ORIGINAL ARTICLE

Outcomes of *Clostridium difficile* Infection in Hospitalized Leukemia Patients: A Nationwide Analysis

Ruihong Luo, MD, PhD;[1] Alan Greenberg, MD;[2] Christian D. Stone, MD, MPH[3]

BACKGROUND. The incidence of *Clostridium difficile* infection (CDI) has increased among hospitalized patients and is a common complication of leukemia. We investigated the risks for and outcomes of CDI in hospitalized leukemia patients.

METHODS. Adults with a primary diagnosis of leukemia were extracted from the United States Nationwide Inpatient Sample database, 2005–2011. The primary outcomes of interest were CDI incidence, CDI-associated mortality, length of stay (LOS), and charges. In a secondary analysis, we sought to identify independent risk factors for CDI in leukemia patients. Logistic regression was used to derive odds ratios (ORs) adjusted for potential confounders.

RESULTS. A total of 1,243,107 leukemia hospitalizations were identified. Overall CDI incidence was 3.4% and increased from 3.0% to 3.5% during the 7-year study period. Leukemia patients had 2.6-fold higher risk for CDI than non-leukemia patients, adjusted for LOS. CDI was associated with a 20% increase in mortality of leukemia patients, as well as 2.6 times prolonged LOS and higher hospital charges. Multivariate analysis revealed that age >65 years (OR, 1.13), male gender (OR, 1.14), prolonged LOS, admission to teaching hospital (OR, 1.16), complications of sepsis (OR, 1.83), neutropenia (OR, 1.35), renal failure (OR, 1.18), and bone marrow or stem cell transplantation (OR, 1.27) were significantly associated with CDI occurrence.

CONCLUSIONS. Hospitalized leukemia patients have greater than twice the risk of CDI than non-leukemia patients. The incidence of CDI in this population increased 16.7% from 2005 to 2011. Development of CDI in leukemia patients was associated with increased mortality, longer LOS, and higher hospital charges.

Infect Control Hosp Epidemiol 2015;36(7):794–801

Clostridium difficile infection (CDI) is a common cause of diarrhea in hospitalized patients. With new highly pathogenic, treatment-resistant strains emerging and an expanding epidemiological niche, the prevalence of CDI has increased.[1] The cost of this disease in the United States has been estimated to exceed $1.1 billion annually, accounting for significant morbidity and mortality in hospitalized patients.[2]

Risk factors for CDI include older age, prolonged hospitalization, recent antibiotic use, systemic comorbidities, and immunosuppression.[3] Patients with hematological malignancies are also susceptible to CDI, with risk attributable in part to chemotherapy-induced neutropenia and prolonged hospitalization in the case of bone marrow transplant recipients. As reported previously, CDI often complicates the care of patients with hematological malignancies after myelosuppressive chemotherapy.[4] Neutropenic enterocolitis is a severe complication of aggressive chemotherapy, with *C. difficile* being the underlying pathogen in ~6% of these patients.[5] Antibiotic exposure further compounds the risk of CDI in leukemia patients. Notably, neutropenic fever warrants empirical antibiotic therapy, which in turn can suppress resident bowel flora and thus permit overgrowth of *C. difficile*.[6] Lastly, cytotoxic chemotherapy such as Ara-C, used in leukemia, may also induce *C. difficile* colitis.[7]

There is a paucity of data on the nationwide incidence of CDI in leukemia patients and the effects of CDI on their in-hospital outcomes. In this study, we aimed to determine the trend of incidence of CDI in hospitalized leukemia patients, to evaluate the impact of CDI on mortality and expense, and to identify the risk factors for developing CDI in this population.

METHODS

Data Source

We performed a retrospective cohort study using data from the Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS) from 2005 to 2011. NIS is an all-payer inpatient care database representing a 20% stratified sample of non-federal acute-care hospitals in the United States, including

Affiliations: 1. Department of Internal Medicine, University of Nevada School of Medicine, Las Vegas, Nevada; 2. Infectious Disease Specialists, University Medical Center, Las Vegas, Nevada; 3. Section of Gastroenterology and Hepatology, University of Nevada School of Medicine, Las Vegas, Nevada.

Received October 18, 2014; accepted February 20, 2015; electronically published March 24, 2015

 0899-823X/2015/3607-0006. DOI: 10.1017/ice.2015.54

community, general, and academic centers but not long-term care facilities. It contains data from ~8 million hospital stays per year. Each discharge is weighted to allow for estimates projected to a national level. Each individual hospitalization is deidentified and maintained in the NIS as a unique entry with one primary discharge diagnosis and up to 24 secondary diagnoses.[8]

Patient Selection

International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes were used to identify subjects from the database. We included adults, aged ≥18 years, with a primary diagnosis code for leukemia (all ICD-9-CM codes used in this study are listed in the Appendix). We excluded cases with a primary diagnosis of CDI and leukemia as a secondary diagnosis. A comparison group was generated by a 10% random selection of non-leukemia patients from NIS, 2005–2011.

Study Variables

The variables of age, gender, ethnicity, teaching status of hospital, in-hospital death or survival, length of hospital stay (LOS), and total hospital charges were extracted from the NIS dataset to provide subject characteristics. Other variables including leukemia, CDI, pneumonia, urinary tract infection (UTI), sepsis, and bone marrow or stem cell transplant were identified by ICD-9-CM diagnosis codes (Appendix). The subgroups of acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphoid leukemia (ALL), and chronic lymphoid leukemia (CLL) as well as disease in relapse or remission were identified and analyzed separately. Age, LOS, and hospital charges were collected as continuous variables. Age was categorized initially into the following subgroups: 18–25, 26–35, 36–45, 46–55, 56–65 and >65 years old. All other variables were analyzed as categorical variables.

Outcomes

The main outcomes of interest were the trend of incidence of CDI in hospitalized leukemia patients, mortality, LOS, and inflation-adjusted hospital charges in leukemia patients with CDI. In our secondary analyses, we investigated risk factors for developing CDI and the impact of CDI on subject mortality. Hospital charges refer to the charges that the hospital levied to the patients. All dollar amounts in this report were adjusted to inflation based on the year 2011. The LOS refers to the total number of continuous days a patient was hospitalized.

Statistical Analysis

Descriptive statistics were used to describe the baseline characteristics of all patients. The 7-year incidence of CDI was calculated by the number of cases with secondary diagnosis of CDI divided by the total number of hospitalizations from 2005 to 2011. The CDI incidence of all hospitalized patients was compared to that of leukemia patients. CDI incidence was similarly calculated for the 10% randomly selected non-leukemia patients from 2005 to 2011 and compared to that of leukemia patients after adjusting for LOS. To identify risk factors for CDI in leukemia patients, patients were divided into 2 groups based on the presence or absence of a diagnosis of CDI during hospitalization. To evaluate the effect of CDI on in-hospital mortality, subjects were divided into 2 groups based on death or survival. Categorical and continuous variables were compared using a χ^2 test and the Mann-Whitney U test, respectively.

A logistic regression model was developed to determine risk factors for developing CDI in leukemia patients using CDI as the dependent variable. To determine the impact of CDI on mortality, the in-hospital outcome of survival or death was used as the dependent variable. The following potential confounding factors were included in the final regression model: age (reference group [Ref]: age ≤ 65), gender (Ref: male), race (Ref: Caucasian), Charlson index score (Ref: 0), teaching status of hospital (Ref: non-teaching hospital), the presence of complications or comorbidities (eg, hypertension, diabetes, pneumonia, etc.), and the performance of bone marrow or stem cell transplant during hospitalization.

All analyses were performed using the Statistical Program for Social Sciences version 19.0 (SPSS, Armonk, NY: IBM Corp.). The discharge weight variable assigned to each discharge was used to project to national estimates. All statistical tests were 2-sided, and $P < .01$ was considered statistically significant. The University of Nevada School of Medicine Office of Human Research Protection has deemed that research using the NIS and similar deidentified datasets is exempt from institutional approval.

RESULTS

Incidence of CDI in Patients with Leukemia

A total of 1,243,107 cases with a primary discharge diagnosis for leukemia were identified, including 42,438 cases with diagnoses of both leukemia and CDI. Overall, the incidence of CDI in leukemia patients was 3.4%, which was significantly greater than the incidence of CDI in all hospitalized patients (0.85%). During the 7 years studied, the total number of leukemia patients diagnosed with CDI increased by 45.5%. The incidence of CDI in leukemia patients was 3.0% in 2005 and 3.5% in 2011, an increase of 16.7%. By comparison, the incidence of CDI in all hospitalized patients increased by 30.3% (from 7.6 to 9.9%). The increasing trend in CDI was slower in leukemia patients compared to all hospitalized patients. The incidence of CDI in leukemia patients remained 2.3 to 2.8 times higher than in non-leukemia patients after adjusting for LOS (Table 1).

The most common leukemia type identified within the database was CLL (44.6%), followed by AML (32.5%). The incidence

https://doi.org/10.1017/ice.2015.54 Published online by Cambridge University Press

TABLE 1. *Clostridium difficile* Infection Trend in Hospitalized Leukemia Patients, 2005–2011

	2005	2006	2007	2008	2009	2010	2011
CDI incidence, all patients, %	0.76	0.80	0.81	0.87	0.85	0.89	0.99
Leukemia patients with CDI, no.	4,647	4,993	6,200	6,910	6,594	6,335	6,760
CDI incidence in leukemia patients, %	3.0	3.2	3.5	3.6	3.5	3.4	3.5
Risk of CDI, leukemia vs non-leukemia patients, OR (95% CI)[a]	2.5 (2.1–3.1)	2.9 (2.4–3.6)	2.3 (1.8–2.8)	2.5 (2.1–3.0)	2.8 (2.3–3.3)	2.5 (2.1–3.0)	2.8 (2.4–3.3)

NOTE. CDI, *Clostridium difficile* infection; CI, confidence interval; OR, odds ratio.
[a]Comparison after adjusting for length of hospital stay.

TABLE 2. Differences in CDI Incidence Based on Type of Leukemia

Leukemia type, no. (%)	Total, %	No remission, %	Remission, %	Relapse, %	*P* Value
ALL, 142,978 (11.5)	3.9	3.7	4.0	5.9	<.001
CLL, 554,987 (44.6)	2.5	2.5	2.4	2.8	.173
AML, 403,545 (32.5)	4.7	4.7	4.1	5.8	<.001
CML, 141,598 (11.4)	2.9	2.9	2.4	5.4	<.001

NOTE. CDI, *Clostridium difficile* infection; ALL, acute lymphoid leukemia; AML, acute myeloid leukemia; CLL, chronic lymphoid leukemia; CML, chronic myeloid leukemia.

of CDI was highest in AML (4.7%), followed by ALL (3.9%), CML (2.9%) and CLL (2.5%), and the difference among these groups was significant ($P < .001$). Patients with ALL, AML, or CML had a significantly higher incidence of CDI when they were in relapse compared to remission ($P < .001$). In contrast, while subjects with CLL exhibited a numerical difference in CDI between relapse and remission, this difference was not statistically significant (Table 2).

Tables 3 and 4 summarize the subject demographic and clinical features as well as in-hospital outcomes in leukemia patients with or without CDI. Because the CDI incidences in leukemia patients among all of the age subgroups below age 65 were nearly identical, the final analysis regarding age was dichotomized as ≤ 65 and >65 years old.

Risk Factors for CDI in Leukemia Patients

Logistic regression analysis revealed that age > 65 years (OR,1.13; 95% CI, 1.10–1.16) and male gender (OR, 1.14; 95% CI, 1.11–1.17) minimally increased the risk for CDI. White race was associated with a higher risk for CDI than for Blacks or Asian/Pacific Islanders. CDI diagnoses occurred during hospitalizations as short as 2 days and incidence increased consistently with increasing LOS. Patients in teaching hospitals had 16% higher risk for CDI compared to those in non-teaching hospitals. CDI risk was higher for acute (ALL and AML) vs. chronic leukemias (CLL and CML). The occurrence of sepsis (OR,1.83; 95% CI, 1.78–1.88) and neutropenia (OR, 1.35; 95% CI, 1.31–1.38) were major clinical complications that significantly increased the risk of CDI. Patients undergoing bone marrow or stem cell transplantation during hospitalization also had increased risk for CDI (OR, 1.27; 95% CI, 1.22–1.32). With regard to comorbidities, congestive heart failure (OR, 1.33; 95% CI, 1.27–1.40), renal failure (OR, 1.18; 95% CI, 1.09–1.28), and lymphoma (OR, 1.12; 95% CI, 1.05–1.20) were significantly associated with CDI. However, increased Charlson index was not associated with the development of CDI (Table 5).

Effect of CDI on Mortality in Leukemia Patients

Logistic regression analysis revealed that CDI independently increased mortality of leukemia patients (OR, 1.17; 95% CI, 1.13–1.22). Other factors that increased mortality were age > 65 (OR, 1.90; 95% CI, 1.86–1.94), sepsis (OR, 5.79; 95% CI, 5.69–5.90), pneumonia (OR, 2.14; 95% CI, 2.11–2.18), CHF (OR, 1.13; 95% CI, 1.09–1.16), coagulopathy (OR, 1.85; 95% CI, 1.82–1.89), liver disease (OR, 1.22; 95% CI, 1.15–1.28), and lymphoma (OR, 1.24; 95% CI, 1.19–1.30). Higher Charlson index was associated with increased mortality in leukemia patients.

DISCUSSION

CDI is frequently identified as a cause of diarrhea in the hospital setting. Its incidence ranges from 4.8% to 9% in patients with AML, but this rate is as high as 14%–30.4% in patients with allogenic hemotopoietic stem cell transplant.[9,10] A recent study reported an incidence of CDI of 3.1% in hematologic patients.[9] These data are in agreement with our study, in which CDI incidence varied from 2.5% to 4.7%, depending on type of leukemia. As in general hospitalized patients, the incidence of CDI in leukemia patients increased from 2005 to 2011. CDI is considered among the most common hospital-acquired infections with a documented increase in frequency and severity beginning ~10 years ago.[11,12] The increase is attributed in part to the emergence of a hypervirulent strain of *C. difficile* known as NAP1/BI/027.[12] Leukemia has been identified as an

https://doi.org/10.1017/ice.2015.54 Published online by Cambridge University Press

TABLE 3. Comparison of Demographic Characteristics between Patients with Leukemia and Patients with Leukemia and *Clostridium difficile* Infection

	Leukemia	Leukemia and CDI	*P* Value
Number	1,200,669	42,439	…
Age, y			
Age (mean ± SD)	65.23 ± 18.35	63.09 ± 18.36	<.001
≤65, no. (%)	515,757 (43.0)	20,930 (49.3)	<.001
>65, no. (%)	684,913 (57.0)	21,509 (50.7)	
Gender, no. (%)			
Female	526,534 (43.9)	19,997 (47.1)	<.001
Male	673,813 (56.1)	22,437 (52.9%)	
Race, no. (%)			<.001
Caucasian	774,917 (79.3)	27,903 (78.3)	
African American	79,407 (8.1)	2,839 (8.0)	
Hispanic	76,079 (7.8)	3,098 (8.7)	
Asian/Pacific Islander	19,392 (2.0)	674 (1.9)	
Native American	3,519 (0.4)	151 (0.4)	
Other	24,248 (2.5)	979 (2.7)	
Hospital teaching status, no. (%)			<.001
Non-teaching hospital	508,241 (42.6)	14,064 (33.4)	
Teaching hospital	683,525 (57.4)	27,989 (66.6)	
Outcomes			
Mortality, no. (%)	89,789 (7.5)	5,566 (13.1)	<.001
LOS, mean (range)	5 (0–365)	13 (0–288)	<.001
Charges, mean (range)	27,625 (38–2,669,472)	71,178 (195–3,167,459)	<.001

NOTE. CDI, *Clostridium difficile* infection; LOS, length of stay; SD, standard deviation.

independent risk factor for CDI.[13] Antibiotic prophylaxis with fluoroquinolones is common in patients with hematologic malignancies given that it reduces mortality, febrile episodes, and bacterial infections in neutropenic patients.[14–16] With the emergence of a new fluoroquinolone-resistant *C. difficile* strain, this class of antibiotic represents a risk factor for occurrence and may be responsible for specific outbreaks of CDI.[11,17,18] In addition to antibiotic exposure, chemotherapy, neutropenia, frequent hospitalization, and performance of bone marrow or peripheral stem cell transplantation have also been found to confer risk of CDI in leukemia patients.[4,7,19]

In our study, leukemia patients with CDI had higher mortality than patients without CDI, though the mortality may not be related directly to CDI. After adjusting for age, comorbidities, and other complications, CDI was found to independently increase the in-hospital mortality by 17%. A recent multi-institutional study reported that the crude mortality in nosocomial *C. difficile* hospitalized patients was 24.8% and that the CDI-contributable mortality was 6.9%.[11] CDI has been associated with higher mortality in many disease states such as inflammatory bowel disease, liver cirrhosis, and solid organ transplant.[20–22] In addition to the emergence of hypervirulent *C. difficile* strains,[23,24] other factors that may account for increased mortality in leukemia patients with CDI include greater severity of leukemia, more comorbidities, and complications like neutropenia and different infections.[12]

Our study also found that CDI substantially increased LOS with accompanying higher hospital charges. This result mirrors that of several studies that examined the burden of CDI in patients with hematologic diseases, inflammatory bowel disease, and cirrhosis.[22,25–27] However, determining to what degree CDI contributed to prolonged LOS has been studied only rarely. The issue is problematic because LOS and CDI influence each other and a cause–effect relationship may be bidirectional.[19,25,28] A recent study using multistate models found that CDI had little additive effect on LOS.[29] To investigate LOS further in the current study, we adjusted for LOS in a regression model and found that the incidence of CDI was still 2.6-fold greater in leukemia than in non-leukemia patients, indicating that factors other than LOS are responsible for the risk of CDI.

We found that women with leukemia had a 14% increased risk for CDI compared to men and that Caucasians patients had a higher risk for CDI compared to Asian/Pacific Islanders and Blacks. A few publications examining the issue of sex and race disposition in CDI have reported variable findings,[4,21] which may reflect results occurring by chance. The role of sex and race on CDI susceptibility requires further research.

To our knowledge, the comparison of CDI incidence between teaching and non-teaching hospitals has rarely been reported previously. We found that leukemia patients in teaching hospitals were more likely to be diagnosed with CDI and had higher mortality compared with those in non-teaching hospitals. This result may stem from the facts that patients referred to teaching hospitals tend to have more complex illness, greater severity of disease, and higher risk of infection and may receive more acid suppressants and antibiotics.[30]

https://doi.org/10.1017/ice.2015.54 Published online by Cambridge University Press

TABLE 4. Comparison of Clinical Features between Patients with Leukemia and Patients with Leukemia and *Clostridium difficile* Infection

	CDI Absent	CDI Present	*P* Value
Number	1,200,669	42,438	
Unweight	243,239	8,567	
Leukemia, N (%)			<.001
ALL	137,375 (11.4)	5,603 (13.2)	
CLL	541,179 (45.1)	13,808 (32.5)	
AML	384,647 (32.0)	18,897 (44.5)	
CML	137,469 (11.4)	4,130 (9.7)	
Complication/comorbidities, no. (%)			
Sepsis	108,688 (9.1)	9,198 (21.7)	<.001
Pneumonia	208,964 (17.4)	9,634 (22.7)	<.001
UTI	4,606 (0.4)	170 (0.4)	.579
Neutropenia	154,872 (12.9)	9,684 (22.8)	<.001
Hematopoietic cell transplantation	63,127 (5.3)	4,285 (10.1)	<.001
Deficiency anemia	267,501 (22.3)	9,195 (21.7)	.003
Collagen vascular diseases	23,844 (2.0)	806 (1.9)	.208
CHF	131,224 (10.9)	6,181 (14.6)	<.001
COPD	198,244 (16.5)	6,522 (15.4)	<.001
Coagulopathy	224,119 (18.7)	9,419 (22.2)	<.001
DM (Uncomplicated)	211,122 (17.6)	6,293 (14.8)	<.001
DM with chronic complications	337,840 (2.8)	1,232 (2.9)	.275
HTN	520,665 (43.4)	16,722 (39.4)	<.001
Hypothyroidism	130,983 (10.9)	4,084 (9.6)	<.001
Liver disease	22,928 (1.9)	41,430 (2.4)	<.001
Lymphoma	32,779 (2.7)	1,222 (2.9)	.064
Obesity	52,148 (4.3)	41,023 (3.3)	<.001
PVD	49,316 (4.1)	1,458 (3.4)	<.001
Renal failure	124,882 (10.4)	4,813 (11.3)	<.001
Solid tumor without metastasis	27,242 (2.3)	677 (1.6)	<.001
Metastatic cancer	18,964 (1.6)	41,908 (1.3)	<.001
Valvular disease	53,145 (4.4)	2,066 (4.9)	<.001
Charlson Index, no. (%)			<.001
0	648,627 (54.0)	23,217 (54.7)	
1	283,698 (23.6)	9,422 (22.2)	
2	139,126 (11.6)	5,271 (12.4)	
3	66,646 (5.6)	2,325 (5.5)	
4	29,649 (2.5)	1,113 (2.6)	
≥5	32,924 (2.7)	1,090 (2.6)	

NOTE. CDI, *Clostridium* difficile infection; ALL, acute lymphoid leukemia; AML, acute myeloid leukemia; CLL, chronic lymphoid leukemia; CML, chronic myeloid leukemia; UTI, urinary tract infection; DM, diabetes mellitus; HTN, hypertension; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease.

Comparisons of CDI rates between acute and chronic leukemia have rarely been published. We found that acute leukemia had higher incidence of CDI than chronic leukemia. Exposure to antibiotics, use of certain chemotherapeutic agents, prolonged or repeat hospitalization, sustained neutropenia, and allogenic stem cell transplantation are all more common in patients with acute leukemia[4,31] and may explain the higher risk of CDI. In addition, we found that patients with leukemia relapse had higher incidence of CDI than patients in remission, which possibly reflects greater disease severity or more exposure to known CDI risks factors.

Our results confirm the previously described links between CDI and older age, prolonged hospitalization, and immunodeficiency-related complications of leukemia, such as neutropenia, lymphoma, and bone marrow or stem cell transplant.[4,31] We also found a higher risk of CDI associated with sepsis, CHF or renal failure. This is not surprising given the extensive antibiotic use that accompanies sepsis and the fact that CHF and renal failure are associated with a higher risk of MRSA infection, prolonged LOS, ICU admission[31] and presence of NAP strain infection.[32] In addition, our results reveal statistically significant associations with other clinical factors such as deficiency anemia, coagulopathy, uncomplicated diabetes, etc. (Table 5). However, the absolute difference between leukemia and non-leukemia patients with regard to these factors is very small and probably clinically insignificant.

https://doi.org/10.1017/ice.2015.54 Published online by Cambridge University Press

TABLE 5. Demographic and Clinical Features Independently Associated with *Clostridium difficile* Infection in Hospitalized Patients with Leukemia

Characteristic	Reference	OR (95% CI)	*P* Value
Age	≤65 years	1.13 (1.10–1.16)	<.001
Gender	Male	1.14 (1.11–1.17)	<.001
Race	Caucasian		
Black		0.92 (0.88–0.95)	<.001
Hispanic		0.97 (0.93–1.01)	.102
Asian/Pacific Islander		0.72 (0.66–0.78)	<.001
Native American		1.16 (0.98–1.38)	.077
LOS (days)	1 day		
2		1.68 (1.51–1.86)	<.001
3–5		2.78 (2.54–3.04)	<.001
6–10		5.13 (4.69–5.62)	<.001
11–15		7.58 (6.91–8.32)	<.001
≥16		12.89 (11.79–14.10)	<.001
Hospital teaching status	Non-teaching hospital	1.16 (1.14–1.19)	<.001
Leukemia	ALL		
CLL		0.77 (0.74–0.80)	<.001
AML		1.01 (0.98–1.05)	.451
CML		0.84 (0.80–0.88)	<.001
Complications	None		
Sepsis		1.83 (1.78–1.88)	<.001
Pneumonia		0.92 (0.90–0.95)	<.001
UTI		0.82 (0.69–0.98)	.032
Neutropenia		1.35 (1.31–1.38)	<.001
Bone marrow/stem cell transplant		1.27 (1.22–1.32)	<.001
Deficiency anemia		1.07 (1.04–1.10)	<.001
PVD		0.98 (0.90–1.07)	.710
CHF		1.33 (1.27–1.40)	<.001
COPD		1.03 (0.98–1.09)	.185
Coagulopathy		0.96 (0.93–0.98)	.001
DM, uncomplicated		0.92 (0.87–0.96)	.001
DM, complicated		0.99 (0.90–1.09)	.803
Hypertension		0.99 (0.97–1.01)	.425
Hypothyroidism		0.94 (0.91–0.98)	.001
Liver disease		1.04 (0.96–1.13)	.291
Lymphoma		1.12 (1.05–1.20)	.001
Obesity		0.69 (0.65–0.73)	<.001
Renal failure		1.18 (1.09–1.28)	<.001
Solid tumor without metastasis		0.76 (0.68–0.86)	<.001
Cancer metastasis		0.94 (0.77–1.15)	.548
Valvular disease		1.04 (0.99–1.10)	.114
Charlson index	0		
1		0.97 (0.93–1.02)	.300
2		1.08 (0.99–1.17)	.085
3		0.97 (0.86–1.09)	.596
4		1.03 (0.88–1.21)	.749
≥5		0.94 (0.76–1.15)	.536

NOTE. CDI, *Clostridium difficile* infection; OR, odds ratio; LOS, length of hospital stay; ALL, acute lymphoid leukemia; AML, acute myeloid leukemia; CLL, chronic lymphoid leukemia; CML, chronic myeloid leukemia; UTI, urinary tract infection; DM: diabetes mellitus; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease.

Our study has several limitations. First and foremost, we were not able to adjust for the severity of underlying leukemia. Patients with severe leukemia are typically at greater risk of acquiring CDI and develop worse outcomes after CDI. However, there are no validated measures of determining leukemia severity within large administrative databases or retrospective analyses using hospital discharge codes. A second limitation inherent to administrative data is the possibility of

https://doi.org/10.1017/ice.2015.54 Published online by Cambridge University Press

coding errors leading to missed or erroneous diagnoses. Nevertheless, we do not suspect a systematic bias toward any particular diagnosis or error. Third, a major limitation of the NIS is that it lacks information on readmission rates and medication use including antibiotic classification and acid suppressants, which are known to increase the risk of CDI.[4] Moreover, the choice of treatment regimen for CDI like metronidazole, vancomycin and/or fidaxomicin, which may affect patient outcomes, is also missing from NIS. Like most dataset studies, study design cannot adjust for this systematic error. However, the risk factors found in our study have been demonstrated previously,[4,31,32] and risk assessment was not the primary objective of the current study. Fourth, CDI cases were identified using administrative diagnostic codes but not confirmed by laboratory data, thus we could not validate the accuracy of the ICD-9-CM codes in NIS data. Nevertheless, studies have shown that ICD-9-CM coding was an accurate indicator of CDI with sensitivity of 82% and specificity of 99% compared to microbiological data,[33] and good correlation has been shown between a *C. difficile* toxin assay and ICD-9-CM coding ($\kappa = .72$).[34] In addition, the similarity of CDI incidence in our study to the published data that used laboratory assays for case ascertainment supports the accuracy of CDI diagnostic administrative codes.[9]

In summary, this large, nationwide study investigating risk factors for CDI in hospitalized leukemia patients identified an overall 3.4% prevalence of CDI but a marked difference between acute and chronic leukemia patients. Leukemia itself was found to be independently associated with CDI, which predicts a higher healthcare burden and higher cost. By independently increasing the risk of mortality in hospitalized leukemia patients, CDI serves as a negative prognostic factor on oncology wards. Gender, race, and admission to teaching hospitals are additional factors that may be explored more in the future to assess their potential impact on CDI risk in these patients.

ACKNOWLEDGMENTS

Financial support: No financial support was provided relevant to this article.

Potential conflicts of interest: All authors report no conflicts of interest relevant to this article.

Address all correspondence to Christian D. Stone, MD, MPH, Associate Professor of Medicine, Section of Gastroenterology and Hepatology, University of Nevada School of Medicine, 2040 W. Charleston Blvd, Suite 300, Las Vegas, NV 89102 (cdstone@unr.edu).

REFERENCES

1. Kelly CP, LaMont JT. *Clostridium difficile*—more difficult than ever. *N Engl J Med* 2008;359:1932–1940.
2. Kyne L, Hamer MB, Polavaram R, Kelly CP. Health care costs and mortality associated with nosocomial diarrhea due to *Clostridium difficile*. *Clin Infect Dis* 2002;34:346–353.
3. Bignard GE. Risk factors for *Clostridium difficile* infection. *J Hosp Infect* 1998;40:1–15.
4. Schalk E, Bohr UR, Konig B, Scheinpflug K, Mohren M. *Clostridium difficile* associated diarrhea, a frequent complication in patients with acute myeloid leukemia. *Ann Hematol* 2010;89:9–14.
5. Cartoni C, Dragoni F, Micozzi A, et al. Neutropenic enterocolitis in patients with acute leukemia: prognostic significance of bowel wall thickening detected by ultrasonography. *J Clin Oncol* 2001; 19:756–761.
6. Ballett JG, Gerding DN. Clinical recognition and diagnosis of *Clostridium difficile* infection. *Clin Infect Dis* 2008;46:S12–S18.
7. Anand A, Glatt AE. *Clostridium difficile* infection associated with antineoplastic chemotherapy: a review. *Clin Infect Dis* 1993;17: 109–113.
8. Agency for Healthcare Research and Quality, Rockville, MD. Nationwide Inpatient Sample (NIS)-HCUP Coding Practices. http://www.hcup-us.ahrq.gov/db/coding.jsp. Published 2008. Accessed January 29, 2015.
9. Spadao F, Gerhardt J, Guimaraes T, et al. Incidence of diarrhea by *Clostridium difficile* in hematologic patients and hematopoietic stem cell transplantation patients: Risk factors for severe forms and death. *Rev Inst Med Trop Sao Paulo* 2014;56:325–331.
10. Alonso CD, Treadway SB, Hanna DB, et al. Epidemiology and outcomes of *Clostridium difficile* infections in hematopoietic stem cell transplant recipients. *Clin Infect Dis* 2012;54:1053–1063.
11. Loo VG, Poirier L, Miller MA, et al. A predominantly clonal multi-institutional outbreak of Clostridium difficile-associated diarrhea with high morbidity and mortality. *N Engl J Med* 2005;353:2442–2449.
12. Cohen SH, Gerding DN, Johnson S, et al. 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 Hosp Epidemiol* 2010;31:431–455.
13. Dubberke ER, Reske KA, Yan Y, Olsen MA, McDonald LC, Fraser VJ. *Clostridium difficile*-associated disease in a setting of endemicity: identification of novel risk factors. *Clin Infect Dis* 2007;45:1543–1549.
14. Gafter-Gvili A, Fraser A, Paul M, Leibovici L. Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients. *Ann Intern Med* 2005;142:979–995.
15. Bucaneve G, Micozzi A, Menichetti F, et al. Grouppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) Infection Program. Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. *N Engl J Med* 2005;353:977–987.
16. Cullen M, Steven N, Billingham L, et al. Simple Investigation in Neutropenic Individuals of the Frequency of Infection after Chemotherapy +/- Antibiotic in a Number of Tumours (SIGNIFICANT) Trial Group. Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. *N Engl J Med* 2005;353:988–998.
17. Pepin J, Saheb N, Coulombe MA, et al. Emergence of fluoroquinolones as the predominant risk factor for *Clostridium difficile* associated diarrhea: a cohort study during an epidemic in Quebec. *Clin Infect Dis* 2005;41:1254–1260.
18. McDonald LC, Killgore GE, Thompson A, et al. An epidemic, toxin gene-variant strain of *Clostridium difficile*. *N Engl J Med* 2005;353:2433–2441.
19. Dettenkofer M, Ebner W, Bertz H, et al. Surveillance of nosocomial infections in adult recipients of allogeneic and autologous

bone marrow and peripheral blood stem-cell transplantation. *Bone Marrow Transpl* 2003;31:795–801.
20. Pant C, Anderson MP, O'Connor JA, Marshall CM, Deshpande A, Sferra TJ. Association of *Clostridium difficile* infection with outcomes of hospitalized solid organ transplant recipients: results from the 2009 Nationwide Inpatient Sample database. *Transpl Infect Dis* 2012;14:540–547.
21. Ali M, Anathakrishnan AN, Ahmad S, Kumar N, Kumar G, Saeian K. *Clostridium difficile* infection in hospitalized liver transplant patients: a nationwide analysis. *Liver Transpl* 2012;18:972–978.
22. Nguyen GC, Kaplan GG, Harris ML, Brant SR. A national survey of the prevalence and impact of *Clostridium difficile* infection among hospitalized inflammatory bowel disease patients. *Am J Gastroenterol 2008*;103:1443–1450.
23. Miller M, Gravel D, Mulvey M, et al. Health care-associated Clostridium difficile infection in Canada: patient age and infecting strain type are highly predictive of severe outcome and mortality. *Clin Infect Dis* 2010;50:194–201.
24. He M, Miyajima F, Roberts P, et al. Emergence and global spread of epidemic healthcare- associated Clostridium difficile. *Nat Genet* 2013;45:109–113.
25. Apostolopoulou E, Raftopoulos V, Terzis K, Elefsiniotis I. Infection probability score: a predictor of *Clostridium difficile*-associated disease onset in patients with haematological malignancy. *Eur J Oncol Nurs* 2011;15:404–409.
26. Rodemann JF, Dubberke ER, Reske KA, Seo Da H, Stone CD. Incidence of *Clostridium difficile* infection in inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2007;5:339–344.
27. Bajaj JS, Ananthakrishnan AN, Hafeezullah M, et al. *Clostridium difficile* is associated with poor outcomes in patients with cirrhosis: A national and tertiary center perspective. *Am J Gastroenterol* 2010;105:106–113.
28. Micek ST, Schramm G, Morrow L, et al. *Clostridium difficile* infection: a multicenter study of epidemiology and outcomes in mechanically ventilated patients. *Crit Care Med* 2013;41:1968–1975.
29. Mitchell BG, Gardner A, Barnett AG, Hiller JE, Graves N. The prolongation of length of stay because of *Clostridium difficile* infection. *Am J Infect Control* 2014;42:164–167.
30. Leung S, Metzger BS, Currie BP. Incidence of *Clostridium difficile* infection in patients with acute leukemia and lymphoma after allogeneic hematopoietic stem cell transplantation. *Infect Control Hosp Epidemiol* 2010;31:313–315.
31. McKinnell JA, Miller LG, Eells SJ, Cui E, Huang SS. A systematic literature review and meta-analysis of factors associated with methicillin-resistant Staphylococcus aureus colonization at time of hospital or intensive care unit admission. *Infect Control Hosp Epidemiol* 2013;34:1077–1086.
32. Pant C, Sferra TJ, Deshpande A, Minocha A. Clinical approach to severe *Clostridium difficile* infection: update for the hospital practitioner. *Eur J Intern Med* 2011;22:561–568.
33. Scheurer DB, Hicks LS, Cook EF, Schnipper JL. Accuracy of ICD-9 coding for *Clostridium difficile* infections: a retrospective cohort. *Epidemiol Infect* 2007;135:1010–1013.
34. Dubberke ER, Reske KA, McDonald LC, Fraser VJ. ICD-9 codes and surveillance for *Clostridium difficile*-associated disease. *Emerg Infect Dis* 2006;12:1576–1579.

APPENDIX. ICD-9 Codes for Leukemia and Its Complications

Disease	ICD-9 Codes
Acute lymphoid leukemia	204.00–204.02
Chronic lymphoid leukemia	204.10–204.12
Acute myeloid leukemia	205.00–205.02
Chronic myeloid leukemia	205.10–205.12
Sepsis	995.90–995.94
Pneumonia	480–486
Urinary tract infection	590.0–590.9

https://doi.org/10.1017/ice.2015.54 Published online by Cambridge University Press