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LETTER TO THE EDITOR

Risk factors associated with *Clostridium difficile* infection in adult oncology patients with a history of recent hospitalization for febrile neutropenia

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Clostridium difficile infection (CDI) is a growing problem in the hospitalized population [1]. Recent studies estimate 333 000 new cases of CDI per year, with an annual mortality between 15 000 and 20 000 [2]. The most vulnerable populations are the elderly and the chronically ill [2]. The most important risk factor for CDI is exposure to antibiotics, which decreases commensal flora in the gastrointestinal tract and facilitates the growth of pathogenic strains [3]. Some other risk factors include exposure to known *C. difficile* carriers and prolonged duration of hospitalization [2,4]. The Infectious Diseases Society of America (IDSA) guidelines for empiric treatment of febrile neutropenia (FN) recommend broad-spectrum antimicrobial coverage even if no source of infection is identified [4]. Given the rise in CDI over the past decade with increased virulence, judicious antibiotic usage policies are becoming popular [5,6]. In the case of FN, postponing the administration of antibiotics is not feasible given the possibility of rapid progression of infection and death. The main objective of the present study was to evaluate risk factors for the development of CDI after a hospital admission for FN in oncology patients.

Rhode Island Hospital and The Miriam Hospital are tertiary-care university-affiliated institutions located in Providence, Rhode Island, USA. Medical records from patients admitted to either hospital between January 2005 and December 2009 that included ICD-9 (International Classification of Diseases, Ninth Revision) codes for fever (780.6) and neutropenia (288) were selected for extraction. The subset of these records coded for CDI (008.45) was then identified. Medical records were then reviewed. The extracted variables were patient age at time of admission, type of malignancy, duration of neutropenia, duration of hospitalization, and duration and choice of antimicrobial agents used. The dependent variable was identification of *C. difficile* in the stool (Meridian Premier EIA kit; Meridian Biosciences, Inc., Cincinnati, OH) in adult patients with diarrhea within 3 months of hospital admission for FN. The institutional review board approved the present study. De-identified patient characteristics were compared using Mann–Whitney and χ^2 tests for continuous and categorical variables, respectively. Univariate regression models were used to calculate odds ratios (ORs) with 95% confidence intervals (CIs) of developing CDI within 3 months of a hospital admission for FN in oncology patients. p-Values < 0.05 were considered statistically significant. All calculations were performed with MedCalc Software (Mariakerke, Belgium).

Between January 2005 and December 2009, we identified a total of 294 admissions for FN at our institution. After excluding patients who did not meet criteria for FN ($n = 73$), had a non-malignant cause of neutropenia ($n = 28$) or had incomplete data ($n = 50$), 143 patients were included in our study. Twenty-nine patients (20%) had a positive *C. difficile* assay in the setting of diarrhea within 3 months of an FN episode (CDI group). One hundred and fourteen patients (80%) did not develop CDI within 3 months of a FN episode (non-CDI group). The patients who developed CDI had longer average hospital stays (16 days vs. 9 days; $p = 0.001$), received longer courses of antibiotics (21 days vs. 12 days; $p = 0.002$) and more likely had a diagnosis of hematological malignancy (72% vs. 48%; $p = 0.03$) than patients without CDI. There were no differences in age, sex, degree of neutropenia or number of neutropenic days between the CDI and non-CDI groups. Selected characteristics of the patients included in the study are shown in Table I. In the univariate regressional analysis, number of hospitalization days (OR 1.05, 95% CI 1.01–1.09; $p = 0.008$), number of antibiotic days (OR 1.04, 95% CI 1.01–1.07; $p = 0.004$) and a diagnosis of hematological malignancy (OR 2.82, 95% CI 1.15–6.88; $p = 0.02$) were identified as risk factors for CDI in patients with FN (Table II). Patients' age, sex, degree of neutropenia and duration of neutropenia were not significant risk factors for the development of CDI. When evaluating antibiotic exposure (Table II), administration of cefepime (OR 1.10, 95% CI 1.03–1.19; $p = 0.005$) or levofloxacin (OR 1.46, 95% CI 1.09–1.96; $p = 0.01$) was associated with higher odds of CDI in oncology patients with FN.

The character of CDI in immunosuppressed patients is a topic of growing interest. Importantly, our study shows a nearly three-fold increase in the odds of CDI in patients with

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Table I. Selected characteristics of the patients.

	All cases	CDI	Non-CDI	*p*-Value
Number of patients	143	29	114	—
Median age, years (IQR)	63 (52–74)	62 (50–74)	63 (53–73)	0.77
Male sex (%)	65 (45%)	17 (59%)	48 (42%)	0.16
Mean ANC, cells/mm^3 (SD)	178 (± 167)	221 (± 170)	167 (± 166)	0.12
Mean hospital days (SD)	10 (± 12)	16 (± 19)	9 (± 8.2)	0.001
Mean antibiotic days (SD)	13 (± 14.5)	21 (± 17.2)	12 (± 13.1)	0.002
Mean neutropenia days (SD)	21 (± 47.7)	32 (± 61.7)	18 (± 43.3)	0.16
Hematological malignancy	76 (53%)	21 (72%)	55 (48%)	0.03
Acute myeloid leukemia	23 (30%)	7 (33%)	16 (29%)	—
Diffuse large B-cell lymphoma	14 (18%)	5 (24%)	9 (16%)	—
Solid tumor	67 (47%)	8 (28%)	59 (52%)	0.03
Breast cancer	20 (30%)	2 (25%)	18 (31%)	—
Lung cancer	13 (19%)	1 (13%)	12 (20%)	—

CDI, *Clostridium difficile* infection; IQR, interquartile range; ANC, absolute neutrophil count; SD, standard deviation.

a diagnosis of hematological malignancy, which is consistent with previous studies showing increased risk of CDI in patients with leukemia and lymphoma [7-10]. Subsequent studies suggested that this association may be due to the intensity of chemotherapy involved in treating these conditions [11], supported by a recent study which identified chemotherapy, irrespective of malignancy type, as an independent risk factor for CDI [12]. Our study also found increased odds of CDI in patients with FN with longer hospital stays and longer antibiotic regimens. Both factors have been previously associated with a high risk of CDI in the general population [1,2]. Our multivariate analysis, however, failed to identify independent risk factors for CDI in our cohort of oncology patients hospitalized for FN, which could be a reflection of the multifactorial etiology of CDI in this population or, most likely, the need for larger studies to adequately quantify outcome effects. Current IDSA guidelines recommend selecting from piperacillin/tazobactam, a carbapenem, cefepime or ceftazidime, with further guidance from the regional or local antibiogram [13]. Our study shows that the use of cefepime for the treatment of FN in oncology patients increases the odds of developing CDI. A recent study showed an increased risk of mortality with the use of cefepime in patients with FN, although this was not specifically attributed to CDI [13]. The indicated study also showed an increased risk of CDI with the use of meropenem, which was not evident from our data. It is difficult, however, to determine whether the increased risk of developing CDI with the use of cefepime found in our study is due to a significantly disproportionate usage of this agent in our population. Our study also shows increased odds of CDI with levofloxacin. Previous studies have shown an increased risk of CDI in patients with FN with the use of fluoroquinolones [14], and the importance of judicious use of these agents is emphasized by the increase in virulence observed in *C. difficile* over the past two decades [15]. Given our findings and the recently published IDSA guidelines recommending the use of cefepime, a carbapenem or piperacillin/tazobactam in treatment of FN, we believe that there may be a benefit to avoiding the use of cefepime as initial monotherapy in oncology patients. Our institution does not mandate the use of any specific agent or agents other than those recommended by the IDSA when treating febrile neutropenia. We believe that this makes the findings of our study generally applicable in other institutions following IDSA guidelines. Our study, however, has several limitations. First, during our data extraction period, our laboratory used a relatively insensitive assay to detect CDI [16], which could have introduced a detection bias. Despite this fact, the

Table II. Risk factors and antibiotics for *Clostridium difficile* infection in oncology patients with febrile neutropenia.

		Univariate analysis	
	No. of patients (CDI/non-CDI)	OR (95% CI)	*p*-Value
Characteristic			
Age at presentation	29/114	0.99 (0.97–1.02)	0.51
ANC at presentation		1.002 (1.000–1.004)	0.12
Number of hospital days		1.05 (1.01–1.09)	0.008
Duration of neutropenia		1.00 (0.99–1.01)	0.18
Number of antibiotic days		1.04 (1.01–1.07)	0.004
Hematologic malignancy	21/55	2.82 (1.15–6.88)	0.02
Antibiotic			
Azithromycin	4/11	1.02 (0.86–1.20)	0.85
Aztreonam	2/4	1.03 (0.85–1.25)	0.75
Cefepime	24/94	1.10 (1.03–1.19)	0.005
Ciprofloxacin	9/21	1.15 (0.92–1.44)	0.21
Clindamycin	2/3	1.07 (0.74–1.56)	0.71
Gentamycin	1/4	1.09 (0.83–1.43)	0.55
Levofloxacin	7/3	1.46 (1.09–1.96)	0.01
Linezolid	3/3	1.07 (0.95–1.20)	0.25
Meropenem	4/5	1.00 (0.82–1.22)	0.99
Piperacillin/tazobactam	7/15	1.06 (0.92–1.21)	0.41
Vancomycin	20/43	1.08 (1.00–1.17)	0.06

CDI, *Clostridium difficile* infection; OR, odds ratio; CI, confidence interval; ANC, absolute neutrophil count.

incidence of CDI in our cohort of oncology patients with FN was 20%, which is higher than in previous reports [17,18]. It is also likely that by excluding patients with incomplete data from our study ($n = 50$) we could have introduced a selection bias. The direction in which these biases would affect our results, however, is unknown. Another limitation is the small sample size of our cohort. Hence, our results should be considered preliminary and be taken with caution.

Further studies are needed to assess the risk of CDI against the therapeutic benefit of certain antibiotic regimens in the management of oncology patients with FN. Our study supports an increased risk of CDI in patients with hematological malignancies, and suggests that exposure to cefepime and levofloxacin may increase that risk. However, a larger study, ideally using propensity scoring, is needed to bring greater clarity to this issue in the hope of effectively managing FN in oncology patients with antibiotics that are least likely to lead to CDI. The necessity of judicious antibiotic use is becoming clear across all disciplines of medicine. There are no studies describing safe cessation of antibiotics in the setting of febrile neutropenia. Well-designed prospective studies are needed to develop recommendations for the duration of treatment in this patient population, especially when no source of infection is identified.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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