original article

Clostridium difficile infection in an academic medical center in Saudi Arabia: prevalence and risk factors

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BACKGROUND: *Clostridium difficile* infection is one of the most common causes of diarrhea in healthcare facilities. More studies are needed to identify patients at high risk of *C difficile* infection in our community.
OBJECTIVES: Estimate the prevalence of *C difficile* infection among adult patients and evaluate the risk factors associated with infection.
DESIGN: Retrospective record review.
SETTING: Tertiary academic medical center in Jeddah.
PATIENTS AND METHODS: Eligible patients were adults (≥18 years old) with confirmed *C difficile* diagnosis between January 2013 and May 2018.
MAIN OUTCOME MEASURES: Prevalence rate and types of risk factors.
SAMPLE SIZE: Of 1886 records, 129 patients had positive lab results and met the inclusion criteria.
RESULTS: The prevalence of *C difficile* infection in our center over five years was 6.8%. The mean (SD) age was 56 (18) years, and infection was more prevalent in men (53.5%) than in women (46.5%). The most common risk factors were use of proton-pump inhibitors (PPI) and broad-spectrum antibiotics. The overlapping exposure of both PPIs and broad-spectrum antibiotics was 56.6%. There was no statistically significant difference between the type of PPI (P=.254) or antibiotic (P=.789) and the onset of *C difficile* infection.
CONCLUSION: The overall *C difficile* infection prevalence in our population was low compared to Western countries. The majority of the patients who developed *C difficile* infection were using PPIs and/or antibiotics. No differences were observed in the type of antibiotic or PPI and the onset of *C difficile* infection development. Appropriate prescribing protocols for PPIs and antibiotics in acute settings are needed.
LIMITATIONS: Single center and retrospective design.
CONFLICT OF INTEREST: None.

Clostridium difficile is a gram-positive spore-forming anaerobic bacteria that causes *C difficile* infection, one of the most common causes of diarrhea in healthcare facilities.[1-3] Its virulence arises from its ability to produce toxin A (TcdA) and toxin B (TcdB).1 Both toxins are pro-inflammatory and cytotoxic and cause extensive damage in the large intestine.[4] More than 40 risk factors are known to be involved in the development of the disease.[5] Host-related characteristics, including age, sex, race, and comorbidities, are well-described risk factors.[5]

A study conducted in 2011 to estimate the incidence across 34 counties in 10 geographic areas of the United States found that the incidence was higher in older people (aged ≥ 65 years), women, and white people.[6] Moreover, a meta-analysis conducted by Vardakas et al aimed at identifying the risk factors associated with a high-virulence strain of *C difficile* (BI/NAP1/027) found an increase in age (65 years and older) was associated with a greater risk of *C difficile* infection (BI/NAP1/027).[7] Other comorbidities, including but not limited to diabetes mellitus, tumors, and inflammatory bowel disease, are involved in the pathogenesis of the disease.[5]

Gastric suppressant agents such as proton pump inhibitors (PPIs) and histamine-2-receptor antagonists are widely used, and their association with *C difficile* infection has been evaluated.[8,9] PPIs increase the risk of *C difficile* infection by 38.6% compared to histamine-2-receptor antagonists.[8] In 2012, a meta-analysis (n=202 965) revealed that PPI use could increase the risk of *C difficile* infection two-fold.[10] Moreover, a case-control study including approximately 35 000 critically ill patients reported that an increased duration of PPI use (≥ 2 days) is considered a significant risk factor for *C difficile* infection.[11] Another case-control study found that PPIs are significantly associated with recurrence of *C difficile* infection.[12]

In addition to PPIs, broad-spectrum antibiotic use is a risk factor for *C difficile* infection infection due to the disruption of normal flora that in turn facilitates the proliferation of *C difficile*.[13,14] A systematic review and meta-analysis, which aimed to confirm the association between antibiotic use and *C difficile* infection, indicated that clindamycin and third-generation cephalosporins were most strongly linked with healthcare facility-associated *C difficile* infection.[15] Furthermore, the risk remains post-antibiotic exposure.[16] A multi-center case-control study conducted to identify the *C difficile* infection risk interval after stopping antibiotics found that during the first month the risk of *C difficile* infection was increased seven- to ten-fold.[16] *C difficile* infection has become an increasingly common infection with an increased severity over the past years. Data on risk factors for *C difficile* infection and disease epidemiology in Saudi Arabia are limited. Therefore, more studies are needed to identify patients at high risk of *C difficile* infection in our community. Hence, the objective of this study was to estimate the prevalence of *C difficile* infection in our institution (a tertiary academic medical center) in Saudi Arabia and to evaluate the common risk factors that influence the development of *C difficile* infection. In addition, we assessed the duration of exposure to risk factors and the relationship with onset of *C difficile* infection.

PATIENTS AND METHODS

We conducted this retrospective record review at King Abdulaziz University Hospital, a tertiary medical center in Jeddah. This study was approved by the Institutional Review Board at King Abdulaziz University (Reference No. 320-18). All medical records of adults (≥18 years old) who were admitted to the hospital between 2013 and 2018 in all wards were reviewed. The toxin A and B test was performed for patients who experienced diarrhea and were suspected of having *C difficile* infection. The inclusion criteria were adult patients with positive toxin A and B results. The exclusion criteria were patients who had diarrhea due to chronic *C difficile* infection before hospital admission or diarrhea due to any other bacterial or non-bacterial infection.

The data collected included demographics such as sex, age, and race, and infection markers such as body temperature, white blood cell (WBC) count, and the date of positive toxin A and B test results. We collected risk factors that were documented in the medical records. Such risk factors included ward (intensive care unit [ICU] vs. non-ICU), PPI use (yes vs. no), type of PPI administered during hospitalization, date of starting PPI, broad-spectrum antibiotics received during the 90 days before developing *C difficile* infection (yes vs. no), type of antibiotic, and the duration of antibiotic use. The primary outcome was the prevalence of *C difficile* infection, while other outcomes of interest included the risk factors and the duration of exposure until the onset of *C difficile* infection.

The data were protected in a secured spreadsheet to which only the researchers had access. Statistical analyses were performed using SPSS version 21 (IBM Corp., Armonk, NY). Descriptive statistics are presented using mean (standard deviation) and number (percent) . Quantitative variables were compared using an independent sample *t* test and one-way ANOVA assuming a normal distribution. A *P* value <.05 was considered statistically significant.

RESULTS

The mean (SD) age of the 129 cases that met inclusion criteria was 56 (18) years. Men accounted for (53.5%) of the cases (n=69). The majority of the patients were from non-ICU wards. Although the baseline WBC was elevated due to infection, the baseline body temperature was normal (**Table 1**). During the five years (2013–2018), the toxin A and B test was performed in 1885 hospitalized adult patients. Only 129 patients had positive test results and were diagnosed with *C difficile* infection. The prevalence rate of *C difficile* infection was 6.8%.

The two most common risk factors for *C difficile* infection were the use of PPIs and broad-spectrum antibiotics.More than half of the population received both agents simultaneously, followed by approximately a third who were either on antibiotics or PPIs alone. The category with the lowest percentage (7.8%) were patients who had not received any of the agents (**Table 2**).

Two types of PPIs were used by patients: omeprazole followed by pantoprazole. However, several broad-spectrum antibiotics were prescribed. Piperacillin-tazobactam was the most frequently used broad-spectrum antibiotic followed by ceftriaxone. The mean duration from the start of PPI use until *C difficile* infection onset was not significantly different between omeprazole and pantoprazole (*P*=.254). Additionally, the mean duration from the start of antibiotic use until *C difficile* infection onset was not significantly different between the types of antibiotics (*P*=.789). However, the comparison of duration of PPIs vs. duration of antibiotics indicated that PPI use led to an earlier onset of *C difficile* infection than antibiotics (**Table 3**).

DISCUSSION

The prevalence rate of *C difficile* infection from 2013 to 2018 was 6.8%. A similar low rate was documented previously in 2010 in the eastern region of Saudi Arabia.[17] Our results indicate that *C difficile* infection cases are limited, and the disease is not widespread. In contrast, Giancola and colleagues reported a 22% prevalence rate of a certain virulent strain in the United States between 2012 and 2016.[18] In addition, the inci-

Table 2. Risk factor exposure.

Patients not receiving any agents	10 (7.8)
Patients received proton pump inhibitors only	17 (13.2%)
Patients received broad-spectrum antibiotics only	29 (22.5%)
Patients received bothproton pump inhibitors and broad-spectrum antibiotics	73 (56.6%)

Table 1. Demographic and clinical characteristics of study group (n=129).

Age (years)	56 (18)
Gender	
Male	69 (53.5)
Female	60 (46.5)
Race	
White	105 (81.4)
Black	24 (18.6)
Hospital ward	
Non-ICU	113 (87.6)
ICU	16 (12.4)
Body temperature (°C) (median and interquartile range)	36.8 (0.4)
Leucocytes (WBC/L)	11.2 (6.7)

Data are number (%) or mean (standard deviation) unless noted otherwise.

Table 3. Duration of risk factor exposure and the onset to Clostridium difficile infection.

Risk factor		Duration from starting agent to infection onset of diagnosis	P value
Proton-pump inhibitors			
Omeprazole	68 (75.6)	6.41 (19)	.254
Pantoprazole	22 (24.4)	6.43 (19)	
Antibiotics			
Piperacillin-tazobactam	38 (37.3)	19 (33)	.789
Ceftriaxone	26 (25.6)	19 (33.5)	
Cefuroxime	15 (14.7)	20.2 (34.4)	
Ciprofloxacin	12 (11.8)	19.6 (32.9)	
Amoxicillin-clavulanic acid	6 (5.88)	21 (35.8)	
Ampicillin	4 (3.9)	13.8 (25.7)	
Clindamycin	1 (1)	-	

Data are number (%).

dence of *C difficile* infection in Europe has been increasing in recent years.[19] A possible explanation for the low prevalence reported in our study is daily hand hygiene related to religious practices. Hands are considered one of the main routes of pathogen transmission, and it has been reported that the hands of up to 59% of healthcare workers are contaminated with *C difficile*.[20] A study of an education program to improve patient hand hygiene reported that *C difficile* infection decreased significantly after the program was implemented.[21] However, proper handwashing technique should include soap and water.[22] Besides hand hygiene, another explanation for the low prevalence rate in Saudi Arabia vs. other countries is the lower sensitivity and specificity of the rapid enzyme immunoassay which is usually used to confirm the diagnosis of *C difficile* infection.[19] Low positive rates can overestimate the number of *C difficile* infection cases in some institutions leading to false prevalence rates.[23]

In our population, the number of male *C difficile* cases was higher than the number of female cases, whereas no significant sex differences were reported previously.[24] However, asymptomatic colonization was more prevalent in men than in women.[25] Another characteristic observed in our population is that mean ages tended to be older adults. *C difficile* infection is known to be more prevalent in older people due to their poorer health status.[26] In addition, hypertoxic strains, such as BI/NAP1/027, are strongly associated with older age.[7]

Other identified risk factors were PPI and antibiotic use. The percentage of patients receiving both broad-spectrum antibiotics and PPIs (56.6%) was higher than that of patients who were receiving only one agent. The finding that broad-spectrum antibiotic or PPI exposure leads to similar rates of *C difficile* infection may indicate that the combination of these risk factors markedly increases the risk of developing *C difficile* infection. Although we did not study the combined effect of broad-spectrum antibiotics and PPIs on *C difficile* infection, this association is consistent with the literature where it was found that hospitalized patients at the highest risk of developing *C difficile* infection were exposed to both antibiotics and PPIs.[27,28]

Regarding antibiotics, piperacillin/tazobactam (n=38, 37.3%) was the most frequently used broad-spectrum antibiotic among our sample followed by third-generation cephalosporins including ceftriaxone (n=26, 25.6%) and cefuroxime (n=15, 14.7%). It is believed that piperacillin-tazobactam is a strong risk factor for *C difficile* infection due to its broad-spectrum activity and impact on anaerobic bacteria, thus having the greatest effect on the large colon and normal flora.[29] In addition, third-generation cephalosporin use was previously documented to increase the risk of *C difficile* infection.[30]

The association between the duration of antibiotic use and *C difficile* infection is a directly established relationship.[31] In our study, the duration of use for all antibiotics before the occurrence of *C difficile* infection were approximately the same except for ampicillin and there was no difference between the type of antibiotics and the onset of *C difficile* infection. Similar results were reported by Thabit et. al for many antibiotics except for cefepime and cefazolin as both were significantly associated with *C difficile* infection occurrence after a median duration 8,6 days.[32]

PPI use is an independent risk factor for *C difficile* infection development.[33-35] In addition, after controlling for several risk factors such as age, sex, and antibiotics exposure, PPI use still increases the risk of *C difficile* infection.[36] Despite this, more than half of the patients in our study were using PPIs, either omeprazole or pantoprazole. Moreover, omeprazole use was 36% higher than pantoprazole use; however, there was no statistically significant difference between the type of PPI (omeprazole or pantoprazole) and *C difficile* infection onset. All the previously mentioned studies and our study included PPI use during hospitalization only; thus, all the patients were in an acute setting. In contrast, a population-based study conducted in Canada to estimate the association between outpatient PPI therapy and hospitalization with *C difficile* infection reported that PPI is not a risk factor in an outpatient setting.[37]

The retrospective design was a limitation. In addition, the study was conducted in a single center, and only adult patients were included; thus, the findings may not be generalizable.

In summary, the *C difficile* infection prevalence rate in our center was low compared to international rates, although the exposure to well-established risk factors was high. Furthermore, there were no differences in the type of antibiotic or PPI and the onset of *C difficile* infection. Institutional protocols for antibiotic and PPI use are highly recommended to prevent *C difficile* infection.

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