


Characteristics, Risk Factors, and Prevalence of *Clostridioides difficile* Among Hospitalized Patients in a Tertiary Care Hospital in Palestine

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Purpose: *Clostridioides difficile* is one of the most important nosocomial infection pathogens. It is linked with many risk factors. Unfortunately, many studies have been conducted in different countries to address the *Clostridioides difficile* infections (CDI), and no studies have been conducted in Palestine. This study aims to identify the prevalence and possible risk factors associated with CDI.

Patients and Methods: This was a retrospective descriptive study conducted at the An-Najah National University Hospital (NNUH) in Palestine. Data were collected for patients diagnosed with CDI who tested positive for GDH, toxins A and B between January 2018 and April 30, 2021. In addition, patient characteristics and risk factors associated with CDI were analyzed.

Results: A total of 593 participants were included in the study; 53% had hospital-acquired CDI. There was an insignificant association between participant age and CDI risk. Most patients had mild to moderate infections. Sixty-three percent of the participants were immunocompromised. About 58.5% used an antibiotic agent two weeks before CDI, and 67% were on a proton pump inhibitor (PPI). About 61.3% of patients were treated according to IDSA 2017 guidelines, and 94% responded adequately to the treatment provided.

Conclusion: There was an increased prevalence of community-acquired CDI, with a prevalence almost equal to that of hospital-acquired. In addition, most of the participants were immunocompromised. The risk factors for CDI, such as antibiotics and PPI use, were also observed with high prevalence among positive patients. Antimicrobial stewardship and the appropriate use of acid suppressors are warranted.

Keywords: *Clostridium difficile* infection, *Clostridium difficile* risk factors, community-acquired CDI, hospital-acquired CDI, PPI, antibiotics

Introduction

Clostridioides difficile is a gram-positive spore-forming anaerobic bacterium that causes gastrointestinal tract infection due to disruption of the normal microbiota of the colon caused by antimicrobial agents. CDI has been associated with the most nosocomial diarrheal infections among hospitalized patients,¹ causing substantial public health threats associated with higher morbidity and mortality worldwide.²

Symptoms related to CDI are associated with the production and release of different toxins.³ Symptoms of CDI include watery diarrhea (at least three watery stools within 24 hours), abdominal pain, fever and nausea. *C. difficile* is transmitted from person to person via the fecal-oral route. Healthcare facilities are at the highest

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risk of infection transmission due to environment, surfaces, and health worker contamination. Therefore, good hygiene among healthcare workers and surface disinfection are essential to minimize CDI. In addition, CDI patients must be isolated from other patients to prevent transmission.

CDI is classified as community-acquired (CA) or hospital-acquired (HA). According to the Infectious Disease Society of America (IDSA) guidelines, CDI is considered community-acquired if the diagnosis was without exposure to the healthcare facility after 12 weeks of discharge. On the other hand, it is regarded as hospital-acquired if the diagnosis was after 3 days of admission or within four weeks of release.⁴

Several factors increase the likelihood of CDI, including antibiotic exposure, older age, and hospitalization.¹ Antibiotic use and previous exposure to *C. difficile* are the two main risk factors for CDI. Fluoroquinolones, cephalosporins, carbapenems, and clindamycin have the highest risk of CDI.^{5,6} Other potential risk factors include; stomach acid suppression medications, immunocompromised patients, irritable bowel syndrome and chronic kidney disease, prolonged exposure to healthcare facilities, and enteral feeding (tube feeding) have the potential to cause CDI.^{7,8}

Treatment for CDI includes vancomycin, fidaxomicin, and metronidazole. The most recent guidelines update in 2017 by the IDSA and the society for healthcare epidemiology (SHEA) recommend vancomycin or fidaxomicin as first-line agents for initial treatment of CDI while metronidazole is preserved as an alternative therapy.⁴

During the last few years, there has been an increase in CDI rates due to the emergence of new strains.⁹ According to the Centers for Disease Control and Prevention (CDC), approximately half a million infections are estimated to occur in the United States each year. In addition, according to the National Institutes of Health (NIH), CDI increases morbidity, mortality, and healthcare costs. Hence, the total annual *C. difficile* attributable cost in the United States is approximately \$6.3 billion.

Minimal data are available on the prevalence and characteristics of CDI infections in Palestine. Therefore, this retrospective descriptive study aimed to determine CDI prevalence among hospitalized patients in a Palestinian teaching hospital by examining infection characteristics, risk factors, comorbidities, and treatment.

Methods

A retrospective descriptive study at the An-Najah National University Hospital (NNUH) in Palestine was conducted for all patients diagnosed with CDI from January 2018 to April 30, 2021. A laboratory-confirmed CDI was a patient with positive ELISA test detection of A or B CDI toxins. The CoproStrep *C. difficile* GDH + Toxin A + Toxin B rapid test was used to aid in CDI diagnosis. Patients with positive antigen results and negative toxin A or B results were excluded from the study due to the lack of other tests such as PCR for test result confirmation. In addition, patients who had laboratory test results with incomplete patient documentation or records were also excluded from the study.

Data on patient information, diagnosis, treatment, comorbidities, risk factors, and symptoms associated with CDI were collected and analyzed using the Statistical Package for Social Sciences (SPSS) version 22. Data collected included patient demographic information, hospitalization length, CDI symptoms such as diarrhea and abdominal pain, and the type of CDI community or hospital acquired. Prior antibiotics, proton pump inhibitors (PPIs), H2 receptor antagonists, and laxatives use were also collected. In addition, patients' comorbidities were considered and if the patient was immunocompromised. Data were recorded and categorized as required. Frequencies and percentages were used to represent the data. Pearson's Chi-square test was performed to assess the association between the possibility of being a CD-infected patient and patients' age and sex as potential risk factors.

Ethical Committee

This was a retrospective observational study conducted at the An-Najah National University Hospital (NNUH) in Palestine. The IRB committee approved the study design at Birzeit University and An-Najah Medical Hospital reference number BZUPNH2102. The requirement to obtain written informed consent from each patient was waived because this was an observational retrospective study. The patients were anonymized. Their information was non-identifiable. This study complied with the ethical guidelines of the Declaration of Helsinki and patient data.

Results

Data from 593 patients were extracted from the files for the current study. Laboratory test results revealed that 105 (17.7%) had a positive *C. difficile* antigen, 79 (13.3%) had

Table 1 Patient Characteristics of *Clostridium difficile* Toxins Test Result

Characteristic		Participants n(%)	Toxin A/Toxin B Test Result		P- value
			Positive n(%)	Negative n(%)	
Sex	Male	281 (47.4)	53 (17)	259 (83)	0.195
	Female	312 (52.6)	37 (13.2)	244 (86.8)	
Age	2–18	54 (9.1)	13 (24.1)	41 (75.9)	0.257
	19–44	195 (32.9)	29 (14.9)	166 (85.1)	
	45–64	202 (34.1)	30 (14.9)	172 (85.1)	
	65 or more	142 (23.9)	18 (12.7)	124 (87.3)	

a positive toxin A test, and 77 (13%) had a positive result for toxin B. A total of 90 patients had a positive result for toxin A or B; 8 patients were excluded due to incomplete records. In addition, 38 (46.9%) were community-acquired infections, while 43 (53.1%) were acquired due to hospital admission.

Half of the patients, 312 (52.6%), were females. 53 (17%) male and 37 (13.2%) female patients had a positive result for the *C. difficile* toxin test, as shown in Table 1, with no significant difference between the two groups ($P=0.195$) (Table 1).

Regarding age groups, findings demonstrated that most patients aged between 19 and 64 years with the highest percentage with positive CDI toxin test were among patients aged 2–18 years 13 (24.1%). No significant differences were found between the four age groups and their possibility of being infected ($P=0.275$) (Table 1).

The characteristics, risk factors, and symptoms with a confirmed diagnosis are presented in Table 2. Among 82 patients, 58.5%, 65.8%, 4.9%, 7.3% had used antibiotics, PPIs, H2 antagonists, and laxatives during the six weeks before CDI, respectively. The percentages of patients who suffered from abdominal pain and diarrhea

were 46.9% and 90.1%. In addition, 84.1% were treated as inpatients and 63.4% were immunocompromised.

Table 3 shows antibiotics administered within six weeks prior to the confirmation of CDI diagnosis. The antibiotics used most were Piperacillin-tazobactam 20 (24.1%), aminoglycosides 19 (23.2%), and cephalosporins 18 (22%).

Of the 82 patients with a confirmed diagnosis of CDI, 80 had a complete record of the treatment regimen, 49 (61.3%) had a treatment based on 2017 treatment guidelines (the latest guideline), while in 31 (38.7%) of the cases, the treatment guidelines were not followed. In evaluating patients' outcomes, in one case (1.5%), there was no indication for treatment, 75 (93.8%) responded to therapy while 4 (5%) were still untreated.

Among the total 82 patients with positive CDI results, 43% were found to have moderate CDI. 31.6% had mild, 16.5% had severe, and only 8.9% had Fulminant CDI (Figure 1).

The usage of antibiotics and PPIs among participants with *C. difficile* toxin tests was compared based on CDI severity. The results show that 84.6% of severe cases, more than 60% of mild and 50% of fulminant cases have used both antibiotics and a PPI before developing CDI (Figure 2).

Table 2 Participant's Characteristics and Symptoms (N=82)

Characteristics		n (%)
Prior antibiotic use	Yes	48 (58.5%)
PPI use	No	28 (34.2%)
	4 days or less	12 (14.6%)
	>4 day	42 (52.4%)
Anti H2 use	Yes	4 (4.9%)
Laxative	Yes	6 (7.3%)
Abdominal pain	Yes	43 (46.9%)
Diarrhea	Yes	73 (90.1%)
Treatment	Inpatient	69 (84.1%)
Immunocompromised	Yes	52 (63.4%)

Table 3 The Frequency of Antibiotics Used Prior Diagnosis (N=82)

Prior antibiotic use	n (%)
Piperacillin-tazobactam	20 (24.4%)
Aminoglycosides	19 (23.2%)
Cephalosporins	18 (22%)
Vancomycin	18 (22%)
Fluoroquinolones	16 (19.5%)
Carbapenems	11 (13.4%)
Colistin	5 (6.1%)
Metronidazole	3 (3.7%)
Penicillin	2 (2.4%)
Clindamycin	2 (2.4%)

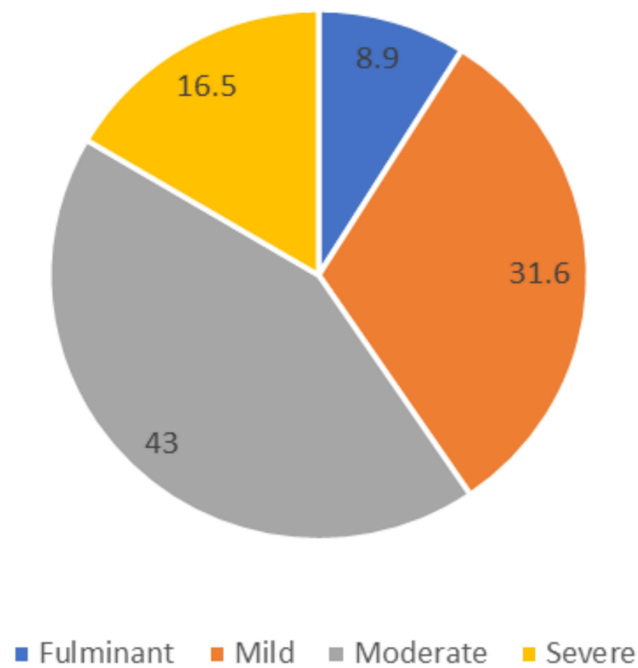


Figure 1 CDI classifications as percentages (N=82).

In this study, 93% of hospital-acquired CDI (HA-CDI) cases were treated with PPI, and 88.4% were also on antimicrobial agents. On the other hand, 36.8% of the community-acquired CDI (CA-CDI) cases used PPI, and 23.7% had taken antibiotics prior to CDI (Figure 3).

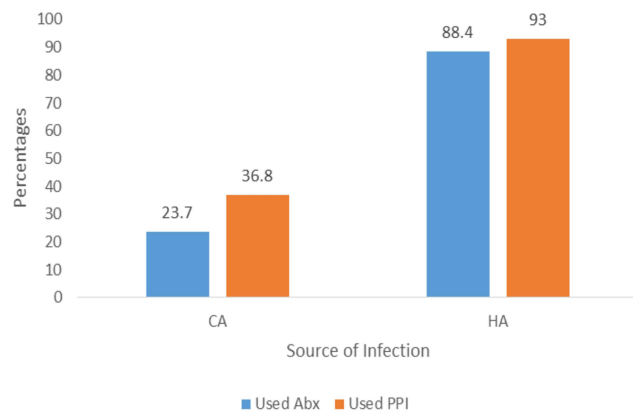


Figure 3 CA-CDI/HA-CDI and medication use (N=82).

Discussion

This study was the first to address CDI’s prevalence and risk factors among hospitalized and admitted patients in a teaching hospital in Palestine. According to many studies conducted in different countries, CDI has always been associated with many risk factors. The main risk factors for CDI are antibiotic exposure, stomach acid suppression medications, increased age, type of feeding, and extended hospitalization. These factors were also very evident in the study population.

Three-year hospital admission data revealed a total of 593 patients suspected of having a CDI infection, with only 90 patients tested positive for CDI toxin, which represents a very low prevalence of CDI infection. In addition, the

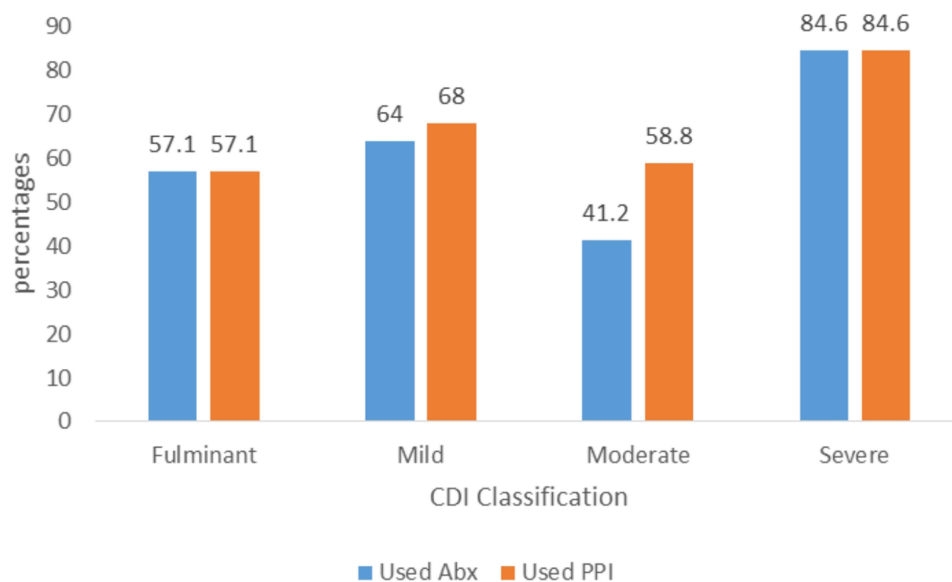


Figure 2 CDI classification and medication use (N= 82).

results of the CDI toxin test revealed no significant gender difference between male and female patients p-value 0.195. The result is similar to the Michigan university study finding, showing no gender difference in prevalence among patients infected with CDI.⁹

A recent review in 2017 at the Center for Anti-Infective Research and Development, Hartford Hospital, Hartford, USA, reported increased age as a risk factor for CDI.¹⁰ In 2015 the CDC reported that one out of every three CDIs occurred in patients aged 65 years or older. In addition, two out of every three healthcare-associated CDIs occurred in patients aged 65 years or older.⁸ Older ages are at increased risk for CDI due to the comorbidities usually seen in the elderly and physiological changes in the body, such as changes in immune system reactions and normal gastrointestinal flora. In contrast to the above, although the results indicated that the highest percentage with positive CDI toxin test (24%) was among patients aged 2–18 years, there was no significant difference among different patients based on age. This finding disagrees with other studies or CDC reporting due to the social characteristics of the elderly in Palestine and the lack of nursing home utilization increasing the risk among the elderly.¹¹ In addition, studies have shown that children are at an increased risk of developing CDI, especially community-acquired CDI.^{12,13}

A Washington University School of Medicine study for risk factors within the elderly group showed that elderly individuals with other risk factors such as overall health status affect the patient's risk of CDI.¹⁴ Another study by the Memorial Sloan Kettering Cancer Center in New York revealed that patients with comorbidities, such as hematologic malignancies are at a higher risk of developing CDI.¹⁵ This finding is evident in our study, in which more than 63% of the diagnosed patients were immunocompromised. An Oxford University study suggests that immunocompromised patients experience a high incidence of CDI, ranging from 6% to 33% distributed over cancers, HIV patients and solid organ transplant recipients.¹⁶ Immunocompromised patients with suppressed immune systems cannot prevent or delay the binding of either the bacterium or the secreted toxins to the bowel tract epithelial cells where they can cause damage.¹⁷

The CDC reported that antibiotics are a well-known cause of CDI and increase the likelihood of a patient catching *C. difficile*.¹⁸ An analysis of the FDA Adverse Event Reporting System showed that patients who took

penicillin combinations, carbapenems, cephalosporins, tetracyclines, macrolides, fluoroquinolones and trimethoprim-sulfamethoxazole were at higher risk of developing CDI.¹⁹ More than half of the participants in this study used antibiotics in the prior six weeks to CDI diagnosis. This finding is similar to recent regional studies conducted in Lebanon and Saudi Arabia to assess the risk factors for CDI revealed that the majority of participants diagnosed with CDI received antibiotics prior to the infection.^{20,21} A recent study in Egypt reported that patients with antibiotic treatment are at higher risk for CDI.²² The pathophysiology of antimicrobial agents disrupts the normal gastrointestinal flora, resulting in decreased body defenses against *C. difficile*, making it easier for *C. difficile* to produce toxins that cause CDI disease.²³ Nearly all antibiotics have the potential to cause CDI with varying probabilities. Piperacillin-tazobactam, cephalosporins, vancomycin and aminoglycosides had the highest rates of positive CDI toxin tests. According to the National Institute of Health and Care Excellence (NICE), piperacillin-tazobactam is associated with a 1.5 times increase in CDI risk.²⁴ Cephalosporins are among the highest risk categories of antibiotics that cause CDI. Fluoroquinolones, clindamycin, and penicillin are categorized as high-risk antibiotics for CDI.⁶ Although vancomycin and metronidazole are some of the treatment options for CDI, they have been associated with CDI, as shown in the results. There have been cases in which patients develop CDI after vancomycin or metronidazole.^{25,26} Although aminoglycosides do not usually cause CDI, all antibiotics are associated with a risk of CDI. Other factors boost this risk, such as the duration of exposure, dose, number of antibiotics, and other patient factors.²³

PPIs and H2 receptor antagonists are used for many gastrointestinal disorders such as gastroesophageal reflux, heartburn, and peptic ulcer disease. Acid suppressors have been reported in many studies to increase the risk of CDI. A systematic review in Canada showed that acid-suppressing drugs are associated with an increased risk of CDI.²⁷ In addition, many hypotheses have suggested that rising PH disrupts the normal flora; meanwhile, *C. difficile* spores are acid-resistant and survive.²⁸ Other proposed hypotheses related to PPI include leukopenia²⁹ and some antimicrobial properties of PPIs.²⁹

In this study, approximately two-thirds of the patients used PPI, and half used a PPI for more than four days. The

study results showed a clear association between PPI use and CDI, with a higher prevalence among patients on a PPI for more than four days. These results agree with an Egyptian study where patients who received PPIs were at higher risk of developing CDI.²² A meta-analysis also supports this observation where a PPI was associated with a 70% increase in CDI risk.³⁰ H2 blockers were only used by 4.9% of study participants and in comparison between H2 blockers and PPIs, the studies showed that H2 blockers have a lower risk of causing CDI than PPIs.³¹ PPI has been reported to increase the risk and severity of CDI.³² This study revealed that 84.6% of patients who had a severe form of CDI and 57.1% who had fulminant CDI were taking PPIs. Furthermore, PPI has been shown to increase the risk of hospital-acquired CDI (HA-CDI).³³ These facts are very evident in our study; 93% of HA-CDI patients were taking PPIs.

CA and HA CDI prevalence were almost the same in this study, with 53.1% HA-CDI and 46.9% CA-CDI. This represents a change in the dynamics of CDI, which is known to be nosocomial. This increase in the prevalence of CA-CDI indicates a new disease pattern. This finding is similar to a USA study conducted in 2018.¹⁶ This change could be due to inappropriate self-treatment with antimicrobial agents without the supervision of physicians and the availability of PPIs and antacids secretory agents over the counter. However, HA-CDI patients suffer from a more severe form of the disease,³⁴ moreover, it is associated with higher mortality rates.³⁵ CDI is also classified by the IDSA guidelines based on the severity into mild, moderate, severe and fulminant.⁴ The current study showed that mild and moderate cases had the highest prevalence. Diarrhea was the chief complaint of most patients, with a prevalence of 90.1% in study participants, while 46.1% complained of abdominal pain.

Toxin A (TcdA) and toxin B (TcdB) are the primary markers for diagnosing CDI. Toxins are detected in the unformed stool of patients that grow in an anaerobic environment by tests such as glutamate dehydrogenase detection, toxin enzyme immunoassay, Nucleic Acid Amplification Tests (NAAT), and toxigenic stool culture.³⁶ “The researchers recommended that NAAT be used as the primary diagnostic method for CDI.” However, the optimal test for laboratory diagnosis remains controversial.³⁷ These toxins cause symptoms of infection,³⁸ as the results show in our study. Of the 593 participants, 17.7% had a positive *C. difficile*

antigen, 13.3% had a positive toxin A test, and 13% had a positive result for toxin B. Based on the guidelines, treatment should be administered to patients with positive toxins A and B.⁴ One important note is that toxin tests were performed on asymptomatic patients, which is unnecessary and not cost-effective.

According to the IDSA, vancomycin and fidaxomicin are the first treatment options for CDI, and metronidazole is used as an alternative if first-line options cannot be used. In the case of a fulminant form of CDI, vancomycin is still the first choice, but the route of administration differs and if ileus is present, IV metronidazole should be used. Of the patients with a confirmed diagnosis of CDI, 84.6% were treated as inpatients in-hospital settings. IDSA recommendation was only followed in 62% of patients due to formulary restrictions or an attractive medication cost of metronidazole. However, 94% of the patients responded to the treatment, regardless of the guideline recommendations.

Limitations

This retrospective descriptive study has potential limitations. First, we used previously documented patient files over three years. More than one doctor wrote notes about the same patient, so we read all the physician notes to answer questions and obtain accurate information. Thus, it was not easy to obtain data due to the hospital documentation system. Second, the sample size in our study was small due to different reasons, CDI has a low overall prevalence, and we also used information from one hospital. Because of the small sample size, we could not generalize the results to a broader population.

Conclusion

The prevalence, risk factors, and characteristics of CDI infections have similarities and differences between different countries. Although CDI prevalence is very low in Palestine, antibiotics, PPIs, and patient immune status continues to be the leading risk factors for acquiring CDI in hospitals or communities. *C. difficile* is one of the most important nosocomial infections worldwide. Nevertheless, the prevalence of CDI in community settings has been increasing. Most participants had a mild-to-moderate form of the disease. In addition, there was an insignificant association between CDI and different genders or age groups. This finding cannot be generalized; however, more studies should be conducted on these factors to ensure association. Finally, complete

patient assessments, awareness of CDI risk factors, appropriate utilization of PPIs, and antimicrobial stewardship are essential steps that healthcare providers can utilize to prevent or minimize CDI.

Disclosure

The authors report no conflicts of interest in this work.

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