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The Epidemiology of *Clostridium difficile* Infections among Oncology Patients

M.P.H. Thesis
Department of Epidemiology of Microbial Diseases
Yale School of Public Health

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April 2015

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Acknowledgements

I would like to thank Dr. Louise-Marie Dembry and Dr. David Banach for their patience, support and mentorship throughout the past year. I am immensely grateful for their generous donation of their time and for their constant willingness to make availabilities in their busy schedules for me. Without their steadfast encouragement and guidance, this thesis would not have been possible. I would also like to thank Peter Longley from the Yale-New Haven Hospital's Data Analytics Team and Linda Sullivan for their help in obtaining data for the study. Finally, I would like to thank my adviser Dr. Sunil Parikh for advising me throughout the MPH program and for his help in connecting me to this research opportunity.

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Abstract

Clostridium difficile is the leading cause of hospital-acquired diarrhea. Oncology patients are a group of immunosuppressed patients who are at increased risk for *C. difficile* infection. The primary objective of this study was to describe the demographic factors, medical history, and clinical characteristics and identify risk factors for *C. difficile* infection among oncology patients. A retrospective chart review was conducted for this case-control study. Seventy-seven cases were compared to two control groups; one control group of patients with diarrhea but whose stool samples were tested and were negative for *C. difficile* (n=77), and a second control group of patients matched to cases based on hospital ward and date of discharge (n=152). Multivariate analyses were performed using logistic regression. Adjusting for all other variables, days of hospitalization prior to test (OR=1.075, 95% CI 1.027, 1.124), fever on test date (OR=5.232, 95% CI 1.460, 18.755), history of *C. difficile* (OR=32.433, 95% CI 3.513, 299.445), and hypotension on test date (OR=9.245, 95% CI 1.232, 69.183) were significantly associated with *C. difficile* infection in cases compared to the negative test control group. When cases were compared to the matched control group, age (OR=1.042, 95% CI 1.006, 1.079), history of any co-infection (OR=5.614, 95% CI 1.878, 16.787), blood transfusion (OR=3.200, 95% CI 1.251, 8.183), prior receipt of cephalosporins (OR=4.214, 95% CI 1.371, 12.952) or metronidazole (OR=16.005, 95% CI 3.958, 64.713), chemotherapy (OR=5.069, 95% CI 1.609, 15.972), history of *C. difficile* (OR=27.806, 95% CI 2.484, 311.290), and use of a nasogastric tube (OR=6.988, 95% CI 1.339, 36.477) were significantly associated with *C. difficile* infection. Risk factors for *C. difficile* infection differed when comparing cases to the negative test control group and to the matched control group; however, prior history of *C. difficile* was a common risk factor. Based on the analysis of the matched control group, reduction in cephalosporin and metronidazole use, particularly among patients with a history of *C. difficile* infection, recent chemotherapy or blood transfusions, or presence of a nasogastric tube, may reduce the risk of *C. difficile* infection and should be a focus of future study and intervention.

Introduction

Clostridium difficile is a gram-positive, anaerobic bacterium that is the leading cause of hospital-acquired diarrhea [1]. *C. difficile* has a wide variety of clinical presentations, ranging from asymptomatic carriage to mild self-limited diarrhea, pseudomembranous colitis, toxic megacolon perforation, and sepsis [2]. Since 2002, there has been a consistent rise in the rates of *C. difficile* in Canada, the United States, and Europe. In 2011, over 450,000 incident cases of *C. difficile* and 29,000 deaths were estimated to have occurred in the United States [3]. This is a significant increase in the number of *C. difficile* cases in just five years. In 2006, United States hospitals reported a *C. difficile* diagnosis discharge rate of 300,000 cases per year, a doubling of cases since 2000 [4]. Thus, *C. difficile* cases have been steadily increasing over the recent decades, which represent significant patient mortality and morbidity nationwide. This increase in the number of *C. difficile* cases has been attributed to a newly identified strain, *C. difficile* BI/NAP1/027, which may be more virulent than previous strains [4]. There have been other changes in the epidemiology of *C. difficile* in recent years that exacerbate its economic and health consequences. Currently, *C. difficile*-associated disease is estimated to incur costs of up to $4.8 billion per year [2, 3].

C. difficile has the ability to form spores, which contributes to transmission due to environmental contamination, particularly in healthcare settings. The spores are able to persist on environmental surfaces for up to several months [5]. The spores are heat and alcohol resistant, and contamination of surfaces often remains after cleaning and disinfection with standard disinfectants [6, 7]. Environmental transmission contributes to the exogenous acquisition of *C. difficile* which occurs through the fecal-oral transmission of spores. In hospital or healthcare settings, transmission through contact with contaminated residual spores present on healthcare professionals' hands and clothing is common [5]. Acquisition of *C. difficile* can also be endogenous as well. Antibiotic use

results in the disruption of normal colonic flora which facilitates the proliferation of *C. difficile* and subsequent illness when toxigenic strains proliferate [6].

More than 90% of *C. difficile* infections have been shown to occur either during or after antibiotic treatment, likely as a result of the disruption of the normal microbiota [5]. However, host factors also play a role in the development of illness. Even if a toxigenic strain is acquired, illness may not result if the host is able to mount an IgG antibody response, which would result in asymptomatic colonization. Asymptomatic colonization with *C. difficile* also occurs if a non-toxigenic strain is acquired [4]. It has been estimated that 3% of the general, healthy population is asymptomatically colonized with *C. difficile*, but carriage rates are higher in patients who have been previously hospitalized or have received antibiotics [5].

Pathogenicity of *C. difficile* is attributable to two main endotoxins, toxin A and toxin B. Non-toxigenic strains of *C. difficile* are generally not pathogenic [8]. In most cases, both toxins A and B are produced during *C. difficile* infection [9]. Once *C. difficile* proliferates and is endocytosed in the colon, toxins A and B induce fluid secretion, inflammation, and mucosal damage [5]. Cell death results from the production of tumor necrosis factor-alpha and pro-inflammatory interleukins. The combined tissue damage results in diarrhea or pseudomembranous colitis [5, 8]. Typical treatment for first occurrence of mild to moderate *C. difficile* is metronidazole. Oral vancomycin is recommended for more severe infections and for second or later recurrent episodes. Severely ill patients are typically identified as such if they present with leukocytosis, elevated creatinine levels, elevated lactate levels, hypotension, shock, ileus, colonic perforation, or megacolon, and a colectomy may be necessary for these patients [6]. Recently, fecal microbiota transplant has also been suggested as a possible treatment for *C. difficile*, particularly for patients with recurrent *C. difficile* infection and antimicrobial treatment failure. Fecal microbiota transplantation involves the infusion of healthy donor feces in the patient in order to restore the intestinal microbiota, and thus,

prevent *C. difficile* colonization. Fecal microbiota transplantation has been shown to have a very high efficacy, with no further recurrence of *C. difficile* seen in 92% of treated cases [10, 11]. However, further research into fecal microbiota transplantation is needed as there have been limited controlled studies to elucidate the benefits and potential adverse effects of this treatment.

There are many risk factors for *C. difficile* infection. A systematic review found consistent evidence that increasing age, severity of underlying diseases, non-surgical gastrointestinal procedures, nasogastric tubes, anti-ulcer medications, increasing duration of hospital stay, increasing duration of antibiotic course, and the use of multiple antibiotics are associated with increased risk of *C. difficile* infection [12]. However, older age and severity of underlying illnesses may have a confounding association with risk of *C. difficile* infection, as older patients and patients with more severe illnesses are more likely to have an increased length of hospital stay and subsequently, increased potential exposure to *C. difficile* [13]. Among antibiotics, broad-spectrum antibiotics – in particular, cephalosporins, clindamycin, and fluoroquinoloes – as well as penicillin have been the most frequently associated with increased risk of *C. difficile* infection. A proposed mechanism has been that these particular antibiotics or antibiotics classes have a large disruptive impact on the normal intestinal flora, and thus, facilitate colonization of toxigenic *C. difficile* strains [5, 13]. Gastrointestinal stimulants, stool softeners, and enemas have also been associated with increased risk of *C. difficile*-associated diarrhea for the similar proposed mechanism of the disruption of the normal intestinal flora [13].

Immunosuppression is another risk factor for *C. difficile* infection and has been associated with severe *C. difficile*-associated illness. One study showed that patients who had been immunosuppressed due to medications such as corticosteroids and chemotherapeutic drugs or due to underlying conditions such as hematologic malignancies, HIV, and other autoimmune disorders were at higher risk of developing severe *C. difficile* infection resulting in fulminant colitis,

colectomy, or death [14]. Of the immunosuppressed patients, patients who had received lung transplants were particularly susceptible to developing fulminant *C. difficile* colitis [14]. Kidney-pancreas transplant recipients have also been shown to have a high incidence of *C. difficile* colitis [15]. Another single hospital-based study also found higher rates of infections in the nephrology, hematology, and organ transplantation wards compared to other wards, corroborating studies that suggest transplant recipients may be more susceptible to *C. difficile* infections due to their immunosuppressed state [16].

Cancer patients are another group of immunosuppressed individuals susceptible to *C. difficile* infection. A case report implicated chemotherapeutic agents as a risk factor for *C. difficile* infection, independent of previous antibiotic exposure [17]. A review of published cases of *C. difficile* infection in patients who have received chemotherapeutic agents reported on various classes of chemotherapeutic agents associated with *C. difficile* colitis. Methotrexate was the most commonly received chemotherapeutic drug among patients who developed *C. difficile*, followed by doxorubicin and cyclophosphamide, and then fluorouracil. There were no significant associations among *C. difficile* infection and type of cancer [18]. Although the pathogenesis of chemotherapeutic agents in facilitating *C. difficile* infections is yet unclear, chemotherapeutic agents have been known to cause extensive inflammatory damages in the bowel and alter the normal gut flora. Many chemotherapeutic agents cause desquamation and necrosis, which may result in an adequate anaerobic environment for the proliferation of *C. difficile* [18]. In an outpatient case-control study that examined risk factors for *C. difficile* infections among cancer patients, no significant association between any chemotherapy or treatment and the development of *C. difficile* was found. The only significant associations found in this study were exposure to clindamycin and third-generation cephalosporins and recent prolonged hospitalization [19]. Another case-control study examined risk factors for *C. difficile* during an outbreak in an oncology unit. Compared to patients

in the unit with diarrhea but negative for *C. difficile*, patients with *C. difficile* infection were more likely to have received chemotherapy. Receipt of both chemotherapy and exposure to antibiotics increased the risk of *C. difficile* infection [20].

Although studies have shown that *C. difficile* has been associated with significant mortality and morbidity and that there are many risk factors for *C. difficile* infection, there have been limited studies examining *C. difficile* in cancer patients. Incidences of *C. difficile* in cancer patients have previously been published as case reports, but there have been few comprehensive studies examining risk factors among cancer patients. Additionally, current research has been limited in showing consistent associations between specific chemotherapeutic drugs, other types of cancer treatments, types of cancers, and specific antibiotics with *C. difficile* infections in cancer patients. This study will address this gap in the current literature and aim to identify risk factors associated with *C. difficile* infections in cancer patients by assessing various demographic and clinical variables as well as previous medical history including prior antibiotic use and types of cancer treatment received.

Methods

Study design and subjects

The study utilized a retrospective medical records review. Medical records of patients over the age of 18 years admitted to the oncology wards at Yale-New Haven Hospital between February 1, 2013 and June 4, 2014 were eligible for enrollment in the study. The exclusion criterion was patients aged 18 years or younger without an oncology diagnosis.

The study design was case-control with two separate control arms. Cases were defined as inpatient oncology patients whose stools tested positive for *C. difficile* through the Yale-New Haven Hospital Microbiology Laboratory. The Yale-New Haven Hospital Microbiology Laboratory performs a rapid glutamate dehydrogenase (GDH) antigen enzyme immunoassay (EIA) test on all stool samples, and if positive, performs a reflex cell culture cytotoxin test. If both tests are negative, then the patient is determined to be negative for *C. difficile*. If both tests are positive, then the patient is determined to be positive for *C. difficile* infection. However, if the GDH antigen EIA test is positive but the toxin EIA test is negative, a cytotoxin neutralization test in cell culture is performed on the sample. If this is positive, then the patient is determined to have *C. difficile* disease, while if it is negative, then the patient is determined to be colonized with *C. difficile* and is not indicative of disease or active infection.

There were two control groups in this study. The first control group consisted of patients presenting with loose stools during the admission period and whose stools were submitted to the Microbiology Laboratory but tested negative for *C. difficile*. This control group was selected in order to determine risk factors for *C. difficile* infection compared to oncology patients who presented with loose stools but did not have *C. difficile*. The negative *C. difficile* test control subjects were selected at random using the random number generator function on Microsoft Excel from a computer-generated list of all patients who had been tested for *C. difficile* during the study period and whose stools had been submitted from the oncology wards.

A second control group consisted of oncology patients matched to cases based on hospital ward and dates of admission in order to control for environmental exposure to *C. difficile* [21]. This control group was matched to cases on a 1:2 case-control ratio. From a computer-generated list of all patients discharged from the oncology wards during the study period, patients were matched to cases manually, first by hospital ward, and then by discharge date. Control patients were matched to

cases using a discharge date range of ±3 days. If a case had more than two control patients matched by hospital ward and discharge date, two control patients were selected at random using the random number generator function on Microsoft Excel.

Data Collection

All subjects, cases and controls, were assigned a subject identification number, which was used for data entry in order to eliminate patient identifiable information on data forms. All patient medical records were accessed through the electronic medical record system. Data was stored both on paper and electronically. Paper forms were kept in a locked storage cabinet. Electronic data was entered on a Microsoft Excel spreadsheet and stored on a HIPAA-secured network accessed through an encrypted computer.

Multiple demographic and clinical variables were abstracted from patient medical records. The relevant risk period for *C. difficile* infection was established as 90 days prior to *C. difficile* test for the cases and the negative test control group, and 90 days prior to admission date for the matched control group. Demographic data such as age of subject and sex were collected. Dates of index admission and discharge and cumulative days of hospitalization in the 90 days prior to the *C. difficile* test (for the cases and negative test control group) or the index admission (for the matched control group) were recorded. Previous medical history such as prior history of *C. difficile*, type of cancer, stage of cancer, and cancer treatment (chemotherapy, surgery, stem cell therapy, blood transfusion, radiation therapy) received in the 90 days prior to the test or the index discharge were also recorded. Clinical variables included vancomycin-resistant enterococcus (VRE) colonization status, co-infections, indwelling medical devices on current admission, clinical presentation, and clinical outcome and treatment. For clinical presentation, the variables of elevated creatinine, fever, hypotension, and tachycardia were assessed at the time of the *C. difficile* test, while elevated lactic

acid, loose bowel movements, and neutropenia were assessed in the 90 days prior to the test. Elevated creatinine was defined as equal to or greater than 1.5 times the creatinine level on index admission, elevated lactic acid was defined as greater than 1.2 mmol/L, fever was defined as equal to or greater than a temperature of 100.4°F, hypotension was defined as systolic blood pressure equal to or less than 90 mmHg, and tachycardia was defined as heart rate equal to or greater than 110 beats per minute. Antibiotics received in the risk period were noted, as well as whether they were received at the time of the test, prior to index admission, or discontinued after diagnosis.

Univariate analysis was conducted for all variables to determine the descriptive statistics such as mean, frequencies, and standard deviations for each patient group. For the categorical variables, logistic regression and the Fisher's exact test was used to determine whether variables were significantly associated with *C. difficile* infection. For continuous variables, the Student's *t* test was used to determine association. Conditional logistic regression was used to find associations between the cases and the matched control group. For the multivariate model, all variables were input into the model and a backward stepwise elimination strategy was used to obtain the final model. All tests were two-tailed with a significance level of α=0.05. Data were processed and analyzed using Microsoft Excel (version 14.32, Microsoft Corporation) and SAS (version 9.3, SAS Institute, Inc.) software.

Study Approval

The study design and all protocols were reviewed and approved by the Institutional Review Board at Yale University.

Results

Eighty-one cases had a positive *C. difficile* test from the oncology wards during the period February 1, 2013 to June 4, 2014. Four cases were excluded because the patients did not have cancer, and a total of 77 cases met the eligibility criteria and were included in the study as cases. Six hundred seventy patients had a negative *C. difficile* test while on one of the oncology wards during the study period. Of this group of patients, 77 controls were selected for the negative test control group through randomization. A total of 6,933 patients were discharged during the study period from the oncology wards. Of this patient population, patients were matched to cases based on ward and discharge date as described in the methods. Two control subjects were matched to each case with the exclusion of two cases. For these two cases, only one control for each case was found to meet the matching criteria. The study included 306 subjects in total, with 77 cases, 77 patients in the negative test control group, and 152 patients in the matched control group.

Table 1 summarizes the demographic and clinical characteristics of subjects in all three groups. Clinical presentation on the *C. difficile* test date was recorded for cases and the negative test control group but not the matched control group since the matched control group was not tested for *C. difficile*. Significant differences between cases and the negative test control group were found in the proportion of subjects with prior history of *C. difficile* ($p=0.0026$), mean days of hospitalization in the 90 days prior to the test ($p=0.0028$), history of stem cell therapy ($p=0.0046$), and fever on the test date ($p=0.0032$). Significant differences between cases and the matched control group were found in mean age ($p=0.0011$), proportion of subjects with prior history of *C. difficile* ($p<0.0001$), history of blood transfusion ($p=0.0134$), any co-infection ($p<0.0001$), bloodstream infection ($p=0.0438$), wound/skin infection ($p=0.0033$), urinary tract infection ($p=0.0171$), and pneumonia ($p=0.0059$). The difference in proportion of subjects in each group who received chemotherapy in

the 90 days prior to the test date or index discharge was not significant between cases and the two groups. However, the most common chemotherapeutic agents received in each group varied. For cases, the most common chemotherapeutic drugs received were cytarabine (7.14%), doxorubicin (5.56%), cyclophosphamide (5.56%), irinotecan (5.56%), and paclitaxel (5.56%). In the negative test control group, the most common chemotherapeutic drugs received were cytarabine (7.69%), idarubicin (6.92%), cyclophosphamide (6.15%), and melphalan (6.15%), while in the matched control group, they were cytarabine (7.28%), cisplatin (7.28%), cyclophosphamide (6.80%), etoposide (6.63%), and methotrexate (5.53%).

Table 2 displays various antibiotics received in all three groups. A significantly greater number of cases received clindamycin (p=0.0314) and metronidazole (p=0.0329) in the 90 days prior to their *C. difficile* test compared to the negative test control group. There was also a significantly higher proportion of individuals who received beta-lactams/beta-lactamase inhibitor (BLI) (p=0.0018), clindamycin (p=0.0065), and fluoroquinolones (p=0.0069) prior to admission in the cases compared to the negative test control group. Beta-lactams/BLI (p=0.0205) and cephalosporins (p=0.0230) were discontinued after diagnosis in significantly higher numbers in the cases compared to the negative test control group. There were no significant differences in antibiotics received at the time of the test between the cases and the negative test control group. For antibiotics received in the 90 days prior to the test or index discharge in cases compared to the matched control group, proportions of patients who received beta-lactams (p=0.0182), beta-lactams/BLI (p=0.0002), cephalosporins (p=0.0364), metronidazole (p<0.0001), and intravenous vancomycin (0.0002) were significantly higher in cases. Additionally, a significantly higher number of cases received beta-lactams (p=0.0187), beta-lactams/BLI (p<0.0001), cephalosporins (p=0.0028), clindamycin (p=0.0079), fluoroquinolones (p<0.0001), metronidazole (p<0.0001),

sulfonamides (p=0.0438), and intravenous vancomycin (<0.0001) prior to admission compared to the matched control group.

Table 1: Demographic Factors, Medical History, and Clinical Factors by Group

Characteristics	Case (n=77)		Negative Test Control (n=77)		Matched Control (n=152)	
	%	No.	%	No.	%	No.
Mean age (years)	63.37 ± 13.24		61.41 ± 13.85		56.68 ± 14.80	
Male	40.26	31	40.26	31	38.16	58
Mean days of hospitalization	15.97 ± 18.81		8.88 ± 8.13		13.37 ± 14.11	
Prior history of *C. difficile*	18.18	14	2.6	2	0.66	1
VRE colonization	20.69	12	12.96	7	14.29	13
Cancer type						
Solid tumors	72.73	56	61.04	47	72.37	110
Hematologic cancers	32.47	25	44.16	34	27.63	42
Cancer treatment						
Blood transfusion	38.96	30	37.66	29	23.03	35
Chemotherapy	67.53	52	72.73	56	60.53	92
History of stem cell therapy	3.90	3	19.48	15	7.24	11
Radiation therapy	7.79	6	9.09	7	10.53	16
Surgery	36.36	28	23.38	18	36.18	55
Indwelling medical devices						
Central venous catheter	63.64	49	68.83	53	52.63	80
Enteral feeding	3.90	3	6.49	5	5.92	9
Mechanical ventilation	3.90	3	6.49	5	4.61	7
Nasogastric tube	15.58	12	12.99	10	7.24	11
TPN	6.49	5	3.9	3	3.95	6
Co-infections						
Any co-infection	51.95	40	48.05	37	19.74	30
Blood stream-infection	11.69	9	5.19	4	3.95	6
Pneumonia	12.99	10	9.09	7	2.63	4
Urinary tract infection	14.29	11	15.58	12	1.97	3
Would/skin infection	11.69	9	10.39	8	4.61	7
Clinical presentation						
Elevated creatinine	1.30	1	2.6	2		
Elevated lactic acid	12.99	10	3.9	3		
Fever	24.68	19	6.49	5		
Hypotension	11.69	9	2.60	2		
Loose bowel movements	41.56	32	29.87	23		
Neutropenia	33.77	26	31.17	24		
Tachycardia	28.57	22	22.08	17		

Table 2: Antibiotics Received by Group

Antibiotic	Case (n=77)		Negative Test Control (n=77)		Matched Control (n=152)	
	%	No.	%	No.	%	No.
Antibiotic received in 90 days prior to test						
Beta-lactams	11.69	9	9.09	7	3.29	5
Beta-lactams/BLI	58.44	45	45.45	35	32.24	49
Carbapenems	5.19	4	1.30	1	1.32	2
Cephalosporins	59.74	46	49.35	38	44.74	68
Clindamycin	12.99	10	2.60	2	5.92	9
Colistin	0.00	0	0.00	0	0.66	1
Daptomycin	1.30	1	0.00	0	1.32	2
Fluoroquinolones	53.25	41	50.65	39	44.08	67
Fosfomycin	2.60	2	0.00	0	0.00	0
Metronidazole	37.66	29	20.78	16	9.21	14
Sulfonamides	14.29	11	12.99	10	9.87	15
Tigecycline	0.00	0	0.00	0	0.66	1
Vancomycin (intravenous)	49.35	38	41.56	32	24.34	37
Vancomycin (oral)	2.60	2	0.00	0	0.00	0
Antibiotic received prior to admission [a]						
Beta-lactams	7.79	6	2.60	2	1.32	2
Beta-lactams/BLI	33.77	26	11.69	9	7.89	12
Carbapenems	1.30	1	0.00	0	0.00	0
Cephalosporins	28.57	22	16.88	13	11.84	17
Clindamycin	10.39	8	0.00	0	1.97	3
Daptomycin	1.30	1	0.00	0	1.32	2
Fluoroquinolones	46.75	36	24.68	19	14.47	22
Fosfomycin	2.60	2	0.00	0	0.00	0
Metronidazole	10.39	8	12.99	10	1.97	3
Sulfonamides	11.69	9	9.09	7	3.95	6
Vancomycin (intravenous)	24.68	19	11.69	9	5.26	8
Vancomycin (oral)	1.30	1	0.00	0	0.00	0
Antibiotic received at time of test [a]						
Beta-lactams	5.19	4	3.90	3		
Beta-lactams/BLI	24.68	19	28.57	22		
Carbapenems	1.30	1	0.00	0		
Cephalosporins	6.49	5	11.69	9		
Fluoroquinolones	7.79	6	19.48	15		
Metronidazole	10.39	8	12.99	10		
Sulfonamides	5.19	4	5.19	4		
Vancomycin (intravenous)	23.38	18	15.58	12		
Antibiotic discontinued after diagnosis [a]						
Beta-lactams	25.00	1	33.33	1		
Beta-lactams/BLI	38.10	8	4.76	1		
Cephalosporins	80.00	4	11.11	1		
Clindamycin	14.29	1	0.00	0		
Metronidazole	0.00	0	40.00	4		
Vancomycin (intravenous)	35.29	6	0.00	0		

[a] Antibiotics with zero frequencies across all groups were omitted

Table 3 displays the odds ratios from a univariate, unadjusted logistic regression of demographic, medical history, and clinical risk factors in cases compared to the negative test control group and the matched control group. For cases compared to the control group with negative *C. difficile* test results, days of hospitalization in the 90 days prior to the test date, prior history of *C. difficile*, fever on the test date, and hypotension on the test date were all significantly associated with *C. difficile* infection in cases compared to the negative test control group. Increasing days of hospitalization in the past 90 days prior to the *C. difficile* test was associated with 1.054 (95% CI 1.017, 1.092) times the odds of having a positive *C. difficile* infection. Prior history of *C. difficile* was associated with 8.333 (95% CI 1.824, 38.063) times the odds of *C. difficile* infection. For clinical presentation on the test date, the odds of *C. difficile* infection were 4.717 (95% CI 1.661, 13.400) for fever and 4.963 (95% CI 1.036, 23.781) for hypotension. In contrast, history of stem cell therapy was negatively associated with *C. difficile* infection. Patients with a history of stem cell therapy were significantly less likely (OR=0.168, 95% CI 0.046, 0.606) to have positive *C. difficile* infection.

For the univariate analysis of cases compared to the matched control group, age, prior history of *C. difficile,* blood transfusion, having any co-infection, as well as the co-infections of blood-stream infection, pneumonia, urinary tract infection, and would/skin infection were significantly associated with risk of *C. difficile infection*. Increasing age was associated with 1.036 (95% CI 1.013, 1.060) times the odds of having positive *C. difficile* infection. Patients with a prior history of *C. difficile* had 27-fold higher odds of having *C. difficile* infection (OR=27.035, 95% CI 3.551, 205.826). Patients who received blood transfusion for cancer treatment in the 90 days prior to index admission were 2.168 (95% CI 1.161, 4.048) times as likely to have *C. difficile* infection. Having any co-infection was associated with a 3.830 (95% CI 2.113, 6.944) times the odds of having *C. difficile* infection. For specific co-infections, the odds were 3.221 (95% CI 1.102, 9.411)

for blood stream infections, 5.522 (95% CI 1.672, 18.242) for pneumonia, 3.452 (95% CI 1.281, 9.303) for urinary tract infections, and 6.574 (95% CI 1.725, 25.048) for wound/skin infections.

Table 3: Univariate Logistic Regression of Potential Risk Factors in Cases Compared to Control Groups

	Negative Test Control (n=77)	Matched Control (n=152)
	OR (95% CI)	OR (95% CI)
Age	1.010 (0.987, 1.034)	1.036 (1.013, 1.060)
Gender		
Male	1.000	1.000
Female	1.000 (0.525, 1.904)	0.895 (0.488, 1.641)
Days of hospitalization	1.054 (1.017, 1.092)	1.011 (0.993, 1.030)
Prior history of *C. difficile*	8.333 (1.824, 38.063)	27.035 (3.551, 205.826)
VRE colonization	1.752 (0.634, 4.842)	1.532 (0.624, 3.760)
Cancer type		
Hematologic	0.608 (0.316, 1.171)	1.490 (0.625, 3.548)
Solid tumors	1.702 (0.863, 3.357)	1.123 (0.494, 2.553)
Cancer treatment		
Blood transfusion	1.056 (0.552, 2.023)	2.168 (1.161, 4.048)
Chemotherapy	0.780 (0.390, 1.558)	1.515 (0.760, 3.017)
History of stem cell therapy	0.168 (0.046, 0.606)	0.442 (0.115, 1.705)
Radiation therapy	0.845 (0.271, 2.641)	0.702 (0.247, 1.997)
Surgery	1.873 (0.927, 3.783)	1.048 (0.503, 2.183)
Indwelling medical devices		
Central venous catheter	0.792 (0.406, 1.548)	1.700 (0.913, 3.165)
Enteral feeding	0.584 (0.135, 2.533)	0.537 (0.104, 2.786)
Mechanical ventilation	0.584 (0.135, 2.533)	0.843 (0.204, 3.491)
Nasogastric tube	1.237 (0.500, 3.060)	2.315 (0.962, 5.572)
TPN	1.713 (0.395, 7.433)	1.667 (0.509, 5.461)
Co-infections		
Any co-infection	1.169 (0.621, 2.199)	3.830 (2.113, 6.944)
Blood stream infection	2.415 (0.711, 8.205)	3.221 (1.102, 9.411)
Pneumonia	1.493 (0.537, 4.149)	5.522 (1.672, 18.242)
Urinary tract infection	0.903 (0.372, 2.192)	3.452 (1.281, 9.303)
Would/skin infection	1.141 (0.416, 3.132)	6.574 (1.725, 25.048)
Clinical presentation		
Elevated creatinine	0.493 (0.044, 5.558)	
Elevated lactic acid	3.682 (0.972, 13.946)	
Fever	4.717 (1.661, 13.400)	
Hypotension	4.963 (1.036, 23.781)	
Loose bowel movements	1.670 (0.858, 3.250)	
Neutropenia	1.126 (0.573, 2.211)	
Tachycardia	1.412 (0.680, 2.933)	

A univariate, unadjusted logistic regression was also analyzed for use of various antibiotics as risk factors in cases compared to both control groups (Table 4). In cases compared to the negative test control group, receipt of clindamycin and metronidazole in the 90 days prior to test were significantly associated with risk of *C. difficile* infection, while receipt of beta-lactams/BLI, clindamycin, fluoroquinolones, metronidazole, and intravenous vancomycin prior to index admission were significantly associated with increased risk of *C. difficile* infection. Clindamycin was associated with 5.596 (95% CI 1.184, 26.457) times the odds of *C. difficile* infection if received at any time in the 90 days prior to test and 18.939 (95% CI 1.074, 333.333) times the odds of *C. difficile* infection if received prior to index admission. Metronidazole was associated with 2.303 (95% CI 1.123, 4.723) times the odds of *C. difficile* infection if received in 90 days prior to test and 5.978 (95% CI 1.927, 18.541) times the odds of *C. difficile* infection if received prior to index admission. The odds of *C. difficile* infection for antibiotics received prior to admission were 3.852 (95% CI 1.662, 8.926) for beta-lactams/BLI, 2.680 (95% CI 1.351, 5.315) for fluoroquinolones, and 2.475 (95% CI 1.040, 5.889) for intravenous vancomycin.

A greater number of antibiotics were significantly associated with higher risk of *C. difficile* infection in cases compared to the matched control group. The odds of *C. difficile* infection for antibiotics received in the 90 days prior to index discharge were 4.165 (95% CI 1.271, 13.653) for beta-lactams, 3.160 (95% CI 1.704, 5.858) for beta-lactams/BLI, 1.870 (95% CI 1.048, 3.336) for cephalosporins, 6.754 (95% CI 2.924, 15.599) for metronidazole, and 3.048 (95% CI 1.659, 5.600) for vancomycin. The odds of *C. difficile* infection for antibiotics received prior to admission were 6.000 (95% CI 1.211, 29.727) for beta-lactams, 8.242 (95% CI 3.126, 21.727) for beta-lactams/BLI, 2.728 (95% CI 1.376, 5.409) for cephalosporins, 5.333 (95% CI 1.415, 20.103) for clindamycin, 5.457 (95% CI 2.669, 11.158) for fluoroquinolones, 33.103 (95% CI 4.412, 248.357) for

metronidazole, 3.000 (95% CI 1.068, 8.428) sulfonamides, and 8.087 (95% CI 2.722, 24.029) for intravenous vancomycin.

Table 4: Univariate Logistic Regression of Antibiotic Use in Cases Compared to Control Groups

	Negative Test Control (n=77)	Matched Control (n=152)
	OR (95% CI)	OR (95% CI)
Antibiotic received in 90 days prior to test		
Beta-lactams	1.324 (0.467, 3.754)	4.165 (1.271, 13.653)
Beta-lactams/BLI	1.687 (0.892, 3.193)	3.160 (1.704, 5.858)
Carbapenems	4.164 (0.455, 38.139)	4.000 (0.733, 21.838)
Cephalosporins	1.523 (0.804, 2.882)	1.870 (1.048, 3.336)
Clindamycin	5.596 (1.184, 26.457)	2.788 (0.983, 7.908)
Daptomycin	3.039 (0.122, 75.757)	1.000 (0.091, 11.028)
Fluoroquinolones	1.110 (0.590, 2.089)	1.430 (0.811, 2.521)
Metronidazole	2.303 (1.123, 4.723)	6.754 (2.924, 15.599)
Sulfonamides	1.117 (0.444, 2.806)	1.550 (0.671, 3.582)
Vancomycin (intravenous)	1.370 (0.725, 2.589)	3.048 (1.659, 5.600)
Antibiotic received prior to admission		
Beta-lactams	3.169 (0.619, 16.221)	6.000 (1.211, 29.727)
Beta-lactams/BLI	3.852 (1.662, 8.926)	8.242 (3.126, 21.727)
Cephalosporins	1.969 (0.908, 4.273)	2.728 (1.376, 5.409)
Clindamycin	18.939 (1.0743, 333.333)	5.333 (1.415, 20.103)
Daptomycin	3.039 (0.122, 75.757)	1.000 (0.091, 11.028)
Fluoroquinolones	2.680 (1.351, 5.315)	5.457 (2.669, 11.158)
Metronidazole	5.978 (1.927, 18.541)	33.103 (4.412, 248.357)
Sulfonamides	1.324 (0.467, 3.754)	3.000 (1.068, 8.428)
Vancomycin (intravenous)	2.475 (1.040, 5.889)	8.087 (2.722, 24.029)
Antibiotic received at time of test		
Beta-lactams	1.352 (0.292, 6.251)	
Beta-lactams/BLI	0.819 (0.400, 1.676)	
Carbapenems	3.039 (0.122, 75.757)	
Cephalosporins	0.525 (0.167, 1.645)	
Fluoroquinolones	0.349 (0.128, 0.955)	
Metronidazole	0.777 (0.289, 2.088)	
Sulfonamides	1.000 (0.241, 4.151)	
Vancomycin (intravenous)	1.830 (0.800, 4.190)	

In a multivariate logistic regression model comparing cases to the negative test control group (Table 5), days of hospitalization in the 90 days prior to the test, fever on the test date, prior

history of *C. difficile*, and hypotension were all significantly associated with higher likelihoood of *C. difficile* infection, adjusting for all other variables. Increasing days of hospitalization was associated with slightly increased odds of *C. difficile* infection, at an odds ratio of 1.075 (95% CI 1.027, 1.124). Fever on the test date was associated with a five-fold increase in likelihood of *C. difficile* (OR=5.232, 95% CI 1.460, 18.755) and hypotension on the test date was associated with a nine-fold increase in likelihood of *C. difficile* infection (OR=9.245, 95% CI 1.235, 69.183). Prior history of *C. difficile* carried the highest likelihood of *C. difficile* infection of the variables in the model, at a 32-fold increase in likelihood of *C. difficile* infection (OR=32.433, 95% CI 3.513, 299.445). In the same model, history of stem cell therapy and radiation therapy as cancer treatment in the 90 days prior to the test were significant for reduced likelihood of *C. difficile* infection. History of stem cell therapy was associated with 0.043 times (95% CI 0.006, 0.313) the odds of *C. difficile* infection, and patients who received radiation therapy for cancer treatment in the 90 days prior to the *C. difficile* test were nine-fold less likely to have *C. difficile* infection (OR=0.096, 95% CI 0.016, 0.594). All significant variables in the multivariate, adjusted model were also significant in the univariate model with the exclusion of radiation therapy. Antibiotics that were significantly associated with increased likelihood of *C. difficile* in the univariate analysis, however, were not significant in the multivariate, adjusted model.

Table 5: Multivariate Logistic Regression Compared to Negative Test Control Group

Characteristic	OR (95% CI)
Days of hospitalization	1.075 (1.027, 1.124)
Fever	5.232 (1.460, 18.755)
History of *C. difficile*	32.433 (3.513, 299.445)
History of stem cell therapy	0.043 (0.006, 0.313)
Hypotension	9.245 (1.235, 69.183)
Radiation therapy	0.096 (0.016, 0.594)

For cases compared to the matched control group, the multivariate logistic regression model showed that age, any co-infection, blood transfusion, cephalosporins, chemotherapy, prior history of *C. difficile* infection, metronidazole, and the presence of a nasogastric tube were significantly associated with higher risk of *C. difficile* infection. Fluoroquinolones, mechanical ventilation, radiation therapy, and TPN were associated with lower risk of *C. difficile* infection, adjusting for all other variables. Increasing age was associated with slightly increased odds of *C. difficile* infection of 1.042 (95% CI 1.006, 1.079). Patients with any co-infection were 5.614 (95% CI 1.878, 16.787) times more likely to have *C. difficile* infection. Certain cancer treatments were associated with increased risk of *C. difficile*. Blood transfusion was associated with 3.200 (95% CI 1.251, 8.183) times the odds of *C. difficile* infection, while chemotherapy was associated with 5.069 (95% CI 1.609, 15.972) times the odds of *C. difficile* infection. Patients who received cephalosporins in the 90 days prior to the index discharge were 4.214 (95% CI 1.371, 12.952) times more likely to have *C. difficile* infection, and patients who received metronidazole were 16.005 (95% CI 3.958, 64.713) times more likely to have *C. difficile* infection. Prior history of *C. difficile* was associated with an almost 28-fold increase (OR=27.806, 95% CI 2.484, 311.290) in likelihood of *C. difficile* infection during the index admission. The presence of a nasogastric tube during the index admission was associated with a seven-fold increase (OR=6.988, 95% CI 1.339, 36.477) in likelihood of *C. difficile* infection. In contrast, receiving fluoroquinolones was associated with a reduced likelihood of *C. difficile* infection (OR=0.286, 95% CI 0.097, 0.846), and mechanical ventilation was also associated with a reduced likelihood (OR=0.056, 95% CI 0.004, 0.817) of *C. difficile* infection. Patients who received radiation therapy were 0.117 (95% CI 0.016, 0.872) times as likely to have *C. difficile* infection, and patients who received TPN were 0.108 (95% CI 0.015, 0.834) times as likely. The co-infections of blood stream infection, pneumonia, urinary tract infection, and wound/skin infections were each individually significantly associated with *C. difficile* infection in the univariate analysis

but were not significant in the multivariate, adjusted model. In contrast, chemotherapy, mechanical ventilation, nasogastric tube, radiation therapy, and TPN were not significant in the univariate model but were significant in the multivariate, adjusted model. Of the antibiotics that were found to be significant in the univariate model, only receipt of cephalosporins, fluoroquinolones, and metronidazole in the 90 days prior to the index discharge were significant in the multivariate, adjusted model.

Table 6: Multivariate Logistic Regression Compared to Matched Control Group

Characteristic	OR (95% CI)
Age	1.042 (1.006, 1.079)
Any co-infection	5.614 (1.878, 16.787)
Blood transfusion	3.200 (1.251, 8.183)
Cephalosporins	4.214 (1.371, 12.952)
Chemotherapy	5.069 (1.609, 15.972)
Fluoroquinolones	0.286 (0.097, 0.846)
History of *C. difficile*	27.806 (2.484, 311.290)
Mechanical ventilation	0.056 (0.004, 0.817)
Metronidazole	16.005 (3.958, 64.713)
Nasogastric tube	6.988 (1.339, 36.477)
Radiation therapy	0.117 (0.016, 0.872)
TPN	0.108 (0.014, 0.834)

Discussion

The study found several significant associations between *C. difficile* infection and various demographic characteristics, clinical factors, antibiotics, and medical history. By using two control groups, this study was able to find distinct associations for *C. difficile*-associated diarrhea in oncology patients presenting with diarrhea (the negative test control group) and for *C. difficile* infection in a more general group of oncology patients (the matched control group).

Cases Compared to the Negative Test Control Group

Between the cases and the negative test control group, univariate, unadjusted analyses found that the days of hospitalization in the 90 days prior to test, prior history of *C. difficile,* fever on test date, hypotension on test date, receipt of clindamycin in 90 days prior to *C. difficile* test, receipt of metronidazole in 90 days prior to *C. difficile* test, receipt of beta-lactams/BLI prior to admission, receipt of clindamycin prior to admission, receipt of fluoroquinolones prior to admission, receipt of metronidazole prior to admission, and receipt of intravenous vancomycin prior to admission were significantly associated with increased likelihood of *C. difficile* infection. Surprisingly, history of stem cell therapy was significantly associated with reduction in likelihood *C. difficile* infection. However, the associations between the cases and the negative test control group may reflect the likelihood of positive *C. difficile* test rather than the odds of disease, as testing bias may impact the associations.

Days of hospitalization in the 90 days prior to test may be associated with *C. difficile* infection for multiple reasons. First, days of hospitalization may reflect severity of underlying cancers, and subsequently, increased host susceptibility to infection. Recent hospitalization may also indirectly represent recent exposure to other risk factors, such as antibiotic use and immunosuppressive therapies, both of which have been implicated as risk factors for *C. difficile* infection in previous studies [12, 14]. Days of hospitalization may also correlate to increased exposure to *C. difficile* in the healthcare setting through increased length of exposure to any environmental spores or exposure to asymptomatic carriers of toxigenic strains of *C. difficile*. Although most asymptomatic carriage of *C. difficile* is with non-toxigenic strains, studies have shown that there are individuals who are asymptomatic and carry toxigenic strains of *C. difficile*. If there were patients in the study wards who were asymptomatically colonized with toxigenic strains, they may have contributed to nosocomial transmission of *C. difficile* [22, 23]. Prior history of *C.*

difficile is another factor in patients' medical histories that has previously been identified as a risk factor for *C. difficile* infection; recurrent *C. difficile* is common. Relapse rates have been found to range from 5-23% for metronidazole-treated *C. difficile* and 9-24% for patients treated with oral vancomycin [24]. Re-infections are common as well. A study found that 56% of clinical recurrences of *C. difficile* are due to re-infections rather than relapses [25]. Thus, patients with prior history of *C. difficile* may have been susceptible to re-infection or relapse upon index admission.

In terms of clinical presentation, cases were more likely to present with fever and hypotension on the day of the *C. difficile* test compared to patients in the negative test control group, and these associations were statistically significant. There were higher proportions of cases with elevated lactic acid in the 90 days prior to test, loose bowel movements in the 90 days prior to test, neutropenia in the 90 days prior to test, and tachycardia on the test date compared to the negative test control group, but these differences in proportions were not significant. This finding has implications for clinicians who are treating cancer patients with diarrhea. Poorer clinical presentation, particularly fever and hypotension, on days of diarrhea may increase suspicion for *C. difficile* infection.

All antibiotics assessed in this study were received in higher proportions in cases compared to the negative test control group if received in the 90 days prior to the test or prior to admission, though only a few associations were statistically significant. Receipt of clindamycin and metronidazole in the 90 days prior to the test were significantly associated with *C. difficile* infection in cases compared to the negative test control group, and receipt of beta-lactams/BLI, clindamycin, fluoroquinolones, metronidazole, and intravenous vancomycin prior to admission (i.e., on a previous hospitalization within 90 days prior to the index admission) were significantly associated with *C. difficile*. The associations between clindamycin, fluoroquinolones, and beta-lactams/BLI with *C. difficile* infection are consistent with previous studies [26]. Metronidazole, however, is often

used as treatment for *C. difficile* infections, so the association between metronidazole use and *C. difficile* may be confounded by recent history of *C. difficile*, particularly since prior history of *C. difficile* was also significantly associated with positive *C. difficile* test. Intravenous vancomycin has also previously not been commonly associated with *C. difficile* infection. However, intravenous vancomycin is a commonly prescribed antibiotic particularly for empirical use, so the frequency of intravenous vancomycin received in cases may be more reflective of general antibiotic prescription practices based on the patients' poorer clinical presentation or their increased days of hospitalization prior to *C. difficile* infection [27].

Of the cancer treatments, history of stem cell therapy was the only significant association, and the association between history of stem cell therapy and *C. difficile* infection was negative. This was an unexpected finding, as stem cell therapy is typically performed in conjunction with immunosuppressive agents, and immunosuppression is an established risk factor for *C. difficile* infection [14, 28]. However, the association found in this study may reflect the higher percentage of patients in the negative test control group with hematologic cancers compared to the cases. Additionally, diarrhea is a frequent complication of stem cell transplantation for patients with lymphoma and multiple myeloma, so there may have been selection bias in the negative test control group. Patients with lymphoma and multiple myeloma who had a history of stem cell therapy may have been selected more frequently into the negative test control group because they exhibited greater frequency of diarrhea than patients with other cancers, which resulted in their stool samples being tested more frequently [29].

Adjusting for all other variables, the multivariate model comparing cases to the negative case control group found days of hospitalization, fever on the test date, hypotension on the test date, and prior history of *C. difficile* to be significantly associated with *C. difficile* infection. History of stem cell therapy was once again associated with reduced likelihood of *C. difficile* infection, as well

as radiation therapy in 90 days prior to *C. difficile* test, which was not significant in the univariate analysis. Radiation therapy, like stem cell therapy, is typically associated with immunosuppression and has been associated with decreased intestinal microflora, which is a risk factor for acquisition of toxigenic *C. difficile* strains [30]. Thus, this finding was unexpected and a similar association has not been found in previous studies. Further studies should be conducted to assess for possible confounders in the negative association between radiation therapy and *C. difficile* infection. None of the antibiotics were independently associated with increased risk of *C. difficile* infection in the adjusted model that controlled for all other variables; however, this finding does not necessarily indicate that antibiotic use is not a risk factor for *C. difficile* infection.

Cases Compared to the Matched Control Group

Between the cases and the control group matched to cases based on hospital ward and date of discharge, increasing age, prior history of *C. difficile*, blood transfusion, any co-infection, blood stream infection, pneumonia, urinary tract infection, and wound/skin infection were significantly associated with *C. difficile* infection in the univariate, unadjusted analysis. For the univariate, unadjusted analysis examining antibiotic use between cases and the matched control group, receipt of beta-lactams, beta-lactams/ BLI, cephalosporins, metronidazole, and intravenous vancomycin in the 90 days prior to test were significantly associated with *C. difficile* infection, and receipt of beta-lactams, beta-lactams/BLI, cephalosporins, clindamycin, fluoroquinolones, metronidazole, sulfonamides, and intravenous vancomycin prior to admission were significantly associated with *C. difficile*.

The study's finding of a positive association between increasing age and *C. difficile* infection is consistent with previous studies that identified increasing age to be a risk factor for *C. difficile* [12]. All co-infections that were assessed in the study were significantly associated with *C.*

difficile infection in the univariate analyses, and this is also consistent with previous associations found between *C. difficile* and severity of underlying disease [12]. Of cancer treatments, only blood transfusion was significantly associated with *C. difficile* infection. Blood transfusion has been known to cause immunomodulation in the recipient, and in particular, immunosuppression [31]. It is possible that blood transfusion increased the likelihood of *C. difficile* infection through immunosuppression, thereby increasing host susceptibility. Additionally, a study found that in children with cancer, *C. difficile* infection was significantly associated with blood transfusions, possibly due to immunosuppression following blood transfusions [32]. Although our study did not enroll children under the age of 18, it is possible that in both pediatric and adult oncology patients, there is a similar mechanism that increases susceptibility to *C. difficile* infection after receiving recent blood transfusion; however, the exact mechanism is yet unknown and warrants further research.

Beta-lactams, beta-lactams/BLI, cephalosporins, clindamycin, and fluoroquinolones have all been previously associated with *C. difficile* infection [33]. Although a study has found a significant association between sulfonamides and *C. difficile* infection, sulfonamides are a class of antibiotics that have typically been less frequently associated with *C. difficile* infection [34]. Intravenous vancomycin has also previously been rarely associated with *C. difficile* infection, but in this study, recent receipt of intravenous vancomycin was significantly associated with *C. difficile* infection in univariate analyses in cases compared to both control groups. The identification of antibiotics that have previously been less commonly associated with *C. difficile* in this study could reflect changes in prescription practices or the identification of novel antimicrobial risk factors in *C. difficile*.

There were several unexpected effects found in the multivariate regression model comparing the cases to the matched control group. First, receipt of fluoroquinolones in the 90 days prior to the test appeared to have a negative association with *C. difficile* infection. However, fluoroquinolones

have been previously identified as a risk factor for *C. difficile* infection in several studies [35, 36]. Consistent with previous studies, the univariate analysis showed an insignificant but positive association between fluoroquinolones and *C. difficile* infection for fluoroquinolones received in the 90 days prior to the test, and a significant, positive association between fluoroquinolones received prior to admission and *C. difficile*. In our study, antibiotics received in the 90 days prior to the test was a distinct variable from antibiotics received prior to admission, since the antibiotics received prior to admission excluded the antibiotics received prior to test but during the index admission. In the multivariate model, antibiotics used in the 90 days prior to test was included but not the antibiotics received prior to admission as these variables were overlapping for many of the subjects; however, the reversal of association found in the multivariate model is still surprising given prior studies. It is possible that the negative association in the multivariate model is due to multicollinearity, in which the variable of fluoroquinolones is strongly correlated with another variable in the multiple regression model, or there could be a confounder in the model. However, it is not readily apparent whether any of the variables in the model lies in the causal pathway between fluoroquinolones and *C. difficile* and would be a confounder of this association. Another possible explanation is the reversal paradox, also known as the Simpson's paradox, Lord's paradox, or the suppression effect. This paradox refers to the phenomenon in which the association between two variables is reversed, diminished, or enhanced when additional variables are controlled for [37]. This paradox is commonly observed in conditional analyses in particular, which is consistent with the use of the conditional multivariate logistic regression for the model comparing cases to the matched control group [38]. It is possible that the reversal in association for fluoroquinolones and *C. difficile* is due to this paradox; however, there is a lack of consensus in the literature regarding the correct interpretation of results when the reversal paradox occurs, so it is unclear whether the univariate results or the multivariate results should be considered the true association. However,

because there have been numerous studies showing a positive association between fluoroquinolones and *C. difficile* infection, it is likely that the positive association found in this study's univariate analyses may be more reflective of the true association. The negative association between total parenteral nutrition and *C. difficile* also appears to be affected by the reversal paradox in the multivariate model, as the univariate analysis shows a non-significant but positive association between TPN and *C. difficile*. The interpretation of this is less clear, as there have been limited previous studies examining the association between TPN and *C. difficile*. This is an association that warrants further investigation.

Other factors that were not affected by the reversal paradox but negatively associated with *C. difficile* infection in the multivariate model comparing cases to the matched control group were mechanical ventilation on index admission and radiation therapy in the 90 days prior to index discharge. Radiation therapy was also found to be significantly associated with reduced likelihood of *C. difficile* infection in the multivariate analysis comparing cases to the negative test control group, and poses an unexpected finding. The negative association between *C. difficile* and mechanical ventilation was also unexpected, as mechanical ventilation often indicates more severe underlying disease. Additionally, the association between nosocomial pneumonia and ventilators has been well established, and ventilators have long been implicated as a major cause of nosocomial bacterial colonization [39]. Radiation therapy and mechanical ventilation both require further research to determine the association between these factors and risk of *C. difficile* infection.

The multivariate model found several significant positive associations for *C. difficile* infection. Increasing age, any co-infection, recent blood transfusion, receipt of cephalosporins in the 90 days prior to the index discharge, recent chemotherapy, prior history of *C. difficile*, receipt of metronidazole in the 90 days prior to the index discharge, and presence of a nasogastric tube were associated with increasing likelihood of *C. difficile* infection. All of these variables were also

significantly associated with *C. difficile* infection in the univariate analyses with the exception of chemotherapy and nasogastric tube. Both chemotherapy and nasogastric tubes have been associated with *C. difficile* in previous studies, and this study shows a consistent association [12, 17]. This study did not examine associations between specific chemotherapeutic agents and *C. difficile*, but previous studies have shown particular chemotherapeutic agents to be associated with *C. difficile*. Thus, grouping all chemotherapeutic agents as a single variable in this study may have resulted in a diminished association, and future studies may benefit from examining the associations between specific chemotherapy drugs and *C. difficile* infection.

Limitations

There are several limitations to this study. First, the study design was a retrospective, case-control chart review. Patient medical records may be incomplete, and missing data can lead to biased results. In particular, several variables were difficult to find and often incompletely and inconsistently documented in patient medical records, such as indwelling medical devices and cancer staging information. Cancer staging data were so sparsely found in patients' medical records that the variable was omitted in the analysis, but future studies may find analysis of cancer stage to be informative in exploring an association between *C. difficile* and severity of cancer. Patients who were transferred from outside facilities also often had inconsistently or incompletely documented charts. There may also be bias due to differential reporting and documentation between cases and controls. Case patients tended to have poorer prognosis and more complications during their hospitalizations than control patients, particularly compared to the matched control group. Thus, it may have been more likely for control patients to have incomplete documentation for various medical history and clinical factors while cases had more extensive documentation in their charts.

The selection of control groups also posed a limitation. Subjects for the negative test control group were selected from a randomized list of patients whose stool samples were submitted to the Microbiology Lab for *C. difficile* testing and found to be negative for *C. difficile* toxin. However, it is possible that not all patients with diarrhea were tested for *C. difficile*, as there were no universal criteria for *C. difficile* testing in patients with diarrhea in the study hospital. This could have resulted in selection bias in which more clinically severely ill patients were enrolled as both cases and as negative test controls, because patients exhibiting milder diarrheal symptoms may not have had stool samples collected for *C. difficile* testing, and consequently, not enrolled in the study. Finally, the matching criteria for the matched control group were kept minimal to two factors – same hospital ward and date of discharge – in order to identify as many potential risk factors as possible. Although the matching criteria used in our study were selected to control for environmental factors, incorporating additional matching criteria may have been able to adjust for possible confounding variables.

Another limitation with the negative test control group was that *C. difficile* carriage status was not documented. Patients who were positive for *C. difficile* antigen but were negative for *C. difficile* toxin in the clinical microbiology laboratory test results were identified to be negative for *C. difficile* infection but colonized with non-toxigenic *C. difficile*. Although patients with *C. difficile* colonization are not clinically indicated for treatment and are not considered to have active infection, studies have shown both common and distinct risk factors for *C. difficile* colonization compared to *C. difficile* infection. Healthcare-associated *C. difficile* colonization has been associated with previous hospitalization, chemotherapy, proton-pump inhibitors, H_2 blockers, antibodies against toxin B, stool softeners, and antacids [40, 41]. Thus, by not distinguishing between *C. difficile* colonized patients and un-colonized patients in our control groups, this study may have overlooked the distinct risk factors that may influence *C. difficile* colonization versus infection.

The risk period during used in this study was 90 days; however, different studies have used shorter periods of 60 days or 30 days prior to infection to assess relevant exposures associated with *C. difficile* [42, 43, 44]. The use of a longer risk period may have resulted in the identification of some exposures that may not have been directly associated with *C. difficile* by the time of diagnosis for the cases. Finally, this study was conducted in a single institution with a relatively low sample size. Thus, the results of the study may not be applicable to a larger population of oncology patients, particularly in different settings where overall *C. difficile* prevalence may be different than that of our center.

Conclusions

In conclusion, this study identified several risk factors for *C. difficile* infection in oncology patients, both with and without diarrhea and suspicion of *C. difficile*. These findings may guide clinicians in selecting appropriate testing for oncology patients who may be at higher risk for *C. difficile* infection. Although diarrhea is a common complication in cancer patients, the comparison between the cases and the negative test control group shows that cancer patients exhibiting diarrhea with a fever and hypotension may be indicative for *C. difficile* infection. Additionally, patients with diarrhea who have lengthy recent hospitalization records and a prior history of *C. difficile* may be at increased risk of current *C. difficile* infection. Based on the analysis of the matched control group, reduction in cephalosporins and metronidazole use, particularly among patients with any co-infections, presence of a nasogastric tube, a history of *C. difficile* infection, recent chemotherapy or blood transfusions may reduce the risk of *C. difficile* infection and should be a focus of future study and intervention.

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Appendix: Data Collection Form

Data Collection Form – *C. difficile* in Oncology Patients

Subject type: CASE NEGATIVE TEST CONTROL HOSPITAL TIME CONTROL

Date of *C. difficile* test confirmation (cases) or negative test (controls): ____/____/____

Age of subject at test confirmation or at time of hospital admission: _____

Sex: MALE FEMALE

Date of index admission: ____/____/____

Date of index discharge: ____/____/____

Days of YNHH hospitalization in 90 days prior to culture: _____

_____

_____

History of *C. difficile*: YES NO If yes, date of prior diagnosis:_____

Type of Cancer: _____

Stage: I II III IV Not staged

Cancer treatment 90 days prior to test:

Chemotherapy 90 days prior to culture: YES NO Date of last chemotherapy treatment: _____/_____/_____ Type:_____
Surgery: YES NO If yes, site(s): _____
History of stem cell therapy: YES NO
Blood transfusion: YES NO
Radiation therapy: YES NO

VRE colonization status: YES NO UNKNOWN

Co-infections: YES NO

Blood stream infections Urinary tract infections

Wound/skin infections Pneumonia

Other: _____

Indwelling medical devices on current admission:

Central Venous Catheter YES NO UNKNOWN

Urinary Catheter YES NO UNKNOWN

Mechanical Ventilation YES NO UNKNOWN

Nasogastric Tube YES NO UNKNOWN

TPN YES NO UNKNOWN

Enteral feeding YES NO UNKNOWN

Antibiotic received 90 days prior to test or discharge:

Antibiotic	**Received (YES/NO)**	**At time of test (YES/NO)**	**Prior to index admission (YES/NO)**	**Discontinued after diagnosis? (YES/NO)**
Beta-Lactam				
Beta-Lactam + BLI				
1st or 2nd generation cephalosporin				
3rd generation cephalosporin				
4th generation cephalosporin				
Carbapenem				
Fluoroquinolone				
Tigecycline				
Vancomycin (intravenous)				
Vancomycin (oral)				
Daptomycin				
Linezolid				
Metronidazole				
Clindamycin				
Sulfonamide				
Rifaxamin				
Fosfomycin				
Colistin				
Other _____				

Clinical presentation:

Temperature on test date: _____

T_{max} 90 days prior to test: _____

Max heart rate: _____

Min blood pressure: _____

WBC count: _____

Creatinine on admission: _____

Creatinine on test date: _____

Neutropenia 90 days prior to test: YES NO

Lactic acid 90 days prior to test: YES NO

Loose stool 90 days prior to test: YES NO

Clinical outcome/treatment:

Treatment: _____

Transferred to ICU: YES NO UNKNOWN

Abdominal X-Ray: YES NO

CAT Scan: YES NO

If yes, evidence of colitis?: YES NO

Colectomy: YES NO

Death: YES NO