# Antibiotics and Nosocomial *Clostridioides difficile*, a Retrospective Chart Review

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## ABSTRACT

*C. difficile* is a complication of antibiotic therapy. Certain antibiotics are associated with a higher rate of developing *C. difficile*. The charts of 54 patients with nosocomial *C. difficile* were reviewed and very few had received a high-risk antibiotic. Seven (13%) of 54 patients had not received any antibiotics in the hospital prior to the positive stool test for *C. difficile*. Moreover, 6 of the 7 had no documentation of receiving an antibiotic in the 56 days prior to admission suggesting that they might be colonized with *C. difficile*.


**KEYWORDS:** *Clostridioides difficile*, antibiotics, healthcare-associated infections

## INTRODUCTION

Clostridioides difficile (formerly Clostridium difficile) infection is a rare, but potentially devasting, complication of antibiotic therapy. Since about one-half of all hospitalized patients receive an antibiotic, a rare complication can affect many patients.[1] In 2017 there were 223,900 people hospitalized with *C. difficile* in the United States with 12,800 deaths.[2]

Certain antibiotics such as clindamycin and cefotaxime, a third-generation cephalosporin, are associated with a higher risk of developing *C. difficile* infection.[3] Doxycycline, penicillin, macrolides, trimethoprim/sulfamethoxazole and cefazolin, a first-generation cephalosporin, are low-risk antibiotics. Ciprofloxacin, levofloxacin, meropenem (a carbapenem) and certain cephalosporins are medium risk. In addition to antibiotics, proton pump inhibitors may increase the risk of developing *C. difficile* infection.

The rate of nosocomial *C. difficile* in the state of Rhode Island is among the highest in the country. At The Miriam Hospital, a 247-bed teaching hospital in Providence, RI, numerous interventions were used to decrease the rate of nosocomial *C. difficile* (See accompanying article, "Safety and Nosocomial *Clostridioides difficile* Infections", Steeves S, et al). As part of a quality improvement project to further reduce the rate of nosocomial *C. difficile*, a retrospective chart review was performed to determine which antibiotics were received by patients with nosocomial *C. difficile*. This data may help to determine if antibiotic use could be optimized to reduce the rate of nosocomial *C. difficile* infection.

## METHODS

This descriptive study includes data from persons admitted to The Miriam Hospital (TMH) in Providence, RI who developed hospital onset *C. difficile* infection using National Healthcare Safety Network (NHSN) Laboratory-identified data from January 1, 2018 through December 31, 2018. Electronic medical records were reviewed. This study was a retrospective chart review conducted for internal quality improvement at TMH and thus was exempted from needing Institutional Review Board approval.

### Case Definition

A case of hospital onset *C. difficile* was defined as per the NHSN criteria of a positive laboratory diagnostic test >3 days after admission. The date of admission to an inpatient unit was coded as hospital day 1. The Microbiology laboratory uses a PCR-based diagnostic test. As per NHSN, an incident case was defined as a patient without symptom onset or a positive laboratory test in the previous eight weeks (56 days). A recurrent case was defined as a patient with a positive *C. difficile* test within the previous 56 days. Patients diagnosed with a second hospital-onset *C. difficile* infection >56 days after their first infection during the period of study were counted as separate incident cases.

### Variables of Interest

Patient data were de-identified and patients were assigned a code for analysis. All data were extracted from patients' electronic medical record unless otherwise noted. Age was recorded in years as the age of the patient at the time of *C. difficile* diagnosis. Sex was defined as male or female per patient chart. The admission date was defined as the admission date of the hospitalization to an inpatient unit during which the patient was diagnosed with *C. difficile*. The location from which the patient was admitted was defined as the location in which the patient had spent the previous 24 hours and was coded as home, nursing home or transfer from another hospital. Home included any private residence. Nursing home included patients who were admitted from rehabilitation facilities and skilled nursing facilities. Patient charts were also reviewed to identify if patients had undergone a surgical procedure or been hospitalized during the eight weeks prior to the index admission. Hospitalization was defined as an overnight admission of a minimum of

one day; emergency department visits that did not result in admission were excluded. Surgical procedures were defined as invasive surgical procedures done in the operating room and excluded procedures such as bedside central line/PICC line placement, suturing of wounds, etc. Hospitalizations and surgical procedures that were performed outside of The Miriam Hospital but documented in patients' electronic medical record were included.

Previous antibiotic use was defined as any antibiotic for which the patient was prescribed at least one dose in the previous 56 days. Antimicrobial agents during hospitalization were defined as any antibiotic of which patient received at least one dose prior to the patient's *C. difficile* diagnosis during the hospitalization of interest. Number of days received was defined as the number of days patient received each antibiotic prior to diagnosis with *C. difficile*. The day the *C. difficile* specimen was collected was not counted as a "day received" for antimicrobial agents. One dose of antibiotic was counted as one day independent if patient received the full therapeutic amount of antibiotic for that day.

Proton pump inhibitor (PPI) use was coded as "yes" if patients had one or greater doses of PPI documented in the chart at any time in the six months prior to *C. difficile* infection. Site of infection was defined as the documented infection site for which antimicrobials were prescribed. The culture site was the site from which positive cultures were obtained. Negative cultures were not recorded. Culture organism was the organism(s) that grew from the positive culture sites; some sites grew more than one organism and all organisms were recorded. Sepsis was defined as "yes" when patients had a diagnosis of sepsis recorded during the hospitalization in which they were diagnosed with *C. difficile*. Other positive tests were defined as other positive microbial tests, including, MRSA/VRE screen positive patients and positive respiratory pathogen panels.

### Data Quality

Charts were reviewed in a standardized manner and data were extracted from the same location in the chart when possible. In addition, outpatient records were reviewed for all patients with such data included in their electronic medical record to ensure that all possible information on prior hospitalizations, surgical procedures, antibiotic and PPI use, etc. was recorded. A list of operational definitions for each variable was created to ensure standardization in the interpretation and documentation of all variables. Any discrepancies or ambiguities were reviewed with the senior author, who made a final decision.

### Data Analysis

Data were entered into a spreadsheet and descriptive statistics were run. The mean, minimum and maximum values were calculated for patient age and days between admission and *C. difficile* diagnosis. Percent distributions were calculated for all other variables.

## RESULTS

### Demographics

There were a total of 54 hospitalizations with hospital onset incident *C. difficile* cases from January 1, 2018–December 31, 2018 representing 52 unduplicated patients. Two patients were diagnosed with *C. difficile* twice in separate hospitalizations >56 days apart during the study period. Thus, each *C. difficile* diagnosis was counted as a separate incident case for the purposes of this analysis. Of the 54 incident cases, 26 (48%) were male and 28 (52%) were female. The average age of patients was 72.6 years (range 42 – 94 years) at the time of *C. difficile* diagnosis. The majority (n=43; 80%) of patients were admitted from home with ten (19%) admitted from a nursing home and one patient (2%) transferred from another hospital.

Forty-three percent (n=23) of patients were neither hospitalized nor had a surgical procedure in the eight weeks prior to their *C. difficile* diagnosis. A total of 41 percent were hospitalized and almost a quarter (n=12; 22%) had a surgical procedure in the previous eight weeks. Eight patients (15%) had a previous *C. difficile* infection >56 days prior to the incident case; the remaining 46 (85%) had no previous *C. difficile* infection documented in their electronic medical records. One half (n=27) had taken a proton pump inhibitor in the six months prior to diagnosis.

Almost sixty percent (n=33; 61%) of patients did not have documented antibiotic use in the eight weeks (56 days) prior to admission. Of those who did receive antibiotics, the most commonly used were intravenous vancomycin (15%), followed by ceftriaxone (13%) and piperacillin/tazobactam (11%). The remaining antibiotics used were taken by less than ten percent of patients (**Table 1**).

### Admission Clinical Data

The average number of days between admission and *C. difficile* diagnosis was seven (range 3 – 25; median 5 days). The vast majority (n=47; 87%) of patients took at least one antibiotic during admission prior to being diagnosed with *C. difficile*. Of those who used antibiotics, the most common site of infection for which the antibiotics were prescribed was the lower respiratory tract (22%) followed by the urinary tract (19%) and the bloodstream (15%). Approximately ten percent of infections were in the skin and soft tissue (9%), gastrointestinal tract (11%) or undetermined/empirical (11%) respectively. Of note, the undetermined/empirical category included peri-operative antibiotic administration. Seven (13%) patients had a documented diagnosis of sepsis during the admission. Five patients had more than one site of infection (**Table 2**).

A total of twenty-six patients had a positive infection site culture. Eleven patients (20%) had positive urine cultures, seven (13%) had positive blood cultures, four (7%) had positive abscess site cultures and four (7%) had positive sputum cultures.

The most commonly used antibiotics during admission

**Table 1.** Antibiotics used in the 56 days prior to admission of patients diagnosed with *C. difficile*, January 1–December 31, 2018.

| Antibiotic | Number (percent) |
|---|---|
| Vancomycin (intravenous) | 8 (15) |
| Ceftriaxone | 7 (13) |
| Piperacillin/tazobactam | 6 (11) |
| Cefazolin | 4 (7) |
| Levofloxacin | 4 (7) |
| Amoxicillin/clavulanate | 3 (6) |
| Ampicillin/sulbactam | 2 (4) |
| Cefepime | 2 (4) |
| Ciprofloxacin | 2 (4) |
| Metronidazole (intravenous) | 2 (4) |
| TMP/SMX | 2 (4) |
| Metronidazole (oral) | 1 (2) |
| Cefuroxime axetil | 1 (2) |
| Azithromycin | 1 (2) |
| Meropenem | 1 (2) |
| Penicillin | 1 (2) |

**Table 2.** Admission clinical data of patients diagnosed with *C. difficile*, January 1–December 31, 2018

| Site of infection* | Number (percent) |
|---|---|
| Lower respiratory tract | 12 (22) |
| Urinary tract | 10 (19) |
| Bloodstream | 8 (15) |
| Sepsis | 7 (13) |
| None | 7 (13) |
| Gastrointestinal tract | 6 (11) |
| Undetermined/empirical** | 6 (11) |
| Skin and soft tissue | 5 (9) |
| Bone and joint | 1 (2) |
| Hepatobiliary system | 1 (2) |
| Asymptomatic bacteriuria | 1 (2) |
| Fever and neutropenia | 1 (2) |
| Other*** | 1 (2) |

* Five patients had more than one site of infection
** Includes empiric peri-operative antibiotics
*** Respiratory pathogen panel positive for Coronavirus HKU1

**Table 3.** Antibiotics used during hospitalization of patients diagnosed with *C. difficile*, January 1–December 31, 2018.

| Antibiotic | Number (percent) | Average Number of Days Used |
|---|---|---|
| Piperacillin/tazobactam | 27 (50) | 4.1 |
| Vancomycin (IV) | 25 (46) | 3.4 |
| Ceftriaxone | 11 (20) | 2.8 |
| Cefazolin | 8 (15) | 3.0 |
| Cefepime | 8 (15) | 3.5 |
| Azithromycin | 6 (11) | 3.5 |
| Metronidazole I.V. | 4 (7) | 1.3 |
| Aztreonam | 3 (6) | 2.3 |
| TMP/SMX | 2 (4) | 2.0 |
| Doxycycline | 2 (4) | 2.0 |
| Ciprofloxacin | 2 (4) | 1.5 |
| Levofloxacin | 2 (4) | 3.0 |
| Ertapenem | 2 (4) | 7.0 |
| Meropenem | 2 (4) | 3.0 |
| Ampicillin/sulbactam | 1 (2) | 4.0 |
| Amoxicillin/clavulanate | 1 (2) | 2.0 |
| Clindamycin | 1 (2) | 1.0 |

were piperacillin/tazobactam (50%), followed by vancomycin IV (46%), ceftriaxone (20%), cefazolin (15%), cefepime (15%) and azithromycin (11%). All other antibiotics administered were used in less than ten percent of the patients *C. difficile* (**Table 3**).

Seven (13%) patients did not receive any antibiotics during their hospital stay prior to the positive test for *C. difficile*. One patient recently completed an outpatient course of amoxicillin/clavulanate prior to admission. Three of the seven had a prior positive test 22, 297 and 682 days prior to admission. The patient with the positive test 22 days earlier was an inpatient at an outside hospital. One patient received oral magnesium oxide which can cause diarrhea.

## DISCUSSION

*C. difficile* infection is a complication of antibiotic therapy. Certain antibiotics, such as clindamycin, are associated with a higher risk for developing *C. difficile* infection. One strategy to reduce the rate of nosocomial *C. difficile* is to reduce the use of high-risk antibiotics. At The Miriam Hospital during 2018 very few patients with nosocomial *C. difficile* received a high-risk antibiotic.

Approximately 30-50% of prescribed antibiotics may be inappropriate or unnecessary.[4] In this study of patients with nosocomial *C. difficile*, very few received unnecessary antibiotics.

If *C. difficile* is solely a complication of antibiotic therapy, then it is remarkable that seven patients (13%) classified by NHSN as having hospital-acquired *C. difficile* did not receive any antibiotics while in the hospital. Moreover, six of the seven did not receive any antibiotics in the 56 days prior to their admission. Three of the seven had a prior positive stool test for *C. difficile*. Hence, they may be chronically colonized and did not acquire *C. difficile* while in the hospital. Four-percent to 15% of healthy adults are colonized with *C. difficile*.[5] Hence, if a colonized patient is admitted to the hospital and develops diarrhea for some other reason, when a stool sample is tested it will be positive for *C. difficile* even though the diarrhea is not due to *C. difficile*.

This study has several limitations. The data were collected via retrospective chart review. While every effort was made to extract data for each variable in a systematic manner, the data completeness and quality for each patient was limited by what was documented. Additionally, some variables, such as antibiotic use and surgery/hospitalization in the prior 56 days depended on access to and completeness of outpatient records. For the sake of consistency in operational definitions and analytical purposes, "PPI use" was coded as a dichotomous variable with one recorded use of any PPI coded as "yes". This is not, however, representative of how these medications are used in clinical practice, with the vast majority of conditions requiring multi-day/week courses.

*C. difficile* infection is a complication of antibiotic therapy. At The Miriam Hospital during 2018 use of high-risk antibiotics or unnecessary use of antibiotics was found in very few of the cases of nosocomial *C. difficile*. Moreover, 13 percent of patients did not receive an antibiotic in the hospital. Hence, some of the patients classified as having nosocomial *C. difficile* may be colonized but not infected.

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