January 2013

Comparisons Of Patients With Recurrent Vs. Incident-Only Clostridium Difficile-Associated Diarrhea: A Case-Control Study Of Treatment Effectiveness At Yale New Haven Hospital, 2010-2011

Mark Stuntz
Yale University, markestuntz@gmail.com

Comparisons of Patients with Recurrent vs. Incident-only *Clostridium difficile*-Associated Diarrhea: A Case-Control Study of Treatment Effectiveness at Yale New Haven Hospital, 2010-2011

Mark E. Stuntz

Epidemiology of Microbial Diseases
Yale School of Public Health
May 2013

Acknowledgements

I would like to thank Dr. Jim Hadler and Dr. Linda Niccolai for their advice and guidance throughout the process of writing this thesis. I would also like to thank Carol Lyons for her patience throughout my summer internship while I gathered the data. Jim Meek also provided invaluable feedback and suggestions, as well as figuring out a way to pay me during the summer, for which I am forever grateful. Danyel Olsen and the student members of the CT EIP FoodCORE team provided me with much needed personal support and compassion, and I cannot thank them enough.

I would also like to thank my professors at Yale School of Public Health. I am so incredibly proud to have attended this school, and that is completely due to my wonderful teachers over the course of my time here.

Table of Contents

Abstract

Background *Clostridium difficile* infection (CDI) is the most frequent cause of hospital-acquired infectious diarrhea in developed countries. Approximately 19-20% of affected patients will experience a symptomatic recurrence following their first episode of *Clostridium difficile*-associated diarrhea (CDAD). Risk factors for the initial CDAD episode have been well-documented, however, epidemiologic risk factors for recurrent CDAD have not been described in as much detail. It is hypothesized that initial treatment could be a risk factor for recurrent CDAD. The CT Emerging Infections Program (EIP) conducts laboratory-based surveillance for CDAD in New Haven County, however, routine surveillance does not collect treatment data. Therefore, we conducted a pilot case-control study on CDAD patients at Yale New Haven Hospital (YNHH) during the years 2010-2011 to examine initial CDAD treatment as a risk factor for recurrent CDAD.

Methods Cases and control patients were identified from CT EIP CDI surveillance data. A patient with recurrent CDAD is defined as having had another positive *C. difficile* stool specimen between two to eight weeks after the last positive *C. difficile* stool specimen. Both cases and controls were persons hospitalized at YNHH in 2010-2011; cases had recurrent disease, controls had only a single (incident-only) episode of CDAD. Cases and controls were matched within +/- two years of age. Medical charts of cases and controls were reviewed to collect treatment information related to the incident CDAD episode and severity of the incident case of CDAD, as defined by the Society for Healthcare Epidemiologists of America. Cases and controls were compared on categorical variables with the Fisher's Exact Test or the chi-squared test. Differences in continuous variables were analyzed with the Student's *t* test. Stratified analyses were conducted by severity of incident infection and sex, using the Mantel-Haenszel chi-squared test.

Results Eighty-one persons with recurrent CDAD were eligible cases, matched to 122 controls with incident-only CDAD. Persons starting on vancomycin as compared to metronidazole were found to have a lower risk of recurrence, regardless of initial disease severity. Persons treated with a course of vancomycin <10 days had a higher risk of recurrence than those treated longer. Initial treatment with vancomycin appeared to substantially reduce the risk of recurrence: recurrent cases were less likely to have received initial vancomycin therapy (odds ratio [OR]: 0.59; 95% confidence interval [CI]: 0.20, 1.76) and received shorter courses of vancomycin (OR: 2.11; 95% CI: 0.57, 7.82) than controls.

Conclusions Persons started on vancomycin as compared to metronidazole have a lower risk of recurrence, regardless of initial CDI severity. Vancomycin is being underused at YNHH to initially treat severe CDAD. Our sample size was too small to demonstrate statistically significant differences between recurrent and control cases, but in light of these point estimates, YNHH may want to revisit their established clinical practices for treatment of CDAD. Ongoing surveillance for CDAD and recurrent CDAD may also want to include initial treatment information.

Introduction

Clostridium difficile is a gram-positive, cytotoxin-producing anaerobic bacterium first identified in 1935 from the stool of healthy newborn infants[1]. It was not shown to be a cause of diarrhea until the late 1970s[2]. Following its recognition as a pathogen, it was found to be a normal part of gut flora in up to 3% of healthy adults and in 24% of hospitalized patients[3]. Today, *Clostridium difficile* infection (CDI) is the most frequent cause of hospital-acquired infectious diarrhea in developed countries[4], and also accounts for 20-30% of antibiotic-associated diarrhea[5,6]. The case fatality rate in the US is 10.1% overall and 15.4% in those over 70 years of age[7]. Costs for care of individual cases of *Clostridium difficile*-associated diarrhea (CDAD) ranges from $3006 per case[8] to as high as $15,397[9], with the annual cost of hospital care for patients with CDAD in the United States ranging from $1 billion[10] up to as much as $4.8 billion[11].

This spore-forming bacillus produces two toxins, toxin A and toxin B, which are pathogenic to intestinal epithelial cells and mediate the resulting disease[12]. Growing evidence suggests the emergence of a hypervirulent, epidemic strain as an important factor in the recent increases in incidence and severity. In multiple locations in the United States, a previously uncommon strain of *C. difficile* was found to be responsible for multiple, near-simultaneous outbreaks of hospital infection[13,14]. It is characterized as North American Pulsed Field Type 1 (NAP1), restriction enzyme analysis type "BI", and PCR ribotype 027[15]. The emergence of a previously uncommon strain of *C. difficile* that is more resistant and potentially more virulent than other strains indicates that inpatient health care facilities in North America need advances in available treatments, therapeutic management strategies, and diagnostics.

The presentation of CDAD is highly variable, ranging from symptomless carriage, to mild or moderate diarrhea with abdominal pain and cramps, to sudden and sometimes fatal pseudomembranous colitis[7]. Clinical findings often include fever and lower abdominal tenderness with leukocytosis and hypoalbuminemia which can progress to toxic megacolon, a life-threatening widening or dilation of the large intestine, and septic shock[16]. The typical clinical course is for resolution of symptoms within days of beginning antibiotic treatment. However, approximately 19-20% of affected patients will experience a symptomatic recurrence following their first episode of CDAD[17]. This is typically defined for surveillance purposes as having a second positive test for *C. difficile* between two and eight weeks after successful therapy for the initial episode is completed[18].

The choice of initial antibiotic therapy for CDAD depends on the severity of disease. Metronidazole (500mg by mouth three times per day for 10-14 days) is the drug of choice for an initial episode of mild-to-moderate CDAD, while vancomycin (125mg by mouth four times per day for 10-14 days) is the drug of choice for an initial episode of severe CDAD. A severe episode is defined as having leukocytosis with a white blood cell count of 15,000 cells/μL or higher and/or a serum creatinine level greater than or equal to 1.5 times the premorbid level[12]. Decreased response rates and slower responses for metronidazole compared to vancomycin have been noted since 2004[19,20,21].The antibiotic used to treat the initial infection is one of the few risk factors for recurrent CDAD that is modifiable, and these studies suggest that vancomycin may be the preferred drug of choice for treating an initial episode of CDAD in order to prevent recurrence.

Some epidemiologic surveillance studies have suggested that 0.5%-1.5% of all hospitalized patients in the United States may develop CDAD[22,23,24]. However, the number of

cases of both healthcare- and community-associated CDAD has increased dramatically in recent years[25,26].One study has shown that the incidence rate of healthcare-associated CDAD has more than doubled in recent years, from 31 cases per 100,000 patients in 1996 to 84 cases per 100,000 patients in 2005[27]. This increase in incidence is possibly due both to the overuse of certain antibiotics and the emergence of new virulent strains of the bacterium.

Risk factors for the initial symptomatic CDAD episode have been well documented and include advanced age (typically defined as over 65 years), prolonged duration of hospital stay, prolonged use of certain antibiotics, and the presence of underlying medical conditions such as inflammatory bowel disease (IBD), diabetes, immunodeficiency and HIV infection[15]. However, epidemiologic risk factors for recurrent CDAD have not been described in as much detail. A recent review found that important risk factors were similar to the established risk factors for the incident CDAD episode, including advanced age, long hospital stays, and continuation of antimicrobial therapy following the initial episode of CDAD[28]. A study examining data collected through surveillance by the Yale Emerging Infections Program (EIP) found older age, high white blood cell count prior to the first incident infection, use of H2 blockers (medicines that work by reducing the amount of stomach acid secreted by glands in the lining of your stomach), and previous antibiotic use to be risk factors for recurrence[29].

The previous Yale EIP study was based on data that did not include actual treatment given. Because recurrent CDAD is both common and costly, identifying modifiable risk factors is important. The objective of this study was to build on this previous work to further investigate risk factors for CDAD recurrence, especially with regards to the choice of antibiotic used to treat the initial infection.

Methods

The Emerging Infections Programs (EIP) were established in 1995 in response to the Centers for Disease Control and Prevention's (CDC) 1994 strategy, Addressing Emerging Infectious Disease Threats: A Prevention Strategy for the United States[30]. The EIP is a network of 10 state health departments and their collaborators in local health departments, academic institutions, other federal agencies, and public health and clinical laboratories; hospital infection preventionists; and healthcare providers. The EIP network is a national resource for surveillance, prevention, and control of emerging infectious diseases.

C. difficile infection surveillance is being conducted in seven EIP sites throughout the United States. The surveillance system is designed to determine the population-based incidence of CDAD and describe the epidemiology of CDAD and generate hypotheses for future research activities using EIP CDAD surveillance infrastructure. The Connecticut EIP conducts active surveillance for CDAD through laboratory reporting in two population-based catchment areas: the New Haven and Waterbury, Connecticut metropolitan areas. This surveillance includes the collection of antibiotic history in the three months prior to the incident case of CDAD, but currently the CDC does not request the treatment information for this incident case. The Connecticut EIP routinely receives lists of toxin-positive CDAD cases from all clinical laboratories and diagnostic laboratories throughout the New Haven and Waterbury areas. These lists are evaluated to determine individual cases and classify the cases as either community onset (CO) cases that can be health care facility-associated (HCFA) or community associated (CA) or health care onset (HO, fig. 1). Selected laboratories save stool samples on all cases of CDAD for further laboratory evaluation at the CDC including culture and toxinotype testing.

This was a pilot matched case-control study to look at differences in initial antibiotic treatment between CDAD patients reported to the Connecticut EIP who had a recurrent episode and those who only had a single episode (i.e. incident only). The study population was limited to persons reported from and treated at Yale-New Haven hospital during 2010-2011 inclusive because of feasibility related to data collection. Recurrent cases eligible for this study were the 81 persons $\geq$ 1 year of age reported with *C. difficile* infections who had another positive *C. difficile* stool specimen between 2 to 8 weeks after the last positive specimen. Persons with only a single episode of CDAD were eligible to be controls and included patients with a *C. difficile* infection, defined as a positive *C. difficile* toxin assay or a positive *C.difficile* molecular assay (e.g., PCR), on a stool specimen who was 1 year of age or older, and who did not have a laboratory-documented recurrent episode. Since age is one of the leading risk factors for CDAD, controls were matched to cases on this variable, within +/-two years of age at the time of incident infection. Each case was matched with two controls whenever possible. Chart reviews were done on all cases and controls, using Yale New Haven Hospital's online medical records software, MDLink. All HIPAA regulations were adhered to during the chart review process, and patient information was de-identified for analysis. In this system, specific prescription orders were only available online for patients who were admitted to the hospital.

Cases and controls were compared on categorical variables with the Fisher's Exact Test or the chi-square test. Differences in continuous variables were analyzed with the Student's *t* test. Stratified analyses were conducted by severity of incident infection and sex. All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC).

Results

Of the 81 patients with a recurrent episode of *C. difficile*, 68 were included in this analysis. Eight cases were excluded due to a lack of treatment information in the online medical records (e.g., outpatients, emergency room visits), and five due to a lack of age-matched controls. At least one control, matched on age, was used for each case, and two were used wherever possible, resulting in a total study population of N=190.

There were no significant differences between cases and controls for any of the general demographic and treatment variables studied, including ethnicity, number of underlying conditions, incident disease status, and treatment regimen used for the incident case (Table 1). There were several notable findings nonetheless. Females made up a greater proportion of cases than controls (67.7% of cases, 55.7% of controls, p=0.108). Recurrent cases were nearly 70% less likely to have been treated initially with vancomycin than controls (7.4% vs 11.5%, OR: 0.59; 95% CI: 0.20-1.26). In addition, recurrent cases who received vancomycin were 1.64 times more likely than controls not to have received a full standard course (29.2% vs 16.3%, OR: 1.64; 95% CI: 0.57, 4.73).

The data was stratified by the incident disease severity because there are different initial treatment recommendations depending on CDAD severity. There were 22 severe cases and 40 severe controls (Table 2). None of the main demographic or treatment variables was statistically significant among severe cases, although sex was marginally significantly different (p=0.079) with recurrent cases being more likely than controls to be females (81.8% vs 60.0%). Among all 62 severe cases, only 5 (8.1%) were initially treated with vancomycin. Recurrent cases were less than half as likely as controls to be initially treated with vancomycin (OR: 0.44; 95% CI: 0.04-

4.38). They were also more likely when treated to have a less than full standard course of treatment (OR:3.00; 95% CI 0.46-19.49). Sex did not appear to be a confounder among severe cases and controls, as the adjusted odds ratios for all the variables remained fairly consistent with the crude odds ratios.

There were 41 cases and 77 controls with mild/moderate incident disease severity (Table 3). Similar to the severe cases, none of the main demographic variables had a statistically significant difference between the groups. The number of underlying conditions was marginally significant (p=0.055); a higher proportion of cases than controls had at least one underlying condition. One notable treatment finding was that among those treated with metronidazole, recurrent cases were less likely (p=0.029) than controls to have received a less than standard course (i.e., more likely to have received a full course. OR: 0.32; 95% CI: 0.12, 0.85). Sex did not appear to be a confounder among the mild/moderate cases and controls, as the adjusted odds ratios for all the variables remained consistent with the crude odds ratios.

Because female sex was a predictor for recurrence in this study, stratified analyses by disease severity and sex variables were conducted. For the severe patients, there were no significant differences with regards to demographic or outcome variables among males or females (Table 4) and there was little confounding of any of the treatment variables by sex (data not shown). Among the mild/moderate patients, the finding that recurrent cases were more likely than controls to have had a full course of metronidazole was driven mainly by females (Table 5). A total of 90% of female recurrent patients treated with metronidazole had a full treatment course compared to 57.9% of controls (p=0.011).

Discussion

Recurrent *Clostridium difficile* infection is becoming more common in healthcare settings, and is quite costly. This single institution pilot study aimed to identify modifiable risk factors, especially with regards to the treatment of the incident CDAD, and to inform whether treatment data should be collected for future CDAD surveillance.

There are several important findings of this study based on the magnitude of the point estimate for differences with respect to treatment of initial infection as a risk factor for recurrent CDAD infection, despite the lack of statistical significance of them. First, initial treatment with vancomycin appeared to substantially reduce risk of recurrence: recurrent cases were 70% less likely to have received vancomycin for the initial infection. Second, regardless of when it is used in the initial treatment of CDI, having anything less than 10-14 days of treatment with vancomycin, the recommended regimen, is associated with a higher risk of recurrence. Recurrent cases were nearly twice as likely to have less than 10 days of vancomycin. Third, recurrent cases who initially had mild/moderate CDAD were more than twice as likely to have been treated with a full course of metronidazole.

In a prospective, randomized, double-blind, placebo-controlled trial, it was shown that metronidazole and vancomycin were equally effective for the treatment of mild CDAD, but vancomycin was superior for treating patients with severe CDI[31]. Our results suggest that vancomycin may be superior as the initial treatment, regardless of disease severity. Prospective trials of metronidazole and vancomycin therapy have not looked at the risk of recurrence with regards to the duration of treatment[25]. It is possible that a patient receiving a full course of metronidazole did not receive vancomycin, and thus would have greater odds of recurring.

An additional and somewhat surprising finding was that vancomycin was being underused for initial treatment of severe CDAD according to the clinical practice guidelines put forth by the Society for Healthcare Epidemiology of America. The 2010 update stipulates that vancomycin is the recommended antibiotic for treating incident CDI deemed severe, which is defined as leukocytosis with a white blood cell count of 15,000 cells/μL or higher within one day before or after date of incident stool collection. However, this study showed that a very small proportion of all severe cases received vancomycin as initial treatment (8.1%). Many factors go into a doctor's choice of antibiotic that could not be obtained from the online medical records, and such factors could shed additional light on treatment decisions. However, based solely on the recommended treatment guidelines for CDAD, it appears that vancomycin is being underused for initial treatment of severe CDI.

One possible reason for the lack of vancomycin use is cost. The major advantage of metronidazole over vancomycin is its much lower price. Cost of a 10-day course of metronidazole is ~$20, whereas the cost of a 10-day course of oral vancomycin (Vancocin) increased from $300 to $600 when the drug became more widely used in the United States. Some hospitals have avoided this issue by compounding the intravenous formulation into an oral formulation, thus reducing the price of a 10-day course to $45.[32] However, this practice is not common. Furthermore, it is also possible that the additional costs incurred by vancomycin therapy would be compensated by savings on the management of CDAD recurrence. As mentioned earlier, the cost per patient with CDI requiring admission to the intensive care unit $3006 per case to as high as $15,397. A more formal study of the cost effectiveness of using metronidazole versus vancomycin is needed, especially taking into account recurrent disease and the costs associated with it.

This pilot study brings to light information that should be addressed in the future, especially in routine surveillance. Currently the CDC-funded EIP surveillance does not collect treatment information. Additional collection of antibiotic treatment information on all incident cases of CDAD for routine surveillance could inform best practices.

The results of this study are insufficient to make treatment recommendations, however in light of these findings Yale New Haven Hospital may want to revisit their practices for treating CDAD. Examining the reasons of low use of vancomycin for severe CDAD goes beyond the scope of this study, and greater in-depth analysis of CDAD treatment would need to be conducted by the hospital epidemiologist, or someone on site, in order to truly understand the lack of vancomycin use.

This study had additional limitations, including the small sample size. This lack of statistical power made it difficult to observe any significant differences among the cases and controls, or risk factors for recurrence. Increasing the duration of the study and/or the number of hospitals could increase statistical power and generalizability. Other limitations include the fact that this was an observational study that did not permit full assessment of all potential confounders. This study was also limited to inpatients, who could not be included due to a lack of information in their online medical records. Results and conclusions are also based on what the patients were prescribed and information about whether patients completed their treatment regimens as ordered by the physician was not known.

Despite the small sample size and lack of statistical power, our study suggests that vancomycin is the superior treatment for CDAD, yet it is being underused at Yale New Haven Hospital. Persons started on vancomycin as compared to metronidazole have a lower risk of

recurrence, regardless of initial disease severity. An initial treatment with vancomycin appeared to substantially reduce the risk of recurrence, yet only a small proportion of patients are receiving this antibiotic for reasons that remain unknown. The results of this study have potential impacts on the future of surveillance and altering treatment regimens. Surveillance for recurrent CDAD should include information on treatment of the initial infection, and future studies should be conducted on the cost-benefit of using vancomycin instead of metronidazole for the initial treatment of CDAD, taking into account the potential for recurrence.

Tables and Figures

Table 1. Comparison of cases and controls by selected demographic and risk factors, *Clostridium difficile*-associated diarrhea (CDAD) patients, YNHH, 2010-11[a]

Characteristic	Recurrence, n=68 (%)[b]	Incident only, n=122(%)[b]	Odds Ratio	p[c]
Age at incident stool collection (years)	66.4±19.5	67.3±19.2		0.759
Sex				0.108
Male	22 (32.4)	54 (44.3)	ref	
Female	46 (67.7)	68 (55.7)	1.66 (0.89, 3.09)	
Incident Disease Status[d]				0.626
Mild/Moderate	41 (60.3)	77 (63.1)	ref	
Severe	22 (32.4)	40 (32.8)	1.03 (0.54, 1.97)	
Ethnicity				0.158
Non-Hispanic or Latino	64 (94.1)	107 (87.7)	ref	
Hispanic or Latino	4 (5.9)	15 (12.3)	0.45 (0.14, 1.40)	
Underlying conditions				0.649
0	7 (10.3)	17 (13.9)	ref	
≥1	61 (89.7)	105 (86.1)	1.41 (0.55, 3.59)	
Treatment for Incident Case				0.632
Received Metronidazole IV/PO only	44 (64.7)	73 (59.8)	ref	
Received Vancomycin PO only	5 (7.4)	14 (11.5)	0.59 (0.20, 1.76)	
Received Combination	19 (27.9)	35 (28.7)	0.90 (0.46, 1.76)	
Received Vancomycin?				0.508
Yes	24 (35.3)	49 (40.2)	ref	
No	44 (66.7)	73 (59.8)	1.23 (0.67, 2.28)	
Received Metronidazole?				0.952
Yes	60 (88.2)	108 (88.5)	ref	
No	8 (11.8)	14 (11.5)	1.03 (0.41, 2.59)	
Vancomycin duration				0.202
At least standard	17 (70.8)	41 (83.7)	ref	
Less than standard	7 (29.2)	8 (16.3)	2.11 (0.67, 6.74)	
Metronidazole duration				0.111
At least standard	45 (75.0)	68 (63.0)	ref	
Less than standard	15 (25.)	40 (37.0)	0.58 (0.29, 1.15)	

[a] Table values are mean ± SD for continuous variables and n (column %) for categorical variables.
[b] Numbers may not sum to total due to missing data, and percentages may not sum to 100% due to rounding.
[c] P-value is for t-test (continuous variables) or χ^2 test or Fisher's exact test (categorical variables).
[d] Clinical definition (Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America):

Mild or moderate: Leukocytosis with a white blood cell count of less than 15,000 cells/µL within 1 day before or after date of incident stool collection

Severe: Leukocytosis with a white blood cell count of 15,000 cells/µL or higher within 1 day before or after date of incident stool collection

Table 2.
Comparison of severe cases and controls by selected demographic and risk factors, *Clostridium difficile*-associated diarrhea (CDAD) patients, YNHH, 2010-11[a]

Characteristic	Recurrence, n=22 (%)[b]	Incident only, n=40(%)[b]	Crude Odds Ratio	Adjusted Odds Ratio[c]	p[d]
Age at incident stool collection (years)	71.9±22.2	70.7±15.2			0.825
Sex					0.079
Male	4 (18.2)	16 (40.0)	ref		
Female	18 (81.8)	24 (60.0)	3.00 (0.86, 10.52)		
Ethnicity					0.889
Non-Hispanic or Latino	20 (90.9)	36 (90.0)	ref	ref	
Hispanic or Latino	2 (9.1)	4 (10.0)	0.90 (0.15, 5.35)	0.74 (0.12, 4.72)	
Underlying conditions					0.513
0	5 (22.7)	5 (12.5)	ref	ref	
≥1	17 (77.3)	35 (87.5)	0.49 (0.12, 1.91)	0.48 (0.12, 1.97)	
Treatment for Incident Case					0.850
Received Metronidazole IV/PO only	12 (54.6)	21 (52.5)	ref	ref	
Received Vancomycin PO only	1 (4.6)	4 (10.0)	0.44 (0.04, 4.38)	0.76 (0.20, 2.97)	
Received Combination	9 (40.9)	15 (37.5)	1.05 (0.35, 3.12)	1.24 (0.40, 3.84)	
Received Vancomycin?					0.823
Yes	10 (45.5)	19 (47.5)	ref	ref	
No	12 (54.6)	21 (52.5)	1.09 (0.38, 3.08)	0.97 (0.33, 2.86)	
Received Metronidazole?					0.993
Yes	21 (95.5)	36 (90.0)	ref	ref	
No	1 (4.6)	4 (10.0)	0.43 (0.05, 4.09)	0.83 (0.25, 2.80)	
Vancomycin duration					0.775
At least standard	7 (70.0)	17 (89.5)	ref	ref	
Less than standard	3 (30.0)	2 (10.5)	3.00 (0.46, 19.49)	2.40 (0.29, 19.80)	
Metronidazole duration					0.900
At least standard	13 (61.9)	23 (63.9)	ref	ref	
Less than standard	8 (38.1)	13 (36.1)	1.19 (0.40, 3.54)	1.29 (0.41, 4.10)	

[a] Table values are mean ± SD for continuous variables and n (column %) for categorical variables.
[b] Numbers may not sum to total due to missing data, and percentages may not sum to 100% due to rounding.
[c] Adjusted for sex
[d] P-value is for t-test (continuous variables) or χ^2 test or Fisher's exact test (categorical variables). The corrected Mantel-Haenszel p-value is used for variables where a sex-adjusted Odds Ratio was calculated.

Table 3.
Comparison of mild/moderate cases and controls by selected demographic and risk factors, *Clostridium difficile*-associated diarrhea (CDAD) patients, YNHH, 2010-11[a]

Characteristic	Recurrence, n=41 (%)[b]	Incident only, n=77(%)[b]	Crude Odds Ratio	Adjusted Odds Ratio[c]	p[d]
Age at incident stool collection (years)	63.9±18.3	66.9±19.8			0.426
Sex					0.443
Male	16 (39.0)	36 (46.8)	ref		
Female	25 (61.0)	41 (53.3)	1.37 (0.64, 2.97)		
Ethnicity					0.283
Non-Hispanic or Latino	39 (95.1)	67 (87.0)	ref	ref	
Hispanic or Latino	2 (4.9)	10 (13.0)	0.34 (0.07, 1.65)	0.34 (0.07, 1.64)	
Underlying conditions					0.108
0	1 (2.4)	11 (14.3)	ref	ref	
≥1	40 (97.6)	66 (85.7)	6.67 (0.83, 53.60)	6.34 (0.78, 51.80)	
Treatment for Incident Case					0.815
Received Metronidazole IV/PO only	29 (70.7)	50 (64.9)	ref	ref	
Received Vancomycin PO only	3 (7.3)	7 (9.1)	0.74 (0.18, 3.08)	0.76 (0.18, 3.24)	
Received Combination	9 (22.0)	20 (26.0)	0.78 (0.31, 1.93)	0.77 (0.32, 1.88)	
Received Vancomycin?					0.643
Yes	12 (29.3)	27 (35.1)	ref	ref	
No	29 (70.7)	50 (64.9)	1.31 (0.58, 2.96)	1.32 (0.59, 2.96)	
Received Metronidazole?					0.432
Yes	35 (85.4)	71 (92.2)	ref	ref	
No	6 (14.6)	6 (7.8)	2.03 (0.61, 6.75)	1.98 (0.59, 6.65)	
Vancomycin duration					0.687
At least standard	8 (66.7)	21 (77.8)	ref	ref	
Less than standard	4 (33.3)	6 (22.2)	1.28 (0.34, 4.82)	1.86 (0.40, 8.68)	
Metronidazole duration					0.052
At least standard	29 (82.9)	44 (62.0)	ref	ref	
Less than standard	6 (17.1)	27 (38.0)	0.32 (0.12, 0.85)	0.35 (0.13, 0.93)	

[a] Table values are mean ± SD for continuous variables and n (column %) for categorical variables.
[b] Numbers may not sum to total due to missing data, and percentages may not sum to 100% due to rounding.
[c] Adjusted for sex
[d] P-value is for t-test (continuous variables) or χ^2 test or Fisher's exact test (categorical variables). The corrected Mantel-Haenszel p-value is used for variables where a sex-adjusted Odds Ratio was calculated.

Table 4.
Comparison of severe cases and controls, stratified by recurrence status and sex, *Clostridium difficile*-associated diarrhea (CDAD) patients, YNHH, 2010-11[a]

	Males, n=20				Females, n=42			
Characteristic	Recurrence, n=4 (%)[b]	Incident only, n=16	OR	p	Recurrence, n=18 (%)[b]	Incident only, n=24	OR	p[c]
Age at incident stool collection (years)	71.0±23.8	67.69±15.99		0.740	72.11±22.56	72.8±14.6		0.912
Ethnicity				1.000				1.000
Non-Hispanic or Latino	4 (100.0)	15 (93.8)	ref		16 (88.9)	21 (87.5)	ref	
Hispanic or Latino	0	1 (6.25)	<0.		2 (11.1)	3 (12.5)	0.88 (0.13, 5.87)	
Underlying conditions				0.509				0.438
0	1 (25.0)	2 (12.5)	ref		4 (22.2)	3 (12.5)	ref	
≥1	3 (75.0)	14 (87.5)	0.43 (0.03, 6.41)		14 (77.8)	21 (87.5)	0.50 (1.00, 2.58)	
Treatment for Incident Case				1.000				0.731
Received Metronidazole IV/PO only	2 (50.0)	7 (43.8)	ref		10 (55.6)	14 (58.3)	ref	
Received Vancomycin PO only	0	1 (6.3)	<0.01		1 (5.6)	3 (12.5)	0.47 (0.04, 5.17)	
Received Combination	2 (50.0)	8 (50.0)	0.88 (1.00, 7.95)		7 (38.9)	7 (29.2)	1.40 (0.37, 5.27)	
Received Vancomycin?				1.000				1.000
Yes	2 (50.0)	9 (56.3)	ref		8 (44.4)	10 (41.2)	ref	
No	2 (50.0)	7 (43.8)	1.29 (0.14, 11.54)		10 (55.6)	14 (58.3)	0.89 (0.26, 3.07)	
Received Metronidazole?				1.000				0.623
Yes	4 (100.0)	15 (93.8)	ref		17 (94.4)	21 (87.5)	ref	
No	0	1 (6.3)	<0.01		1 (5.6)	3 (12.5)	0.41 (0.04, 4.33)	
Vancomycin duration				1.000				0.608
At least standard	2 (100.0)	9 (100.0)	ref		5 (62.5)	8 (80.0)	ref	
Less than standard	0	0	N/A		3 (37.5)	2 (20.0)	2.20 (0.33, 14.79)	
Metronidazole duration				0.303				1.000
At least standard	1 (25.0)	9 (60.0)	ref		12 (70.6)	14 (66.7)	ref	
Less than standard	3 (75.0)	6 (40.0)	5.00 (0.42, 59.64)		5 (29.4)	7 (33.3)	0.93 (0.24, 3.63)	

[a] Table values are mean ± SD for continuous variables and n (column %) for categorical variables.
[b] Numbers may not sum to total due to missing data, and percentages may not sum to 100% due to rounding.
[c] P-value is for t-test (continuous variables) or χ^2 test or Fisher's exact test (categorical variables).

Table 5.
Comparison of mild/moderate cases and controls, stratified by recurrence status and sex, *Clostridium difficile*-associated diarrhea (CDAD) patients, YNHH, 2010-11[a]

	Males, n=52				Females, n=66			
Characteristic	Recurrence, n=16 (%)[b]	Incident only, n=36	OR	p	Recurrence, n=25 (%)[b]	Incident only, n=41	OR	p[c]
Age at incident stool collection (years)	62.1±21.1	64.7±19.8		0.670	65.0±16.6	68.7±19.9		0.415
Ethnicity				1.000				0.239
Non-Hispanic or Latino	15 (93.8)	32 (88.9)	ref		24 (96.0)	35 (85.4)	ref	
Hispanic or Latino	1 (6.3)	4 (11.1)	0.53 (0.06, 5.19)		1 (4.0)	6 (14.6)	0.24 (0.03, 2.15)	
Underlying conditions				0.409				0.289
0	1 (6.3)	7 (19.4)	ref		0	4 (9.8)	ref	
≥1	15 (93.8)	29 (80.6)	3.62 (0.41, 32.21)		25 (100.0)	37 (90.2)	>999.99	
Treatment for Incident Case				0.500				0.295
Received Metronidazole IV/PO only	10 (62.5)	26 (72.2)	ref		19 (76.0)	24 (58.5)	ref	
Received Vancomycin PO only	1 (6.3)	4 (11.1)	0.65 (0.07, 6.55)		2 (8.0)	3 (7.3)	0.84 (0.13, 5.56)	
Received Combination	5 (31.3)	6 (16.7)	2.17 (0.54, 8.73)		4 (16.0)	14 (34.2)	0.36 (0.10, 1.28)	
Received Vancomycin?				0.527				0.188
Yes	6 (37.5)	10 (27.8)	ref		6 (24.0)	17 (41.5)	ref	
No	10 (62.5)	26 (72.2)	0.64 (0.18, 2.23)		19 (76.0)	24 (58.5)	2.24 (0.74, 6.80)	
Received Metronidazole?				1.000				0.242
Yes	15 (93.8)	33 (91.7)	ref		20 (80.0)	38 (92.7)	ref	
No	1 (6.3)	3 (8.3)	0.73 (0.07, 7.64)		5 (20.0)	3 (7.3)	3.17 (0.69, 14.63)	
Vancomycin Duration				0.125				1.000
At least standard	4 (66.7)	10 (100.0)	ref		4 (66.7)	11 (64.7)	ref	
Less than standard	2 (33.3)	0	>999.99		2 (33.3)	7 (35.3)	0.51 (0.09, 2.73)	
Metronidazole Duration				0.746				0.012
At least standard	11 (73.3)	22 (66.7)	ref		18 (90.0)	22 (57.9)	ref	
Less than standard	4 (26.7)	11 (33.3)	0.76 (0.20, 2.88)		2 (10.0)	16 (42.1)	0.14 (0.03, 0.66)	

[a] Table values are mean ± SD for continuous variables and n (column %) for categorical variables.
[b] Numbers may not sum to total due to missing data, and percentages may not sum to 100% due to rounding.
[c] P-value is for t-test (continuous variables) or χ^2 test or Fisher's exact test (categorical variables).

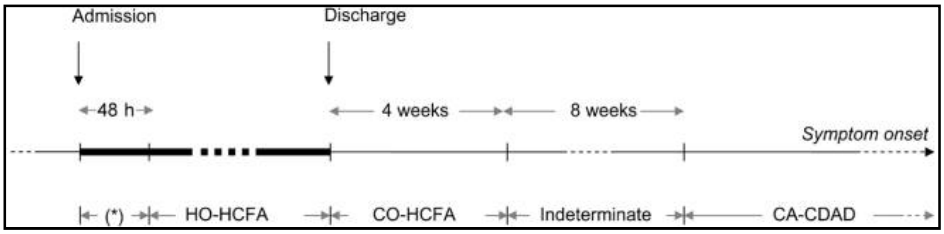

Figure 1.Time line for definitions of *Clostridium difficile*–associated disease (CDAD) exposures. Case patients with symptom onset during the window of hospitalization marked by an asterisk (∗) would be classified as having community-onset, healthcare facility–associated disease (CO-HCFA), if patient was discharged from a healthcare facility within the previous 4 weeks; would be classified as having indeterminate disease, if the patient was discharged from a healthcare facility between the previous 4-12 weeks; or would be classified as having community-associated CDAD (CA-CDAD), if the patient was not discharged from a healthcare facility in the previous 12 weeks. HO-HCFA, healthcare facility–onset, healthcare facility–associated CDAD. [33]

References

[1] Hall IC, O'Toole E. Intestinal flora in new-born infants: with a description of a new pathogenic anaerobe, Bacillus difficilis. Am J Dis Child 1935;49:390-402.

[2] Bartlett JG, Moon N, Chang TW, Taylor N, Onderdonk AB. Role of Clostridium difficile in antibiotic-associated pseudomembranous colitis. Gastroenterology. 1978 Nov;75(5):778-82.

[3] Gould CV, McDonald LC. Bench-to-bedside review: Clostridium difficile colitis. Crit Care. 2008;12(1):203. Epub 2008 Jan 18. Review.

[4]Barbut F, Gariazzo B, Bonné L, Lalande V, Burghoffer B, Luiuz R, Petit JC. Clinical features of Clostridium difficile-associated infections and molecular characterization of strains: results of a retrospective study, 2000-2004. Infect Control HospEpidemiol. 2007 Feb;28(2):131-9. Epub 2007 Jan 24.

[5]Bartlett JG. Antibiotic-associated colitis. Dis Mon. 1984 Dec;30(15):1-54. Review.

[6]Tillotson GS, Tillotson J. Clostridium difficile--a moving target. F1000 Med Rep. 2011;3:6. Epub 2011 Mar 1.

[7]Henrich TJ, Krakower D, Bitton A, Yokoe DS. Clinical risk factors for severe Clostridium difficile-associated disease. Emerg Infect Dis. 2009 Mar;15(3):415-22.

[8]Dubberke ER, Reske KA, Olsen MA, McDonald LC, Fraser VJ. Short- and long-term attributable costs of Clostridium difficile-associated disease in nonsurgical inpatients. Clin Infect Dis. 2008 Feb 15;46(4):497-504.

[9]O'Brien JA, Lahue BJ, Caro JJ, Davidson DM. The emerging infectious challenge of clostridium difficile-associated disease in Massachusetts hospitals: clinical and economic consequences. Infect Control HospEpidemiol. 2007 Nov;28(11):1219-27. Epub 2007 Oct 3.

[10]Kyne L, Hamel MB, Polavaram R, Kelly CP. Health care costs and mortality associated with nosocomial diarrhea due to Clostridium difficile. Clin Infect Dis. 2002 Feb 1;34(3):346-53. Epub 2001 Dec 17.

[11]Dubberke ER, Olsen MA. Burden of Clostridium difficile on the healthcare system. Clin Infect Dis. 2012 Aug;55Suppl 2:S88-92.

[12]Pothoulakis C, LaMont JT. Clostridium difficile colitis and diarrhea. GastroenterolClin North Am. 1993 Sep;22(3):623-37. Review.

[13] Loo VG, Poirier L, Miller MA, et al. A predominantly clonal multi-institutional outbreak of Clostridium difficile-associated diarrhea with high morbidity mortality. N Engl J Med 2005;353:2442-9.

[14] McDonald LC, Killgore GE, Thompson A, et al. An epidemic, toxin gene-variant strain of Clostridium difficile. N Engl J Med 2005;353:2433-41.

[15] Warny M, Pepin J, Fang A, et al. Toxin production by an emerging strain of Clostridium difficile associated with outbreaks of severe disease in North America Europe. Lancet 2005;366:1079-84.

[16]Lo Vecchio A, Zacur GM. Clostridium difficile infection: an update on epidemiology, risk factors, and therapeutic options. CurrOpinGastroenterol. 2012 Jan;28(1):1-9. Review.

[17]Aslam S, Hamill RJ, Musher DM. Treatment of Clostridium difficile-associated disease: old therapies and new strategies. Lancet Infect Dis. 2005 Sep;5(9):549-57. Review.

[18]Garey KW, Sethi S, Yadav Y, DuPont HL. Meta-analysis to assess risk factors for recurrent Clostridium difficile infection. J Hosp Infect. 2008 Dec;70(4):298-304.

[19]Fernandez A, Anand G, Friedenberg F. Factors associated with failure of metronidazole in Clostridium difficile-associated disease. J ClinGastroenterol. 2004 May-Jun;38(5):414-8.

[20]Musher DM, Aslam S, Logan N, Nallacheru S, Bhaila I, Borchert F, Hamill RJ. Relatively poor outcome after treatment of Clostridium difficile colitis with metronidazole.Clin Infect Dis. 2005 Jun 1;40(11):1586-90. Epub 2005 Apr 25.

[21]Pepin J, Alary ME, Valiquette L, Raiche E, Ruel J, Fulop K, Godin D, Bourassa C. Increasing risk of relapse after treatment of Clostridium difficile colitis in Quebec, Canada.Clin Infect Dis. 2005 Jun 1;40(11):1591-7.

[22]Olson MM, Shanholtzer CJ, Lee JT Jr, Gerding DN. Ten years of prospective Clostridium difficile-associated disease surveillance and treatment at the Minneapolis VA Medical Center, 1982-1991. Infect Control HospEpidemiol. 1994 Jun;15(6):371-81.

[23]Samore MH, DeGirolami PC, Tlucko A, Lichtenberg DA, Melvin ZA, Karchmer AW. Clostridium difficile colonization and diarrhea at a tertiary care hospital. Clin Infect Dis. 1994 Feb;18(2):181-7.

[24]McCarter MD, Abularrage C, Velasco FT, Davis JM, Daly JM. Diarrhea and Clostridium difficile-associated diarrhea on a surgical service. Arch Surg. 1996 Dec;131(12):1333-7.

[25]Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, Pepin J, Wilcox MH; Society for Healthcare Epidemiology of America; Infectious Diseases Society of America. 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 HospEpidemiol. 2010 May;31(5):431-55.

[26]CDC. Surveillance for community-associated *Clostridium difficile*—Connecticut, 2006. MMWR, 2008; 57(13):340-3.

[27]McDonald LC, Owings M, Jernigan DB. Clostridium difficile infection in patients discharged from US short-stay hospitals, 1996-2003. Emerg Infect Dis. 2006 Mar;12(3):409-15.

[28]Johnson S. Recurrent Clostridium difficile infection: a review of risk factors, treatments, and outcomes. J Infect. 2009 Jun;58(6):403-10. Epub 2009 Apr 5. Review.

[29] Paccha B. Epidemiology and risk factors for secondary incidents of *Clostridium difficile* infection in selected New Haven and Litchfield County catchment areas. (Unpublished graduate thesis, Yale School of Public Health). 2012.

[30]http://www.cdc.gov/ncezid/dpei/eip/

[31] Zar FA, Bakkanagari SR, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile-associated diarrhea, stratified by disease severity. Clin Infect Dis. 2007 Aug 1;45(3):302-7.

[32] Pepin J. Vancomycin for the treatment of Clostridium difficile Infection: for whom is this expensive bullet really magic? Clin Infect Dis. 2008 May 15;46(10):1493-8.

[33] McDonald LC, Coignard B, Dubberke E, Song X, Horan T, Kutty PK; Ad Hoc Clostridium difficile Surveillance Working Group. Recommendations for surveillance of Clostridium difficile-associated disease. Infect Control HospEpidemiol. 2007 Feb;28(2):140-5. Epub 2007 Jan 25.