From the Intensive Care Unit (L.L., C.N., J.M., J.L.I., J.J.J., R.S., M.M.M., and M.L.M.) and the Research Unit (A.J.), Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain

Address reprint requests to Leonardo Lorente, MD, PhD, Intensive Care Unit, Hospital Universitario de Canarias, Ofra s/n, La Cuesta, La Laguna, 38320, Santa Cruz de Tenerife, Spain (lorentemartin@msn.com).

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Incidence of *Clostridium difficile* Infection in Patients with Acute Leukemia and Lymphoma after Allogeneic Hematopoietic Stem Cell Transplantation

To the Editor—Patient risk factors for *Clostridium difficile* infection (CDI) include antibiotic exposure, exposure to certain chemotherapeutic agents, prolonged hospital stay, and previous hospitalization. These risk factors are common attributes of patients with hematological malignancies who are undergoing high-dose chemotherapy and allogeneic stem cell transplantation (SCT). These patients often experience diarrhea as a complication. In spite of the potential for increased risk of diarrhea and CDI among patients undergoing allogeneic SCT, this association has not been rigorously evaluated. This study evaluates CDI among allogeneic SCT recipients to determine the incidence of and risk factors for CDI and investigates the possibility that different hematological malignancies may be associated with different risks of CDI after allogeneic SCT.

We retrospectively reviewed the medical records of all patients who underwent their first allogeneic SCT at our academic medical center during the period from May 2003 through December 2007. A total of 26 patients were identified; 12 had underlying acute myeloid leukemia, 4 had acute lymphoid leukemia, and 10 had lymphoma disease. All of the patients received high-dose bone marrow ablation chemotherapy before SCT, as well as antimicrobial prophylaxis, which consisted of valacyclovir, ciprofloxacin or gatifloxacin, and fluconazole, from marrow ablation through engraftment. Chart review identified patients who experienced diarrhea, defined as experiencing 3 or more loose bowel movements within a 24-hour period, and recorded the results of *C. difficile* tests. Collected data for each patient included age, sex, body weight, serum albumin level, and creatinine level 2 days prior to the onset of diarrhea; total number of neutropenic days; any history of recent hospitalization within 30 and 60 days before hospital admission; antibiotic use within 30 and 60 days before hospital admission; and all chemotherapy exposure within 60 days prior to hospital admission and during hospitalization. Other medications investigated as potential CDI risk factors included receipt of granulocyte-colony stimulating factor, proton pump inhibitors, and H2 blockers.

Only stool samples that took the shape of the container were tested for *C. difficile*, because it is our institution's microbiology laboratory policy to only accept such samples for *C. difficile* testing. Samples were evaluated for the presence of either *C. difficile* enterotoxin A or cytotoxin B by enzyme linked immunosorbent assay (Premier Toxins A & B kit; Meridian Bioscience). The Fisher exact test was used for univariate analysis, which included a comparison of patient characteristics between the leukemia and lymphoma patient groups and between the *C. difficile*–positive and *C. difficile*–negative groups.

Diarrhea was reported in 23 patients (88.5%), all of whom were tested for *C. difficile*. The onset of diarrhea ranged from 8 to 41 days after patient admission. Seven patients (30.4%) received a diagnosis of CDI. Among these 7 patients, 6 had acute myeloid leukemia, and 1 had acute lymphoid leukemia. No patients with lymphoma received a diagnosis of CDI. This difference was statistically significant ($P = .02$).

Comparison of *C. difficile*–positive and *C. difficile*–negative

TABLE. Patient Demographic Characteristics, Clinical Characteristics, and Antibiotic and Chemotherapy Regimen Exposure, Categorized by Disease

Characteristic	AML plus ALL group (n = 14)	Lymphoma group (n = 9)	P
Age, years, mean ± SD	48.1 ± 19.6	46.2 ± 12.8	.80
White race	3 (21.4)	2 (22.2)	>.99
Female sex	12 (85.7)	4 (44.4)	.07
Clostridium difficile toxin positive	7 (50.0)	0 (0)	.02
Hospitalization			
Within prior 60 days	13 (92.9)	4 (44.4)	.02
Within prior 30 days	10 (71.4)	1 (11.1)	.01
Time of onset of diarrhea after admission, days, mean ± SD	18.6 ± 10.1	14.6 ± 8.1	.33
Albumin level 2 days prior to onset of diarrhea, g/dL, mean ± SD	3.3 ± 0.5	3.4 ± 0.4	.92
Serum creatinine level 2 days prior to onset of diarrhea, mg/dL, mean ± SD	0.74 ± 0.4	0.8 ± 0.8	.69
Total no. of neutropenic days prior to onset of diarrhea, mean ± SD	9.6 ± 7.1	13.5 ± 9.5	.27
Antibiotic exposure			
Preceding 60 days prior to admission			
All	13 (92.9)	3 (33.3)	.01
Cefepime	9 (64.3)	2 (22.2)	.09
Ciprofloxacin/gatifloxacin	7 (50.0)	1 (11.1)	.09
Vancomycin	8 (57.1)	1 (11.1)	.04
Metronidazole	7 (50.0)	0 (0)	.02
Daptomycin	4 (28.6)	0 (0)	.13
Preceding 30 days prior to admission			.01
All	10 (71.4)	1 (11.1)	
Cefepime	6 (42.9)	1 (11.1)	.18
Ciprofloxacin/gatifloxacin	5 (35.7)	0 (0)	.34
Vancomycin	5 (35.7)	0 (0)	.12
Metronidazole	5 (35.7)	0 (0)	.12
Daptomycin	2 (14.3)	0 (0)	.50
During hospitalization			
Ciprofloxacin/gatifloxacin	13 (92.9)	9 (100)	>.99
Vancomycin	9 (64.3)	4 (44.4)	.42
Cefepime	8 (57.1)	4 (44.4)	.68
Imipenem	3 (21.4)	0 (0)	.25
Amphotericin	4 (28.6)	4 (44.4)	.66
Chemotherapy exposure			
Preceding 60 days prior to admission	10 (71.4)	4 (44.4)	.38
During hospitalization			
Cyclophosphamide	7 (50.0)	1 (11.1)	.09
Dexamethasone	13 (92.9)	8 (88.9)	>.99
Tacrolimus	13 (92.9)	9 (100)	>.99
Methotrexate	11 (78.6)	8 (88.9)	>.99
Fludarabine	7 (50.0)	5 (55.6)	>.99
Melphalan	2 (14.3)	8 (88.9)	<.001
Other medications received during hospitalization			
Granulocyte-colony stimulating factor	12 (85.7)	9 (100)	.50
Proton pump inhibitor and/or H2 blockers	12 (85.7)	9 (100)	.50

NOTE. Data are no. (%) of patients, unless otherwise indicated. ALL, acute lymphoid leukemia; AML, acute myeloid leukemia; SD, standard deviation.

patients only identified inpatient use of imipenem as a risk factor for CDI (P = .02). Prior hospitalization and prior antibiotic exposure, especially exposure to intravenous vancomycin (P = .04) and metronidazole (P = .02), within 60 days before admission were significantly higher in the acute leukemia group relative to the lymphoma group (P = .02 and P = .005, respectively) (Table). Exposure to granulocyte-colony stimulating factor, proton pump inhibitors, or H2

blockers did not seem to be a risk factor for CDI in patients who underwent allogeneic SCT.

Diarrhea was a very common complication of hematologic malignancy in patients who underwent SCT. In fact, only 3 patients did not develop diarrhea during their hospitalization. Almost one-third of the patients who underwent allogeneic SCT also received a diagnosis of CDI. Previous studies have reported increased rates of CDI among allogeneic SCT recipients of 13%[1] and 20%,[2] and a more recent publication[3] reported a CDI rate of 27.3% among such patients—a rate comparable to our reported rate. In our study, all CDI cases occurred among leukemic patients, and 60% of the patients with acute myeloid leukemia developed CDI. This association was evident over a 4.5-year period and was not associated with any temporal clustering of CDI cases. However, leukemia was also associated with higher rates of prior hospitalization and prior antibiotic use.

To our knowledge, this study is the first to report an association between CDI and acute myeloid leukemia in patients undergoing allogeneic SCT. The principal limitation of our study is its small sample size, which did not allow us to perform multivariate analysis. Our findings will need to be investigated in a multicenter study that encompasses a sample size large enough to allow multivariate analysis to control for confounding. Despite the small sample size and the complex nature of the patient population, we determined that leukemic patients undergoing allogeneic SCT have a very high risk of developing CDI. Clinicians should maintain a high degree of suspicion for CDI when caring for leukemic patients (and for those with acute myeloid leukemia in particular) who have undergone allogeneic SCT and subsequently develop diarrhea, and they should aggressively pursue this diagnosis, which will allow for early recognition and treatment of CDI.

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Sharon Leung, MD; Brian S. Metzger, MD, MPH; Brian P. Currie, MD, MPH

From the Divisions of Critical Care Medicine (S.L.) and Infectious Disease (B.S.M. and B.P.C.), Montefiore Medical Center and Albert Einstein College of Medicine, Bronx, New York; and Foundation for Applied Epidemiology, Northvale, New Jersey (B.P.C.).

Address reprint requests to Sharon Leung, MD, Div of Critical Care Medicine, Montefiore Medical Center, 111 E 210th St, Gold Zone, Main Floor, Bronx, NY 10467 (sleung@montefiore.org).

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Cryptococcus Neoformans as a Rare Cause of Hospital Infection

To the Editor—Cryptococcosis is a systemic mycosis caused by varieties of *Cryptococcus neoformans* and is predominantly an opportunistic infection observed in adults with AIDS or in other cellular immunodeficiency conditions. Most cryptococcal infections are acquired primarily by inhalation of infectious propagules, and there are occasional cases of direct traumatic inoculation.[1,2] Nosocomial transmission of cryptococcosis has been reported previously and is considered to be quite rare.[2-4] We report a case suggestive of nosocomial transmission of cryptococcosis and review the cases reported in the medical literature.

A 65-year-old woman (patient A) was hospitalized because of fever, cough, and headaches on March 28, 2008. The patient underwent liver transplantation because of end-stage chronic hepatitis C liver disease in 2003. Chest radiography revealed an infiltrate with pulmonary nodules in the right lung. *C. neoformans* was isolated from pulmonary nodule biopsy specimens and cerebrospinal fluid specimens on April 24, 2004. She received mechanical ventilation and was transferred to the medical intensive care unit on May 4, 2008. Despite receiving treatment with amphotericin B (50 mg/day) and 5-flucytosine (7250 mg/day), the patient died of refractory respiratory failure on July 27, 2008.

A 67-year-old woman (patient B) was admitted to the same medical intensive care unit (ICU) in a close but not contiguous bed to patient A. Before her admission in the ICU on June 19, 2008, the patient underwent valve replacement and developed hemorrhagic shock. Patient B had previously been healthy, without any underlying diseases, and was not receiving any immunosuppressive therapy. Because refractory respiratory failure and persistent fever occurred despite receipt of broad-spectrum antibiotic treatment, multiple blood samples were drawn for culture, which yielded *C. neoformans* on July 10, 2008. *C. neoformans* was also isolated from cer-