Trends in the Incidence and Outcomes of Hospitalized Cancer Patients With *Clostridium difficile* Infection: A Nationwide Analysis

Arjun Gupta, MBBS^a; Raseen Tariq, MBBS^b; Ryan D. Frank, MS^c; Gary W. Jean, PharmD^d; Muhammad S. Beg, MBBS^{a,e}; Darrell S. Pardi, MD^b; David H. Johnson, MD^a; and Sahil Khanna, MBBS, MS^b

Abstract

Background: Patients with cancer have several risk factors for *Clostridium difficile* infection (CDI), but the impact of CDI on outcomes in this population needs elucidation. We analyzed the incidence of CDI and its impact on outcomes in patients with cancer using the National Hospital Discharge Survey (NHDS) database from 2001 to 2010. **Methods:** Diagnosis codes were used to identify patients with cancer and CDI events. Demographics, diagnoses, length of stay (LOS), and discharge information were abstracted. Multivariate linear and logistic regression models with weighted analysis were conducted to study CDI incidence and CDI-associated outcomes. Analyses were performed using SAS version 9.4. **Results:** During the 10-year study period, 20.1 million discharges had a cancer diagnosis. CDI developed in 1.09% of patients with cancer versus 0.77% of patients without cancer (adjusted odds ratio [aOR], 1.28; 95% CI, 1.28–1.29; $P < .001$). The incidence of CDI in patients with cancer increased during the 10-year study period (64.7 per 10,000 discharges in 2001–2002 to 109.1 in 2009–2010; $P < .001$). In multivariable analysis, compared with patients with cancer without CDI, patients with cancer and CDI had a longer mean LOS (5.67 days; 95% CI, 5.39–5.94) and higher rates of in-hospital mortality (aOR, 1.18; 95% CI, 1.16–1.20) and discharge to a care facility (aOR, 1.74; 95% CI, 1.72–1.75; all $P < .001$). **Conclusions:** In this national database, CDI incidence increased significantly in patients with cancer over the study period and was associated with prolonged hospitalization, increased mortality, and discharge to a care facility. Despite increased attention, CDI remained a serious infection and merits appropriate prevention and management.

J Natl Compr Canc Netw 2017;15(4):466–472

Clostridium difficile infection (CDI) is the most common nosocomial infection in the United States,¹ with increasing recognition in the community.^{2,3} An increase in incidence and severity of CDI has been observed despite increased awareness, prevention strategies, and newer treatment modalities for CDI.^{4–9} Patients with cancer are particularly vulnerable to CDI, which is attributed to traditional risk factors such as age; cancer itself; hospitalization and health care exposure; chemotherapy and its side effects, such as neutropenia; and infection leading to antibiotic exposure.^{4,8} Additionally, graft-versus-host disease (GVHD) has been associated

with CDI.^{10–12} A study using the National Inpatient Sample from 2005 to 2011 reported that patients with leukemia have a 2.6-times higher incidence of CDI than those without leukemia, and that CDI was associated with higher mortality and length of stay (LOS).¹³ A similarly increased rate of CDI has also been reported in stem cell transplant recipients, who have a unique risk factor profile given profound immunosuppression, use of prophylactic antibiotics, mucositis, and GVHD.¹⁴ Although high rates of CDI in patients with cancer have been recognized since the 1980s, the existing literature has focused on CDI in hematologic malignancies.¹⁵ The

From ^aDepartment of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas; ^bDivision of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota; ^cDepartment of Health Sciences and Research, Mayo Clinic, Jacksonville, Florida; ^dDepartment of Pharmacy Practice, Texas Tech University Health Sciences Center School of Pharmacy, Dallas, Texas; and ^eDivision of Oncology, University of Texas Southwestern Medical Center, Dallas, Texas.

Submitted October 25, 2016; accepted for publication December 5, 2016.

The authors have disclosed that they have no financial interests, arrangements, affiliations, or commercial interests with the manufacturers of any products discussed in this article or their competitors.

Abstract was presented at the 2017 ASCO Gastrointestinal Cancers Symposium; January 19–21, 2017; San Francisco, California.

Correspondence: Sahil Khanna, MBBS, MS, Division of Gastroenterology and Hepatology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905. E-mail: khanna.sahil@mayo.edu

epidemiology of CDI in other patients with cancer remains largely understudied.^{16,17} CDI may also be more refractory to standard therapy in patients with cancer than in those without.¹⁸ Thus, elucidating the epidemiology of CDI and its impact on outcomes in patients with cancer is imperative.

We used the National Hospital Discharge Survey (NHDS) database to evaluate the incidence of CDI in patients with both solid organ and hematologic cancers, incidence trends over time, and outcomes in these patients compared with those with cancer without CDI.

Methods

Data Source

The NHDS is a national survey that collects discharge information from nonfederal short-stay hospitals (average LOS, <30 days) conducted annually since 1965.^{19–21} Available information includes patient diagnosis codes, demographics, type of admission (ie, emergent/urgent or elective), LOS, in-hospital mortality, and discharge location. The database is accessible online at <http://www.cdc.gov/nchs/nhds.htm>. All diagnoses are based on ICD-9-CM codes.

Data Collection

Data collected and analyzed included age, sex, race, admission type (urgent/emergent vs elective), hospital characteristics, LOS, discharge location, and mortality for all patients discharged between January 1, 2001, and December 31, 2010. Patients <18 years of age were excluded from analyses.

Definitions of Variables

Patients with cancer, CDI, and those with both diseases were identified by ICD-9-CM diagnosis codes. The codes to capture patients with cancer are presented in supplemental eTable 1 ([available with this article at JNCCN.org](#)). We included both solid and hematologic cancers. The broad categories of solid cancers included gastrointestinal, genitourinary, breast, lung, head and neck, and cranial cancers; melanoma; and Kaposi sarcoma, whereas hematologic cancers included leukemia and lymphoma. Subgroup analyses for solid and hematologic cancers were performed separately, because the epidemiology and outcomes of CDI may be different in these populations. ICD-9-CM code 008.45 was used to

identify patients with CDI, which has been validated in previous studies.^{22–24}

The NHDS classifies discharges into one of several categories: routine and/or discharged home, discharged to a short-term healthcare facility, discharged to a long-term healthcare facility, left against medical advice, death during hospitalization, or unknown discharge status. Patients discharged to healthcare facilities (either short- or long-term) were classified as “discharged to a care facility” (DTCF).

Comorbidities including congestive heart failure, valvular disease, pulmonary circulatory disease, peripheral vascular disease, diabetes mellitus with complications, hypertension, liver disease, and obesity were identified using ICD-9 diagnosis codes and diagnosis-related group codes.

Statistical Analyses

Demographic and clinical data were summarized using frequencies and percentages for categorical variables and means/medians for continuous variables. There were 2 continuous variables reported in our study: age and LOS. We reported the median with age because the median is unbiased. For LOS, we reported the mean because we used a linear regression to analyze LOS, which uses the mean LOS. To determine whether there were any outliers, we repeated the analyses using a logarithmic transformation on LOS and had similar results. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). Weighted analyses were used in all regression models to obtain nationwide estimates and account for the stratified sampling process of the NHDS database.^{19,21}

Wilcoxon rank sum tests and chi-square tests were used to compare medians and proportions, respectively, in patients with any cancer with and without CDI (as in Table 1). Logistic regression (and linear regression for LOS) was used to calculate *P* values adjusted for age, sex, admission type, congestive heart failure, valvular disease, pulmonary circulatory disease, peripheral vascular disease, diabetes mellitus with complications, hypertension, liver disease, and obesity. Logistic regression was also used to examine associations between CDI incidence rates per 10,000 discharges and the presence of cancer diagnoses. Trends in rates of CDI across calendar periods by cancer diagnosis were calculated using a proportional odds model.

Table 1. Demographic Characteristics from the National Hospital Discharge Survey (2001–2010)^{a,b}

	Cancer Patients With CDI (n=0.2 x 10 ⁶)	Cancer Patients Without CDI (n=19.9 x 10 ⁶)	P Value
Median age (interquartile range), y	71 (61–78)	68 (57–77)	<.001
Sex			<.001
Female	49.0%	48.5%	
Age distribution			<.001
18–49	10.8%	13.5%	
50–65	27.1%	31.4%	
>65	62.1%	55.1%	
Race			<.001
White	67.8%	64.4%	
African American	6.1%	10.7%	
Asian	0.7%	1.5%	
Others	3.6%	2.3%	
Not stated	21.7%	21.2%	
Geographic region			<.001
Northeast	26.8%	22.7%	
Midwest	23.5%	22.9%	
South	33.4%	37.1%	
West	16.4%	17.3%	
Admission type			<.001
Emergent/Urgent	75.1%	57.3%	
Elective	18.9%	32.2%	
Not stated	6.0%	10.5%	
Hospital ownership			<.001
Nonprofit	83.0%	78.5%	
Proprietary	6.5%	8.4%	
Government	10.5%	13.2%	
Number of beds			<.001
6–99	11.1%	16.5%	
100–199	18.8%	18.5%	
200–499	52.5%	47.4%	
>500	17.6%	17.6%	

Abbreviation: CDI, *Clostridium difficile* infection.
^aAll data are proportion of cases unless otherwise stated.
^bP value adjusted for age, sex, admission type, congestive heart failure, valvular disease, pulmonary circulatory disease, peripheral vascular disease, diabetes mellitus with complications, hypertension, liver disease, and obesity. There is only one P value per variable because it is testing to see whether there is a difference in proportions between those with CDI and those without. The P value used for the categorical variables was a chi-square test. For the continuous variables, a Wilcoxon test was used.

We used linear regression to examine associations between mean LOS and presence of CDI. Finally, logistic regression was used to determine associations with DTCF and in-hospital mortality. Patients with discharge disposition set to unknown/other discharge status were not included in the discharge analysis. Adjusted P values were calculated for all models using the previously listed adjusters; P<.01 was determined to be statistically significant.

When appropriate, continuous variables were reported as mean or median. Categorical variables were reported as percentages and compared using odds ratios (ORs) and adjusted ORs (aORs), and 95% CIs.

Results
Demographics

An estimated 317.9 million adult hospital discharges were evaluated, with a median age of 58 years (61.0% female, 61.6% white). Overall, 64.8% of admissions were classified as emergent/urgent. There were 20.1 million (6.3%) cancer cases, with a median age of 68 years (48.5% female, 64.5% white). According to primary site, gastrointestinal (4.6 million), lung (3.7 million), lymphoma (2.6 million), prostate (2.1 million), and breast (1.7 million) cancers were the most common. These 20.1 million cancer hospitalizations were regarded as the primary study population.

Incidence Data

Overall, there were 2.2 million (0.7%) CDI cases, of which 0.2 million were in patients with cancer (Table 1). The overall incidence of CDI was 109.5 per 10,000 cancer discharges compared with 66.9 per 10,000 in patients without cancer (aOR, 1.28; 95% CI, 1.28–1.29; P<.001). Significant trends were observed in CDI incidence during the study period (Figure 1). In patients without cancer, the incidence of CDI per 10,000 discharges increased from 49.2 in 2001 to 2002 to 83.1 in 2009 to 2010 (P<.001). For patients with cancer, the incidence of CDI per 10,000 discharges increased from 64.7 in 2001 to 2002 to 109.1 in 2009 to 2010, with a peak of 144.7 in 2007 to 2008 (P<.001).

The median age of patients with cancer with and without CDI was 71 and 68 years, respectively (P<.001). A greater proportion of patients with cancer and CDI were elderly (>65 years of age), white,

Cancer and *Clostridium difficile* Infections

Figure 1. Trends in the incidence of *Clostridium difficile* infection (CDI) in patients with and without cancer during the 10-year study period.

had an emergency/urgent admission versus a routine admission, were admitted in the Northeast, and in medium-sized hospitals (bed size, 200–499) compared with patients with cancer without CDI (Table 1). The highest rates of CDI were seen in patients with leukemia (288.9/10,000 discharges), Kaposi sarcoma (242.9/10,000 discharges), and lymphoma (183.9/10,000 discharges) (supplemental eTable 2). This was followed by gastrointestinal (105.1/10,000 discharges), lung cancer (87.6/10,000 discharges), and head and neck cancers (91.2/10,000 discharges). Patients with intracranial neoplasms (43.2/10,000 discharges) and melanoma (30.3/10,000 discharges) had lower rates of CDI than patients without cancer ($P<.001$; supplemental eTable 2).

Outcomes Data

Outcomes data are presented in Table 2. After adjustment for age, sex, admission urgency, and comorbidities, the mean LOS was 5.67 days longer (95% CI, 5.39–5.94) in patients with cancer and CDI than patients with cancer without CDI ($P<.001$). Patients with cancer and CDI had increased risk of DTCTF (aOR, 1.74; 95% CI, 1.72–1.75) and in-hospital mortality (aOR, 1.18; 95% CI, 1.16–1.20) compared with patients with cancer without CDI (after adjustment; $P<.001$).

There were significant trends in outcomes (LOS, DTCTF, and mortality) over time ($P<.001$ for all; Figure 2). Mean difference in LOS between patients with cancer with and without CDI was highest in 2001 to 2002 (8.14 days), decreased sharply from 2005 to 2008, but then increased to 6.11 days in

2009 to 2010. The aOR for DTCTF was >2.0 in the first and last year category, but more moderate (aOR, 1.1–1.9) from 2003 to 2008. Similarly, patients with CDI were at higher risk of in-hospital mortality in 2001 to 2002 and 2003 to 2004 (aOR, 1.24 and 1.72), but slightly decreased risk in 2005 to 2006 ($P<.001$).

Hematologic Cancers

A total of 4.0 million hospitalizations with a diagnosis of leukemia (1.5 million) and/or lymphoma (2.6 million) occurred in the 10-year study period. These patients' had a median age of 69 years, 44.9% were female, and 67.0% were white. CDI was reported in 890,000 of these admissions with a rate of 288.9 per 10,000 discharges in patients with leukemia and 183.9 per 10,000 discharges in those with lymphoma (supplemental eTable 2). aOR for the incidence of CDI in patients with hematologic malignancies (vs no hematologic malignancy) was 2.40 (95% CI, 2.39–2.42; $P<.001$). In adjusted models, CDI (vs no CDI) was associated with longer mean LOS (6.74 days) and increased risk of in-hospital mortality (aOR, 1.73) and DTCTF (aOR, 1.68) in patients with hematologic malignancies (supplemental eTable 3).

Solid Cancers

A total of 16.2 million hospitalizations with a diagnosis of solid cancer occurred in the 10-year study period. These patients had a median age of 68 years, 49.3% were female, and 63.9% were white. CDI was reported in 133,000 of these admissions, with a rate

Table 2. Comparison of Outcomes^{a,b}

	Cancer Patients With CDI	Cancer Patients Without CDI	OR (95% CI)	Adjusted OR (95% CI)	P Value ^a
Mean length of stay, d	6.22	11.86	Mean difference: 6.01 (5.73, 6.29)	Adjusted mean difference: 5.67 (5.39, 5.94)	$<.001$
All-cause in hospital mortality	9.1%	6.3%	1.50 (1.48, 1.52)	1.18 (1.16, 1.20)	$<.001$
Dismissal to care facility ^b	27.3%	15.4%	2.07 (2.05, 2.09)	1.74 (1.72, 1.75)	$<.001$

Abbreviation: CDI, *Clostridium difficile* infection; OR, odds ratio.

^aP value for the adjusted odds ratio. Adjustment was made for age, sex, admission status, and comorbidities.

^bExcluding patients who left against medical advice, who died, or in whom dismissal status was not reported.

Figure 2. Trends in the outcomes of patients with cancer with *Clostridium difficile* infection. (A) Length of stay. (B) Discharge to care facility. (C) In-hospital mortality.

of 82.0 per 10,000 discharges in patients with solid cancers. In adjusted models, CDI (vs no CDI) was associated with longer mean LOS (4.65 days) and increased risk of DTCF (aOR, 1.74) ([supplemental eTable 4](#)).

Discussion

In this large, national, hospitalized patient sample, patients with cancer had a high rate of CDI with a significant increase in incidence from 2001 to 2010. In patients with cancer, CDI was associated with a longer hospitalization, increased inpatient mortality, and increased likelihood of DTCF compared with patients with cancer without CDI.

Prior studies on the epidemiology of CDI in patients with cancer have largely been limited to hematologic malignancies. A study from the National Institute of Science (NIS) found an almost 5-fold higher incidence of CDI in stem cell transplant recipients and identified GVHD as a specific association with CDI.^{14,25} In our study, patients with leukemia, lymphoma, and Kaposi sarcoma had the highest rates of CDI, likely related to prolonged immunosuppression and high rates of chronic antibiotic use.²⁶

In our study, compared with patients with cancer without CDI, those with CDI were more likely to be older, white, and from the Northeast. Age is a known risk factor for CDI,²¹ and higher rates of CDI in whites and the Northeast have been demonstrated previously in the NHDS.^{27,28} CDI rates were

also related to admission status (elective vs not) with patients with cancer and CDI more likely to have emergent/urgent admissions. The rate of CDI in patients with cancer increased overall during the study period, with a peak incidence in 2007 to 2008. Unique environmental sources of CDI in these patients must be considered, because this was observed despite nationwide inpatient prevention strategies. Recent increases in CDI incidence have also been linked to the introduction of more sensitive molecular diagnostic tests (nucleic acid amplification tests or polymerase chain reaction), which detect microbial DNA instead of the toxin itself.²⁹ Because the method of CDI diagnosis was not available in the NHDS, whether the increase in incidence is also related to this is unclear.

In our study, CDI was associated with longer LOS, increased mortality, and DTCE, highlighting the burden that CDI places on patients with cancer. Given the cross-sectional data and lack of data on temporal association, it is plausible that cancer might have led to worse CDI outcomes (vs the hypothesis that CDI worsened cancer outcomes). Using the 2011 NIS database, Kassam et al³⁰ developed a novel *C difficile*-associated risk of death score (CARDS) to predict the risk of mortality in hospitalized patients with CDI, and malignancy was a component of that score, contributing 2 points to a maximum overall score of 19. A study over 7 years covering 186 US hospitals found that cancer was a predictor of longer LOS in hospitalized patients with CDI.³¹ Malignancy has also been shown to be an independent risk factor for CDI recurrence,³² and we were unable to differentiate the first episode versus recurrence of CDI in this study. Poor outcomes may be due to patients with cancer responding less well to standard anti-CDI therapy, including vancomycin.¹⁸ The longer LOS in our study may also represent increased opportunity to acquire CDI, because LOS increases the risk of contracting hospital-acquired infections.^{33,34} Trends in outcomes over the study period reveal a U-shaped relationship with time; the adjusted mean difference

in LOS was at its lowest point during the middle period of the study; it then worsened during the latter part of the study period. The odds of mortality and DTCE in patients with cancer and CDI also hit a nadir in 2005 to 2006. This could be epidemiologically related to the rapid spread of hypervirulent *C difficile* strains over the latter part of the past decade, which contributed to worse outcome during this time.^{2,35}

Our study has important limitations. Although we included all hospitalized patients from the NHDS database, this national survey only represents approximately 1% of all hospitalizations in the United States. Given the nature of the study's cross-sectional design, longitudinal follow-up could not be assessed. We likely underestimated the overall CDI burden, because we solely studied inpatient CDI; a large group of patients with prior healthcare exposure are diagnosed with CDI outpatient. Because the NHDS does not individually identify patients, over the course of the study a patient could appear in the data set multiple times, potentially leading to hierarchical clustering of data. We did not have information about the duration, stage, or treatment modality used (including chemotherapy) for most cancers, or the severity of CDI. We also lacked details on recent antibiotic exposure, CDI treatment, strain type, detection method, or route of CDI acquisition (ie, community- versus hospital-acquired).

Conclusions

Our data support that CDI occurs in higher rates in patients with cancer and is associated with worse morbidity and mortality. Appropriate prevention strategies, treatment, and close clinical follow-up are thus warranted.

Acknowledgments

Drs. Gupta and Khanna had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Magill SS, Edwards JR, Bamberg W, et al. Multistate point-prevalence survey of health care-associated infections. *N Engl J Med* 2014;370:1198–1208.
2. Gupta A, Khanna S. Community-acquired *Clostridium difficile* infection: an increasing public health threat. *Infect Drug Resist* 2014;7:63–72.
3. Khanna S, Pardi DS, Aronson SL, et al. The epidemiology of community-acquired *Clostridium difficile* infection: a population-based study. *Am J Gastroenterol* 2012;107:89–95.
4. Cohen SH, Gerding DN, Johnson S, et al. 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.

5. Evans CT, Safdar N. Current trends in the epidemiology and outcomes of *Clostridium difficile* infection. *Clin Infect Dis* 2015;60(Suppl 2):S66–71.
6. Khanna S, Pardi DS. The growing incidence and severity of *Clostridium difficile* infection in inpatient and outpatient settings. *Expert Rev Gastroenterol Hepatol* 2010;4:409–416.
7. Slimings C, Armstrong P, Beekingham WD, et al. Increasing incidence of *Clostridium difficile* infection, Australia, 2011–2012. *Med J Aust* 2014;200:272–276.
8. Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections. *Am J Gastroenterol* 2013;108:478–498; quiz 499.
9. Taylor G, Gravel D, Matlow A, et al. Assessing the magnitude and trends in hospital acquired infections in Canadian hospitals through sequential point prevalence surveys. *Antimicrob Resist Infect Control* 2016;5:19.
10. Raza S, Baig MA, Russell H, et al. *Clostridium difficile* infection following chemotherapy. *Recent Pat Antiinfect Drug Discov* 2010;5:1–9.
11. Selvey LA, Slimings C, Joske DJ, Riley TV. *Clostridium difficile* Infections amongst patients with haematological malignancies: a data linkage study. *PLoS One* 2016;11:e0157839.
12. Dubberke ER, Reske KA, Srivastava A, et al. *Clostridium difficile*-associated disease in allogeneic hematopoietic stem-cell transplant recipients: risk associations, protective associations, and outcomes. *Clin Transplant* 2010;24:192–198.
13. Luo R, Greenberg A, Stone CD. Outcomes of *Clostridium difficile* infection in hospitalized leukemia patients: a nationwide analysis. *Infect Control Hosp Epidemiol* 2015;36:794–801.
14. Guddati AK, Kumar G, Ahmed S, et al. Incidence and outcomes of *Clostridium difficile*-associated disease in hematopoietic cell transplant recipients. *Int J Hematol* 2014;99:758–765.
15. Heard SR, Wren B, Barnett MJ, et al. *Clostridium difficile* infection in patients with haematological malignant disease. Risk factors, faecal toxins and pathogenic strains. *Epidemiol Infect* 1988;100:63–72.
16. Han XH, Du CX, Zhang CL, et al. *Clostridium difficile* infection in hospitalized cancer patients in Beijing, China is facilitated by receipt of cancer chemotherapy. *Anaerobe* 2013;24:82–84.
17. Hebbard AI, Slavin MA, Reed C, et al. The epidemiology of *Clostridium difficile* infection in patients with cancer. *Expert Rev Anti Infect Ther* 2016;14:1077–1085.
18. Cornely OA, Miller MA, Fantin B, et al. Resolution of *Clostridium difficile*-associated diarrhea in patients with cancer treated with fidaxomicin or vancomycin. *J Clin Oncol* 2013;31:2493–2499.
19. Gupta A, Pardi DS, Baddour LM, Khanna S. Outcomes in children with *Clostridium difficile* infection: results from a nationwide survey. *Gastroenterol Rep (Oxf)* 2016;4:293–298.
20. Keddis MT, Khanna S, Noheria A, et al. *Clostridium difficile* infection in patients with chronic kidney disease. *Mayo Clin Proc* 2012;87:1046–1053.
21. Khanna S, Gupta A, Baddour LM, Pardi DS. Epidemiology, outcomes, and predictors of mortality in hospitalized adults with *Clostridium difficile* infection. *Intern Emerg Med* 2016;11:657–665.
22. 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.
23. 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.
24. Dubberke ER, Butler AM, Yokoe DS, et al. Multicenter study of surveillance for hospital-onset *Clostridium difficile* infection by the use of ICD-9-CM diagnosis codes. *Infect Control Hosp Epidemiol* 2010;31:262–268.
25. Rodriguez Garzotto A, Merida Garcia A, Munoz Unceta N, et al. Risk factors associated with *Clostridium difficile* infection in adult oncology patients. *Support Care Cancer* 2015;23:1569–1577.
26. Yoshida M, Ohno R. Current antimicrobial usage for the management of infections in leukemic patients in Japan: results of a survey. *Clin Infect Dis* 2004;39(Suppl 1):S11–14.
27. Argamany JR, Aitken SL, Lee GC, et al. Regional and seasonal variation in *Clostridium difficile* infections among hospitalized patients in the United States, 2001–2010. *Am J Infect Control* 2015;43:435–440.
28. Argamany JR, Delgado A, Reveles KR. *Clostridium difficile* infection health disparities by race among hospitalized adults in the United States, 2001 to 2010. *BMC Infect Dis* 2016;16:454.
29. Polage CR, Gyorke CE, Kennedy MA, et al. Overdiagnosis of *Clostridium difficile* infection in the molecular test era. *JAMA Intern Med* 2015;175:1792–1801.
30. Kassam Z, Cribb Fabersunne C, Smith MB, et al. *Clostridium difficile* associated risk of death score (CARDS): a novel severity score to predict mortality among hospitalised patients with *C. difficile* infection. *Aliment Pharmacol Ther* 2016;43:725–733.
31. Campbell R, Dean B, Nathanson B, et al. Length of stay and hospital costs among high-risk patients with hospital-origin *Clostridium difficile*-associated diarrhea. *J Med Econ* 2013;16:440–448.
32. Chung MS, Kim J, Kang JO, Pai H. Impact of malignancy on *Clostridium difficile* infection. *Eur J Clin Microbiol Infect Dis* 2016;35:1771–1776.
33. Tess BH, Glenister HM, Rodrigues LC, Wagner MB. Incidence of hospital-acquired infection and length of hospital stay. *Eur J Clin Microbiol Infect Dis* 1993;12:81–86.
34. Klevens RM, Edwards JR, Richards CL Jr, et al. Estimating health care-associated infections and deaths in U.S. hospitals, 2002. *Public Health Rep* 2007;122:160–166.
35. Goorhuis A, Bakker D, Corver J, et al. Emergence of *Clostridium difficile* infection due to a new hypervirulent strain, polymerase chain reaction ribotype 078. *Clin Infect Dis* 2008;47:1162–1170.

See JNCCN.org for supplemental online content.