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Major article

Impact of *Clostridium difficile*-associated diarrhea on acute care length of stay, hospital costs, and readmission: A multicenter retrospective study of inpatients, 2009-2011

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Background: The recent epidemiologic changes of *Clostridium difficile*-associated diarrhea (CDAD) have resulted in substantial economic burden to U.S. acute care hospitals. Past studies evaluating CDAD-attributable costs have been geographically and demographically limited. Here, we describe CDAD-attributable burden in inpatients, overall, and in vulnerable subpopulations from the Premier hospital database, a large, diverse cohort with a wide range of high-risk subgroups.

Methods: Discharges from the Premier database were retrospectively analyzed to assess length of stay (LOS), total inpatient costs, readmission, and inpatient mortality.

Results: Patients with CDAD had significantly worse outcomes than matched controls in terms of total LOS, rates of intensive care unit (ICU) admission, and inpatient mortality. After adjustment for risk factors, patients with CDAD had increased odds of inpatient mortality, total and ICU LOS, costs, and odds of 30-, 60- and 90-day all-cause readmission versus non-CDAD patients. CDAD-attributable costs were higher in all studied vulnerable subpopulations, which also had increased odds of 30-, 60- and 90-day all-cause readmission than those without CDAD.

Conclusion: Given the significant economic impact CDAD has on hospitals, prevention of initial episodes and targeted therapy to prevent recurrences in vulnerable patients are essential to decrease the overall burden to hospitals.

In the last 15 years, the epidemiology of *Clostridium difficile*-associated diarrhea (CDAD) has changed, resulting in increased incidence and severity.[1-3] Between 2000 and 2009, *C difficile* infection hospitalizations increased by 237% in the United States,[4] with nearly 1% of all hospitalizations involving CDAD in 2009.[2] Additionally, nearly 250,000 people require hospital care for CDAD each year.[5] Despite current therapies, CDAD-related morbidity and mortality rates remain high,[6] with worse outcomes and higher acute care costs than in patients without CDAD.[7,8] This is particularly true in patients with risk factors, including renal disease, malignant neoplasms, immunocompromising conditions, inflammatory bowel disease (IBD), or concomitant antibiotic use, where CDAD is associated with substantially increased economic burden.[9,10]

Studies evaluating the U.S. health care costs attributable to CDAD have been limited to individual hospitals, specific populations, and small geographic areas.[11,12] One recent review noted that most

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Conflicts of interest: Magee, Brown, and Baumer performed research contracted by Optimer Pharmaceuticals, Jersey City, NJ, at the time the study was conducted. Thomas and Strauss were employed by Optimer Pharmaceuticals at the time this manuscript was being developed. Strauss was issued Contingent Value Rights Options as part of the acquisition agreement between Optimer and Cubist Pharmaceuticals, Lexington, MA, now Merck & Co., Inc., Kenilworth, NJ. Broderick is an employee of Merck & Co., Inc.

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previous studies included small sample sizes or inadequate control of confounders, such as comorbidities and increased age and illness acuity, factors that are more likely in patients with CDAD than in those without, and that cost differences may vary by region.[11] Another found that attributable outcomes (costs and length of stay [LOS]) were erratic among studies and not consistently reported, making it difficult to draw meaningful conclusions.[12]

The current study was designed to address the shortcomings of earlier assessments of CDAD-related burden on U.S. acute care hospitals. The primary strengths of the Premier hospital database include geographic diversity and its representative sampling of teaching and nonteaching hospitals. Additionally, its large size is likely adequate to provide meaningful conclusions regarding vulnerable subgroups. Our primary aim was to describe the burden attributable to CDAD in hospitalized patients, overall, and in specific vulnerable subpopulations.

MATERIALS AND METHODS

Study design

This retrospective, observational study used data from the Premier hospital database, a deidentified patient database containing a complete census of inpatients from geographically diverse hospitals, with patient demographic information, hospital characteristics, and all discharge ICD-9-CM diagnoses and procedure codes. Date-stamped information was available for all billed services, including medications and diagnostic and therapeutic services in patient daily service records. The database is compliant with the Health Insurance Portability and Accountability Act of 1996.

Patient selection

The inpatient population with CDAD was identified using the first inpatient discharge (index discharge) between January 1, 2009, and December 31, 2011, in which the patient met the following criteria: aged ≥18 years at discharge; principal or secondary discharge diagnosis of ICD-9-CM 008.45 (intestinal infection caused by *C difficile*); received fidaxomicin, metronidazole, or vancomycin during index hospitalization; and no previous hospital admission 90 days before index admission.

The non-CDAD control population was selected using the first inpatient discharge for patients who met the following criteria: index discharge between January 1, 2009, and December 31, 2011; aged ≥18 years at discharge; no previous hospital admission 90 days before index admission; and no record of ICD-9-CM code 008.45.

Patients without CDAD were matched 1:1 to patients with CDAD in a 2-step process. First, patients from both cohorts were categorized by Medicare severity diagnosis-related group. Within each group, individuals were matched using the Mahalanobis caliper method for propensity score matching.[13] All propensity score logistic models used the same covariates: patient demographics (age, sex, race, admission source, admit type, and discharge year) and hospital characteristics (geographic region, teaching status, urban-rural status, and number of beds). All models were assessed for goodness-of-fit using the concordance c statistic. All matched patients were then aggregated, and the data were reviewed for outliers in LOS and total costs, which were removed from the analysis file, from which all analyses were conducted.

Subgroup analysis

Several subgroups were identified from the matched analysis file, most of which were identified by ICD-9-CM codes. These included patients with renal impairment (ICD-9-CM codes: 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.x, 583.0-583.7, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x), malignant neoplasms (140.x-172.x, 174.x-195.8, 200.x-208.x, 238.6), and IBD (556.x, 555.x). The exceptions were patients with immunocompromised status (identified as those exposed to selected alkylating agents, platinum compounds, antimetabolites, antimitotics, epipodophyllotoxins, pegaspargase, asparaginase, DNA topoisomerase inhibitors, biologic response modifiers, monoclonal antibodies, bortezomib, and tyrosine kinase inhibitors) and patients with concomitant antibiotic usage (identified as those exposed to carbapenems, cephalosporins, penicillins, aminoglycosides, tetracyclines, macrolides, fluoroquinolones, and β-lactams). The subgroups were not mutually exclusive, and patients could be included in >1 subgroup.

Outcomes

The impact of CDAD was evaluated by assessing the following outcomes: index hospitalization LOS; total inpatient costs; readmission within 30, 60, and 90 days of index discharge; and inpatient mortality. Costs were reported by hospitals as patient care costs and were not based on charges or cost-to-charge ratios. Readmission rates reflected all-cause readmission to the same hospital within the specified time periods for patients discharged alive from the index hospitalization.

Statistical analysis

Unadjusted baseline characteristics for the matched CDAD and non-CDAD groups were evaluated. Categorical variables were compared using χ^2 test, and continuous variables were evaluated using Student *t* test. Risk-adjusted models were developed for the outcomes of interest. Categorical outcomes were modeled using logistic regression, and continuous variables were modeled using generalized linear models. Because of the skewed distribution of the continuous outcomes (LOS and costs), linear models used a log link with a gamma distribution. Outputs were exponentiated to present results in the original unit of measurement. Covariates used in all models included age, sex, race, admission source, admission type, intensive care unit (ICU) admission, Charlson comorbidity index score, geographic region, teaching status, urban-rural status, and number of beds. All models were assessed for goodness-of-fit. The *P* values <.05 were considered statistically significant. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

After matching, there were 171,586 eligible discharges (85,793 per cohort). There were 2,443 (1.4%) extreme outliers with total costs <$1,000 or >$200,000 or LOS >100 days (CDAD cohort, 1,568 [1.8%]; non-CDAD, 875 [1.0%]). The final analysis dataset included 169,143 discharges (84,225 CDAD; 84,918 non-CDAD).

Patient and hospital characteristics are presented in Table 1. The matching scheme was effective in balancing several characteristics; however, significant differences still existed in part because of the very large patient population. The CDAD cohort had a greater number of patients who were white and who were admitted from skilled nursing facilities (SNFs) (both $P < .01$). Patients with CDAD also had a significantly elevated mean Charlson comorbidity index score ($P < .01$), indicating greater underlying comorbidity. Hospital characteristics were well balanced.

Table 2 presents select subgroup demographics. Although the mean age was slightly lower for patients with CDAD in the renal impairment and neoplasm subgroups and slightly higher for patients with CDAD in the IBD, immunocompromised, and

Table 1
Patient and hospital characteristics

Characteristic	CDAD	Non-CDAD	*P* value*
Patient characteristics			
Total discharges	84,225 (100.0)	84,918 (100.0)	
Age group, y			<.01
18-44	9,114 (10.8)	8,893 (10.5)	
45-64	22,848 (27.1)	24,043 (28.3)	
65-74	17,430 (20.7)	17,551 (20.7)	
75-84	20,808 (24.7)	20,880 (24.6)	
≥85	14,025 (16.7)	13,551 (16.0)	
Age, y	67.7 ± 17.2	67.5 ± 17.0	.31
Sex, female	46,429 (55.1)	46,590 (54.9)	.10
Race			<.01
Black	10,395 (12.3)	10,438 (12.3)	
Other	16,280 (19.3)	18,070 (21.3)	
White	57,550 (68.3)	56,410 (66.4)	
Admission source			<.01
Emergency department	28,683 (34.1)	33,063 (38.9)	
Home	38,034 (45.2)	38,295 (45.1)	
Other	3,487 (4.1)	3,238 (3.8)	
Transfer	7,894 (9.4)	7,912 (9.3)	
SNF	6,127 (7.3)	2,410 (2.8)	
Admission type			.82
Elective	9,761 (11.6)	9,754 (11.5)	
Emergency	60,421 (71.7)	61,093 (71.9)	
Other-unknown	469 (0.6)	469 (0.6)	
Urgent	13,574 (16.1)	13,602 (16.0)	
Discharge status			<.01
Hospice	3,983 (4.7)	2,836 (3.3)	
Transferred	7,746 (9.2)	6,930 (8.2)	
Expired	8,556 (10.2)	6,743 (7.9)	
Home	37,135 (44.1)	51,762 (61.0)	
SNF	25,971 (30.8)	15,623 (18.4)	
Other-unknown	834 (1.0)	1,024 (1.2)	
Charlson comorbidity index score, mean (median) ± SD	2.57 (2.00) ± 2.46	2.19 (2.00) ± 2.33	<.01
Hospital characteristics			
Teaching			.41
Nonteaching	48,870 (58.0)	49,105 (57.8)	
Teaching	35,355 (42.0)	35,813 (42.2)	
No. of beds			.36
<100	2,607 (3.1)	2,514 (3.0)	
100-199	8,264 (9.8)	8,271 (9.7)	
200-299	13,804 (16.4)	13,786 (16.2)	
300-499	31,045 (36.9)	31,377 (36.9)	
≥500	28,505 (33.8)	28,970 (34.1)	

NOTE. Values are n (%), mean ± SD, or as otherwise indicated.
CDAD, *Clostridium difficile*-associated diarrhea; *SNF*, skilled nursing facility.
**P* values indicate differences observed across all groups of each category.

Table 2
Select demographics by subgroup

Description	CDAD	Non-CDAD	*P* value
Total eligible discharges			
Renal impairment	40,232 (100.0)	32,731 (100.0)	
Neoplasm	12,334 (100.0)	10,834 (100.0)	
Immunocompromised	4,632 (100.0)	3,372 (100.0)	
Inflammatory bowel disease	2,972 (100.0)	1,551 (100.0)	
Concomitant antibiotic	55,054 (100.0)	52,524 (100.0)	
Age, y			
Renal impairment	70.9 ± 15.0	71.3 ± 14.7	<.01
Neoplasm	67.7 ± 14.1	68.6 ± 13.5	<.01
Immunocompromised	61.5 ± 17.2	60.3 ± 16.7	<.01
Inflammatory bowel disease	57.7 ± 20.7	52.8 ± 19.8	<.01
Concomitant antibiotic	68.3 ± 16.7	67.7 ± 16.8	<.01
Female sex			
Renal impairment	20,517 (51.0)	16,409 (50.1)	.02
Neoplasm	6,019 (48.8)	5,228 (48.3)	.42
Immunocompromised	2,321 (50.1)	1,652 (49.0)	.32
Inflammatory bowel disease	1,602 (53.9)	854 (55.1)	.44
Concomitant antibiotic	30,143 (54.8)	28,602 (54.5)	.10
SNF transfer admission source			
Renal impairment	3,496 (8.7)	1,229 (3.8)	<.01
Neoplasm	521 (4.2)	153 (1.4)	<.01
Immunocompromised	226 (4.9)	41 (1.2)	<.01
Inflammatory bowel disease	120 (4.0)	13 (0.8)	<.01
Concomitant antibiotic	4,463 (8.1)	1,772 (3.4)	<.01
SNF discharge status			
Renal impairment	13,583 (33.8)	7,345 (22.4)	<.01
Neoplasm	2,660 (21.6)	1,421 (13.1)	<.01
Immunocompromised	1,107 (23.9)	445 (13.2)	<.01
Inflammatory bowel disease	518 (17.4)	118 (7.6)	<.01
Concomitant antibiotic	18,394 (33.4)	10,911 (20.8)	<.01
Charlson comorbidity index, mean (median) ± SD			
Renal impairment	3.52 (3.00) ± 2.39	3.19 (3.00) ± 2.30	<.01
Neoplasm	4.87 (4.00) ± 3.51	4.85 (4.00) ± 3.41	.71
Immunocompromised	4.10 (3.00) ± 3.43	3.87 (3.00) ± 3.36	<.01
Inflammatory bowel disease	1.47 (1.00) ± 2.04	0.86 (0.00) ± 1.57	<.01
Concomitant antibiotic	2.71 (2.00) ± 2.47	2.24 (2.00) ± 2.34	<.01

NOTE. Values are n (%), mean ± SD, or as otherwise indicated.
CDAD, *Clostridium difficile*-associated diarrhea; *SNF*, skilled nursing facility.

concomitant antibiotic subgroups, these differences were not considered clinically meaningful. Throughout the subgroups, patients with CDAD had significantly higher rates of admission from and discharge to SNFs ($P < .01$ for all). Similarly, except for the neoplasm subgroup ($P = .71$), patients with CDAD had higher Charlson comorbidity index scores ($P < .01$).

Compared with controls, patients with CDAD had significantly worse unadjusted outcomes (Table 3), with longer total LOS and higher rates of ICU admission and inpatient mortality. Unadjusted mean patient costs were 46.8% higher and unadjusted 30-day all-cause readmission rates were 8.4% higher for patients with CDAD than for patients without CDAD. Similar results were observed for unadjusted 60- and 90-day all-cause readmission (not presented). Unadjusted outcomes by subgroup were similar to and directionally the same as outcomes of the total population (Table 3).

After adjusting for risk factors, modeled results continued to show significant differences (Table 4). Patients with CDAD had increased odds of inpatient mortality, longer total LOS, longer ICU LOS, increased total patient costs, and increased odds of 30-, 60-, and 90-day all-cause readmission compared with patients without CDAD ($P < .01$ for all). These results were statistically significant overall and in the analyzed subgroups ($P < .01$), with the exception of odds of inpatient mortality for patients with neoplasms ($P = .14$) or immunocompromised status ($P = .26$). Although directionally the same, these results were not statistically significant.

Costs of care for inpatient discharges attributable to CDAD were derived by subtracting the adjusted total costs for non-CDAD patients from those of patients with CDAD. For the eligible population, CDAD-attributable costs were $7,286. CDAD-attributable costs for subgroups are as follows: renal impairment, $8,942; neoplasm, $6,975; immunocompromised status, $8,692; IBD, $5,526; and use of concomitant antibiotics, $8,545.

CONCLUSIONS

The burden of CDAD on resource utilization and total cost to acute care hospitals is significant. This study extends previous research by evaluating a database of all patients treated at 477 U.S. acute care hospitals during a 3-year period. The incremental costs of CDAD observed here, both overall and in individual high-risk subgroups, may provide useful information for cost-benefit analyses of new treatment regimens for CDAD.

Table 3
Unadjusted outcomes of patients with CDAD versus patients without CDAD

Outcome	CDAD		Non-CDAD			
Length of stay, d	Mean ± SD	Median (IQ range)	Mean ± SD	Median (IQ range)	*P* value	Percentage difference
All eligible	14.4 ± 18.3	10 (5-17)	8.7 ± 15.6	6 (3-10)	<.01	65.5
Renal impairment	14.76 ± 12.46	11 (6-19)	9.37 ± 9.26	6 (4-12)	<.01	57.5
Neoplasm	15.30 ± 12.67	12 (7-20)	9.97 ± 9.26	7 (4-13)	<.01	53.5
Immunocompromised	18.78 ± 14.59	15 (6-19)	12.68 ± 11.72	9 (4-12)	<.01	48.1
Inflammatory bowel disease	12.45 ± 11.86	8 (4-16)	7.17 ± 7.82	5 (3-8)	<.01	73.6
Concomitant antibiotic	15.13 ± 12.67	11 (7-20)	9.44 ± 9.38	6 (4-12)	<.01	60.3
ICU admission	n	%	n	%		Percentage-point difference
All eligible	30,942	36.7	26,147	30.8	<.01	5.9
Renal impairment	19,419	48.3	13,398	40.9	<.01	7.3
Neoplasm	4,445	36.0	3,456	31.9	<.01	4.1
Immunocompromised	1,675	36.2	950	28.2	<.01	8.0
Inflammatory bowel disease	1,073	36.1	243	15.7	<.01	20.4
Concomitant antibiotic	24,212	44.0	19,003	36.2	<.01	7.8
Inpatient mortality	n	%	n	%		Percentage-point difference
All eligible	8,556	10.2	6,743	7.9	<.01	2.2
Renal impairment	6,550	16.3	4,345	13.3	<.01	3.0
Neoplasm	1,714	13.9	1,345	12.4	<.01	1.5
Immunocompromised	552	11.9	325	9.6	<.01	2.3
Inflammatory bowel disease	385	13.0	47	3.0	<.01	9.9
Concomitant antibiotic	6,465	11.7	4,765	9.1	<.01	2.7
Total inpatient costs	Mean ± SD	Median (IQ range)	Mean ± SD	Median (IQ range)		Percentage difference
All eligible	$27,408 ± $30,664	$16,353 ($8,269-33,598)	$18,676 ± $24,369	$10,119 ($5,401-$20,992)	<.01	46.8
Renal impairment	$32,552 ± $33,504	$20,565 ($10,644-$41,236)	$22,329 ± $27,579	$12,529 ($6,408-$25,958)	<.01	45.8
Neoplasm	$33,246 ± $33,908	$20,934 ($10,773-$42,907)	$23,579 ± $13,096	$12,868 ($7,174-$28,184)	<.01	41.0
Immunocompromised	$43,078 ± $41,102	$27,655 ($13,050-$59,987)	$32,914 ± $37,001	$18,093 ($7,987-$44,244)	<.01	30.9
Inflammatory bowel disease	$27,387 ± $32,440	$14,787 ($7,089-$34,898)	$14,334 ± $20,341	$7,720 ($4,541-$15,131)	<.01	91.1
Concomitant antibiotic	$33,072 ± $33,754	$20,954 ($10,897-$42,097)	$22,484 ± $27,720	$12,461 ($6,430-$26,134)	<.01	47.1
30-d all-cause readmission	n	%	n	%		Percentage-point difference
All eligible	17,539	23.2	11,536	14.8	<.01	8.4
Renal impairment	8,415	25.0	4,718	16.6	<.01	8.4
Neoplasm	2,707	25.5	1,878	19.8	<.01	5.7
Immunocompromised	1,239	30.4	723	23.7	<.01	6.6
Inflammatory bowel disease	542	21.0	235	15.6	<.01	5.3
Concomitant antibiotic	11,305	23.3	7,066	14.8	<.01	8.5

CDAD, *Clostridium difficile*-associated diarrhea; *ICU*, intensive care unit; *IQ*, interquartile; *SNF*, skilled nursing facility.

The present data are consistent with other studies that found increased LOS, total patient costs, and risk of readmission for patients with CDAD.[11] The increase in LOS with CDAD was 4.7 days, and the total cost attributable was $7,286. These results are broadly similar to those of Kyne et al[8] (attributable LOS, 3.6 days; attributable cost, $3,669) and Song et al[3] (attributable LOS, 5.5 days; attributable cost, $6,326). Both of these studies were conducted at single institutions, whereas the current study used recent, geographically diverse data from several hundred hospitals, presumably providing a more generalizable estimate of current conditions.

The subgroup analysis of vulnerable clinical populations with known increased risk of infection suggested that the effect of CDAD on the reported outcomes is consistent throughout the populations. The effect of CDAD on inpatient mortality and readmission was similar to the overall population analysis. In all subgroups, total inpatient costs were higher for patients with CDAD than for controls, confirming previous findings.[9,10,14,15] The CDAD-attributable cost was slightly higher for patients with renal impairment ($8,942), immunocompromised status ($8,692), and concomitant antibiotic exposure ($8,545), compared with the overall population.

Patients with CDAD had significantly higher 30-day readmission rates than controls in the overall population and in each high-risk subgroup studied. Comparing all-cause readmission rates observed here with previous studies is difficult because of varying definitions used for identifying the CDAD population and differences in sample size, time periods, and definition of readmission. Despite these potential confounding variables, the rates of readmission reported here are comparable with those found in recent studies.[7,11,16,17] Although we have not specifically focused on CDAD recurrence, it is likely a contributor to the increased 30-day all-cause readmission rates and should be considered by hospitals for more accurate estimations of potential future costs. Indeed, a recent study demonstrated that approximately 50% of patients with recurrence were rehospitalized within 3 months.[16] Moreover, it seems that using the appropriate initial treatment for CDAD should be a priority for preventing downstream resource utilization and readmission, specifically in vulnerable patients.

This study adds to previous research in several ways particularly important to acute care hospitals. First, it provides an analysis using data from a large number of geographically diverse hospitals. Previous large-database analyses relied on Medicare data, the National Hospital Discharge Survey, or state databases, whereas other cohort studies relied on retrospective or prospective data from small numbers of acute care facilities. Each approach limits the generalizability of results. Second, we used an easily reproduced definition of CDAD. Use of ICD-9 coding to identify CDAD cases has been shown to have good concordance with cases identified by *C difficile* toxin assays.[18] Inclusion of patients treated with fidaxomicin, metronidazole, or vancomycin helps identify individuals in an

Table 4
Adjusted outcomes of patients with CDAD versus patients without CDAD

Inpatient mortality	Odds ratio	Lower*	Upper*	*P* value
All eligible	1.13	1.09	1.17	<.01
Renal impairment	1.14	1.09	1.19	<.01
Neoplasm	1.06	0.98	1.15	.14
Immunocompromised	1.09	0.94	1.27	.26
Inflammatory bowel disease	2.57	1.84	3.59	<.01
Concomitant antibiotic	1.13	1.08	1.18	<.01
Total length of stay, d	CDAD	Non-CDAD	Percentage difference	*P* value
All eligible	13.2	8.5	55.3	<.01
Renal impairment	14.5	9.4	54.3	<.01
Neoplasm	13.6	8.9	52.8	<.01
Immunocompromised	17.8	12.0	48.3	<.01
Inflammatory bowel disease	10.4	6.9	50.7	<.01
Concomitant antibiotic	14.9	9.5	56.8	<.01
ICU length of stay, d	CDAD	Non-CDAD	Percentage difference	*P* value
All eligible	8.3	6.6	25.8	<.01
Renal impairment	10.3	8.5	21.2	<.01
Neoplasm	4.7	3.7	27.0	<.01
Immunocompromised	6.6	5.5	20.0	<.01
Inflammatory bowel disease	7.8	6.1	27.9	<.01
Concomitant antibiotic	5.0	4.1	22.0	<.01
Total patient cost	CDAD	Non-CDAD	Percentage difference	*P* value
All eligible	$25,804	$18,518	39.3	<.01
Renal impairment	$31,263	$22,321	40.1	<.01
Neoplasm	$24,694	$17,719	39.4	<.01
Immunocompromised	$33,064	$24,372	35.7	<.01
Inflammatory bowel disease	$19,667	$14,141	39.1	<.01
Concomitant antibiotic	$29,581	$21,036	40.6	<.01
30-d all-cause readmission	Odds ratio	Lower*	Upper*	*P* value
All eligible	1.77	1.73	1.82	<.01
Renal impairment	1.66	1.59	1.73	<.01
Neoplasm	1.45	1.36	1.56	<.01
Immunocompromised	1.45	1.30	1.62	<.01
Inflammatory bowel disease	1.33	1.12	1.59	<.01
Concomitant antibiotic	1.70	1.64	1.76	<.01
60-d all-cause readmission	Odds ratio	Lower*	Upper*	*P* value
All eligible	1.83	1.79	1.87	<.01
Renal impairment	1.71	1.65	1.77	<.01
Neoplasm	1.49	1.40	1.58	<.01
Immunocompromised	1.53	1.38	1.70	<.01
Inflammatory bowel disease	1.41	1.21	1.65	<.01
Concomitant antibiotic	1.73	1.68	1.78	<.01
90-d all-cause readmission	Odds ratio	Lower*	Upper*	*P* value
All eligible	1.83	1.79	1.87	<.01
Renal impairment	1.71	1.65	1.77	<.01
Neoplasm	1.48	1.39	1.57	<.01
Immunocompromised	1.58	1.43	1.75	<.01
Inflammatory bowel disease	1.47	1.27	1.71	<.01
Concomitant antibiotic	1.73	1.68	1.78	<.01

CDAD, *Clostridium difficile*-associated diarrhea; *ICU*, intensive care unit.
*95% confidence interval of odds ratio.

empirical manner. Finally, our method for cost calculation was to use patient-care costs reported directly from hospital charge-masters, rather than billed charges or cost-to-charge ratios.

Our study has several limitations. First, the method for identifying CDAD used only ICD-9-CM and antibiotic exposure data and did not require a positive *C difficile* toxin assay. Although the concordance between the 2 is believed to be high, the size of the CDAD population may have been overestimated. Second, our study only considered hospital costs and not physician or treatment costs beyond the index hospitalization. Therefore, our costs were not an estimate of the total cost of CDAD to the health system. Third, readmission rates were calculated based on readmission to the same hospital. Admission to a different hospital and mortality outside of the hospital would not have been identified by the Premier database; therefore, readmission rates may have been underestimated; however, as shown previously, most patients return to the same hospital for continuing care.[19] Because the CDAD population had higher rates of discharge to SNFs, hospices, and other acute care facilities, this limitation may have systematically underestimated the CDAD-related readmission risk. Fourth, our risk adjustment methods relied on patient data, including comorbidities at the time of discharge. Previous studies have observed that mortality associated with CDAD is usually associated with underlying disease.[8,20] Because we were unable to adjust for disease severity at admission, this should be considered when interpreting inpatient mortality risk. Finally, it is unknown whether patients acquired *C difficile* in the community or the hospital; however, most patients were admitted from home or a SNF.[1] The impact of disease origin on acute care LOS, hospital costs, and readmission in patients with CDAD, overall and in high-risk subgroups, could be addressed in future studies.

In summary, after adjustment for risk factors, patients with CDAD had increased odds of inpatient mortality, longer total and ICU LOS, increased total patient costs, and increased odds of 30-, 60- and 90-day all-cause readmission compared with patients without CDAD, overall and in the analyzed high-risk subgroups. These results emphasize the continuing burden CDAD imparts on U.S. hospitals. Efforts focused on preventing initial CDAD episodes, and targeted therapy to prevent recurrences for vulnerable patients, are essential to decrease this burden.

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