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Epidemiology, outcomes, and predictors of mortality in hospitalized adults with *Clostridium difficile* infection

Sahil Khanna[1] · Arjun Gupta[2,4] · Larry M. Baddour[2,3] · Darrell S. Pardi[1]

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Abstract Studies have demonstrated an increasing *Clostridium difficile* infection (CDI) incidence in hospitals and the community, with increasing morbidity and mortality. In this study, we analyzed data from the National Hospital Discharge Survey (NHDS) to evaluate CDI epidemiology, outcomes, and predictors of mortality in hospitalized adults. We identified cases of CDI (and associated comorbid conditions) from NHDS data from 2005 through 2009 using ICD-9 codes. Weighted univariate and multivariate analyses were performed to ascertain CDI incidence, associations between CDI and outcomes [length of stay (LOS), colectomy, all-cause in-hospital mortality, and discharge to a care facility], and predictors of all-cause in-hospital mortality. Of an estimated 162 million adult inpatients, 1.26 million (0.8 %) had CDI. The overall CDI incidence is 77.8/10,000 hospitalizations, with no statistically significant change over the study period. On multivariate analysis, after adjusting for age, gender, and comorbid conditions, CDI is an independent predictor of longer LOS (mean difference, 2.35 days), all-cause mortality [odds ratio (OR) 1.45], colectomy (OR 1.41), and discharge to a care facility (OR 2.12) (all $P < 0.001$). Elderly patients have a higher CDI incidence and worse outcomes than younger adults. The strongest predictors of all-cause mortality in patients with CDI include age 65 years or older, colectomy, and coagulation abnormalities. Despite stable CDI incidence and advances in management, CDI is associated with increased LOS, colectomy, all-cause in-hospital mortality, and discharge to a care facility in hospitalized, especially elderly, adults. Age older than 65 years should be added to the severity criteria for CDI.

Keywords *Clostridium difficile* infection · Diarrhea · Epidemiology · Mortality · Outcomes research

Abbreviations

CDI	*Clostridium difficile* infection
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
LOS	Length of stay
NHDS	National Hospital Discharge Survey
OR	Odds ratio

Introduction

Clostridium difficile is the most common cause of infectious diarrhea in hospitalized adults in the United States [1, 2]. It is now more common than methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococcus [2]. Risk factors associated with *C. difficile* infection (CDI) include hospitalization, advanced age, antibiotic

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✉ Sahil Khanna
khanna.sahil@mayo.edu

[1] Division of Gastroenterology and Hepatology, Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA

[2] Division of Infectious Diseases, Mayo Clinic, Rochester, MN, USA

[3] Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA

[4] Present Address: Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX, USA

exposure, comorbid conditions, and gastrointestinal surgery or procedures [3–5].

Clinical data generated from research investigations and by infection control and prevention departments throughout the United States have been striking, with increasing incidence and severity of CDI [3, 6–13]. The incidence of health care-acquired CDI increased 2- to 2.5-fold from the late 1990s to the early 2000s, with an even higher increase among the elderly [11, 14]. More recently, CDI is now recognized as a common cause of diarrhea in the community; 40 % of patients with community-acquired CDI in one study required hospitalization [15, 16].

Rates of CDI-related complications such as recurrent CDI, severe and severe-complicated CDI, colectomy, and death related to CDI have also increased significantly [11, 17–20]. The US Centers for Disease Control and Prevention estimates that 29,000 deaths annually in the United States are attributed to CDI [21]. However, the predictors of mortality in this population are not completely known. With more aggressive management, CDI is less severe and has a lower mortality, as shown in a recent single-center study [22].

In the current study, we aimed to evaluate national trends in CDI incidence and outcomes, including length of hospital stay, all-cause in-hospital mortality, colectomy, and dismissal to a short- or long-term care facility in adult patients during a 5-year period. Additionally, we evaluated predictors of mortality in hospitalized patients with CDI.

Methods

Data source

The National Hospital Discharge Survey (NHDS) has been conducted annually since 1965. It collects hospital discharge information from nonfederal short-stay hospitals [defined as an average length of stay (LOS) <30 days] throughout the United States with a stratified random-sampling process. The NHDS database contains diagnosis and procedure codes, demographics, admission type, LOS, all-cause in-hospital mortality, and dismissal information. Diagnoses are based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. This database served as the data source for our study.

Selection of cases

We searched the NHDS database for the records of all adult inpatients (age ≥18 years) from 2005 through 2009. Patients for whom an ICD-9-CM code of 008.45 was listed as primary or additional diagnosis (2005–2009) or admitting diagnosis (2008–2009) were classified as having CDI. Since, NHDS does not include patient identifiers, it is likely that patients who were admitted for CDI more than once were included twice or more.

Demographics

For all patients included in the study, demographic data were obtained. Demographics collected by the database include age, sex, and race, which is classified as white, black/African American, American Indian/Alaskan native, Asian, native Hawaiian/other Pacific islander, other, multiple race indicated, or unknown.

Admission and discharge information

Hospitalizations were classified according to geographic area of the United States: Northeast, Midwest, South, and West. In the NHDS, hospital admissions in adult patients are characterized as emergency, urgent, elective, or not available. Hospitalizations were classified by month and year from 2005 through 2009.

The type of hospital discharge was classified as routine or discharged home, discharged to a short-term health care facility, discharged to a long-term health care facility, unknown discharge status, left against medical advice, or death during hospitalization. To analyze the likelihood of dismissal to a care facility, patients who were discharged to a short- or long-term health care facility were combined and compared with patients who had a routine or home dismissal. Patients who died in the hospital or for whom dismissal information was not available were excluded from this aspect of the analysis.

Incidence

The proportion of CDI cases and CDI incidence were calculated to examine differences between races, geographic regions, admission types, discharge years, and discharge months. CDI incidence was calculated as number of cases per 10,000 hospitalizations.

Colectomy

The ICD-9-CM codes used to determine which patients underwent partial or total colectomy included 45.71, 45.72, 45.73, 45.74, 45.75, 45.76, 45.8, 45.81, 45.82, and 45.83, similar to previous studies [23, 24]. The incidence of colectomy was compared between patients with and without CDI.

Length of stay

Hospital LOS data were abstracted electronically and used to calculate differences in LOS among patients with and without CDI.

All-cause in-hospital mortality

Death during hospitalization (all-cause in-hospital mortality) was analyzed as a separate clinical outcome, to evaluate the contribution of CDI to overall mortality. In addition, among all patients with CDI, univariate and multivariate analyses were performed to elucidate predictors of mortality, adjusting for age, gender, and all comorbidities from the Elixhauser comorbidity index.

Comorbid conditions

Patients' comorbid conditions were abstracted from the NHDS database using guidelines from the Healthcare Cost and Utilization Project. Comorbid conditions were assigned using the validated Elixhauser comorbidity index and used for statistical analyses in multivariate models [25].

Statistical analyses

Data extraction and statistical analysis were carried out using SAS software version 9.2 and JMP Pro 11.2.1 (SAS Institute, Inc). The summary database was converted to a JMP file. Weighted analysis was performed throughout to obtain nationwide estimates and to account for the stratified sampling process of the NHDS database. The proportion of CDI cases and CDI incidence were calculated to examine differences between races, geographic regions, admission types, discharge years, and discharge months. Clinical, demographic, and outcomes data were analyzed using the *t* test for normally distributed continuous variables and the Wilcoxon rank sum test for non-normally distributed variables (e.g., age and LOS).

For comparison of continuous data among several groups, analysis of variance was used if the data were normally distributed, and the Kruskal–Wallis test was used if data were skewed. Continuous variables are reported as mean or median (range), as appropriate. Categorical variables are reported as percentages and compared using odds ratios (ORs) and 95 % CIs. Multivariate logistic and linear regression models with weighted analyses were used to analyze the effect of age, gender, and comorbid conditions on CDI-associated outcomes. *P* values of 0.01 or less were considered statistically significant because of the large sample size.

Results

Patient characteristics

From 2005 through 2009, the NHDS database includes an estimated 162 million hospital discharges of adult patients; the median age is 58 years (range 18–99 years), and 60.7 % are women. Overall, 73.3 % of admissions were classified as urgent or emergent. The median LOS is 3 days (range 1–406 days), and 16.0 % of all patients are discharged to a short- or long-term care facility. The overall rate of colectomy is 0.7 %, and overall all-cause in-hospital mortality is 2.3 %.

Among the group of 162 million, there are an estimated 1.26 million cases of CDI (0.8 %), for an overall incidence of 77.8/10,000 hospitalizations (Table 1). The annual CDI incidence rate varies from 69 to 87 cases per 10,000 hospitalizations over the study period, with no significant temporal trend ($P = 0.77$) (Fig. 1). There is no significant variation in CDI incidence by month of the year ($P = 0.08$) (Fig. 2).

Among patients with CDI, no significant trends are seen over the study period in the rates of colectomy, in-hospital mortality, LOS, or dismissal to a care facility (Fig. 3). Among geographic regions, the Northeast has the highest incidence of CDI in hospitalized patients, followed by the Midwest (Table 1). There is a significantly higher incidence of CDI among whites and in emergent or urgent hospital admissions (Table 1).

Outcomes of CDI

The median LOS among all hospitalized adults is 3 days. Patients with CDI have a median LOS of 7 days, compared with 3 days in patients without CDI. After adjusting for comorbid conditions, CDI is the strongest independent predictor of increased LOS (Table 2). The overall rate of colectomy for all hospitalized patients is 0.7 %. After adjusting for comorbid conditions, CDI is independently associated with colectomy in hospitalized patients (Table 2). The overall rate of dismissal to a short- or long-term care facility is 16 %. After adjusting for comorbid conditions, CDI is an independent predictor of discharge to a long- or short-term care facility (Table 2). Overall in-hospital mortality is 2.3 %. After adjusting for comorbid conditions, CDI is an independent predictor of all-cause in-hospital mortality (Table 2).

Predictors of mortality

Overall all-cause in-hospital mortality in patients with CDI is 6.9 %. On univariate analysis, patients with CDI who die

Table 1 Patient characteristics

Characteristic	Patient group[a]		*P* value[b]	CDI incidence/10,000 hospitalizations	*P* value[c]
	CDI ($n = 126 \times 10^6$)	No CDI ($n = 161 \times 10^6$)			
Median age (year)	75	58	<0.001	77.8	…
Sex			<0.001		<0.001
Men	40.7	39.3		80.8	
Women	59.3	60.7		76.1	
Age (year)			<0.001		<0.001
18–64	29.7	58.8		39.5	
≥65	70.3	41.2		132.4	
Race			<0.001		<0.001
White	85.5	78.4		87.2	
Black	9.9	16.3		48.9	
Asian	1.3	2.0		51.6	
Others[d]	3.3	3.3		77.8	
Geographic region			<0.001		<0.001
Northeast	29.7	21.5		107.2	
Midwest	24.3	23.2		81.9	
South	30.8	37.1		64.7	
West	15.2	18.2		65.2	
Admission type			<0.001		<0.001
Emergent/urgent	39.7	72.4		95.3	
Elective	23.2	19.4		38.8	
Unknown	7.1	8.2		48.2	

CDI Clostridium difficile infection

[a] All values are proportion of cases, unless otherwise stated

[b] Comparing patients with and without CDI

[c] Comparing incidence in the various groups

[d] Includes patients for whom race was not stated or multiple races were indicated for the same patient

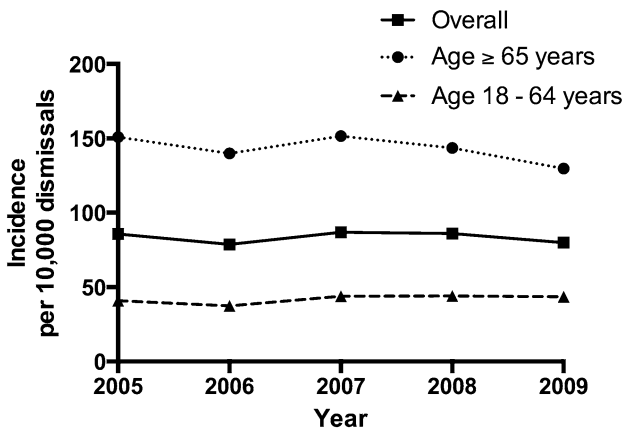

Fig. 1 Incidence rates of *Clostridium difficile* infection (CDI) per calendar year. Graph shows CDI incidence rates from 2005 to 2009 overall and by age group. The incidence is higher in the older (age ≥ 65 year) compared with the younger (18–64 year) population, with no substantial variation over the study period

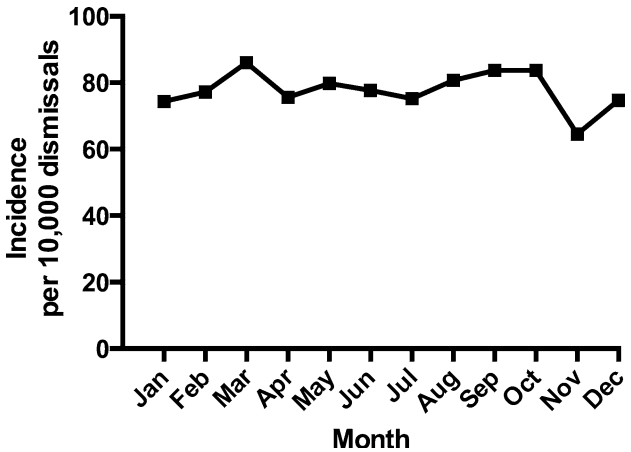

Fig. 2 Incidence rates of *Clostridium difficile* infection (CDI) per calendar month of dismissal. No trend in CDI incidence is seen among calendar months from 2005 to 2009

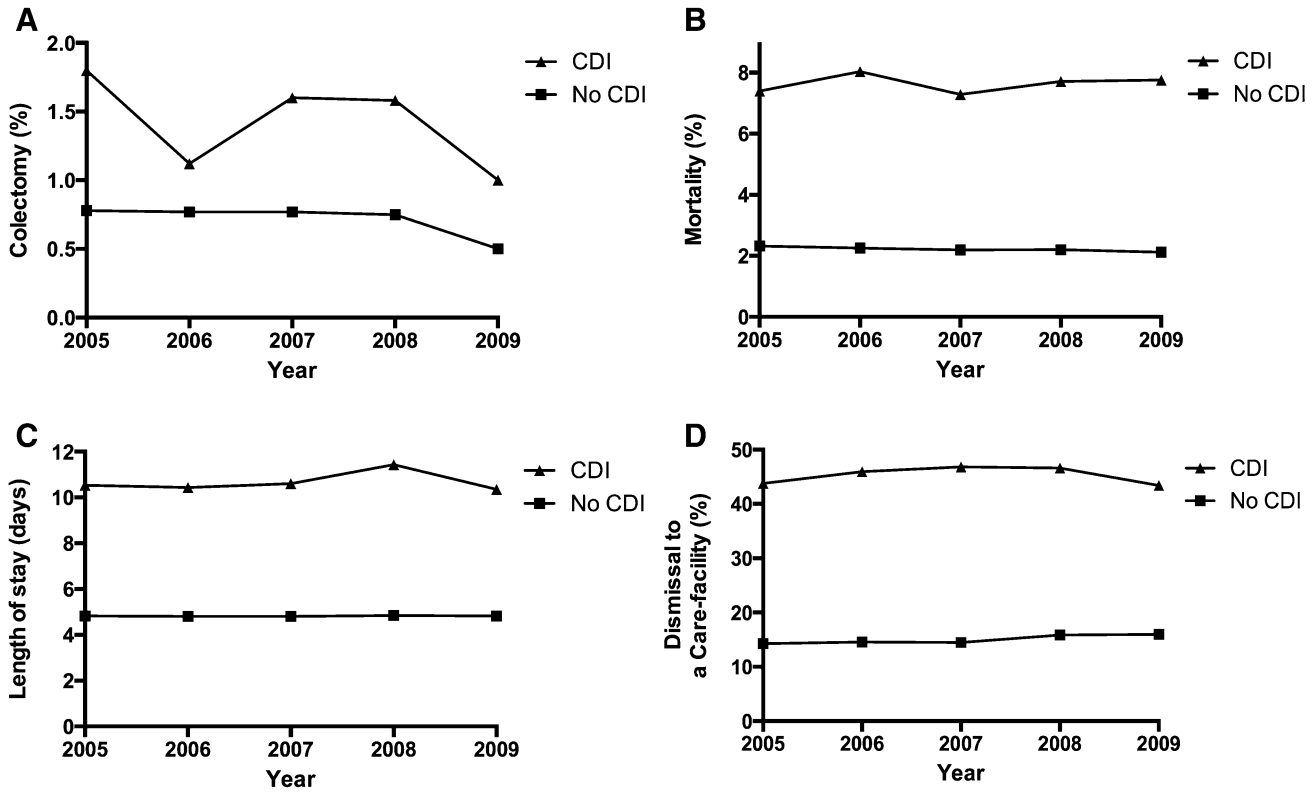

Fig. 3 Outcomes of *Clostridium difficile* infection (CDI) per calendar year. Graphs depicting incidence of colectomy (**a**), all-cause in-hospital mortality (**b**), length of stay (LOS) (**c**), and dismissal to a care facility (**d**) in patients with and without CDI. No temporal trends were seen

Table 2 Outcomes in patients with and without CDI

Outcome	Patient group		OR (95 % CI)		*P* value[a]
	CDI ($n = 1.26 \times 10^6$)	No CDI ($n = 161 \times 10^6$)	Unadjusted	Adjusted	
Median length of stay (day)	7	3		2.35[b] (2.30–2.40)	<0.001
All-cause in-hospital mortality (%)	6.9	2.2	3.22 (3.2–3.3)	1.45 (1.4–1.6)	<0.001
Colectomy (%)	1.3	0.7	1.87 (1.8–1.9)	1.41 (1.39–1.43)	<0.001
Dismissal to care facility (%)[c]	43.6	15.8	4.1 (4.0–4.2)	2.12 (2.10–2.13)	<0.001

CDI Clostridium difficile infection, *OR* odds ratio

[a] *P* value of the adjusted OR. Adjustment was made for age, sex, and comorbid conditions

[b] Adjusted mean difference

[c] Excluding patients who left against medical advice, died, or for whom dismissal status was not reported

in the hospital are older (median age, 80 vs 75 years, $P < 0.001$) and have a longer median LOS (9 vs 7 days, $P < 0.001$) than those who survive. In-hospital mortality in patients with CDI is 8.5 % for those age 65 years or older, compared with 3 % in those younger than 65 years (OR 3.0; 95 % CI 2.4–3.8). There are no differences in mortality on the basis of gender or race. Mortality is lower for routine admissions than for urgent or emergent admissions (3.3 vs 7.4 %; OR 0.42; 95 % CI 0.40–0.43). During the hospitalization, patients who undergo colectomy have a higher mortality (17.3 vs 6.8 %; OR 2.9; 95 % CI 2.7–3.0; $P < 0.001$).

Conditions assigned using the Elixhauser comorbidity index, that are associated (by multivariate logistic regression) with significantly increased mortality among patients with CDI include heart failure, pulmonary circulation disorders (pulmonary hypertension and pulmonary embolism), metastatic cancer, lymphoproliferative disorders, coagulation abnormalities, electrolyte imbalance, and weight loss (all $P < 0.001$). In contrast, valvular heart disease, chronic

lung disease, peripheral vascular disease, diabetes mellitus, hypothyroidism, liver disease, and obesity are not associated with high mortality.

On multivariate analyses, age 65 years or older (adjusted OR 3.51; 95 % CI 3.44–3.59; $P < 0.001$) is the strongest predictor of mortality, followed by colectomy (adjusted OR 3.14; 95 % CI 3.01–3.28; $P < 0.001$) and coagulation abnormalities, likely signifying hemodynamic compromise and possible sepsis (adjusted OR 2.19; 95 % CI 2.12–2.28; $P < 0.001$).

CDI in the elderly

Patients aged 65 years or older have a more than three times higher incidence of CDI compared with patients younger than 65 years (Table 1), whereas patients aged 85 years or older have more than 4 times the incidence. On univariate analysis, elderly patients (age ≥65 years) with CDI have worse outcomes than younger adults with CDI, including a longer median LOS, higher all-cause in-hospital mortality, and need for dismissal to a care facility (Table 3). After adjusting for gender and comorbid conditions, age 65 years or older remain associated with these worse outcomes (Table 3). Elderly patients with CDI have a similar rate of colectomy as younger adults with CDI before and after adjusting for gender and comorbid conditions (Table 3).

Discussion

Clostridium difficile infection is the most common hospital-acquired infection, with disease severity ranging from mild diarrhea to fulminant colitis. CDI is associated with an increasing morbidity, mortality, and economic burden over the past 2 decades [1, 3]. On the basis of our findings from the NHDS database, CDI is associated with poor outcomes, and hospitalized patients with CDI are more likely to undergo colectomy, and to have a prolonged LOS, higher in-hospital mortality, and a higher likelihood of dismissal to a short- or long-term care facility. After adjusting for comorbid conditions, CDI remains the strongest independent predictor of adverse outcomes in hospitalized patients. Hospital LOS has a dual relationship with CDI, since increased hospital LOS is a well-known risk factor for CDI, and patients with CDI tend to stay longer in the hospital. Therefore, it is difficult to separate cause from effect in this association.

The incidence of hospital-acquired CDI increased several fold from the late 1990s to the early 2000s compared with earlier periods [7, 8, 11]. Increasing incidence and outbreaks of CDI are reported from all over the world, with the highest incidence in the elderly [14, 26–28]. In Canada, the incidence rate for CDI in adult patients admitted to hospitals is 4.6 cases per 1000 admissions [29]. CDI-related hospitalizations increased by 23 % per year from 2000 to 2005, but from 2005 through 2006, the rate increased by only 6.7 % [30, 31]. With advances in CDI testing, several laboratories have adapted to polymerase chain reaction (PCR) testing, which is more sensitive than enzyme immunoassay, which can increase CDI incidence both in the inpatient and outpatient settings. In our study, the incidence of CDI in hospitalized patients did not change significantly from 2005 to 2009.

Rates of colectomy, LOS, and mortality related to CDI have increased considerably [17]. It is estimated that CDI may add 3–20 patient-days to hospital stays, with an attributed cost of over $1 billion US per year [32–35]. A retrospective study shows increased CDI incidence and LOS in intensive care settings from 1986 through 2001 [36]. In our study, patients with CDI have a longer LOS, with a median difference of 4 days. After statistical adjustment for age, gender, and more than 25 comorbid conditions, CDI is the strongest predictor of increased hospital LOS. In a French study, it is estimated that the mean extra cost per stay with CDI is €9575 and the extra cost of CDI in public acute-care hospitals is to €163.1 million at the national level, of which 12.5 % is attributed

Table 3 Outcomes in patients with CDI stratified by age

Outcome	Age (year)		OR (95 % CI)		*P* value[a]
	≥65 ($n = 8.9 \times 10^5$)	18–64 ($n = 3.7 \times 10^5$)	Unadjusted	Adjusted	
Median length of stay (day)	8	7		0.7[b] (0.4–0.9)	<0.001
All-cause in-hospital mortality (%)	8.5	3.0	3.0 (2.4–3.8)	3.1 (2.5–3.9)	<0.001
Colectomy (%)	1.3	1.3	1.0 (0.7–1.5)	1.1 (0.8–1.6)	0.7
Dismissal to care facility (%)[c]	53.7	21.6	4.2 (3.8–4.7)	4.1 (3.7–4.6)	<0.001

CDI Clostridium difficile infection, *OR* odds ratio

[a] *P* value of the adjusted OR. Adjustment was made for age, sex, and comorbid conditions

[b] Adjusted mean difference

[c] Excluding patients who left against medical advice, died, or for whom dismissal status was not reported

to recurrent CDI [37]. In a German study, mean length of stay is high at 32 days in primary CDI, compared to 94 days in recurrent CDI to 24 days in controls, resulting in mean overall direct treatment costs per patient of €18,460 in primary CDI, €73,900 in recurrent CDI and €14,530 in controls [38]. In our study, CDI is associated with high colectomy rates, similar to prior studies [39, 40]. Of interest, colectomy rates do not differ in the elderly population compared with younger patients, even after adjusting for comorbid conditions; this could indicate that clinicians may be hesitant to perform surgery in elderly patients.

In a retrospective cohort study that examined national inpatient data, CDI mortality increases by 2.5-fold from 1993 to 2003 [41]. Mortality attributed to CDI is higher in nursing home patients (sevenfold) than in hospitalized patients (4.5-fold), and a higher mortality (3.5-fold) was seen in elderly patients compared with younger patients [28, 42]. In our study, elderly hospitalized patients with CDI have significantly worse outcomes than younger patients with CDI. The mortality attributable to CDI is as high as 6.9 % in different studies [9, 12, 43, 44]. A significant temporal trend in the attributable mortality to CDI is observed in several studies, with 4- to 6-fold changes in CDI-related mortality [42, 45]. In contrast, a recent study demonstrates that CDI from 2009 to 2011 is less severe, and is associated with better outcomes and decreased mortality compared with the years 2006–2008 [22]. CDI is associated with an increased mortality in our study, with CDI being the strongest independent predictor of mortality, but there was no significant change in mortality over the study period.

Predictors of mortality in patients with CDI are described in smaller studies. One study demonstrates increasing age, heart failure, and respiratory failure to be significant risk factors associated with mortality in patients with CDI [46]. Another study shows severe and severe-complicated CDI to be a risk factor for CDI-associated mortality [47]. Similarly, a systematic review demonstrates that mortality is associated with older age, comorbid conditions, hypoalbuminemia, leukocytosis, acute renal failure, and infection with ribotype 027 [48]. In our study, the strongest predictors of all-cause mortality in patients with CDI includes age 65 years or older, colectomy, and coagulation abnormalities.

Our study has several limitations. The data were collected as part of a large national survey, and longitudinal follow-up of patients is not available. Information on potential confounders, such as CDI colonization versus true infection, antibiotic exposure, CDI treatment, *C. difficile* strain, hospital-acquired versus community-acquired CDI, and important laboratory parameters and treatments are lacking. Additionally, it is not possible to distinguish between recurrent and primary CDI, and readmissions for CDI may be counted more than once in the dataset. The NHDS collects only cases from short-stay hospitals, and therefore outpatients and patients being treated in long-term hospitals were excluded from the analysis. The comorbid conditions used for adjustment were based on ICD-9-CM coding and may have lacked precision, which may have affected our findings. The diagnosis of CDI also was made by ICD-9-CM code rather than by clinical symptoms and positive stool assay results. Nevertheless, the ICD-9-CM code for CDI correlates with results of the *C. difficile* toxin assay [49, 50].

Conclusions

Despite advancements and interest in infection control and management, CDI remains a major problem in hospitalized patients, and is an independent predictor of increased LOS, mortality, and likelihood of dismissal to a short- or long-term care facility. Elderly patients with CDI have an increased risk of adverse events, including in-hospital mortality, compared with younger patients with CDI. Therefore, age older than 65 years should be added to the severity criteria for CDI. Several actions are needed to help prevent adverse outcomes and decrease the spread of infection. These actions include more aggressive policies in infection prevention and control, antimicrobial stewardship, and enhanced education to augment the early recognition and prompt treatment of CDI.

Compliance with ethical standards

Conflict of interest SK has served as a consultant to Cubist Pharmaceuticals (Now Merck) in the past and DSP is a consultant for Cubist Pharmaceuticals (Now Merck) and Seres Therapeutics, both related to *C. difficile* infection, but the relationship is unrelated to the work in this manuscript.

Statement of human and animal rights This study was performed using available data from the National Hospital Discharge Survey. No identifiable patient level data was accessed. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was not required as the research was conducted using data collected by the National Hospital Discharge Survey (NHDS) which has a consent waiver. Data collected in the NHDS are consistent with the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA). No personally identifying information, such as patient's name, address, or Social Security number, is collected in the NHDS.

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