American Journal of Infection Control 42 (2014) 1028-32

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Major article

The rise in *Clostridium difficile* infection incidence among hospitalized adults in the United States: 2001-2010

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Key Words:
Mortality
Length of stay
Epidemiology

Background: *Clostridium difficile* infection (CDI) incidence is a growing concern. This study provides national estimates of CDI over 10 years and identifies trends in mortality and hospital length of stay (LOS) among hospitalized adults with CDI.

Methods: We conducted a retrospective analysis of the US National Hospital Discharge Surveys from 2001-2010. Eligible cases included adults aged ≥18 years discharged from a hospital with an ICD-9-CM diagnosis code for CDI (008.45). Data weights were used to derive national estimates. CDI incidence rates were depicted as CDI discharges per 1,000 total adult discharges.

Results: These data represent 2.2 million adult hospital discharges for CDI over the study period. CDI incidence increased from 4.5 CDI discharges per 1,000 total adult discharges in 2001 to 8.2 CDI discharges per 1,000 total adult discharges in 2010. The overall in-hospital mortality rate was 7.1% for the study period. Mortality increased slightly over the study period, from 6.6% in 2001 to 7.2% in 2010. Median hospital LOS was 8 days (interquartile range, 4-14 days), and remained stable over the study period.

Conclusions: The incidence of CDI among hospitalized adults in the United States nearly doubled from 2001-2010. Furthermore, there is little evidence of improvement in patient mortality or hospital LOS.

Several reports have demonstrated a reduction in health care-associated infections, such as central line infections and catheter-associated urinary tract infections, in recent years.[1,2] Conversely, *Clostridium difficile* infection (CDI) continues to be a major public health concern because rates are reportedly rising globally.[3-7] CDI can result in mild diarrhea or more severe clinical manifestations like megacolon, ileus, intestinal perforation, sepsis/shock, or death.[8] Death occurs in approximately 9% of hospitalized patients with CDI, compared with 2% for all other inpatients. The mean cost per hospital stay is $24,400.[7]

Although CDI has been increasingly reported in long-term care facilities and in the community in recent years,[9,10] hospitals remain the primary source of CDI infection due to antibiotic exposure, comorbid illnesses, and environmental factors that facilitate organism transmission. Several reports described increasing CDI incidence in hospitals in the United States (US), Canada, and Europe in the 1990s and early 2000s.[3-6] A more recent report by the Agency for Healthcare Research and Quality showed a steady increase in CDI cases during the past decade.[7]

Few studies have quantified CDI nationally and longitudinally in recent years. Therefore, the objectives of our study were to estimate the national incidence of CDI, identify trends in mortality and hospital length of stay (LOS) among patients with CDI, and compare CDI incidence and outcomes among patients with principal or secondary CDI diagnoses from 2001-2010.

METHODS

Data source

We used data from the US National Hospital Discharge Surveys (NHDS). These surveys are conducted annually by the Centers for Disease Control and Prevention National Center for Health Statistics and provide a national probability sample of inpatients discharged from nonfederal, short-stay hospitals in the US. Hospital discharges are randomly sampled following a 3-stage sample design, including

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Conflicts of interest: None to report.

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http://dx.doi.org/10.1016/j.ajic.2014.06.011

counties, hospitals, and discharges. Because of this complex sampling methodology, the survey data contain a national probability sample of hospital discharges representative of the US population. This enables users to apply data weights to derive national estimates.[11]

NHDS survey data are collected manually or automatically by trained hospital staff, US Census Bureau staff, or National Center for Health Statistics staff. The data collected include patient demographics (age, race, sex, and marital status), year of discharge, expected sources of payment, geographic location in the US, hospital LOS, and hospital discharge status. Diagnoses and procedures are also reported as ICD-9-CM codes. Before 2010, 7 diagnosis and 4 procedure codes were entered for each patient. The 2010 medical abstract form contained 15 diagnosis and 8 procedure codes.[11] The NHDS have been used in several prior infectious diseases epidemiologic studies, including HIV/AIDS,[12] community-associated methicillin-resistant *Staphylococcus aureus*,[13] and health care-associated infections.[1]

Study design and definitions

This was a retrospective analysis of adult patients discharged from US hospitals from 2001-2010. Patients were included if they were aged 18 years or older and had an ICD-9-CM diagnosis code for CDI (008.45).

Patient baseline characteristics were classified based on the categories provided in the NHDS for patient sex (male or female), geographic region as defined by the US Census Bureau (Midwest, West, South, or Northeast), hospital size (6-99 beds, 100-199 beds, 200-299 beds, 300-499 beds, or $\geq$ 500 beds), and admission type (emergency, urgent, or elective). Race was defined using 3 categories: white, black, and other (includes American Indian or Eskimo, Asian or Pacific Islander, and other). Expected primary source of payment was defined as private (includes Blue Cross/Blue Shield, health maintenance organization/preferred provider organization, and other private insurance), Medicare, Medicaid, self-pay, and other (includes no charge, other, other government, and worker's compensation). Finally, admission source was limited to emergency room, transfer (includes transfer from a hospital, skilled nursing facility, or other health care facility), referral (includes physician, clinic, or health maintenance organization referral), and other (includes court/law enforcement or other).

CDI severity indicators were identified by ICD-9-CM codes: shock (639.5, 785.52, and 785.59), sepsis/septicemia (020.2, 038.0-038.9, 995.91, and 995.92), perforated intestine (569.83), prolonged ileus (560.1), megacolon (558.2 and 564.7), acute renal failure (584 and 586), and colectomy (45.73 and 45.81-83). These diagnoses have been used in prior studies to describe CDI severity.[7]

Patient mortality was identified by the Discharge Status item of the NHDS. This represents all-cause, in-hospital mortality for patients with CDI. Hospital LOS was extracted from the Days of Care item of the NHDS and was presented as median (interquartile range).

We stratified our cohort into patients with a principal or secondary CDI diagnosis. Principal CDI refers to CDI as the diagnosis primarily responsible for hospitalization and was defined as an ICD-9-CM code for CDI in the first position. Secondary CDI refers to CDI that contributed to hospitalization, but was not the primary reason for hospitalization. Secondary CDI was defined as an ICD-9-CM code for CDI in any position, except first.

Data and statistical analysis

First, we determined annual incidence rates for CDI using CDI discharges as the numerator and total adult discharges as the denominator. Data weights were applied to derive national estimates and incidence rates were presented as CDI discharges per 1,000 total adult discharges. Baseline patient demographics were summarized using median (interquartile range) for continuous variables and counts (percentages) for categorical variables. Patient outcomes were also presented descriptively and 95% confidence intervals (CIs) were calculated per year of data.

CDI incidence, patient mortality, and hospital LOS were characterized overall and by principal or secondary CDI diagnoses. To compare outcomes among patients with principal or secondary CDI diagnoses, we first compared baseline characteristics between these cohorts using bivariable analyses (χ^2 test for categorical variables and Wilcoxon rank sum test for continuous variables). Statistically significant characteristics, indicated by α level < 0.0001, were inserted into multivariable logistic regression models for mortality and hospital LOS. Hospital LOS was dichotomized into groups ($<$ 7 days vs $\geq$ 7 days) to facilitate logistic regression. Year of discharge, concomitant infectious diseases, and all severity indicators were also included as covariates in the models. JMP 9.0 (SAS Institute Inc, Cary, NC) was used for all statistical comparisons.

Table 1
Baseline characteristics

Demographic	Overall (N = 2,196,446)	Principal CDI (n = 713,761)	Secondary CDI (n = 1,482,685)	*P* value*
Age, y	75 (61-83)	75 (60-83)	75 (62-83)	.0440
Age $\geq$ 65 y	70	68	71	.0164
Sex				<.0001†
Male	41	35	43	
Female	59	65	57	
Race				<.0001†
White	86	87	86	
Black	10	9	10	
Other	4	4	4	
Geographic region				<.0001†
Northeast	29	27	29	
Midwest	24	25	24	
South	32	33	32	
West	15	15	15	
Hospital size				<.0001†
6-99	20	23	18	
100-199	21	21	21	
200-299	24	22	25	
300-499	23	23	23	
Over 500	12	11	13	
Principal payment source				.4827
Medicare	69	68	70	
Medicaid	7	7	6	
Private	21	21	21	
Other	3	4	3	
Admission type				<.0001†
Emergency	66	72	62	
Urgent	21	22	21	
Elective	13	6	17	
Admission source				<.0001†
Emergency room	60	69	55	
Transfer	16	7	20	
Referral	17	17	18	
Other	7	7	7	

CDI, *Clostridium difficile* infection.
NOTE. Values are given as median (interquartile range) or %.
*P values reflect comparisons between principal and secondary CDI diagnosis cohorts.
†Statistically significant at $\alpha < 0.0001$.

RESULTS

Overall, these data represent approximately 2.2 million adult CDI discharges from US hospitals from 2001-2010 (Table 1). Of these patients, 713,461 (33%) had a principal CDI diagnosis and