Characteristics of Patients Infected With Clostridioides Difficile at a Saudi Tertiary Academic Medical Center and Assessment of Antibiotic Duration

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Research

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Abstract

Background

Clostridioides difficile infection (CDI) is a common hospital-associated diarrhea. Several antibiotics commonly associate with CDI; however, limited data are available on the duration of exposure prior to CDI development. Moreover, studies on the characteristics of CDI patients in Saudi Arabia are limited. Therefore, the objective of this study was to characterize CDI patients identified over 10 years and assess antibiotic days of therapy (DOT) prior to CDI.

Methods

This was a retrospective descriptive analysis of CDI patients identified via laboratory testing at a Saudi tertiary academic medical center between December 2007-January 2018. Patients characteristics, prior exposure to known CDI risk factors, and DOT of antibiotics prior to CDI incidence were assessed.

Results

A total of 162 patients were included. Median age was 61.5 years. Most cases were hospital-acquired (70.4%) and admitted to general medical wards (81.5%). Prior exposure to antibiotics and acid suppression therapy were reported with the majority (75.9 and 75.3%, respectively). The most frequently prescribed antibiotics were piperacillin/tazobactam, ceftriaxone, meropenem, and ciprofloxacin with median DOTs prior to CDI incidence of 16.5, 16, 16, and 28 days, respectively. The distribution of DOT was significantly different for piperacillin/tazobactam, ceftriaxone, and ciprofloxacin in different units ($P < 0.05$). Counterintuitively, patients in non-ICU wards had the shortest antibiotic exposure prior to CDI development.

Conclusion

As CDI is a common hospital-acquired infection resulting mainly from antibiotic exposure, results from this study indicate the need to revise antibiotic therapy to assess necessity and discontinue it when deemed unnecessary within the first two weeks.

Background

Clostridioides difficile infection (CDI) is the most common cause of hospital-associated diarrhea.[1] Generally, the acquisition of CDI is categorized based on the exposure to the healthcare system into hospital-onset (HO-CDI), community-acquired (CA-CDI), and community-onset healthcare facility-associated (CO-HCFA) [1]. Some patients with a recurrent CDI episode who get exposed to the healthcare system were found to acquire a strain of CDI that is different from the index strain that caused the initial episode [2]. This finding adds to the evidence that one of the important modes of acquiring CDI is through hospitalization or exposure to healthcare by other means, such as regular hemodialysis or residence in nursing homes.

Certain risk factors are also known to be associated with CDI, such as exposure to antibiotics, older age, use of acid-suppressing agents, and use of antineoplastic agents [3, 4]. Identifying these risk factors in admitted patients can help predicting the risk of acquiring the infection; hence, decreasing the exposure to modifiable factors, such as antibiotics and acid suppression therapy. Some antibiotics or classes of antibiotics are linked to CDI more than others. Penicillins, cephalosporines, carbapebems, fluroquinolones, and clindamycin are associated with CDI incidence that is folds higher than other antibiotics [5-7, 4]. Time from antibiotic exposure to CDI development was reported in two previous studies. One evaluated CDI incidence while patients were still on therapy, whereas the other evaluated the incidence after antibiotic therapy cessation [4, 6]. The studies found an exposure of as short as a few days to as long as three months post therapy discontinuation was followed by CDI.

Data from Saudi Arabia on the characteristics of CDI patients are very limited as only two studies from the same single center were identified. The majority of cases reported from this center had HO-CDI followed by lower rates of CA-CDI and CO-HCFA [8, 9]. Antibiotic exposure within three months was found with 26 of 42 cases (61%) in one of the studies [8]. No additional CDI data from Saudi Arabia were found in the literature, as well as additional data on time to CDI incidence from antibiotic therapy initiation. Therefore, the objective of this study was to describe the characteristics of patients who acquired CDI that was confirmed by a laboratory test for *C. difficile*. The study also aimed to define the duration of antibiotic exposure that preceded CDI incidence in these patients.

Results

Of 170 identified patients with CDI, 162 were included as 8 patients had inconsistent antibiotic administration records. Characteristics of included patients are shown on Table 1. Most of the patients acquired CDI while in the hospital (70.4%), and three-quarters had a prior antibiotic and acid suppression therapy exposure (75.9 and 75.3%, respectively). Only a few patients were on cancer chemotherapy or had a history of a lower gastrointestinal disease, such as inflammatory bowel disease or diverticulitis.

Table 2 presents the frequency of use of antibiotics in the cohort of CDI patients in a descending order with their median days of therapy (DOT). The most frequently prescribed antibiotics were piperacillin/tazobactam, ceftriaxone, meropenem, and ciprofloxacin with median DOTs prior to CDI incidence of 16.5, 16, 16, and 28 days, respectively.

In the subgroup analysis, the distribution of the four most commonly prescribed antibiotics largely followed the distribution of patients in the different categories as reported in Table 1. For example, since most of the patients during the study period were admitted to the medical ward, they represented the group that received most of the antibiotics. The DOT of these antibiotics appear in Figure 1, where the distribution of DOT was significantly different for piperacillin/tazobactam, ceftriaxone, and ciprofloxacin in different units (P = 0.001, 0.02, and 0.02, respectively). Counterintuitively, patients in non-intensive care unit (ICU) wards had the shortest antibiotic exposure prior to CDI development, ranging from a median of 14 days for piperacillin/tazobactam and ceftriaxone to 16.5 and 26 days for meropenem and

ciprofloxacin, respectively. Generally, in all the subgroups, shorter courses of meropenem preceded CDI compared with ciprofloxacin which were given for more days before CDI ensued as illustrated in Figure 1; though, the differences were not statistically significant.

Discussion

CDI tops the reasons behind hospital-associated diarrhea.[1] In fact, the incidence of *C. difficile* colonization in the first days of hospitalization ranges from 16 to 20%; though, it increases with longer hospital stay up to 45.4% [10, 11]. Consistently, HO-CDI was the major mode of CDI acquisition in our patient population despite a lower overall incidence at our center when evaluated over 10 years [12]. On the other hand, CA-CDI has been reported in low-risk populations. For example, younger age, no recent exposure to antibiotic, outpatient visits, acid suppressants, asymptomatic carriers, contaminated food or water, closeness to farms, and hypervirulent strains [13]. However, the presence of any of these factors in non-hospitalized patients can also be linked with CDI development as reported in a study by Chitnis et al. who found that 64.1% of patients with confirmed CA-CDI have received antibiotics in a previous outpatient visit [14].

Patients who are 65 years or older can be at 5-10-fold higher risk for CDI, most likely with poor prognosis compared with younger patients [5, 3]. In our study, half of the patient population were above 61.5 years. Thus, many were already at risk for CDI acquisition. Nonetheless, the presence of other risk factors may have augmented the risk. For instance, the major risk factors of exposure to antibiotics and acid suppression therapy have been reported in about three-quarters of the patients. The latter, especially proton pump inhibitors and H_2-receptor antagonists, is significantly associated with CDI development [15], and most patients who received acid suppression therapy in the current study received more than one kind. Conversely, cancer chemotherapy was reported in a small fraction of patients (13.6%). This can be possibly attributed to the fact that our center is not an oncology specialized center. Nevertheless, if that was the case, more CDI patients would have been included since cancer chemotherapy is another known risk factor for CDI [4, 16]. Similarly, lower gastrointestinal diseases, particularly inflammatory bowel disease, can put patients at risk for CDI [17]. Though, this was also reported in a small number of patients in this study (9.3%).

It was not surprising that many CDI patients in our study were exposed to antibiotics especially that the most frequently prescribed antibiotics belong to culprit antibiotic classes, β-lactams and fluoroquinolones. Similar finding was reported in the other study from Saudi Arabia that evaluated antibiotics use, where cephalosporins and fluoroquinolones were the most used antibiotics [8]. In our study, piperacillin/tazobactam and meropenem were most likely prescribed for empiric purposes. Both, as well as ceftriaxone and ciprofloxacin were significantly associated with CDI in several previous studies. Results from two meta-analyses showed that β-lactams (of all classes), fluoroquinolones, and clindamycin were the antibiotics with the highest likelihood to increase risk of CDI [18, 19]. However, it is important to realize that the exposure to antibiotics alone may not be a factor, but also the duration of that exposure, as well. A short DOT to CDI was reported in a previous study, where an exposure of 6 days

to cefazolin in 80 patients and of 8 days to cefepime in 186 patients preceded CDI [4]. Our study revealed that patients developed CDI after an antibiotic exposure of approximately 2-4 weeks. Interestingly, CDI can still occur even after antibiotic therapy has be discontinued as reported in a study by Hengens et al., where a median of 3.4 days separated the last dose of antibiotic and CDI incidence [6]. They also found that the probability of CDI incidence remains up to three months later.

Our study was limited by a few factors. It was single-centered, which may limit the ability to generalize its results to other centers in Saudi Arabia. Also, there were some inconsistencies in the medication administration records of some patients that resulted in their exclusion. Additionally, the only test utilized at our institution for *C. difficile* detection is toxin immunoassay with reported sensitivity of 88%. Without the utilization of glutamate dehydrogenase for initial screening, about only 12% of the tested population may have been missed due to false negative results. Therefore, a larger, multi-center study utilizing genetic testing or two-step testing for *C. difficile* would be warranted.

Methods

Study design and patients

This was a retrospective descriptive study conducted on adult (≥ 18 years old) CDI patients admitted to King Abdulaziz University Hospital, a tertiary academic medical center. All patients presented to the hospital with CDI during the period from December 2007 to January 2018 were included. The characteristics of these patients, prior exposure to known CDI risk factors at the time of CDI incidence, and the duration of exposure to different antibiotics prior to CDI incidence (expressed as DOT) during or prior to the admission were assessed. Patients with inconsistent medication administration record data were excluded. The study was approved by the Research Committee of The Unit of Biomedical Ethics of Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia.

Definitions

CDI was defined as positive toxin immunoassay in patients with diarrhea (≥ 3 loose stools within one day). CA-CDI is defined according to IDSA as a CDI episode that occurs in a patient with no history of hospitalization within the previous 12 weeks and 48 hours or less of hospitalization. HO-CDI is defined by the US Centers for Disease Control and Prevention as CDI onset three days after admission (on or after day 4). If the symptoms started within 28 days after hospital discharge, the condition is termed CO-HCFA [1]. CDI testing at our institution is done using IMMUNOQUICK Tox A/B (Biosynex, France), which has 88% sensitivity and 99% specificity.[20] According to the protocol of the microbiology laboratory at our institution, all the formed stool samples are rejected; hence, only loose stool samples are accepted for CDI testing. DOT was defined according to the CDC's National Healthcare Safety Network as the aggregate sum of days for which any amount of a specific antimicrobial agent was administered to individual patients as documented in the electronic medical record [21].

Statistical analysis

Data are presented using descriptive statistics as numbers, percentages, and median [interquartile range]. For the most commonly used antibiotics, subgroup analyses using Mann-Whitney U or Kruskal-Wallis test was carried out to determine the difference between the duration of antibiotics in the subgroups. Statistical analysis was carried out using SPSS version 24.0 software (SPSS, Inc., Chicago, Illinois, USA).

Conclusion

CDI is a common hospital-acquired infection, hospitalized patients should be assessed for risk factors, particularly antibiotic exposure. Results from this study indicate the need to revise antibiotic therapy to assess necessity and discontinue it when deemed unnecessary after evaluating microbiological culture results or assuming clinical stability.

Abbreviations

CA-CDI: Community-acquired *Clostridioides difficile* infection

CDC: Centers for Disease Control and Prevention

CDI: *Clostridioides difficile* infection

CO-HCFA: Community-onset healthcare facility-associated *Clostridioides difficile* infection

DOT: Days of therapy

ED: Emergency department

HO-CDI: Hospital-onset *Clostridioides difficile* infection

ICU: Intensive care unit

Declarations

Ethics approval

The study was approved by the Research Committee of The Unit of Biomedical Ethics of Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia (reference 123-18).

Consent for publication

Not applicable.

Availability of data and material

Data are available upon request from the authors.

Competing interests

None.

Funding

Not applicable.

Authors' contribution

KA carried out the data collection and participated in manuscript writing. AT designed the study, performed data analysis and interpretation, and participated and revised the final manuscript.

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Tables

Table 1. Patients characteristics

Characteristic	Total (n=162)
Age, years (median [IQR])	61.5 [48-71]
Sex, male, n (%)	81 (50)
Hospital unit, n (%) • Non-ICU • ICU • ED	 132 (81.5) 19 (11.7) 11 (6.8)
Acquisition, n (%) • CO-CDI • HO-CDI • CO-HCFA	 29 (17.9) 114 (70.4) 19 (11.7)
Time to CDI from admission, days (median [IQR])[a]	8 [3-22]
Non-CDI antibiotic therapy, n (%)	123 (75.9)
Cancer chemotherapy, n (%)	22 (13.6)
Acid suppression therapy, n (%)	122 (75.3)
Type of acid suppression therapy, n (%)[b] • Proton pump inhibitor • H_2-receptor antagonist • Antacid • > 1 type	 47 (29) 2 (1.2) 1 (0.6) 72 (44.4)
Lower gastrointestinal disease, n (%)	15 (9.3)
Number of antibiotics (median [IQR])[c]	3 [1-5]

[a] In hospitalized patients, excluding patients presented to the ED

[b] In the subset of patients who received antibiotics

[c] In the subset of patients who received acid suppression therapy

CA-CDI, community-acquired *C. difficile* infection; CDI, *C. difficile* infection; CO-HCFA, community-onset healthcare facility-associated; DOT, days of therapy; ED, emergency department; HO-CDI, hospital-onset *C. difficile* infection; ICU, intensive care unit; IQR, interquartile range

Table 2. Frequency of antibiotics and their days of therapy (DOT)

Antibiotic	Number of Patients (%)	DOT (median [IQR])
All antibiotics[a]	162 (100)	3.1 ± 3.6
Piperacillin/tazobactam	64 (39.5)	16.5 [8.25-46]
Ceftriaxone	60 (37)	16 [7-47.25]
Meropenem	57 (35.2)	16 [10-32]
Ciprofloxacin	52 (32.1)	28 [14-64]
Cefuroxime	38 (23.5)	18.5 [9-51.75]
Gentamicin	19 (11.7)	21 [6-44]
Imipenem/cilastatin	18 (11.1)	13 [6.75-29]
Ceftazidime	17 (10.5)	14 [10-40]
Amoxicillin/clavulanic acid	16 (9.9)	17.5 [10-34.25]
Clindamycin	15 (9.3)	28 [14-64]
Trimethoprim/sulfamethoxazole	14 (8.6)	38.5 [4.75-74]
Clarithromycin	12 (7.4)	11.5 [7.25-31.75]
Cefazolin	11 (6.8)	13 [7-17]
Cloxacillin	9 (5.6)	43 [12-58.5]
Moxifloxacin	9 (5.6)	38 [10-61]
Azithromycin	7 (4.3)	26 [5-58]
Erythromycin	6 (3.7)	38.5 [16.75-54.5]
Rifampin	5 (3.1)	7 [5.5-36]
Amikacin	4 (2.5)	35 [10.75-54]
Ampicillin	4 (2.5)	8.5 [5.5-11.5]
Tigecycyline	4 (2.5)	48.5 [21.5-54.5]
Cefepime	3 (1.9)	90 [26-90]
Colistimethate sodium	3 (1.9)	26 [9-29]
Ofloxacin	2 (1.2)	38-49[b]
Doxycycline	1 (0.6)	3
Flucloxacillin	1 (0.6)	17
Levofloxacin	1 (0.6)	21

[a] mean ± SD

[b] Range

Figures

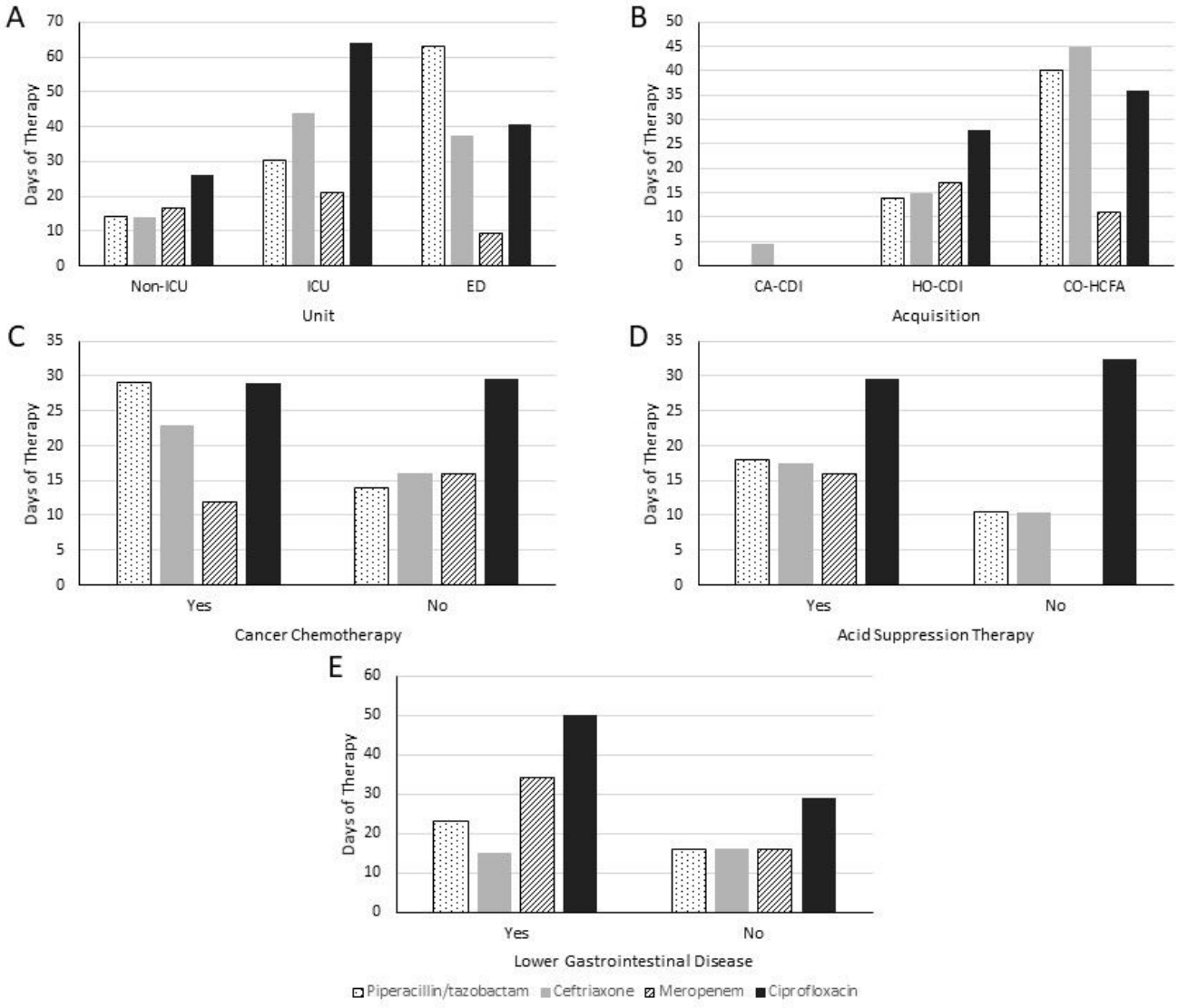

Figure 1

Median days of therapy (DOT) of the four most commonly used antibiotics in the subgroups Significant difference was observed in the distribution of DOT of piperacillin/tazobactam (P = 0.001), ceftriaxone (P = 0.02), and ciprofloxacin (P = 0.02) between the hospital units. CA-CDI, community-acquired C. difficile infection; CO-HCFA, community-onset healthcare facility-associated; ED, emergency department; HO-CDI, hospital-onset C. difficile infection; ICU, intensive care unit