate of 34 confirmed cases per 100 hospital admissions (95% CI: 33.5-34.5), while females were found to have a case rate of 33 confirmed cases of *Clostridium difficile* infection cases per 100 hospital admissions (95% CI: 32.0-34.0) (Table 3). The odds of a case being male are 1.04 times higher than the odds of a case being female (95% CI: 0.188-5.79). With the odds ratio being so

close to 1, this is indicative of there not being a difference in the susceptibility of developing a *Clostridium difficile* infection based on sex. This is further evidenced by the fact that gender was not seen as a statistically significant variable in the model (p=0.9478).

4.3 Race

There was a larger disparity when races were considered. Caucasians were noted to have the highest mortality rate with 17.8 deaths per 100 hospital admissions (95% CI: 17.1-18.5). African Americans registered a mortality rate of almost half that of Caucasians with 9.2 deaths per 100 hospital admissions (95% CI: 8.5-9.7). Other races accounted for 31.7% of hospital admissions and had a mortality rate of 9.2 deaths per 100 hospital admissions as well (95% CI: 8.8-9.6) (Table 2). Caucasians had a higher rate of confirmed *Clostridium difficile* infection cases than African Americans or other races. Caucasians were reported to have a case rate of 38.6 confirmed cases per 100 hospital admissions (95% CI: 37.9-39.3). African Americans had a case rate of 27.3 confirmed cases per 100 hospital admissions (95% CI: 26.6-28.0). Other races exhibited a case rate of 27.5 confirmed cases per 100 hospital admissions (95% CI 26.9-28.1) (Table 3). The odds of a case being Caucasian is 1.63 times higher than a case being another race (95% CI: 1.03-2.58). While Caucasians were not found to be a significant variable (p=0.1549), backwards elimination modeling placed the variable in the final predictive model, suggesting that there is bias or potential clinical significance towards the Caucasian race.

4.4 Hospital Location

The ICU dealt with 31.7% (n=1,847) of the hospital admissions between the fiscal years in question and had a mortality rate of 12.8 deaths per 100 hospital admissions (95% CI: 12.4-13.2). Patients who were admitted to the wards only accounted for 68.3% of the hospital's admissions. The ward recorded a mortality rate of 13.8 deaths per 100 hospital admissions (95% CI: 13.5-14.1) (Table 2). The intensive care unit dealt with 31.6% of the cases of *Clostridium difficile* infection (n=621). The ICU had a case rate of 34.0 confirmed cases per 100 hospital admissions (95% 33.3-34.7). The ward, on the other hand, dealt with 68.4% of the *Clostridium difficile* infection cases during fiscal years 2003 to 2007 (n=1,342). The case rate in the hospital wards was the same as that of the intensive care unit, 34.0 confirmed cases per 100 hospital admissions (95% CI: 33.7-34.3) (Table 3). The odds of a patient being a case who is in the intensive care unit is 0.9197 times the odds of a being a patient in the ICU who is not a case (95% CI: 0.57-1.48), suggesting that there is no significant difference in the location of a patient in terms of susceptibility to acquiring *Clostridium difficile* infection.

4.5 Length of Stay

As previously mentioned, the average length of stay in the hospital for patients was 33 days (standard deviation=28 days) with the median length of stay being 24 days. The shortest stay by a subject was 2 days, with the longest stay by a patient being 248 days (Table 4). Those who were affected by *Clostridium difficile* were found to have the infection on average 25 days after hospital admission. Length of stay was determined to

be a significant variable in the model trying to predict whether a subject had a confirmed case of *Clostridium difficile* or not ($p<0.001$).

4.6 Proton Pump Inhibitors

55.5% (95% CI: 53.2-56.8) of the study's subjects were on proton pump inhibitors (n=3,205). Females had a higher rate of proton pump inhibitor use with 83.1 persons per 100 (95% CI: 82.0-84.2) hospital admissions using proton pump inhibitors during the duration of their hospital admission. Male patients used proton pump inhibitors at a rate of 55.0 persons using per 100 hospital admissions (95% CI: 54.3-55.7). There was not much of a difference in the rates of proton pump inhibitor usage between races. Caucasian patients reported a rate of 55 persons using per 100 hospital admissions (95% CI: 54.6-55.4). African American patients were recorded to have a rate of 51.5 persons using per 100 hospital admissions (95% CI: 51.1-51.9). Other races were seen to have a rate of 57.8 persons using per 100 hospital admissions (95% CI: 57.5-58.1). The intensive care unit demonstrated a higher rate of usage of proton pump inhibitors compared to the rate of usage in the regular hospital wards. In the intensive care unit the rate of usage was 66.5 persons using per 100 hospital admissions (95% CI: 66.1-66.9). The regular hospital wards recorded a rate of 50.4 persons using per 100 hospital admissions (95% CI: 49.9-50.9) (Table 5). Proton pump inhibitors did not show a significant value in predicting whether a subject was a case or not ($p=0.2752$). The subpopulation analysis conducted on the model to predict a case on proton pump inhibitors was not statistically significant with any variable except for fluoroquinolone use ($p<0.0001$) suggesting both a statistical and clinical significance. The odds of a

patient being a case who is on proton pump inhibitors is 1.08 times higher than that of a patient being a case who is not on proton pump inhibitors (95% CI: 0.69-1.69). The odds of a patient who is a confirmed case of *Clostridium difficile* and on proton pump inhibitors passing away is the same (OR 1.00 – 95% CI: 0.63-1.58) as cases who are not on proton pump inhibitors passing away suggesting that proton pump inhibitor use is not a significant factor in developing *Clostridium difficile* infection.

4.7 Other Variables

53.8% of the study subjects were on fluoroquinolones (n=3,105). 18.4% of patients on fluoroquinolones passed away (n=571). 66.9% of confirmed cases were on fluoroquinolones (n=1,314). The mortality rate for patients on fluoroquinolones who were confirmed cases was 82.6 deaths per 100 patients who were on fluoroquinolones and were confirmed cases. The odds of a case being on fluoroquinolones are 2.29 times the odds of a case not being on the fluoroquinolones (95% CI: 1.44-3.65) suggesting the fluoroquinolones could have a causal association with developing *Clostridium difficile* infections. The odds of a patient who was a confirmed case on fluoroquinolones passing away was 2.17 times higher (95% CI: 1.36-3.47) than cases not on fluoroquinolones suggesting fluoroquinolones could exacerbate the *Clostridium difficile* infection and lead to death.

14.2% of the patients in the study were on intravenous vancomycin (n=822). 41.5% of confirmed cases were on intravenous vancomycin (n=815). The mortality rate of confirmed cases were on intravenous vancomycin was 45.5 deaths per 100 confirmed cases on intravenous vancomycin. The odds of a case being on intravenous vancomycin

are 1.65 times higher (95% CI: 1.04-2.62) than the odds of a case not being on intravenous vancomycin. The odds of a case on intravenous vancomycin passing away are 1.57 (0.98-2.50) times higher than the odds of a case not on intravenous vancomycin passing away. However, vancomycin use was not seen to be a significant variable in the model (p=0.1331)

Chapter V

DISCUSSION

The main purpose of the study was to determine whether or not proton pump inhibitors contributed to an increase in risk for patients at the New Haven Veterans' Affairs Hospital to develop *Clostridium difficile* infections. The study was a retrospective cohort study between fiscal years 2003 and 2007 during which 5,773 unique patient admissions were recorded. Patient records were pulled up and various demographical and medical data was collected from these records for each patient. Once the data was collected, analysis using SAS 9.2 was conducted to check for associations between the different variables and confirmed cases of *Clostridium difficile* infections among the study subjects. While proton pump inhibitors were found not to be a significant predictor of *Clostridium difficile* infection amongst patients in the study, other variables were found to be significant predictors. Such variables include the study subject's length of stay in the hospital, whether the patient was on fluoroquinolones, and, to a certain degree, if the patient was Caucasian or not. Through backwards selection, a predictive model was determined:

$$\log\frac{P(Case)}{1-P(Case)} = \beta_0 + \beta_1(Proton\ Pump\ Inhibitor\ Use) + \beta_2(Length\ of\ Stay) + \beta_3(Race = Caucasian) + \beta_4(Fluoroquinolones\ Use)$$

This model suggests that length of stay, the race Caucasian, and the use of fluoroquinolones are important predictors in a patient's risk in contracting *Clostridium difficile* infection.

Gender did not play an important role in predicting whether a subject was a case or not. The rate of subject being a case was almost the same between the sexes. The same observation applies to the mortality rate comparison between the two sexes. Also, because the odds ratio was almost 1.00 (the recorded observation was 1.04) when comparing the odds of a case being one gender or another it suggests that both males and females are equally susceptible to acquiring *Clostridium difficile* infections.

Race however, did appear to be significant in predicting whether a subject was a case or not. Caucasians were noted to have a mortality rate of almost twice as high as other races. The odds ratio also suggested that Caucasians have a higher chance of being a case than other races. However, this could be due to the imbalance of having almost twelve times as many Caucasians as African Americans and three and a half times more subjects than other non Caucasian or African American races. Another possibility is that the enteric bacteria in the gut of Caucasians could be lacking in protecting and responding appropriately to *Clostridium difficile* infections compared to other races.

The location within the hospital – either the regular hospital wards or the intensive care unit – did not show as a significant predictor or have a significant association with *Clostridium difficile* infections. Because the mortality rates as well as the case rates for both the regular hospital wards and the intensive care unit were the same or close to the same, it can be concluded that *Clostridium difficile* does not have an area in the hospital in which it is more prevalent per 100 hospital admissions. The odds ratio implies as much. This is curious because patients who are immunocompromised or on antibiotic treatments – both of which increase the risk of *Clostridium difficile*

infections – tend to be found more in the intensive care unit rather than in the regular hospital wards.

Length of stay was a significant predictor of *Clostridium difficile* infections amongst patients in the study with a very low p-value (p-value < 0.001). This makes sense as the longer a patient is in the hospital, the greater the chance the patient will encounter the bacterium at some point. With patients developing *Clostridium difficile* infection after an average of 25 days in the hospital and the fact that the average length of stay for patients within the hospital being 33 days, it supports the claim that longer lengths of stay increases the chance of developing *Clostridium difficile* infections.

As mentioned before, proton pump inhibitors were the primary variable of interest in the study. What can be concluded from the study is that proton pump inhibitors are not associated with *Clostridium difficile* infections. While females had a higher use of proton pump inhibitors than the male subjects within the study, the rates of *Clostridium difficile* infection were the same between the sexes. There were not significant differences in the rates of proton pump inhibitor usage between the different races. Since Caucasians had a higher rate of *Clostridium difficile* infections, it can be surmised that proton pump inhibitors are not associated with *Clostridium difficile* infections. When considering location and proton pump inhibitor use, it makes sense that the intensive care unit would have a higher rate of proton pump inhibitor use amongst its patients compared to that of the patients in the regular hospital wards. However, that hypothesis would have correlated with an increased rate of *Clostridium difficile* infections in the intensive care unit, which was not seen. This further solidifies the observation that proton pump inhibitors, in fact, do not contribute directly to the development of *Clostridium difficile*

infections. A further look was taken to see if the effect of proton pump inhibitors was in conjunction with another variable, but that, too, came up negative. In this study, it can be confirmed that proton pump inhibitors play no part in an increased risk to the development of *Clostridium difficile* infections.

Fluoroquinolones were observed to be a significant predictor in the development of *Clostridium difficile* infections. While the mortality rate was low, there was a high correlation between cases and subjects being fluoroquinolones. While this is a significant observation, it is an observation that was expected. Literature has long suggested that antibiotics have played a large role in the development of *Clostridium difficile* infections in patients, so the fact that an antibiotic such as fluoroquinolones is a significant variable makes sense.

This logic of antibiotics leading to a higher incidence of *Clostridium difficile* infections is followed with the use of intravenous vancomycin – an antibiotic. While the odds ratio of 1.65 suggests that cases are more likely to be on intravenous vancomycin than not on the antibiotic, it does not appear to be a significant variable in the model to predict cases of *Clostridium difficile* infections. One reason for this apparent discrepancy could be that while cases are more likely to be on the antibiotic, the intravenous vancomycin may not necessarily be a cause for the *Clostridium difficile* infections, but rather a catalyst to allow for the further progression of the infection once the patient is colonized.

Overall, the study was successful. While much of the literature has suggested that proton pump inhibitors play a park in the development of *Clostridium difficile* infections, the study conducted at the Veteran's Affairs Hospital in New Haven, CT has shown

otherwise. While it cannot be definitively said as to what the exact cause of the *Clostridium difficile* infections are, it can be said with assurance that proton pump inhibitors do not play a role in the development of the infections. However, the length of stay of a patient in the hospital does play a role, and to a lesser degree, the race of the patient as well.

This study has great implications for public health. Since *Clostridium difficile* is the leading cause of nosocomial infections, finding ways to prevent infections from occurring is of vital importance. Diarrhea is potentially fatal to patients in the hospital setting, and therefore it is important to control such outbreaks for the good of public health.

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Appendix

TABLES AND FIGURES

Table 1: Number of Hospital Admission by Fiscal Year

Fiscal Year	Number of Admissions
2003	1,244
2004	1,107
2005	1,290
2006	1,005
2007	1,127

Table 2: Mortality Rates by Characteristics of Interest

Characteristic	Deaths	Total Hospitalization	Mortality Rate (95% CI)
Total	785	5,773	13.7 (12.8-14.6)
Sex			
Female	13	101	12.9 (12.4-13.3)
Male	772	5,672	13.6 (13.0-14.2)
Race			
Caucasian	604	3,390	17.8 (17.1-18.5)
Black	51	554	9.2 (8.5-9.7)
Other	168	1,829	9.2 (8.8-9.6)
Location			

ICU	235	1,829	12.8 (12.4-13.2)
Wards	550	3,944	13.8 (13.5-14.1)

Table 3: Rates of *Clostridium difficile* Infections

Characteristic	Deaths	Total Hospitalization	Cases	Case Rate (95% CI)
Total	785	5,773	1,963	34.0 (33.1-34.9)
Sex				
Female	13	101	34	33.0 (32.0-34.0)
Male	772	5,672	1,929	34.0 (33.5-34.5)
Race				
Caucasian	604	3,390	1,309	38.6 (37.9-39.3)
Black	51	554	151	27.3 (26.6 – 28.0)
Other	168	1,829	503	27.5 (26.9-28.1)
Location				
ICU	235	1,829	621	34.0 (33.3-34.7)
Wards	550	3,944	1,342	34.0 (33.7-34.3)

Table 4: Descriptive Statistics on Length of Stay

Number of subjects	5,773
Mean length of stay (days)	32.8
Standard deviation of length of stay (days)	28.1
Median length of stay (days)	24.0

Mode length of stay (days)	17.0
Minimum length of stay (days)	2
Maximum length of stay (days)	248

Table 5: Descriptive Statistics for Proton Pump Inhibitors

Characteristic	Number of Patients on PPIs	Total Hospitalization	Rate of PPI Use (95% CI)
Total	3,205	5,773	55.5 (53.2-56.8)
Sex			
Female	84	101	83.1 (82.0-84.2)
Male	3,121	5,672	55.0 (54.3-55.7)
Race			
Caucasian	604	1,864	55.0 (54.6-55.4)
Black	51	285	51.5 (51.1-51.9)
Other	168	1,056	57.8 (57.5-58.1)
Location			
ICU	1,216	1,829	66.5 (66.1-66.9)
Wards	1,989	3,944	50.4 (49.9-50.9)