Antibiotic Choice and Duration in Association with \textit{Clostridium Difficile} Infection in a Tertiary Academic Medical Center: A Retrospective Case-Control Study

\textbf{Abstract}

\textit{Clostridium difficile} is the major cause of infectious nosocomial diarrhea in the United States. Previous literature has attributed certain antibiotics to cause \textit{C. difficile} infection (CDI); however, a healthcare institution may benefit from knowing its specific antibiotic-associated CDI patterns. We aimed to determine the type and exposure of antibiotic that is associated with the highest CDI incidence at a tertiary academic medical center. We conducted a retrospective, case-control study from January 2010 to December 2012. Patients aged 18 years or older who were initially admitted and received at least one antibiotic were included in the study. Patients were divided into either cases or controls. For cases, CDI was their first episode. Primary outcome was types of antibiotics associated with risk of CDI development and the median time associated with this risk. Of the 601 patients who developed CDI, 313 were included in the study as cases; while 150 patients of 291 who received antibiotics but did not develop CDI were included as controls. Cefepime and Cefazolin were significantly associated with increased risk for CDI development with odds ratios of 3.01 (95\% CI, 1.96-4.65; \(P=0.001\)) and 1.71 (95\% CI, 1.02-2.95; \(P=0.05\)), respectively. Cefepime is estimated to cause CDI after a median time of 8 days, while CDI may occur after 6 days of therapy with cefazolin. Use of Antineoplastic agents was significantly associated with increased CDI risk (odds ratio, 2.32; 95\% CI, 1.35-4.13; \(P=0.01\)). This study concludes that antibiotic use increased the risk of CDI, particularly with cefepime and cefazolin. CDI risk was also increased with the use of antineoplastic agents.

\textbf{Keywords:} \textit{Clostridium difficile} infection; Antibiotic; Antineoplastics; Cefepime; Clindamycin

\textbf{Abbreviations:} CDI- \textit{Clostridium difficile} infection; CI- confidence interval; H\(_2\)RAs- H\(_2\)-receptor antagonists; OR odds ratio; PPIs- proton pump inhibitors

\textbf{Introduction}

\textit{Clostridium difficile} is a Gram-positive spore-forming anaerobic bacillus. It causes toxin-mediated disease by producing two toxins, A and B, which result in the development of diarrhea and colitis [1]. \textit{C. difficile} is the major cause of infectious nosocomial diarrhea in the United States that usually develops after antibiotic therapy, accounting for 20-30\% of cases of nosocomial antibiotic-associated diarrhea [2]. It is estimated that \textit{C. difficile} infection (CDI) is associated with an increased burden to the American healthcare system with a total exceeding \$3 billion per year [3].

Two rationales for CDI pathogenesis currently exist. It is assumed that \textit{C. difficile} presents a small part of the normal intestinal flora. Consequently, upon exposure to antibiotics, intestinal normal flora, other than \textit{C. difficile}, become suppressed and disrupted allowing \textit{C. difficile} to overgrow. On the other hand, exogenous acquisition of \textit{C. difficile} creates the basis for the second rationale [4]. As a result, the development of CDI requires two major components, exposure to antibiotic therapy and exposure to toxigenic \textit{C. difficile} [4]. Symptomatic diarrhea was reported in 96\% of patients who had received antibiotic therapy within 14 days before the onset of diarrhea [2]. Temporal relation of CDI and the initiation of antibiotics were reported to have a median onset of 2-3 days [2].

Antibiotics that are mostly implicated in causing CDI are Clindamycin, quinolones, and cephalosporins; whereas parenteral aminoglycosides, vancomycin, and metronidazole are less frequently associated with CDI [4]. A healthcare institution may benefit from knowing its specific antibiotic-associated CDI patterns based on the institution’s antibiotic formulary and patient population [4,5].

In addition to antibiotic use, several factors were reported to increase the risk of CDI. Such factors include age equal to or greater than 65 years, antineoplastic therapy, infection with human immunodeficiency virus, gastrointestinal (GI) surgery or manipulation of the GI tract (eg, tube feeding), and suppression of stomach acid production due to the use of proton pump inhibitors (PPIs) or H\(_2\)-receptor antagonists (H\(_2\)RAs) [2]. We conducted this study to investigate antibiotics that were highly implicated in increasing the risk of CDI and the median time associated with the infection.

\textbf{Materials and Methods}

\textbf{Study design and setting}

This retrospective, case-control study was conducted at...
were estimated using Cox proportional hazards regression, with covariate adjustment for the antibiotic administered. Median time until CDI was calculated in cases for each antibiotic administered. For secondary outcomes, ORs and 95% CIs were estimated using Cox proportional hazards regression, with covariate adjustment for the confounding factor in question. We compared select baseline characteristics between cases and controls by estimating ORs and 95% CIs. The characteristic of total duration of hospital stay was presented as a median of days. Logistic regression was used to adjust OR of primary outcome for any confounding factor that showed statistical significant association with CDI development. A P value of < 0.05 was considered statistically significant. We used STATA software package 10.1 (Stata Corp, College Station, TX) and Microsoft Excel 14.0 (Microsoft Inc., Redmond, WA) for our analyses and chart development, respectively.

Results

Patients and characteristics

A total of 892 patients were assessed for eligibility for the study. Of the 601 patients from the cases database, 313 patients were included in the study. Antibiotic treatment before hospital admission was the major cause for exclusion from the study (n=48) followed by the transfer from an outside hospital (n=41). One hundred and fifty patients were included as controls and 141 were excluded out of 291 patients who received antibiotics but did not develop CDI. Most of the excluded patients from this group were aged less than 18 years (n=42) (Figure 1).

Outcomes

The primary outcome was types of antibiotic therapy associated with the development of CDI. We assessed this outcome by looking at the electronic medication administration records and counting the days of therapy of each antibiotic administered. Overall, cases and controls did not significantly differ in their average antibiotic choices and duration. Cases and controls did not significantly differ in their baseline characteristics, except for the use of antineoplastic agents (Table 1). More patients in both groups were admitted to general care units versus critical care units; however, this factor was not statistically significantly different.

Primary outcome

A total of 41 antibiotics were administered to the study population. Two antibiotics showed significant increased risk of CDI development. Cefepime showed the highest OR of 3.01 (95% CI, 2.05-4.65; P < 0.001), while cefazolin had an OR of 1.71 (95% CI, 1.02-2.95; P < 0.05) (Figure 2). The remaining 39 antibiotics did not show significant increase in CDI risk. Ampicillin-sulbactam

Figure 1: Flowchart of study subjects

Overall, cases and controls did not significantly differ in their baseline characteristics, except for the use of antineoplastic agents and the length of hospital stay with P values < 0.01, respectively (Table 1). More patients in both groups were admitted to general care units versus critical care units; however, this factor was not statistically significantly different.

Primary outcome

A total of 41 antibiotics were administered to the study population. Two antibiotics showed significant increased risk of CDI development. Cefepime showed the highest OR of 3.01 (95% CI, 1.96-4.65; P < 0.001), while cefazolin had an OR of 1.71 (95% CI, 1.02-2.95; P < 0.05) (Figure 2). The remaining 39 antibiotics did not show significant increase in CDI risk. Ampicillin-sulbactam
showed a significant level ($P<0.05$) in not increasing the risk of CDI development. Interestingly, antibiotics that are known to increase the risk of CDI development, such as clindamycin and fluoroquinolones, did not show an increased risk in our study. The median duration in days for CDI to occur on all the antibiotics ranged between 2 to 26 days. Once cefepime is administered, CDI was estimated to occur at the eighth day whether the antibiotic was continued or discontinued. It may take up to 6 days for CDI to occur after the first dose of cefazolin is administered (Figure 3).

### Secondary outcomes

Factors that are known to increase the risk of CDI development were assessed in our study population (Figure 4). Increased age and presence of lower GI disease did not have effect on increasing CDI risk. Interestingly, the use of acid suppression therapy did not increase the risk of CDI. This was true for PPIs and H$_2$RAs. The only factor that was considerably associated with increased CDI risk was the use of antineoplastic agents ($OR, 2.32; 95\% CI, 1.35-4.13; P<0.01$).

### Controlling for antineoplastic therapy

ORs of cefepime and cefazolin to increase CDI risk were adjusted for antineoplastic therapy and vice versa. Adjusted OR of cefepime was 1.86 ($95\% CI, 1.38-2.48; P=0.001$), which indicated that cefepime still carried the risk for CDI development even without antibiotic therapy. Similarly, cefazolin adjusted OR was 1.5 ($95\% CI, 1.02-2.21; P=0.04$).

Use of antineoplastic agents showed ORs of 2.08 ($95\% CI, 1.22-3.55; P=0.007$) and 2.49 ($95\% CI, 1.47-4.23; P=0.001$) when adjusted for cefepime and cefazolin therapies, respectively. Therefore, the presence of antineoplastic agents was significantly associated with CDI regardless of therapies with cefepime and cefazolin.

### Discussion

To achieve the objective of our study, we looked into the antibiotics, per our formulary, that were highly implicated in increasing the risk of CDI development. Only cefepime and cefazolin were significantly associated with increasing CDI risk. This finding is similar to a finding reported by Deshpande et al. [5]. in their meta-analysis on community-acquired CDI, where they found that the cephalosporins class was the third to most likely increase the risk of CDI development after clindamycin and fluoroquinolones. The major indication for cefazolin in our study population was perioperative prophylaxis. Others described a risk of CDI development with perioperative antimicrobial prophylaxis [6,7], where cephalosporins were the major class of antibiotics used for this indication. This finding confirms our comparable finding with cefazolin. Although clindamycin is a well-known risk factor for CDI development [8], it did not increase the risk in our study. An analogous outcome was shown with fluoroquinolones. The lack of CDI risk with clindamycin and fluoroquinolones was also reported in a study by Komatsu et al. [9].

Of our secondary outcomes, the use of antineoplastic agents was the only risk factor that was significantly associated with CDI occurrence. A study that was conducted in a Turkish University Hospital showed a similar effect [10]. In this study, Ergen et al. [10] found that more patients with CDI were on cancer chemotherapy compared to patients who did not develop CDI. This is also analogous to the results reported by Blot, et al, where cancer chemotherapy without antibiotic therapy was a major risk factor for CDI development ($P=0.02$) [11]. The addition of antibiotics increased this risk remarkably ($P=0.008$) [11].

Our study was limited by several factors. First, this is a single center study, including patients only admitted to our hospital. Second, some antibiotics were not administered large enough to obtain a larger sample size. This was due to Infectious Diseases formulary restrictions of high-risk antibiotics. For example, piperacillin-tazobactam and linezolid were among the restricted agents. As a result, a mean of 3.5% and 7.3% of the study population received these agents, respectively. Therefore, their effect on CDI risk was not adequately evaluated. Also, cefepime and

---

**Citation:** Thabit AK, Varughese CA, Levine AR, Hooper DC (2016) *Antibiotic Choice and Duration in Association with Clostridium Difficile Infection in a Tertiary Academic Medical Center: A Retrospective Case-Control Study.* Pharm Pharmacol Int J 4(5): 00091. DOI: 10.15406/ppij.2016.04.00091
cefazolin were among the highly utilized antibiotics, with a mean proportion of utilization for all study patients that reached 46% for cefepime (second highly utilized agent) and 21% for cefazolin (fourth highly utilized agent) (data not shown). Third, the acuity of illness within the study population was not adequately captured. For example, patients who were immunocompromised were not specifically identified. Last, the introduction of polymerase chain reaction (PCR) testing of *C. difficile* took place in a late phase during our study period, in September 2012. Overcoming this limitation may have helped increasing the sample size of cases given the high sensitivity and specificity of this test (100% and 99.2%, respectively) [12]. Compared to the toxin assay, which has a sensitivity of 63-94% and a specificity of 75-100% [2]. The number of included CDI cases that were detected by PCR in our study was 32 (10.2%), whereas toxigenic assay detected the rest of the included cases (n = 281, 89.8%).

Table 1: Baseline characteristics of cases and controls

| Characteristic                        | Cases (n=313) | Controls (n=150) | Odds Ratio (95% confidence interval) | P Value |
|--------------------------------------|--------------|-----------------|--------------------------------------|---------|
| Age, n (%)                           |              |                 | 1.41 (0.93-2.12)                     | 0.08    |
| ≥ 65 years                           | 173 (55.3)   | 70 (46.7)       |                                      |         |
| < 65 years                           | 140 (44.7)   | 80 (53.3)       |                                      |         |
| Gender, n (%)                        |              |                 | 0.97 (0.65-1.45)                     | 0.92    |
| Male                                 | 182 (58.1)   | 88 (58.7)       |                                      |         |
| Female                               | 131 (41.9)   | 62 (41.3)       |                                      |         |
| Hospital service, n (%)             |              |                 | 1.54 (0.91-2.67)                     | 0.09    |
| Critical care                        | 74 (23.6)    | 25 (16.7)       |                                      |         |
| General care                         | 239 (76.4)   | 125 (83.3)      |                                      |         |
| Use of acid suppression therapy, n (%) | 241 (77)    | 117 (78)        | 1.4 (0.88-2.2)                       | 0.12    |
| Proton pump inhibitors               | 198 (63.2)   | 92 (61.3)       | 1.08 (0.71-1.65)                     | 0.7     |
| H₂-receptor antagonists              | 43 (13.7)    | 25 (16.6)       | 0.79 (0.45-1.42)                     | 0.4     |
| Underlying lower GI disease, n (%)   | 29 (9.2)     | 14 (9.3)        | 0.99 (0.48-2.1)                      | 0.98    |
| Use of antineoplastic agents, n (%)  | 86 (27.4)    | 21 (14)         | 2.32 (1.35-4.13)                     | 0.001   |
| Total duration of hospital stay, median, days | 22          | 8               | < 0.001                              |         |

Conclusion

Antibiotic use increased the risk of CDI, particularly with cefepime and cefazolin, while ampicillin-sulbactam did not show a high risk of CDI incidence. It may take up to 8 days and up to 6 days for CDI to occur with cefepime and cefazolin, respectively. Use of antineoplastic agents was significantly associated with CDI. However, age, use of acid suppression therapy, and the presence of underlying lower GI disease did not increase CDI risk.

Acknowledgements

We thank Irene Goldenshtein, MD and David Hooper, MD (Massachusetts General Hospital Infection Control Unit) for providing the database of CDI cases. We thank Aaron Sacco, and Robert Tewes (MGH Pharmacy) for providing the databases of antibiotics dispensed by the pharmacy during the study period. We thank Barbra T. Irby, RPh for reviewing the manuscript. We thank Douglas Hayden, PhD and Brian Healy, PhD for providing consults on statistics. This work was conducted with support from Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health Award U81TR000170-05 and financial contributions from Harvard University and its affiliated academic health care centers). The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic health care centers, or the National Institutes of Health.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Leffler DA, Lamont JT (2009) Treatment of *Clostridium difficile*-associated disease. Gastroenterology 136(6): 1899-1912.
2. Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, et al. (2010) Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Infect Control Hosp Epidemiol 31(5): 431-455.
3. O’Brien JA, Lahue BJ, Caro JJ, Davidson DM (2007) The emerging infectious challenge of Clostridium difficile-associated disease in Massachusetts hospitals: clinical and economic consequences. Infect Control Hosp Epidemiol 28(11): 1219-1227.

4. Johnson S, Gerding DN (1998) Clostridium difficile-associated diarrhea. Clin Infect Dis 26(5): 1027-1036.

5. Deshpande A, Pasupuleti V, Thota P, Pant C, Rolston DD, et al. (2013) Community-associated Clostridium difficile infection and antibiotics: a meta-analysis. J Antimicrob Chemother 68(9): 1951-1961.

6. Ye J, Dixon CM, McLean AP, Meakins JL. (1991) Clostridium difficile disease in a department of surgery: the significance of prophylactic antibiotics. Arch Surg 126(2): 241-246.

7. Privitera G, Scarpellini P, Ortisi G, Nicastro G, Nicolin R, et al. (1991) Prospective study of Clostridium difficile intestinal colonization and disease following single-dose antibiotic prophylaxis in surgery. Antimicrob Agents Chemother 35(1): 208-210.

8. Johnson S, Samore MH, Farrow KA, Killgore GE, Tenover FC, et al. (1999) Epidemics of diarrhea caused by a clindamycin-resistant strain of Clostridium difficile in four hospitals. N Engl J Med 341(22): 1645-1651.

9. Komatsu M, Kato H, Aihara M, Shimakawa K, Iwasaki M, et al. (2003) High frequency of antibiotic-associated diarrhea due to toxin A-negative, toxin B-positive Clostridium difficile in a hospital in Japan and risk factors for infection. J Clin Microbiol Infect Dis 22(9): 525-529.

10. Ergen EK, Akalin H, Yilmaz E, Sinirtaş M, Alver O, et al. (2009) Nosocomial diarrhea and Clostridium difficile associated diarrhea in a Turkish University Hospital. Med Mal Infect. 39(6): 382-387.

11. Blot E, Escande MC, Besson D, Barbut F, Granpeix C, et al. (2003) Outbreak of Clostridium difficile-related diarrhea in an adult oncology unit: risk factors and microbiologic characteristics. J Hosp Infect 53(3): 187-192.

12. de Jong E, de Jong AS, Bartels CJ, van der Rijt-van den Biggelaar C, Melchers WJ, et al. (2012) Clinical and laboratory evaluation of a real-time PCR for Clostridium difficile toxin A and B genes. Eur J Clin Microbiol Infect Dis 31(9): 2219-2225.