Published in final edited form as:

Infect Control Hosp Epidemiol. 2017 June ; 38(6): 718–720. doi:10.1017/ice.2017.48.

Risk of *Clostridium difficile* infection in hematology-oncology patients colonized with toxigenic *C. difficile*

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Abstract

The prevalence of colonization with toxigenic *Clostridium difficile* among patients with hematological malignancies and/or bone marrow transplant at admission to a 566-bed academic medical care center was 9.3%, with 13.3% of colonized patients developing symptomatic disease during hospitalization. This population may benefit from targeted *Clostridium difficile* infection control interventions.

Introduction

Clostridium difficile infection (CDI) remains a significant health-care associated infection. Patients with hematologic malignancy (heme) and/or bone marrow transplant (BMT) may represent an important reservoir of *Clostridium difficile*. To better characterize the CDI epidemiology for this patient population, we examined the prevalence of toxigenic *C. difficile* colonization at admission in our heme/BMT unit, and the risk of subsequent CDI during hospital stay.

Methods

We conducted a prospective cohort study at a 566-bed academic medical center. We enrolled all patients admitted to the hospital's heme/BMT unit between May 12 – September 24, 2015 with the following characteristics: 1) an anticipated length of hospital stay of at least one night; 2) not admitted as bone marrow donors; and 3) not diagnosed with CDI within the

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Presented in abstract form at the SHEA conference, Atlanta, GA in May, 2016.

first 24 hours of admission, or at any previous time within the study frame. We defined CDI according to the clinical practice guidelines by Cohen *et al.*¹ The University of Wisconsin, Madison Institutional Review Board exempted this study from review as a quality improvement project.

We extracted demographic and clinically relevant variables from the electronic medical record, including previous history of CDI, comorbidities, and medication use during hospitalization and within the 30 days prior to admission.

For microbiological identification, we inoculated 0.1 g of stool into pre-reduced *Clostridium difficile* Brucella Broth, and incubated anaerobically at 36°C. We plated 50 microliters of broth enrichment to *Clostridium difficile* Brucella Agar and incubated anaerobically at 36°C for 48 hours. Suspected *C. difficile* isolates by gram stain and catalase tests were confirmed by in-house PCR, which was also used to evaluate the presence of toxin genes *tcdA*, *tcdB* and *cdtB*.²

We compared the frequency of variables between patients with and without CDI during one admission for every unique patient. We compared categorical variables by the χ^2 test and the Fischer's exact test, and continuous variables by the Student t-test or Wilcoxon rank sum tests. On bivariate analyses, for patients with multiple admissions during the study period, we included only one admission per patient, as follows: 1) the admission that identified colonization with toxigenic *C. difficile* (TCD) or non-toxigenic *C. difficile* (NTCD) on admission, and/or symptomatic CDI during the hospital stay; 2) otherwise, for patients free of *C. difficile*, we chose the first admission during the study period.

For multivariate analysis, we included all admissions during the study period. We conducted regression analyses using a generalized estimating equations model fit with a binomial family and the exchangeable correlation structure to adjust for correlation between measures of exposures taken from the same patient over multiple admissions. The multivariate model included all variables with a p-value < 0.2 on bivariate analysis, as well as any additional potential confounders deemed clinically relevant. We ran a series of nested models and chose the best fitting model using the quasi-likelihood criterion. We analyzed in STATA 14 (StataCorp, College Station, Texas) and determined statistical significance with a two-tailed p-value of to 0.05.

Results

A total of 358 patients were enrolled in the study, with 322 (90%) sampled for colonization status. A total of 41 (12.7%) of the patients sampled were colonized with *C. difficile*, with TCD present in 9.3% (30/322), and NTCD present in 3.4% (11/322) of the samples, respectively.

Overall, CDI developed in 3.4% (12/358) of patients, with a median hospital stay of 4 days before symptoms. Of the 30 patients colonized with TCD, 4 (13.3%) developed CDI during their hospital stay. None of the patients colonized with NTCD developed CDI. None of the 36 (10%) patients with missing screening samples developed CDI.

Table 1 presents the clinical and demographic characteristics for patients who did and did not develop CDI during their hospital stay on bivariate analyses. We found that patients who developed CDI were more likely to have received a BMT, cephalosporins, or certain chemotherapy agents.

Table 2 shows the independent risk factors associated with CDI development during hospitalization for the 456 total patient admissions included in multivariate analysis. After adjusting for age, gender, BMT status, and significant chemotherapy agents, the odds of developing a CDI was 11.6 times greater in TCD patients than patients not colonized (95% CI 2.9–47.1, $p=0.001$). Other independent risk factors for CDI were BMT status, and significant chemotherapy agents.

Discussion

We found that 9.3% of our patients with hematological malignancies were colonized with toxigenic *Clostridium difficile* at admission, and that colonization with a toxigenic strain was an independent risk factor for developing CDI during hospitalization. Jain T *et al*,³ and Bruminhent *et al*,⁴ reported a 12% and a 10.7% colonization rate at hospital admission, respectively, among their BMT population. Taken together, these studies suggest that the heme/BMT patient population is a significant reservoir of *Clostridium difficile* colonization, at least in large academic medical centers in the Midwest.

This finding has important implications. First, colonized patients are at increased risk of developing symptomatic disease. In our study, this risk was 13.3%. In a recent meta-analysis of *Clostridium difficile* colonization at hospital admission, the risk of developing CDI during hospital stay was 18.4%.⁵ Given the fragile health-status for patients with hematological malignancies, the additional morbidity from CDI development can negatively affect their clinical outcomes.⁶ Second, patients with asymptomatic colonization may contribute to the horizontal transmission of *Clostridium difficile* pathogens within the health-care setting, especially if their colonization status is not recognized.⁷

Therefore, the heme/BMT patient population should be considered for additional infection control measures, such as active surveillance and contact isolation of asymptomatic carriers, at least in hospitals with a high colonization pressure. The study by Lanzas, C *et al* found that active surveillance for *Clostridium difficile* could decrease new colonization by 40–50%, and incidence of hospital-onset CDI by 10–25%, supporting this strategy.⁷ While other interventions aimed at reducing disease incidence, such as intestinal decolonization of asymptomatic carriers with oral vancomycin or metronidazole have been disappointing,⁸ antimicrobial stewardship efforts such as fluoroquinolone restriction⁹ or piperacillin-tazobactam substitutions¹⁰ do show promise. The role of prophylactic probiotics as a strategy to reduce disease incidence in *C. difficile* colonized heme/BMT patients deserves further study.

Our study has several limitations. We did not have strain-specific molecular information to confirm that the CDI and colonizing strain were identical. We had missing admission samples for 10% of our study cohort, which may have led to over or underestimation of our

true colonization rates. As this was an observational study, it is subject to the inherent limitations of this study design. Since diarrhea occurs frequently in these patients due to other factors, such as graft-versus-host-disease or chemotherapy, distinguishing between colonization and symptomatic CDI in a patient already colonized may be difficult, leading to an overestimation of CDI rates. Finally, our study reflects the experience of a single academic medical center, and may have limited generalizability to other settings.

In summary, we found that the heme/BMT patient population is at increased risk for *Clostridium difficile* colonization, and should be considered for specific infection control interventions aimed at reducing the burden of transmission and disease within the hospital setting.

Acknowledgments

Funding came from an R03 and R18 grant from the Agency for Healthcare and Research Quality. All authors report no conflicts of interest relevant to this article.

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Table 1

Clinical and demographic characteristics for patients who did and did not develop symptomatic *Clostridium difficile* infection (CDI) during hospital stay, bivariate analysis

Characteristic	CDI positive N (%) N = 12	CDI negative N (%) N = 346	OR (95% CI)	P
Colonized with TCD on admission	4 (33.3)	26 (8.7)	5.3 (1.5 – 18.6)	0.02
Mean age (SD)	55.6 (13.5)	60.5 (14.8)	0.98 (1.0 – 1.1)	0.26
Race			N/E ^e	0.61
White	12 (100)	316 (91.3)		
Other	0 (0)	30 (8.7)		
Male Gender	4 (33.3)	195 (56.4)	0.4 (0.1 – 1.3)	0.14
Mean BMI (SD)	28 (5)	27.8 (6.6)	1.0 (0.9 – 1.1)	0.92
BMT recipient	5 (41.7)	54 (15.7)	3.8 (1.2 – 12.4)	0.03
Graft vs Host Disease	1 (8.3)	27 (7.9)	1.1 (0.1–8.6)	> 0.99
Hemodialysis	0 (0)	6 (1.7)	N/E ^e	> 0.99
Previous history of CDI ^a	2 (16.7)	10 (2.9)	6.7 (1.3 – 34.8)	0.06
Mean number of prior hospitalizations ^b (SD)	2.2 (3.2)	1.2 (1.8)	1.2 (1.0 – 1.5)	0.06
Antibiotics ^c				
Penicillins	1 (8.3)	48 (13.9)	0.6 (0.1 – 4.5)	> 0.99
Cephalosporins	10 (83.3)	165 (47.7)	5.5 (1.2 – 25.4)	0.02
Carbapenems	2 (16.7)	16 (4.6)	4.1 (0.8 – 20.4)	0.12
Fluoroquinolones	2 (16.7)	92 (26.6)	0.6 (0.1 – 2.6)	0.74
Glycopeptides	5 (41.7)	72 (20.8)	2.7 (0.8 – 8.8)	0.14
Chemotherapy agents ^d	10 (83.3)	184 (41.4)	7.1 (1.5 – 32.6)	0.03
H ₂ Blockers	8 (66.7)	116 (33.5)	4.0 (1.2 – 13.4)	0.03

OR = Odds Ratio; CI = Confidence Interval; TCD = toxigenic *Clostridium difficile* strain; SD = Standard Deviation; BMT = Bone Marrow Transplant; LTCF = Long Term Care Facility;

^{a,b} within previous year;

^c within previous 30 days;

^d includes alkylating agents, antimetabolites, and endocrine therapies;

^e not estimable.

Table 2

Independent risk factors for the development of symptomatic *Clostridium difficile* during hospital stay, multivariate analysis (N = 456 patient admissions)

Risk factor	Adjusted Odds Ratio * (95% CI)	P value
Colonization with TCD on admission	11.6 (2.9 – 47.1)	0.001
Bone Marrow Transplant Recipient	3.5 (1.1 – 12.1)	0.044
Chemotherapy agents ^a	7.9 (1.2 – 53.4)	0.034

* Risk adjusted by age and gender.

TCD = Toxigenic *Clostridium difficile* strain;

^a within previous 30 days