

ORIGINAL ARTICLE

Clostridium difficile Infection and Limitations of Markers for Severity in Patients with Hematologic Malignancy

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OBJECTIVE. To describe characteristics of *Clostridium difficile* infection (CDI) and markers of severe CDI among patients with hematologic malignancies.

DESIGN. Case-control study.

SETTING. Tertiary care teaching hospital.

PATIENTS AND METHODS. Inpatients with hematologic malignancies and CDI were age and time matched with 2 control inpatients without hematologic malignancies. Chart reviews were performed, and *C. difficile* isolates were strain typed.

RESULTS. Case patients ($n = 41$) and control patients ($n = 82$) patients were different in respect to receipt of immunosuppressive agents within 2 months (92.7% vs 25.6%; $P < .0001$); neutropenia within 2 months (75.6% vs 3.7%; $P < .0001$) and mean (\pm standard deviation) white blood cell (WBC) count at diagnosis (4.9 ± 14.1 vs $11.8 \pm 6.8 \times 10^3$ cells/mL; $P = .0002$); baseline mean creatinine level (0.89 ± 0.1 vs 1.6 ± 2.4 mg/dL; $P = .003$), mean creatinine level at diagnosis (0.83 ± 0.4 vs 1.85 ± 1.9 mg/dL; $P = .004$), and creatinine increases of 1.5 times over baseline (2.4% vs 15.1%; $P = .02$). Immunosuppressive agents and creatinine level remained significant in multivariable analysis ($P = .03$ for both variables). Severity correlated with mortality when measured by alternate severity criteria but not when measured by the Society for Healthcare Epidemiology of America/Infectious Diseases Society of America criteria, which are based solely on WBC count and creatinine elevation. The prevalence of the epidemic BI/NAP1/027 strain was similar in both groups.

CONCLUSIONS. Patients with hematologic malignancies had lower creatinine levels at the time of CDI diagnosis compared with control patients. WBC counts also tended to be lower in case patients. CDI severity criteria based on WBC count and creatinine level may not be applicable to patients with hematologic malignancies.

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Clostridium difficile infection (CDI) is a major cause of diarrhea and colitis, and multiple hospital outbreaks of CDI have been reported since 2001, coincident with the emergence of the BI/NAP1/027 (BI) strain.^{1,2} The most important risk factors for CDI due to the BI strain or to any *C. difficile* strain include advanced age, healthcare facility admission, and disruption of the indigenous colonic flora by antibiotic therapy or chemotherapy.^{4,5}

Patients with leukemia and lymphoma are at increased risk for CDI.⁶ Specific risk factors for CDI in this population include chemotherapy and hospitalization.^{6,7,15-17} In addition, patients with hematologic malignancies are often exposed to fluoroquinolones, which have a particularly strong association with CDI⁶ and with outbreaks due to the epidemic BI strain.^{8,9} We conducted a case-control study of CDI on a hematology ward and general medicine and surgery wards at a large tertiary referral hospital to determine the epidemiologic features of CDI and markers of severe CDI among patients with hematologic malignancies.

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METHODS

Patients with CDI were identified by reviewing the Loyola University Medical Center (LUMC) clinical microbiology laboratory log of all positive *C. difficile* toxin assay results from January 2007 through December 2008. LUMC is a 570-bed tertiary care center in the western suburbs of Chicago, and the *C. difficile* toxin assay used during this period was the Premier *C. difficile* toxin A and B immunoassay (Meridian Bioscience). Case patients were defined as patients with a positive stool toxin assay result who had a hematologic malignancy and who received treatment for CDI. Control patients were also identified from the microbiology log and were defined as patients with a positive stool toxin assay result who did not have a hematologic malignancy but who received

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nosis. As a result of these differences, control patients were more likely to meet the criteria for severity given in the 2010 SHEA/IDSA guidelines. However, because of the high prevalence of neutropenia among case patients, this finding may not truly reflect differences in CDI severity. In addition, disease severity as defined by these guidelines did not correlate with mortality. In contrast, disease severity as defined by the Zar or the Belmares criteria correlated with both overall mortality and CDI-related mortality among patients with hematologic malignancies. The Zar and Belmares criteria might be more helpful than the SHEA/IDSA guidelines in predicting outcome and guiding treatment decisions in this population. The Belmares criteria have been shown to have a strong correlation with CDI severity in other settings.²³ As shown by Zar et al,¹¹ the choice of treatment regimens for CDI may affect outcome in patients with severe CDI. Overall, metronidazole and oral vancomycin treatment regimens were similar between the 2 groups, and very few patients received vancomycin as initial therapy or at any time, which is consistent with the then-current National Comprehensive Cancer Network clinical practice guidelines, which emphasized use of metronidazole.²¹ Publication of the SHEA/IDSA guidelines, which recommended vancomycin treatment for severe CDI, occurred after the time period of this study, and this treatment preference for metronidazole regardless of disease severity may be changing.

The presence of the BI strain has had a profound impact on the epidemiology and clinical impact of CDI,²⁰ and differences among the predominant infecting strains could have influenced the outcome of our case-control study. We had hypothesized that the strain types might be different between the 2 populations, in part as a result of differences in antibiotic exposure. A study of CDI in hematopoietic stem cell transplant recipients demonstrated exposure to high-risk *C. difficile* antibiotics, including fluoroquinolones, to be an independent risk factor for CDI.²² Earlier outbreaks of the BI/NAP1/027 strain have been linked to fluoroquinolone use.¹⁴ Because of the high prevalence of fluoroquinolone use in patients with hematologic malignancies, one may have expected the incidence of the BI strain to be higher in that population. However, we did not find the prevalence of the BI strain to differ between populations. This finding may relate to an overall high prevalence of BI within our institution and is consistent with the results from another recent CDI study in a population of patients with cancer¹⁸ and the documented high prevalence of the BI strain in the Chicago area.¹⁹

There are several limitations to this study. Case patients and control patients were located on different wards. The toxin assay may not have been optimally sensitive. Most importantly, this was a single-center study in a tertiary care inpatient ward of patients with hematologic malignancies. As a result, our findings may not be applicable to all clinical settings, including outpatients or patients with other malignancies.

In conclusion, this study demonstrates differences in CDI between patients with hematologic malignancies and those without hematologic malignancies, including prediagnosis antibiotic patterns, fever, neutropenia, and baseline creatinine level. Patients without hematologic malignancies were more likely to meet criteria for severity based on the SHEA/IDSA criteria, although the significance of this finding is questionable because of the frequency of neutropenia in patients with hematologic malignancies. Additional studies and alternative definitions of severe CDI that include more than WBC count and creatinine level should be considered in patients with hematologic disorders.

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Potential conflicts of interest. D.N.G. holds patents for the treatment and prevention of CDI licensed to ViroPharma; is a consultant for ViroPharma, Optimer, Cubist, Merck, Pfizer, TheraDoc, Astellas, BioRelix, Cangene, Medicines Company, and Actelion; and holds research grants from GOJO, Merck, Optimer, Sanofi Pasteur, Eurofins Medinet, Actelion, and ViroPharma. S.J. is a consultant for Optimer and Bio-K+. All other authors report no conflicts of interest relevant to this article. All authors submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and the conflicts that the editors consider relevant to this article are disclosed here.

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