Association between omeprazole use and *Clostridium difficile* infection among hospitalized patients: A case–control study of the Saudi population

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**ABSTRACT**

Background: While few international studies have assessed the association between omeprazole use and the risk of *Clostridium difficile* infection (CDI), research into this is lacking in Saudi Arabia and the Middle East region. The aim of this study was to determine whether exposure to omeprazole is associated with the risk of *Clostridium difficile* infection in a sample of hospitalized Saudi patients.

Methodology: A retrospective matched case–control study was conducted at the King Abdulaziz Medical City in Riyadh, Saudi Arabia, from 1 August 2010 through 31 July 2015. The analysis included a total of 200 patients: 100 CDI cases and 100 matched controls.

Results: The majority (60%, 120 out of 200) of patients had received proton pump inhibitors (PPIs), and a minority (18.5%, 37 out of 200) had received omeprazole. The PPI use was insignificantly higher in CDI cases than in controls. However, the use of omeprazole was significantly higher in CDI cases compared with controls. Specifically, patients receiving omeprazole were two times more likely to develop CDI compared with controls (aOR = 2.1, 95% confidence interval (CI) = (1.007–4.437)). After adjusting for potential predictors of CDI, watery diarrhea (aOR = 59.1, 95% CI = 19.831–175.974) and abdominal pain (aOR = 7.5, 95% CI = 2.184–25.445) were found to be independent predictors of CDI.

Conclusions: The data suggests that PPIs were commonly used in patients admitted to King Abdulaziz Medical City in Riyadh: six out of ten patients received PPIs. The findings support a possible association...
between the use of omeprazole and a high risk of CDI. To confirm causality, the link between omeprazole and CDI should be assessed in a large interventional study.

Keywords: *Clostridium difficile* infection, omeprazole, watery diarrhea, abdominal pain, Saudi Arabia

**BACKGROUND**

*Clostridium difficile* infection (CDI) is characterized by a wide range of symptoms from diarrhea to life-threatening or severe colitis. Over the last decade, the prevalence and severity of CDI has increased significantly worldwide, and it is a major and unpleasant complication of antibiotic therapy, especially in older patients.

The recent use of proton pump inhibitors (PPIs) has increased tremendously and causes major public health implications. Although PPIs reduce gastric-acid-related disorders, they may also increase the risk of CDI. Many published studies have revealed that PPI use increases the risk of CDI among patients; however, there are conflicting findings as some studies have not obtained sufficient evidence that PPIs increase the risk of CDI. One systemic review and meta-analysis found insufficient evidence for the association between the use of PPIs and CDI. Furthermore, Lowe et al., and Naggie et al., reported that the relationship between PPI use and CDI may depend on antibiotic use. This includes the number of antibiotics received, antibiotic class, and the timing of antibiotic therapy.

The incidence of CDI continues to increase in patients admitted to King Abdulaziz Medical City in Riyadh, as well as the use of gastrointestinal drugs (e.g., omeprazole and esomeprazole). In this study, we assess the association between gastrointestinal drug use and CDI among hospitalized Saudi patients who had been treated with antibiotics.

Few studies have assessed the relationship between different classes of PPIs and CDI, namely omeprazole (Losec 20 mg tablet, AstraZeneca UK) and esomeprazole (Nexium 20, 40 mg tablet and 40 mg vial for IV injection, AstraZeneca UK) therapies. The use of omeprazole therapy was associated with increased risk of CDI in hospitalized patients. Hegarty et al., reported that omeprazole therapy reduces the gene expression, which may promote CDI. In a study conducted in Bangkok, Thailand, on patients with confirmed CDI toxin A, almost half of the population studied (44.6%, 25 out of 55) received either ranitidine or omeprazole. More epidemiological investigations in different populations are needed to examine PPIs separately for each therapy (esomeprazole and omeprazole) as potential risk factors for CDI.

No previous study was found to examine the association between gastrointestinal drugs (including omeprazole and esomeprazole) and CDI in Saudi Arabia or the Middle East. The study tested whether there was sufficient evidence that PPI (omeprazole or esomeprazole therapy) use increases the risk of CDI in a sample of hospitalized Saudi patients who had taken antibiotics during the previous 30 days.

**METHODOLOGY**

A retrospective matched case-control study was completed at the King Abdulaziz Medical City in Riyadh (KAMC-R), Ministry of National Guard, Saudi Arabia. KAMC-R was established in May 1983 and initially provided medical, obstetrical, surgical, and critical care services to the National Guard population and their dependents. Expansion of services over the years has resulted in more than 1800 beds, as well as specialized services such as oncology and organ transplant. This study was approved by the IRB office at King Abdullah International Medical Research Center (KAIMRC), Research Protocol #SP15/116.

**Study subjects**

The study included hospitalized patients with suspected CDI who had taken antibiotics during the previous 30 days. The study population (CDI cases and controls) was selected by screening microbiology laboratory databases from 1 August 2010 to 31 July 2015. The Microbiology Laboratory at KAMC-R uses stool cultures to diagnose the presence of CDI and its toxins. Positive CDI results were identified using the A04.7 code, in accordance with the guidelines found in the International Statistical Classification of Diseases and Related Health Problems. Cases were defined as hospitalized antibiotic users suspected of CDI, whose stool cultures, based on real-time polymerase chain reaction (PCR) assays, were positive for CDI. Controls were defined as hospitalized antibiotic users suspected of CDI or other types of infections, whose stool cultures, based on real-time PCR assays, were negative for CDI. The controls were matched with the cases in terms of age, gender, and length of hospital stay.
We excluded patients whose stool culture results were not available, who were aged less than 14 years, who were admitted to ICU because of complications with suspicion of infection by many organisms, who used antacids such as ranitidine or sucralfate, and patients who used laxative medications – to prevent confusing diarrhea with CDI. The exclusion criteria also included patients who used systematic antibiotics for more than 30 days and patients with Crohn’s disease, ulcerative colitis, short bowel syndrome, or any type of cancer. Patients who had been exposed to PPI drugs for less than 14 days were also excluded from this study.

**Sample size**

nQuery Advisor was used to calculate the required sample size in each group. The power analysis showed that for an odds ratio of 2.27, the anticipated probability of exposure to PPIs given a CDI of 65%, and an anticipated probability of exposure to PPIs given a no CDI of 45%, would require a sample size of 96 in each group. A total of 315 patients admitted to King Abdulaziz Medical City in Riyadh were retrieved and included in the matching process. The study included 100 patients admitted and diagnosed with CDI based on real-time PCR assays. Confirmed CDI cases were matched with the no CDI group on gender, age (± 5 years), and the length of hospital stay (± 7 days) on the basis of 1:1 to patients admitted who tested negative for CDI on real-time PCR assays. The PPIs, omeprazole, and esomeprazole were used as exposures. The final data included 200 eligible subjects (100 CDI cases and 100 controls).

**Data collection**

QuadraMed and Pharmacy computer systems as well as medical records (charts review) were reviewed retrospectively to retrieve the required variables for the controls and CDI cases. The following demographic data were collected: age and gender. Data on different classes of PPI drugs (including esomeprazole and omeprazole) were collected. The following clinical data were also collected: length of hospital stay, chronic diseases, diabetes (DM), hypertension (HTN), heart failure (HF), renal failure (acute or chronic), dyslipidemia, and organ transplants. Data on the type of feeding by mouth (PO) were collected (nasogastric tubes (NGT) and percutaneous endoscopic gastrostomy (PEG)). Clinical symptoms of CDI were collected: watery diarrhea (Yes/No), abdominal pain (Yes/No), fever (Yes/No), blood or pus in the stool (Yes/No), nausea and vomiting (Yes/No), and high white blood cell count (Yes/No).

**Data analysis**

We performed statistical analyses using IBM SPSS Statistics (IBM Corp. Armonk, NY, USA). Continuous data were expressed as mean and standard deviation (mean ± SD), whereas categorical data were expressed as counts (n) and percent (%) (Table 1). Differences in age and length of hospital stay across CDI cases and controls were tested using independent two-sample t-tests (Table 1). The primary analysis was to examine whether CDI is associated with the PPIs, esomeprazole, or omeprazole. The associations between the final diagnosis status (CDI cases and controls) across clinical and exposure data were assessed by a Chi-square test (Table 1). In order to identify independent risk factors for CDI, we assessed the relationship between CDI and PPIs (including esomeprazole and omeprazole), adjusting for potential confounders (Table 2). The level of significance was set at 0.05.

**RESULTS**

Table 1 shows that the distributions of age, gender, and length of hospital of stay were fairly similar in CDI cases and controls. The overall mean age (± SD) was 67.3 ± 18.2 years for both groups (67.8 ± 18.6 CDI cases vs. 66.8 ± 17.9 controls, p = 0.679) and the length of hospital stay for both groups was 19.2 ± 32.0 days (18.7 ± 23.6 CDI cases vs. 19.7 ± 38.8 controls, p = 0.826). The majority of the sample (67.5%, 135) were 65 years old or over however, no relationship between patients aged 65 years or over and CDI was observed. Male gender was distributed evenly between groups (42% CDI cases vs. 42% controls, p = 1.0).

The majority (85.5%) of the patients had a chronic disease, 62.5% had diabetes mellitus, 74% had hypertension, and 12.5% had heart failure. The most common feeding was PO (74.9%). Out of the 200 patients, 120 (60%) received PPIs, 84 (42%) received esomeprazole, and 37 (18.5%) received omeprazole. On examining the association between PPI use and CDI, we observed no significant association with CDI risk. There was a similar proportion of patients who had exposure to PPIs: 65% (65 out of 100) in the CDI group, relative to 55% (55 out of 100) in the control group (p = 0.149). There was also a similar proportion of patients who had...
exposure to esomeprazole: 41% (41 out of 100) in the CDI group, relative to 43% (43 out of 100) in the control group ($p = 0.774$). However, the use of omeprazole was more common, 24% (24 out of 100) in CDI cases compared to 13% (13 out of 100) in controls ($p = 0.045$).

Watery diarrhea was a more common symptom in CDI cases (74%, 74 out of 100) compared with the controls (7%, 7 out of 100) ($p = 0.001$). CDI patients were more likely to have abdominal pain (28%, 28 out of 100), compared to controls (9%, 9 out of 100) ($p = 0.001$). CDI case subjects were more likely to have blood or pus in the stool (8%, 8 out of 100) compared with the controls (1, 1 out of 100) ($p = 0.035$). The risk of nausea and vomiting increased in CDI cases (37%, 37 out of 100) compared to the control group (20%, 20 out of 100) ($p = 0.008$).

It was found that patients with a chronic disease were more likely to use PPIs. The use of PPIs were common in patients with a chronic disease (64.3%, 110 out of 171), compared to those without a chronic disease (34.5%, 10 out of 29) ($p = 0.002$). However, the risk of CDI was insignificantly low in patients with a chronic disease (48%, 82 out of 171), compared to those without a chronic disease (62.1%, 18 out of 29) ($p = 0.160$).

Table 2 shows independent risk factors for contracting CDI using the multivariate logistic models. Watery diarrhea (OR = 59.1, 95% confidence intervals (CI): 19.831 – 175.974) and abdominal pain (OR = 7.5, 95% CI: 2.184 – 25.445) were identified as primary factors associated with a high risk of CDI.

**DISCUSSION**

We used a retrospective matched case–control study to identify potential risk factors of CDI in a sample of hospitalized Saudi patients who received antibiotics during the previous 30 days. Each CDI case was matched with one control subject in terms of age,
gender, and length of hospital stay. We tested 
hypotheses to determine whether there was suffi-
cient evidence that PPI use (including esomeprazole 
or omeprazole therapy) increases the risk of 

**CDI.**

In both the **CDI** cases and controls, a total of 120 
(60%) of the patients received PPIs. The study finding 
suggests that PPI use was not independently 
associated with an increased risk of **CDI** in a sample of 
hospitalized Saudi patients. Similar results were found 
in a few reports assessing the independent association 
between PPI use and the risk of **CDI.**5,6,16,17 The 
consistency in findings between our study and these 
reports could be due to removing the confounding 
effects of antibiotics as the association between PPI 
use and **CDI** may depend on antibiotic use.6,16

Moreover, patients were relatively older in the 
cohorts of these studies, including our study. 

The association between PPI use and **CDI** is still being 
debated, as most previous studies suggest an 
association between PPI use and **CDI.**7–15 Our study 
revealed inconsistent findings with these reports. This 
could be due to methodological issues such as the 
characteristics of the selected cohorts (e.g., older 
age) and confounding effects.6,16 In our study, we 
removed the confounding effects of antibiotics by 
including patients (**CDI** cases and controls) who 
received antibiotics during the previous 30 days. 
Moreover, when we categorized patients by age to at 
least over and below 65 years of age, the data failed 
to demonstrate an association between PPI use and 
**CDI** in patients 65 years of age or older. This is 
consistent with the findings of Lowe et al.6

We assessed PPIs esomeprazole and omeprazole 
separately for each therapy as potential risk factors of 
**CDI.** We found that the use of omeprazole was 
significantly more prevalent in the **CDI** cases than in 
the controls. According to our study, patients 
receiving omeprazole were two times more likely to 
develop **CDI** compared with controls. Similar findings 
were noted in other studies,19,20,21 which reported 
that omeprazole therapy might play an important role 
in increasing the risk of **CDI.** Nath et al.,19 evaluated 
the association between gastrointestinal drugs 
(omeprazole, ranitidine, cimetidine, famotidine, or 
sucralfate) and the risk of **CDI** in hospitalized patients. 
According to their study, patients receiving

**Table 2. Risk factors of CDI using multivariate logistic model.**

| Factors                | B   | SE    | Wald | P    | OR  | 95% CI for OR |
|------------------------|-----|-------|------|------|-----|---------------|
| Age                    | 0.01| 0.01  | 1.08 | 0.299| 1.0 | 0.987 1.043   |
| Length of stay/days    | 0.00| 0.01  | 0.54 | 0.463| 1.0 | 0.993 1.015   |
| Male                   | 0.42| 0.48  | 0.77 | 0.379| 1.5 | 0.599 3.855   |
| Diabetes mellitus      | 0.30| 0.59  | 0.26 | 0.613| 1.3 | 0.423 4.294   |
| Hypertension           | -0.08| 0.70 | 0.01 | 0.904| 0.9 | 0.234 3.608   |
| Heart failure          | 0.99| 0.67  | 2.17 | 0.140| 2.7 | 0.722 10.024  |
| Renal failure          | 0.45| 0.51  | 0.79 | 0.373| 1.6 | 0.580 4.278   |
| Organ transplant       | 2.18| 1.20  | 3.33 | 0.068| 8.9 | 0.852 92.370  |
| Dyslipidemia           | 0.65| 0.61  | 1.13 | 0.288| 1.9 | 0.578 6.330   |
| Watery diarrhea        | 4.08| 0.56  | 53.64| 0.001*| 59.1 | 19.831 175.974 |
| Abdominal pain         | 2.01| 0.63  | 10.29| 0.001*| 7.5  | 2.184 25.445  |
| Fever                  | 0.28| 0.49  | 0.33 | 0.568| 1.3 | 0.507 3.456   |
| Blood or pus in the stool | 2.64 | 1.44| 3.36 | 0.067| 14.0 | 0.834 235.512 |
| Nausea                 | 0.10| 0.54  | 0.04 | 0.850| 1.1 | 0.383 3.202   |
| High WBC               | -0.94| 0.57 | 2.78 | 0.095| 0.4 | 0.128 1.180   |
| Feeding – PO vs. PEG   | -0.77| 0.66 | 1.37 | 0.242| 0.5 | 0.126 1.686   |
| Feeding – NGT vs. PEG  | 0.41| 0.89  | 0.21 | 0.644| 1.5 | 0.264 8.626   |
| Esomeprazol            | 0.25| 0.52  | 0.22 | 0.640| 1.3 | 0.46 3.57     |
| Omeprazol              | 0.67| 0.70  | 0.94 | 0.330| 2.0 | 0.50 7.66     |
| Constant               | -2.39| 1.49| 2.58 | 0.108| 0.1 |             |

*Significant at α = 0.05. WBC: white blood cells; PO: feeding by mouth; NGT: nasogastric tubes; PEG: percutaneous endoscopic gastrostomy; PPI: proton pump inhibitor; **CDI**: Clostridium difficile infection.
gastrointestinal drugs were 3.2 times more likely to develop CDI compared with controls. The significance of our study is that not all previous studies have assessed the use of omeprazole separately as a risk factor of CDI.

Clinical symptoms show significant differences between cases and controls, especially watery diarrhea and abdominal pain, because those are the signs and symptoms of CDI. However, fever and a high white blood cell count were not significant because both groups had infections.

This study has several notable limitations. The observational case–control study is limited by a random sampling error of control patients. However, in order to prevent selection bias, we selected our patients (cases and controls) from the same period of time and the same population. Both groups were from a microbiology lab (which revealed CDI and other infections), and all patients had used antibiotics during the previous 30 days. However, in a hospital-based study, we learned that patients are more likely to be exposed to multiple antibiotic therapies, but we did not collect data on the number of antibiotics received, antibiotic class, and the timing of the antibiotics. Another limitation is that KAMC-R emergency department treats urgent medical conditions without knowing the patients’ full medication history (particularly PPIs), which could have resulted in adverse drug reactions. This can lead to serious adverse events that are life-threatening or have other negative health effects. Due to the small sample size retrieved, the patients were matched 1:1 instead of one case per two controls. A large hospital-based study excluding patients taking antibiotics is needed to examine more closely the association between PPIs (omeprazole, esomeprazole) and CDI. To our knowledge, this study is the first in Saudi Arabia and the Middle East region to report the association between PPIs (omeprazole, esomeprazole) and the risk of CDI. However, more research studies on each type of PPI, route of administration, and duration of use in larger populations are needed.

CONCLUSION
The study findings suggest that PPIs were commonly used in patients admitted to the King Abdulaziz Medical City in Riyadh, as six out of ten hospital patients with infection received PPIs. PPI use was not an independent risk factor for CDI. The results support a possible association between the use of omeprazole and a high risk of CDI. To confirm causality, the link between omeprazole and CDI should be assessed in a large interventional study. Clinical symptoms such as watery diarrhea and abdominal pain were associated with a high risk of CDI.

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COMPETING INTERESTS
The authors declare no competing interests.

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