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Proton Pump Inhibitor Association with Increased Risk of Clostridium difficile Associated Diarrhea

Kitty Earley
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Proton Pump Inhibitor Association with Increased Risk of Clostridium difficile Associated Diarrhea

Abstract
Background: Proton Pump Inhibitor use is increasing in the hospital setting. This has coincided with an increase in Clostridium difficile-associated diarrhea (CDAD). C. difficile is a growing problem in hospitals, despite health care workers taking extra steps to wash hands and use personal, protective equipment in patient rooms. Known risk factors for the development of C. difficile infection are being carefully reviewed and considered. Upset of the normal intestinal flora is a known risk factor for the development of CDAD. In addition, a controversial risk factor has been proposed: Proton Pump Inhibitors (PPI).

Hypothesis: Hypochlorhydria from PPI is a risk factor for developing CDAD.

Study Design: Systematic review of available medical literature and reviews.

Methods: An extensive literature search was conducted on Medline-OVID, CINAHL (EBSCOhost), and PubMed using the search terms “proton pump inhibitor and Clostridium difficile”, “Proton Pump Inhibitors”, and “Clostridium difficile”. Relevant references were retrieved and references from the reviewed clinical trials listed were used as sources for this paper.

Results: The majority of the clinical trials in the literature today show a strong association with PPI-induced hypochlorhydria inducing CDAD. Of the nine papers discussed in this review, seven showed strong associations with significance, while only two trials showed no association with PPI use and CDAD.

Conclusion: There is a strong correlation between PPI-induced hypochlorhydria and CDAD. With this confirmation of such a strong association, a randomized controlled trial should be done to confirm these results.

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Keywords
Proton Pump Inhibitors, Clostridium difficile, hypochlorhydria

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Proton Pump Inhibitor Association with Increased Risk of *Clostridium difficile* Associated Diarrhea

Kitty Earley

A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 15, 2009

Faculty Advisor: Annajanette Sommers MS, PAC
Clinical Graduate Project Coordinators: Rob Rosenow PharmD, OD & Annjanette Sommers MS, PAC
Biography

Kitty Earley is a native of Montana. She grew up in Billings where she graduated from Billings Central Catholic High School. She moved to Portland, Oregon in 2002, where she majored in Biology at Concordia University. After completion of her undergraduate degree, she worked as a clinical research coordinator at Oregon Health & Science University, and as a nursing assistant in Vancouver, Washington. She continued volunteering at the Free Clinic in Vancouver, and working for the Winter Housing Organization for the homeless in Portland and Vancouver, until she was accepted at Pacific University to work toward her Physician Assistant degree. She enjoys traveling, running, reading novels, and spending time with friends and family as often as she can.
Abstract

Background: Proton Pump Inhibitor use is increasing in the hospital setting. This has coincided with an increase in *Clostridium difficile*-associated diarrhea (CDAD). *C. difficile* is a growing problem in hospitals, despite health care workers taking extra steps to wash hands and use personal, protective equipment in patient rooms. Known risk factors for the development of *C. difficile* infection are being carefully reviewed and considered. Upset of the normal intestinal flora is a known risk factor for the development of CDAD. In addition, a controversial risk factor has been proposed: Proton Pump Inhibitors (PPI). Hypothesis: Hypochlorhydria from PPI is a risk factor for developing CDAD. Study Design: Systematic review of available medical literature and reviews. Methods: An extensive literature search was conducted on Medline-OVID, CINAHL (EBSCOhost), and PubMed using the search terms “proton pump inhibitor and *Clostridium difficile*”, “Proton Pump Inhibitors”, and “*Clostridium difficile*”. Relevant references were retrieved and references from the reviewed clinical trials listed were used as sources for this paper. Results: The majority of the clinical trials in the literature today show a strong association with PPI-induced hypochlorhydria inducing CDAD. Of the nine papers discussed in this review, seven showed strong associations with significance, while only two trials showed no association with PPI use and CDAD. Conclusion: There is a strong correlation between PPI-induced hypochlorhydria and CDAD. With this confirmation of such a strong association, a randomized controlled trial should be done to confirm these results. Keywords: Proton Pump Inhibitors, *Clostridium difficile*, hypochlorhydria
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List of Abbreviations

PPI.................................................................Proton Pump Inhibitors
C. difficile.........................................................Clostridium difficile
CDAD..............................................................Clostridium difficile-associated diarrhea
H2 Blocker......................................................Histamine 2 receptor antagonist
GARD.............................................................Gastric Acid Reducing Drug
Abx.................................................................Antibiotic
ICU.................................................................Intensive Care Unit
OR.................................................................Odds Ratio
CI.................................................................Confidence Interval
HR.................................................................Hazard Ratio
RCT............................................................Randomized Controlled Trial
Introduction

The use of Proton Pump Inhibitors (PPIs) and outcomes of *Clostridium difficile* associated diarrhea (CDAD) have come under close investigation over the past 10 years. Recent literature is showing the likelihood for the PPIs inducing hypochlorhydria which, in turn, might be inducing CDAD. A good practitioner of medicine should have a sound evidence base from which to practice. The questions must be postulated: What is the association between PPI use and CDAD? Is there good evidence to show an association? Does a clinical trial need to be run to provide an answer?

Overview and history of Proton Pump Inhibitors

Wolfe’s article shows that Proton Pump Inhibitors have been used for the treatment of acid-related disorders both in outpatient and inpatient settings since their introduction in the late 1980s. Currently, PPIs are indicated by the FDA for use in the following acid-related disorders: Peptic ulcer disease, eradication of *Helicobacter pylori*, treatment and prevention of gastroduodenal ulcers associated with NSAID use, Zollinger-Ellison syndrome, and finally the treatment of gastroesophageal reflux disease.

Use of PPIs has become increasingly common over the past 10 years in the hospital setting. Recently PPIs have been proven to have a well defined role in the prevention of stress ulcers in critical care patients.

Metz demonstrated that PPIs have potential adverse effects that fall into four main categories. The first is idiosyncratic reactions to PPI-induced interstitial nephritis, hepatitis, or allergy which are unpredictable and very uncommon. The second is drug-to-drug interactions, and is very predictable. Drug-induced reflex hyper-gastrinemia is expected when gastric acid secretion is inhibited and is the third potential adverse effect. The fourth, and the focus of this paper, is a drug-induced hypochlorhydria.
Hypochlorhydria is a low chloride amount in the gastric secretions, which causes an increase in gastrointestinal pH to more alkaline levels.

**Overview and history of Clostridium Difficile-Associated Diarrhea**

According to UpToDate, *Clostridium difficile* is an anaerobic gram-positive, spore-forming, toxin-producing bacillus that was first described in 1935. *C. difficile* exists in spore and vegetative forms. It survives in spore form outside the colon. The bacillus spores are resistant to heat, acid, and antibiotics. Once spores are in the colon, they convert to their fully functional vegetative, toxin-producing forms and become susceptible to destruction by antimicrobial agents.\(^1\) CDAD has been an increasing problem in hospitalized patients. McFarland, Mulligan, Kwok, and Stamm showed that nosocomial, or hospital acquired, *C. difficile* infections are frequently transmitted among hospitalized patients and that the organism is often present on the hands of hospital personnel caring for such patients.\(^4\) With this, there is strong support for an increase in hand washing and personal protection to stop this increasing incidence in *C. difficile* infection.

There are few risks that are recognized to be causes of *C. difficile* infection. A trial by Poutanen and Simor noted that the most common risk factor associated with *C. difficile* infection is exposure to antibiotics, “especially those with broad-spectrum activity such as penicillins, cephalosporin’s and clindamycin.” They also add that advanced age and severe underlying disease are independent risk factors for changes in fecal flora.\(^5\)

The normal flora of the colon presents a strong defense and resistance to *C. difficile* infection. When the body becomes immunocompromised or there is a change in the normal flora, resistance to the bacterium is lost. Any factor that alters the flora, such as a PPI inducing hypochlorhydria, will increase the risk of CDAD and infection.
Importance of exploring a link between PPI induced *C. difficile*

PPIs are a relatively safe way to control dyspepsia, ulcers, and esophageal reflux. PPIs have recently been added to gastrointestinal protocols within many hospitals around the United States, the United Kingdom, and Canada. With this increased use of PPIs, there has also been an increase in CDAD.\(^6\) PPIs may not change the outcome for patients in the short term, and many argue that they are safe, but with the “coincidental” increase in CDAD with PPI use, the question must be asked if these “harmless” drugs are actually causing harm.

It is well documented that PPIs induce hypochlorhydria thus changing the pH of the colon.\(^3,7\) In fact, in 1982, before the introduction of PPIs, Aslam and Musher demonstrated that hypochlorhydric patients are at greater risk for transmission of CDAD.\(^8\) With the increased use of PPIs, this change in the colon environment is important because risks associated with longer stays in hospital, increased *C. difficile* resistance, and mortality resulting from *C. difficile* infection are all also on the rise. Aslam et al. also demonstrated that *C. difficile* produces one or more toxins that cause colonic inflammation, leading, in extreme cases, to necrosis with perforation. *C. difficile* is an important cause of nosocomial morbidity and mortality and has been implicated in recent epidemics.

Nardino, Vender, and Herbert conducted a trial in 2000, highlighting inappropriate use of GARD therapy in hospitalized patients. The trial determined that in 65% cases, PPIs prescribed, were not indicated. They concluded that a there is a significant overuse of GARD therapy in hospitalized patients.\(^9\) Grube and May did a clinical review in 2007 on stress ulcer prophylaxis in hospitalized patients. Their conclusion was that GARD therapy was misused in the hospital setting and that as many as 71% of all patients on general medicine wards were receiving some sort of GARD therapy without any indication.\(^10\)

The current changes in our healthcare system make it even more important to keep our hospital expenses low and the cost of treatment of disease must be taken into account. Heidelbaugh and
Inadomi stated that the cost of inappropriate stress ulcer prophylaxis in hospitalized medicine patients is approximately $44,096 annually.\textsuperscript{11} In 2008, Vonberg, Reichardt, Behnke, Schwab, Zindler, and Gastmeier looked at the total cost, per patient, of a CDAD positive patient in the hospital setting. They found that it is significantly different in length of hospital stays and in cost per patient. The average patient with CDAD will cost Euro 33,840 (47,257 USD), while a patient without CDAD in the hospital will cost roughly Euro 7,147 (9,980 USD).\textsuperscript{12} With these statistics, it is of the utmost importance to try to decrease the factors that increase the risk of CDAD.

**Methods**

An extensive literature search was conducted on Medline-OVID, CINAHL (EBSCOhost), and PubMed using the search terms “Proton Pump Inhibitor and Clostridium Difficile”, “Proton Pump Inhibitors”, “Clostridium Difficile”. Relevant references were retrieved and references from clinical trials found were used as sources for this paper.

The clinical trials were reviewed and assigned validity numbers according to Tables 2 and 3. Inclusion criteria include studies published in English, adults over age 18, studies conducted after 1993, and currently hospitalized patients. Most of the clinical trials systematically reviewed are from 2007 and 2008, with one initial trial of importance in 1993. Clinical trials with patients both in the ICU and on a general medicine floor were included as well as trials that evaluated prophylactic use of PPIs, and trials that evaluated adverse events to include \textit{C. difficile}. Exclusion criteria include outpatient populations, child based trials, any trials before 1993, and non-English speaking trials. No upper age limit was set.

**Results**

A total of 10 trials (Table 1), including case studies, cohorts, and retrospective/prospective reviews were evaluated in this systematic review. The majority were conducted between 2002 and 2008. The results from one trial, conducted in 1993, were reviewed, as it was one of the first studies to link PPIs
with *C. difficile*. Most of the trials found associations between PPI use and subsequent *C. difficile* infection. The literature addressed hospital inpatients that were exposed to a PPI to see if *C. difficile* was an outcome. Patients with diagnosed *C. difficile* were retrospectively reviewed for PPI use. Two reviews which comment on these associations were included.

**Strong links of PPIs and *C. difficile***

Dial, Alrasadi, Manoukian, Huang, and Menzies ran a cohort trial where the cohort patients were identified from a pharmacy database that included all patients who received antibiotics while hospitalized on two general medical and one surgical ward at Royal Victoria Hospital in Montreal. Cohort patients were taken if their names appeared in the hospital infection control service registry with a positive toxin assay result for *C. difficile*. Of the 1187 patients, eighty one (6.8%) developed CDAD. Five hundred and ninety one patients were on PPIs. Fifty five (9.3%) of the patients on PPI developed CDAD. Five hundred and ninety six patients were not exposed to PPI and only twenty six of them (4.4%) developed CDAD. The relative risk of CDAD was higher among the patients who were prescribed PPIs than among those who were not prescribed those drugs. A multivariate analysis was run to look at the antibiotics with known higher risk of CDAD development, the number of antibiotics given, and the ward. CDAD remained significantly associated with the use of PPI (OR 2.1, 95% CI 1.2-3.5).

Dial et al. also ran a retrospective case control study “to assess the possibility that proton pump inhibitors were prescribed to patients who were sicker and had other risk factors for *C. difficile* infection.” The cases involved included all patients on all wards in the hospital who developed diarrhea with a positive *C. difficile* toxin assay result as diagnosed from a stool sample. The control group was selected from a list obtained from the hospital pharmacy of patients who had been prescribed any antibiotics while in hospital during the study period. Ninety four cases were found with ninety four controls to match. In the case group, sixty or (64%) were receiving PPIs while only thirty
four (36%) from the control group received PPIs. CDAD developed in one patient from the control group not receiving an antibiotic but who did receive a PPI. Use of PPIs was associated with *C. difficile* with an adjusted OR 2.7, 95% CI 1.4-5.2, among other risk factors.\(^{13}\)

Jayatilaka, Eddi, Bakaj, Baddsura, and Debari did a 5 year analysis of *C. difficile* infection in inpatient adult populations. They ran an incidence and correlation study regarding gastric acid-reducing agents, or GARD, and *C. difficile* infection. Relevant discharge summaries were reviewed based on a list of ICD-9 codes for patients positive with *C. difficile*. They observed that the usage of PPI increased substantially over the study period and correlated strongly with CDAD incidence, with a P=0.017, which is statistically significant.\(^{14}\) Any P value less than or equal to 0.05 is said to be statistically significant in all trials.

Jayatilaka et al. also did a simultaneous one year case control study at the same institution during the final year of the five year analysis. Cases selected tested positive test for *C. difficile* toxin A or B and had associated episodes of diarrhea. Two controls were selected for one case, where they were matched for admitting dates, age, and gender. These two groups were further stratified by GARD use into H2 blockers and PPIs. Those two groups were further stratified according to those using GARD before or after admission. Of the 244 controls, 112(46%) were on PPI’s before admission, while eighty four (69%) of the 122 cases were on PPI’s. The association between PPI use and CDAD was analyzed using odds ratios. Univariate analysis was performed for patients on PPIs prior to hospital admission and the OR was 2.61 with a 95% CI of 1.65-4.12, while those on PPIs post-admission had an OR of 2. 57 with a 95% CI of 1.45-4.12.

Aseeri, Schroeder, Kramer, and Zackula looked at whether PPIs are a risk factor for CDAD. They ran a case controlled study of hospitalized patients who developed CDAD. Cases were identified as *C. difficile* toxin positive by Premier Toxin A and B enzyme immunoassay, with new onset of two or more loose bowel movements per day after admission for 3 days. The control group had the same
inclusion criteria, expect no diarrhea, with or without positive toxin. The control group was pair matched by admission date, antibiotic exposure, gender, age groups, ward, and room number at admission. One hundred eighty-eight subjects were identified with ninety four cases and matched control. McNemar’s test for the association between gastric acid suppression therapy and CDAD showed a significant association with a P=0.030. The cases had 72 (76.6%) with PPI exposure, while the controls only had 40 patients or 42.6%. Risk factors were sparse in the results, so a multivariate exact conditional logistic regression was conducted. The results showed that patients exposed to PPIs were 3.6 times more likely to develop CDAD. This result was expressed as OR3.6, 95% CI 1.7-8.3.15

Choudhry, Soran, and Ziglam ran a prospective case series to evaluate the appropriateness of prescribing PPI to patients diagnosed with C. difficile. One hundred thirty eight hospitalized patients who developed CDAD were studied over a four month period. Eighty eight (64%) of the 138 patients who developed CDAD were on PPIs. The mean age was seventy six (ranged 35-97) and forty nine were female (55.7%). 90% of the patients were on a PPI for longer than four weeks. An appropriate indication for use of the PPI was only apparent in forty seven (53.4%) of these patients.6

Cadle, Mansouri, Logan, Kudva, and Musher ran a retrospective case series to evaluate the role of concurrent use of PPIs in the outcomes of treatment for CDAD. This trial was conducted at a Veterans Affairs medical center in which C. difficile was diagnosed. One hundred and thirty eight of the 140 patients were male. The outcomes were evaluated as cured, did not respond to therapy, and disease recurrence to CDAD. Ninety-seven (69%) of patients received a PPI and forty three (31%) did not. Of the patients receiving PPIs, thirty seven (38%) were cured, twenty (21%) did not respond, and 40 (41%) had disease recurrence. Patients were 4.17 times as likely to have a recurrence of CDAD while taking a PPI.16

Nachnani, Bulchandani, and Allen ran a retrospective case series to evaluate whether worse outcomes would result for patients taking PPIs who currently had CDAD or who developed it while in
the hospital. Fifty-five consecutive patients had records reviewed who were diagnosed with CDAD. PPI use was considered if the patient had been on it for seven or more days before *C. difficile* was diagnosed. 26 (53%) of patients were on PPIs at admission. In this study, the use of PPIs were an independent and the ONLY risk factor associated with longer hospital stays by almost 4.5 days, with a P=0.033.17

**No conclusive evidence of PPIs causing CDAD**

Beaulieu, Williamson, Pichette, and Lachaine ran a case series trial to determine whether use of gastric acid-suppressive agents increased the risk of CDAD. The subjects were *C. difficile* positive if they had diarrhea for more than twenty four hours and positive Premier Cytoclone A or B between two days after admission and up to two months after discharge. All patients were selected from the medical ICU. Eight hundred and twenty seven records were included in this trial. The mean incidence of CDAD was 8.4 per 1000 days in the hospital. During the study, 335 patients received a PPI (40.5%), 470 (56.8%) received an H₂-receptor antagonist, while 182 (22%) did not receive either medication. Hazard Ratios (HR) were done to evaluate the risks with PPIs. The adjusted Hazard Ratio (aHR) was 0.89, 95% CI 0.59-1.36. The result indicates that the likelihood of developing CDAD was not significantly different for patients taking PPIs or not taking PPIs.18

Simor, Yake, and Tsimidis ran an epidemiological study at a long-term and chronic care facility during 1981 and 1990. Five hundred and four individuals were submitted for *C. difficile* culture and cytotoxin assays, with 236 specimens from ninety four residents testing positive. The number of patients taking anti-ulcer medications was 20 (of 94), while the number of residents taking anti-ulcer medications and not developing CDAD was 116. The OR was 2.1 with a 95% CI of 0.7-2.1. The P=.5, which is not statistically significant, resulting in evidence for the proposition that anti-ulcer medications do not increase the risk for CDAD.19 However, the anti-ulcer medication probably was not a PPI, a significant piece of to trial.
Discussion

The goal of this systematic review is to evaluate recent primary research to determine if the evidence suggests PPI induced hypochlorhydria is a risk factor for developing CDAD. There is a shortage of cohort and case controlled trials in this area of medicine. There are commentaries and reviews in the literature that suggest an association between PPIs and CDAD, but were not included in this systematic review.

Dial, Aseeri, Jayatilaka, Choudhry, Cadle, and Nachanani had all run trials with showing associations of PPIs and a resultant CDAD. Although a correlation was shown, this does not mean a direct causation. These finding show evidence for further trials to define a direct causal relationship of the PPI causing CDAD. The study done to show deny any association of PPI inducing CDAD by Beulieu holds more weight than the epidemiology study done by Simor. Both trials contradict the association of PPI inducing CDAD and they both identify the need for further study.

The variability among the trials also makes it very difficult to evaluate this clinical question. Validity was difficult to determine on this variation of trials. The necessary questions were asked and evaluated in Table 2 for the cohorts and in Table 3 for the case controls. The cohorts were given a score for each of the questions answered with four of four being optimum score, two and three out of four were acceptable scores, and one or zero as unacceptable scores. Both cohort trials fell in the acceptable range. The case control trials were validated on a scale out of three. Each question had one numerical value, as with the cohort. Three out of three was the best, two out of three was acceptable and one or zero was unacceptable. Both case control studies were in the acceptable.

In the case series studies, a problem arose in determining validity. It is impossible to determine whether the observed outcome would likely have occurred in the absence of exposure during case series studies.\textsuperscript{20}
Thus, the importance of recognizing that the results will generate questions for regulatory agencies and clinicians should not be dismissed. Clinical investigators should make policy based on studies that are determined to be valid. The usefulness of these types of studies, case series, and reviews lies in pointing to future experiments that can be carried out under better conditions.

Most of the trials evaluated showed a link with PPIs as risk factors for CDAD. The literature clearly demonstrates that the response to the critical question in this systematic review is in the affirmative. Dial’s cohort carries the most weight. After all the results were presented, they followed up with a multivariate analysis of antibiotics that are known to cause CDAD, such as cefazolin, florquinolones, Vancomycin, and second and third generation cephalosporin’s. After this multivariate analysis, it was still their conclusion that PPI use was strongly associated with the development of CDAD. Controlling for the known risk factors gives the answers more influence. The editorial on the trial done by Aseeri, written by David Metz, concludes with him proposing that the most important way to reduce risk of CDAD is for careful barrier nursing, hand washing among patients, and limiting unnecessary antibiotic exposure.3

He makes many good points throughout his paper and at the end of his editorial, in his conflict of interest statement, he states he has received grant support and honoraria from, among others, Astra Zeneca and Wyeth, who sell PPIs. The literature is strong to support the association of PPI inducing hypochlorhydria in turn being a risk factor for CDAD. With the evidence to show the poor outcomes on patients, longer hospital stays, and an increased financial burden on patients and on hospitals, this is a risk factor that should be eliminated. Further research must be done for more conclusive evidence, as described in the section for recommended further study.

**Limitations of Study**

The methodological limitations should be minimal, as both trials sponsored by hospitals and pharmaceutical companies were used, although some bias may remain. This is not an RCT to give an
example of a population but a mere sampling of trials in the literature at this point in time. Systematic reviews of this issue alone cannot fully conclude whether or not PPIs should be used in hospital setting. High quality RCTs must be done.

**Recommendations for further study**

Currently, the best types of trials used to explore this topic are cohort and case controls. These are good because studies including extremely large populations have been included. The current gold standard for clinical trials is randomized controlled trials (RCT) which are the best way to evaluate a question with primary research. RCT are ideal because they have the least amount of bias, most control within the trial, and balanced measurements.

Many hospitals have PPIs as part of the GI prophylaxis. If PPIs are out on so many protocols, an RCT should be done to evaluate this use of PPIs. The randomizations should be double-blinded in two groups with PPI use vs. placebo. The PPI should be the same one used for all patients. The patient population should be those admitted to a medical or surgical ward, over the age of 18, and not currently taking a PPI. Patients should be recruited over a span of 2 years, to get accurate patient numbers. Randomization should take place with a blinded randomization, such as an interactive voice response system (IVRS), through a telephone system. The patients should be followed for as long as they are admitted to the hospital and through discharge after 2 months. Patients should be followed to monitor any adverse events from the use of prophylactic PPI. Many other known risk factors, for example, advanced age and antibiotic use, will need to be accounted for in the trial. The results should be monitored and controlled with univariate and multivariate analysis with controls for the known risk factors. Certain antibiotics should be taken into account, especially those known as risk factors for inducing CDAD. All patients should be followed up for evaluation and status.
Conclusion

At this point, the evidence strongly suggests that hypochlorhydria induced by PPIs is a risk factor for CDAD. With the evidence that PPIs are being used inappropriately and even with no indication at all, the risks outweigh the benefits. Something more needs to be done to further evaluate the risks. CDAD is a very important disease associated with nosocomial infections. While hand washing and personal protection are helpful ways to control the spread of disease, health care providers have a responsibility to eliminate any other risk factors for this devastating disease in our hospitals today.
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<td>Choudhury: Overuse and inappropriate prescribing of proton pump inhibitors in patients with C. diff-associated disease/QJM</td>
<td>2008</td>
<td>Hospitalized patients with C. Diff</td>
<td>PPI use</td>
<td>None</td>
<td>PPI use and indication</td>
<td>Prospective Case series</td>
<td>Well done case series</td>
</tr>
<tr>
<td>Mates: Clostridium difficile Colitis: Wash Your Hands Before Stopping the Proton Pump Inhibitor/Am J Gastroenterology</td>
<td>2008</td>
<td>Hospitalized patients with C. Diff and diarrhea</td>
<td>Possible PPI therapy</td>
<td>Hospitalized patients without C. Diff or diarrhea</td>
<td>Risk factors associated with CDAD</td>
<td>Editorial</td>
<td>Editorial on Aseri</td>
</tr>
<tr>
<td>Cunningham: Is over-use of Proton Pump Inhibitors fueling the current epidemic of Clostridium difficile-associated diarrhoea? Journal of Hospital Infection</td>
<td>2008</td>
<td>All pts on PPIs</td>
<td>PPI use</td>
<td>PPI over-use or inappropriate use</td>
<td>CDAD</td>
<td>Systematic Review</td>
<td>Good resources</td>
</tr>
<tr>
<td>Beaucet: Risk of Clostridium difficile-Associated Disease Among Patients Receiving Proton-Pump Inhibitors in Quebec Medical Intensive Care Unit/Infection Control and Hospital Epidemiology</td>
<td>2007</td>
<td>Medical ICU patients</td>
<td>PPI Use</td>
<td>No PPI</td>
<td>CDAD</td>
<td>Cohort</td>
<td>3 out of 4</td>
</tr>
<tr>
<td>Jayatilaka: Clostridium Difficile Infection in an Urban Medical Center: Five-year Analysis of Infection rates among Adult admission and Association with the Use of Proton Pump Inhibitors/Annals of Clinical and Laboratory science</td>
<td>2007</td>
<td>Case Series: Adult inpatients hospital Case Study: Hospitalized pts. With CDAD</td>
<td>Series: H. blockers PPI use Study: Cases with CDAD</td>
<td>Series: Patients with C. Diff, patients without C. Diff, study: Age and gender matched with CDAD cases</td>
<td>Series: Correlation of PPI use with CDAD Study: PPI use before admission vs PPI use after admission</td>
<td>1 Case study</td>
<td>1 Case series</td>
</tr>
<tr>
<td>Sinor: Infection Due to Clostridium Difficile among elderly residents of a long term-care facility/Clinical Infectious Disease</td>
<td>1993</td>
<td>Long-term residents with C.diff</td>
<td>Abx use</td>
<td>None</td>
<td>CDAD vs No infection, review of all possible risks associated</td>
<td>Epidemiology</td>
<td>Good review and compilation of information</td>
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</tbody>
</table>
Table 2 Cohort Validity

<table>
<thead>
<tr>
<th>COHORT</th>
<th>DIAL</th>
<th>Beaulieu</th>
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<tbody>
<tr>
<td>Were patients similar for prognostic factors that are known to be associated with the outcome (stat adjustments made)?</td>
<td>Yes, patients taking PPIs and not taking PPIs were just as likely to be taking two or more, or antibiotics that have a high risk of causing C.diff diarrhea.</td>
<td>Yes, they were all medical ICU patients. Although this, there were not 2 specific groups to compare. It was Cdiff and lists of risk factors involved.</td>
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<tr>
<td>Were the circumstances and methods for detecting the outcome similar</td>
<td>Yes and surveillance bias was ruled out. C.Diff infection was identified by verifying names in the hospital’s infection control registry. Addition to this list was a stool sample identified with a positive toxin assay.</td>
<td>Yes, The study pop was composed of pt's in the MICU for &gt;24hrs.</td>
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<tr>
<td>Was the follow-up sufficiently complete</td>
<td>Yes, Medication data was taken 30 days before c. diff diagnosis. Outcomes were followed for 30 days after C. Diff diagnosis.</td>
<td>Yes, survival analysis was performed instead of logistic regression analysis, to avoid survival bias associated with high mortality rates in the ICU.</td>
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Table 3 Case Control Validity

<table>
<thead>
<tr>
<th>Case-Control</th>
<th>Dial</th>
<th>Aseeri</th>
<th>Jayatilaka</th>
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<tbody>
<tr>
<td>Were cases and controls similar with respect to the indication or circumstances that would lead to exposure?</td>
<td>Yes, control subjects were selected from a list obtained from the hospital pharmacy of patients who had been prescribed any antibiotics while in hospital during the study period—other risk factors were controlled for.</td>
<td>Yes, case and controls were matched on a 1:1 ratio based on the following factors, a) date of hospital admission, b) antibiotic use, c) gender, d) age group e) patient location at time of admission f) room time at admission **with specific antibiotics broken down to number, type and duration.</td>
<td>Yes, they are all hospital inpatients. Although this, some were accepted that were already on PPI's. This would bias the data.</td>
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<tr>
<td>Were the circumstances and methods for determining exposure similar for case and controls?</td>
<td>No, cases were defined as all consecutive ward patients with <em>C. diff</em>. Controls were selected from a list obtained from the hospital pharmacy, but the methods for determining exposure were the same.</td>
<td>Yes, cases and controls were both identified by the inclusion and exclusion criteria. The only difference in the two groups was diarrhea, and/or a positive <em>C. Diff</em> toxin for the cases.</td>
<td>Yes, for each of the cases two controls were found and admitted during the same time period, and age and sex were matched to the <em>C. Diff</em> positive case</td>
</tr>
</tbody>
</table>
1. Wolfe MM. Overview and comparison of the proton pump inhibitors for the treatment of acid-related disorders. Available at: http://www.uptodate.com/online/content/topic.do?topicKey=acidpep/10094&selectedTitle=1~150&source=search_result.


