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Original article

Length of stay and hospital costs among high-risk patients with hospital-origin *Clostridium difficile*-associated diarrhea

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Abstract

Objective:
Hospital-onset *Clostridium difficile*-associated diarrhea (HO-CDAD) has been associated with longer length of stay (LOS) and higher hospital costs among patients in general. The burden of HO-CDAD is unknown among patients who may be at particular risk of poor outcomes: older patients, those with complex or chronic conditions (renal disease, cancer, inflammatory bowel disease [IBD]), and those with concomitant antibiotic (CAbx) use during treatment for CDAD.

Research design and methods:
A retrospective analysis (2005–2011) of the *Health Facts*® database (Cerner Corp., Kansas City, MO) containing comprehensive clinical records from 186 US hospitals identified hospitalized adult patients with HO-CDAD based on a positive *C. difficile* toxin collected $>$48 h after admission. Control patients were required to have total hospital LOS $\geq$2 days. Separate logistic regression models to estimate propensities were developed for each study group, with HO-CDAD vs controls as the outcome. Differences in LOS and costs were calculated between cases and controls for each group.

Results:
A total of 4521 patients with HO-CDAD were identified. Mean age was 70 years, 54% were female, and 13% died. After matching, LOS was significantly greater among HO-CDAD patients (vs controls) in each group except IBD. The significant difference in LOS ranged from 3.0 (95% CI = 1.4–4.6) additional days in older patients to 7.8 (95% CI = 5.7–9.9) days in patients with CAbx exposure. HO-CDAD was associated with significantly higher costs among older patients ($p < 0.001$) and among those with renal impairment ($p = 0.012$) or CAbx use ($p < 0.001$).

Limitations:
Missing cost data and potential misclassification of colonized patients as infected.

Conclusions:
Renal impairment, advanced age, cancer, and CAbx use are associated with significantly longer LOS among HO-CDAD patients, with CAbx users being the most resource intensive. Early identification and aggressive treatment of HO-CDAD in these groups may be warranted.

Introduction

Clostridium difficile-associated diarrhea (CDAD) is a serious condition that is associated with considerable morbidity and mortality. Standard case definitions for surveillance characterize patients by the time of onset and by previous exposure to a healthcare facility (HCF). HCF-onset, HCF-associated CDAD

(HO-CDAD) is defined as CDAD symptom onset more than 48 h after admission to an HCF[1]. Estimates of the increased length of stay (LOS) associated with HO-CDAD range from 2.9[2] to 7 days[3], while the attributable costs range from $3669[4] to $13,675[2]. These differences are due in part to sample size and case-mix variation between studies. Beyond the substantial resources expended during an individual episode of care, recurrent disease occurs in 15–30% of patients[5], requiring additional treatment and often re-hospitalization. This carries a considerable toll both for patients—who tend to be frail, with multiple medical problems—and the healthcare system. Risk factors for recurrence include older age[6–8] and continued use of antibiotics after diagnosis and/or during treatment of CDAD[6–9].

Other patient populations with complex underlying illnesses that may incur particular burden if their hospital stay is complicated by CDAD include patients with inflammatory bowel disease (IBD), renal impairment, and cancer or history of bone marrow transplant (BMT). Unfortunately, there are little data on the resource utilization associated with HO-CDAD in these sub-populations. For example, an analysis of the Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS) data reported that hospitalized patients with IBD and CDAD stayed 3 days longer compared to similar patients without CDAD[10]. However, patients were identified by discharge diagnosis codes and were not stratified by timing of onset of CDAD; the authors state that it is likely that most of the CDAD infections were acquired before the hospitalization. The NIS database was also used in a study of patients with end-stage renal disease. CDAD was independently associated with significantly greater mortality, longer LOS and higher charges, although again, due to this database's limitations, the timing of infection could not be considered[11]. Chronic renal disease has also been identified as a risk factor for severe CDAD[12]. Cancer patients have multiple risk factors for C. *difficile* infection, including prolonged hospitalization and exposure to antibiotics and chemotherapeutic agents[13]. Outcome data on the effect of CDAD in cancer patients or in those with a history of BMT are scarce, although studies have shown high fatality rates in cancer patients with C. *difficile* infection[14]. Following allogeneic hematopoietic stem cell transplant, CDAD was associated with increased risk of graft-vs-host disease and mortality[15,16]. Among all adult hospital discharges in one county in California, diagnosis of cancer was associated with readmission for recurrent C. *difficile* infection[17].

Since patients with these characteristics are known to be at greater risk of poor outcomes once they contract CDAD, understanding the impact of the disease on resource utilization would provide a more complete picture of the total burden of this infection. Thus, the aim of this study was to quantify the incremental hospital LOS and costs in HO-CDAD patients vs propensity-matched controls, among five identified high-risk sub-populations: older patients (age $\geq$ 65 years), those with complex conditions or chronic diseases (renal disease, cancer, IBD) and those with concomitant antibiotic (CAbx) use.

Patients and methods

Study design and data source

This was a retrospective cohort study using data collected from hospitals in the *Health Facts* electronic health record (EHR) database (Cerner Corporation, Kansas City, MO). *Health Facts* contains a comprehensive clinical record for each encounter and includes pharmacy, clinical and microbiology laboratory, admission, and billing information from affiliated patient care locations. Clinical information is date- and time-stamped, providing a temporal relationship between clinical information relating to the drugs dispensed and the results of diagnostic laboratory testing. Cerner Corporation has established Health Insurance Portability and Accountability Act-compliant operating policies to establish de-identification for *Health Facts*.

Population selection

Patients were selected if they were hospitalized between April 1, 2005 and June 30, 2011 and aged 18 years or older upon admission. Cases had a positive C. *difficile* stool toxin assay with collection time more than 48 h after admission time. This definition was based on the surveillance definitions described in the 2010 Society for Healthcare Epidemiology of America-Infectious Diseases Society of America (SHEA/IDSA) guidelines[1]. Controls were defined as patients with no evidence of CDAD by positive toxin test or ICD-9-CM discharge diagnosis code during their hospitalization. Patients with evidence of CDAD who did not meet criteria for HO-CDAD cases (i.e., those with a positive toxin result $\leq$48 h after admission) were excluded from the study. Likewise, controls were excluded if they were admitted for less than 2 days. For patients with multiple eligible encounters in *Health Facts*, only the first encounter was considered if all encounters were free of CDAD to prevent analyzing the same patient more than once. If multiple encounters qualified as HO-CDAD, the first such encounter was analyzed.

Study group definitions and other measures

The index toxin was defined as the first positive stool toxin result; the specimen collection time was used as the basis for timing of laboratory results and for measures of organ dysfunction. Renal impairment was defined by

International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) discharge diagnosis codes during the index encounter or up to 12 months prior, or by an estimated glomerular filtration rate (GFR) (4-variable Modification of Diet in Renal Disease equation) of less than 90 mL/min/1.73 m^2 during the encounter as close as possible to the index toxin time[18]. Among patients who received antibiotic treatment for CDAD, CAbx use was defined as orders for pre-specified antibiotics[19] open concurrently with CDAD treatment defined as metronidazole (any route of administration) or vancomycin (oral or rectal route). Patients in the cancer/BMT study group were identified by ICD-9-CM discharge diagnosis codes for cancer (solid tumor or hematologic malignancy) or by procedure code for BMT during the index encounter or up to 12 months prior. IBD was defined by ICD-9-CM discharge diagnosis codes during the index encounter or up to 12 months prior. Patients could be included in more than one study group (e.g., a patient aged ≥65 with cancer).

Clinical characteristics of interest were derived from ICD-9-CM billing codes, medication orders, and laboratory data. For the determination of chronic conditions, we reviewed the patient's record for 12 months prior to and including the study encounter. Surgical or medical patient type was derived using the assigned diagnosis-related group (DRG). Organ dysfunction measures within a 36-h window surrounding the time of the index culture were derived using a Sepsis-related Organ Failure Assessment score equal to 2 or greater[20]. These included cardiovascular, respiratory, hepatic, hematologic, and renal dysfunction. Critical care exposure was defined as having at least two orders from an intensive care unit 12 or fewer hours apart, or mechanical ventilation. Evidence of impaired immunity included orders for immunosuppressive medications and diagnoses affecting the immune system such as human immunodeficiency virus/acquired immunodeficiency syndrome, auto-immune diseases, and metastatic cancer. Severity of CDAD was based upon the clinical definitions outlined in the 2010 SHEA/IDSA guidelines[1] and modified to leverage the available parameters in *Health Facts*. Severe/complicated CDAD was defined as having orders for vasopressors and/or total parental nutrition, ICD-9-CM discharge diagnosis of megacolon, or procedure codes for intestinal surgery. Severe CDAD was defined by elevated white blood cell count and/or serum creatinine, without any of the indicators of severe/complicated disease. The remaining patients were categorized as having mild/moderate/indeterminate disease.

The study outcomes were total hospital LOS and total hospital costs. The latter were computed from billed charges using a cost-to-charge ratio derived from NIS, HCUP, and the Agency for Healthcare Research and Quality. Billed charges are reported by contributing institutions, and different elements may be included across these institutions. Patient cost sharing, reimbursement adjustments, discounts, or physician fees are generally not included.

Statistical methods

Within each of the five study groups (i.e., renal impairment, age ≥65 years, cancer/BMT, IBD, CABx exposure), we compared HO-CDAD patients vs control patients. HO-CDAD patients were identified by a positive toxin test (the index event) for *C. difficile* after 2 days of hospitalization. To create similar populations and to prevent an immortal time bias, control patients were also required to have at least 2 days of hospitalization. Furthermore, to ensure that we did not over-estimate the LOS differences between HO-CDAD patients and controls, we created a 'pseudo' index event date for the control group (analogous to the first positive toxin test among cases) by multiplying a random uniformly distributed variable (i.e., a variable with a value between 0 and 1 following the uniform distribution) on each control patient's LOS. Control patients were required to have both a total LOS ≥2 days and a 'pseudo' index date ≥2 days after admission. Control patients matched to case patients with CAbx exposure were required to have an order for at least one of the antibiotics used to define the CAbx population[19]; however, control patients were not required to have concurrent open orders for vancomycin or metronidazole.

Descriptive statistics were used to summarize patient characteristics and clinical outcomes of the study population. Propensity score matching was used for multivariate adjustment. For each of the study groups, a separate logistic regression model was used to create the propensity of developing HO-CDAD. For each propensity score, we included covariates related to age, gender, admission source, elective vs urgent admission type, chronic comorbidities during the index admission or up to 12 months prior, common primary diagnoses that were present in the HO-CDAD patients (e.g., septicemia), variables indicative of critical care within the first 48 h, early proton pump inhibitor or H2 blocker use, laboratory values taken at baseline that were transformed into binary variables of 'normal' vs 'abnormal' levels, and hospital level factors. We also included indicator variables for the other study groups when appropriate (e.g., for the four non-CAbx models, CAbx exposure was included as a predictor). Each propensity score also took the admitting hospital into account by adjusting at the hospital level (i.e., in a clustered manner) for possible correlation among patients treated within the same hospital[21]. Importantly, each propensity score also included the pseudo index date for controls and the index event date for cases. This was done to ensure that LOS before the index event was similar in both groups and was thus no

longer a confounder. This methodology was similar to that of Dubberke *et al.*[22,23], but includes an adjustment for the time-varying nature of HO-CDAD. We matched on propensity using the 5:1 Greedy Match algorithm. As a sensitivity analysis, we explored the effect of different matching methods by using the nearest neighbor and caliper matching algorithms.

Results

Patient and clinical characteristics

A total of 4521 patients with HO-CDAD were identified. Study patients were identified from 74 unique hospitals; most were urban institutions in the Midwest (39%) and South (27%), and half were teaching hospitals, reflecting the characteristics of sites contributing data to *Health Facts*. The largest study groups were renal impairment and advanced age, with more than 3000 patients each, while 84 patients had a diagnosis of IBD. Nearly 800 patients had a diagnosis of cancer or a history of BMT, and 1641 patients had CAbx exposure; groups were not mutually exclusive. Select clinical characteristics of each group are summarized in Table 1. Consistent with the profile of IBD patients, this group tended to be younger, female, and Caucasian, and had lower comorbidity burden and lower rates of organ dysfunction compared to other study groups. Approximately two-thirds of patients had a medical DRG. In addition to the required positive *C. difficile* toxin, 70% of patients had an ICD-9-CM discharge diagnosis of pseudomembranous colitis. Thirty per cent of patients had severe CDAD, and 15% of the renal impairment, older age, and cancer/BMT groups had severe/complicated CDAD. In the IBD and CAbx groups, more than 25% of patients required vasopressors, total parenteral nutrition, or colon surgery. Overall, the number of days from admission to first positive toxin test averaged 11.6 (SD = 14.2; median = 7.4).

CDAD treatment

Approximately 70% of patients received an antibiotic active against CDAD (metronidazole or oral vancomycin) (Table 2). In more than 80% of patients, metronidazole was the first antibiotic ordered. The mean dose of the first order for metronidazole was slightly more than 1400 mg/day, which is similar to the guideline-recommended dose of 500 mg three times per day[1]. More than half of patients with vancomycin exposure had orders for an oral 'slurry' formulation, whereby this less-expensive intravenous form of vancomycin is mixed with juice and administered orally. The maximum daily dose of any vancomycin formulation ranged from 866 mg (advanced age group) to 1174 mg (IBD group). The large mean dose seen in the small group of IBD patients exposed to vancomycin was skewed by a single patient whose daily dose was 4000 mg. For both metronidazole and vancomycin, the mean duration of drug exposure ranged from 9–12 days across study groups.

Outcomes–unadjusted

Unadjusted outcome data for the HO-CDAD study groups are presented in Table 3. Mean total hospital LOS was slightly more than 20 days, with the exception of the CAbx exposure group (29 days). Cost data were available for ~75% of patients, and missing data were not imputed. Mean total hospital costs mirrored the pattern of LOS, ranging from $36,834 in the IBD group to $72,349 in CAbx patients. In-hospital mortality rates by study group ranged from 12–16%.

Outcomes–adjusted

In general, the propensity score models had good discrimination, with the area under the ROC curve greater than 0.8. Approximately 90% of case patients were successfully matched to controls using the Greedy Matching algorithm, ranging from 80% of the CAbx group to 93% of the renal impairment group. After matching, the covariates in the propensity score models were not significantly different between cases and controls in every study group analysis. Adjusted total hospital LOS was greater among HO-CDAD patients compared to controls in every study group, with four of the five being statistically significant (all $p < 0.001$): renal impairment, age ≥65, cancer/BMT, and CAbx use (Figure 1; online appendix). Patients exposed to antibiotics (in the HO-CDAD group, antibiotic orders were concomitant with CDAD treatment) had the greatest mean number of days in the hospital (27.1), as well as the greatest marginal difference in LOS (7.8; 95% CI = 5.7–9.9) vs controls. Among IBD patients, HO-CDAD was associated with longer LOS, but the difference did not reach statistical significance.

Similar trends were observed for differences in total hospital costs among patients with vs without HO-CDAD (Figure 2; online appendix). Among older patients and those with antibiotic use, HO-CDAD was associated with significantly greater hospital costs ($p < 0.001$). The highest costs and greatest marginal increase in costs associated with HO-CDAD were observed among patients with CAbx exposure, where HO-CDAD was associated with an additional $17,015. In the renal impairment population, the difference of ~$4600 was statistically significant ($p = 0.012$) as well. Among patients with a diagnosis of IBD and in patients with cancer, differences in costs were not significant.

Table 1. Patient and clinical characteristics (HO-CDAD cases).

	Renal impairment		Age ≥65		Cancer/BMT		IBD		CAbx exposure	
	(*n* = 3236)		(*n* = 3064)		(*n* = 782)		(*n* = 84)		(*n* = 1641)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Patient and encounter characteristics										
Age, years (mean [SD])	72.9 (13.4)		78.7 (7.4)		69.2 (14.0)		61.2 (18.3)		61.2 (14.8)	
Male gender	1427	44.1	1321	43.1	395	50.5	32	38.1	746	45.5
Caucasian race	2596	80.2	2577	84.1	635	81.2	75	89.3	1305	79.5
Patient type surgical (vs medical and unknown)	1068	33.0	937	30.6	267	34.1	32	38.1	629	38.3
Admission source										
Hospital/other care facility	214	6.6	205	6.7	40	5.1	5	6.0	106	6.5
SNF/NH/LTC	241	7.4	277	9.0	34	4.4	4	4.8	134	8.2
Emergency room	1895	58.6	1785	58.3	417	53.3	43	51.2	955	58.2
Other/unknown[a]	886	27.4	797	26.0	291	37.2	32	38.1	446	27.2
Discharge diagnosis of pseudomembranous colitis (ICD-9-CM 008.45)										
Any	2286	70.6	2217	72.4	561	71.7	62	73.8	1179	71.9
As primary Dx	202	6.2	198	6.5	58	7.4	8	9.5	89	5.4
As a secondary Dx	2084	64.4	2019	65.9	503	64.3	54	64.3	1090	66.4
Evidence of impaired immunity	1291	39.9	1062	34.7	585	74.8	84	100	651	39.7
Comorbid conditions[b]										
Charlson Comorbidity Index score, mean (SD)[27]	3.0 (2.4)		2.7 (2.4)		5.0 (2.5)		1.8 (2.2)		2.7 (2.4)	
Heart failure	1443	44.6	1411	46.0	212	29.0	24	28.6	625	38.1
Coronary artery disease	1262	39.0	1276	41.6	233	31.8	15	17.9	533	32.5
Diabetes	1140	35.2	982	32.0	197	26.9	18	21.4	482	29.4
COPD	917	28.3	941	30.7	223	30.5	19	22.6	461	28.1
Cerebrovascular disease	557	17.2	578	18.9	88	12.0	9	10.7	260	15.8
Cirrhosis/chronic liver disease	156	4.8	93	3.0	35	4.8	4	4.8	81	4.9
Severity of illness measures										
Any organ system dysfunction around time of index toxin	2132	65.9	1807	59.0	483	61.8	35	41.7	1076	65.6
Critical care use within 48 h of admission	801	24.8	717	23.4	150	19.2	13	15.5	517	31.5
Severity of CDAD[c]										
Mild/moderate/indeterminate	1645	50.8	1596	52.1	416	53.2	38	45.2	644	39.2
Severe	1088	33.6	1018	33.2	246	31.5	24	28.6	566	34.5
Severe/complicated	503	15.5	450	14.7	120	15.4	22	26.2	431	26.3

BMT, bone marrow transplant; CAbx, concomitant antibiotic; CDAD, *Clostridium difficile*-associated diarrhea; COPD, chronic obstructive pulmonary disease; Dx, diagnosis; IBD, inflammatory bowel disease; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; LTC, long-term care; NH, nursing home; SD, standard deviation; SNF, skilled nursing facility.

[a]Includes physician referral, clinic referral, transfer from home health agency, court/law enforcement.

[b]Comorbid conditions defined by diagnosis codes present during the index encounter or up to 12 months prior to admission.

[c]Variable not included in LOS or cost models.

Table 2. CDAD antimicrobial exposure data (HO-CDAD cases).

	Renal impairment ($n=2315$)[a]		Age ≥65 ($n=2211$)[a]		Cancer/BMT ($n=532$)[a]		IBD ($n=59$)[a]		CAbx exposure ($n=1641$)[a]	
First CDAD antibiotic (*n*, %)										
Vancomycin (oral/nasogastric/rectal)	193	8.3	180	8.1	41	7.7	4	6.8	106	6.5
Metronidazole	1902	82.2	1832	82.9	449	84.4	47	79.7	1372	83.6
Both	220	9.5	199	9.0	42	7.9	8	13.6	163	9.9
Vancomycin exposure										
Exposure to oral slurry[b] (*n*, %)	430	56.8	399	56.4	83	47.7	14	45.2	367	59.3
Maximum daily dose, mg (mean [SD])[c]	880 (519)		866 (503)		912 (458)		1174 (909)		927 (535)	
Total days ordered (mean [SD])	9.7 (10.4)		8.8 (9.3)		9.5 (9.0)		10.6 (9.4)		11.9 (13.5)	
Metronidazole use										
First daily dose ordered, mg (mean [SD])[c]	1419 (273)		1423 (270)		1438 (268)		1417 (287)		1454 (258)	
Total days ordered (mean [SD])	9.1 (8.6)		8.9 (7.9)		9.0 (7.6)		10.9 (9.8)		11.8 (10.3)	

BMT, bone marrow transplant; CAbx, concomitant antibiotic; CDAD, *Clostridium difficile*-associated diarrhea; IBD, inflammatory bowel disease; SD, standard deviation.
[a]Number of patients who had any CDAD-associated antibiotic exposure. The percentage of all patients in each group with any exposure ranged from 68% in the cancer group to 100% in the CAbx use group.
[b]Among patients with any vancomycin exposure.
[c]Among patients with dose data available.

Table 3. Unadjusted clinical and resource utilization outcomes (HO-CDAD cases).

	Renal impairment ($n=3236$)	Age ≥65 ($n=3064$)	Cancer/BMT ($n=782$)	IBD ($n=84$)	CAbx exposure ($n=1641$)
Total hospital LOS, days (mean [SD])	22.7 (28.2)	21.3 (25.3)	21.3 (18.5)	21.0 (19.1)	29.3 (34.7)
Total hospital costs, index admission, 2010$ (mean [SD])[a]	46,358 (66,147)	44,842 (62,066)	44,244 (66,536)	36,834 (41,097)	72,349 (91,402)
In-hospital mortality (*n*, %)[b]	480 (14.83%)	452 (14.75%)	121 (15.47%)	10 (11.90%)	259 (15.78%)

BMT, bone marrow transplant; CAbx, concomitant antibiotic; CDAD, *Clostridium difficile*-associated diarrhea; IBD, inflammatory bowel disease; LOS, length of stay; SD, standard deviation.
[a]Cost data available for ~75% of patients.
[b]Approximately 0.3–0.5% of patients were missing discharge disposition; mortality was calculated among those with available discharge disposition data.

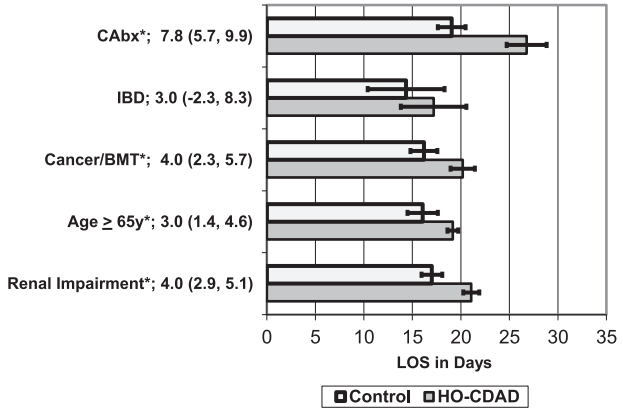

Figure 1. Adjusted total hospital LOS. Data shown are differences (95% confidence interval) in days between HO-CDAD and control patients. BMT, bone marrow transplant; CAbx, concomitant antibiotics; IBD, inflammatory bowel disease. *p-value for difference <0.001.

The sensitivity analysis using the two other matching algorithms produced results consistent with the Greedy Matched algorithm. Namely, significant differences of similar magnitude and direction observed between case and control patients in the primary analysis persisted with at least one other matching algorithm or in both.

Discussion

In a cohort of more than 4500 patients with HO-CDAD, significant differences in hospital LOS and costs were found compared to matched controls on homogeneous, high-risk sub-populations. Notably, these differences varied across sub-populations and the resource burden was particularly high among patients aged 65 or older and among those with CAbx exposure. The increase in LOS ranged from 3 days among elderly patients to more than 1 week for patients with concomitant antibiotic use. It is important to recognize this consequence of HO-CDAD, given that extended hospitalizations can put patients at risk for additional nosocomial infections and venous thromboembolic events due to immobility, and can adversely affect patients' and family members' well-being. Moreover, C. *difficile* infection is recognized as a new measure of hospital-acquired infection in the

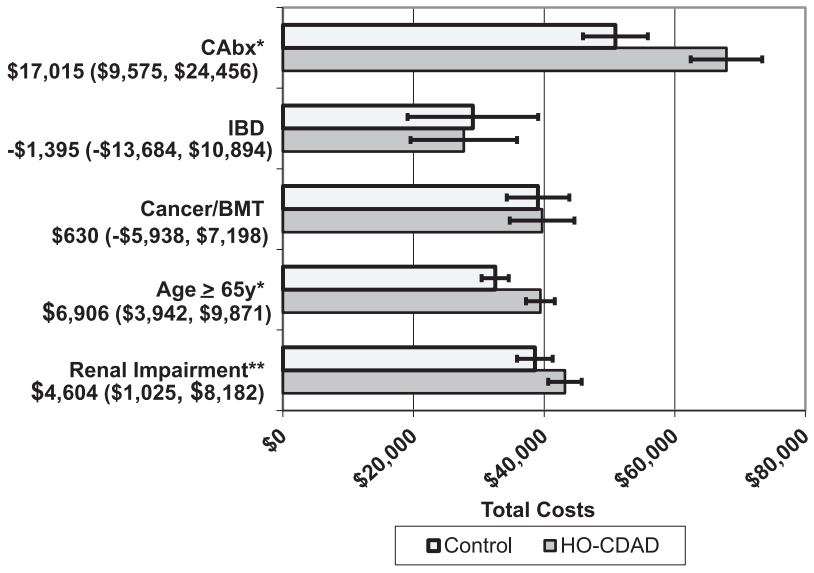

Figure 2. Adjusted total hospital costs. Data shown are differences (95% confidence interval) between HO-CDAD and control patients. BMT, bone marrow transplant; CAbx, concomitant antibiotics; IBD, inflammatory bowel disease. *p-value for difference < 0.001; **p-value for difference $= 0.012$.

Hospital Inpatient Quality Reporting Program, and will soon be subject to payment adjustments.

Our study adds important information to the outcomes literature in HO-CDAD, which is sparse. A recent review of US-based studies of the burden associated with CDAD in acute care facilities yielded only four such papers, noting that most published studies were small and inadequately controlled for confounding[24]. Furthermore, most studies did not distinguish between HO-CDAD and community-onset disease, which is a major shortcoming as the former has Medicare payment restrictions and the two CDAD populations may be clinically different.

The objectives of a prospective cohort study by Kyne *et al.*[4] may be the most closely related to our study, specifically the CAbx exposure group. Kyne *et al.* studied 271 inpatients receiving antibiotics for other infections; 40 developed CDAD while hospitalized. Using linear regression, adjusted LOS was 3.6 days (95% CI = 1.5–6.2) longer and adjusted costs were $3669 (95% CI = $1126–7024) ($5137 in 2010$) greater in CDAD patients. Using our methodology, our estimates of the effect of CDAD in patients with CAbx exposure (LOS 7.8 days; 95% CI = 5.7–9.9) and $17,015 (95% CI = $9575–24,456) are higher than Kyne *et al.*'s, with our sample size considerably larger and from multiple sites. Nevertheless, in both studies, the results were highly statistically significant and show a large impact of HO-CDAD on the healthcare system.

We found no statistically significant effect of HO-CDAD on LOS or hospital costs among patients with IBD. However, this was our smallest cohort, with the least amount of power to detect a significant difference. Ananthakrishnan *et al.*[10] identified hospitalized IBD patients with and without CDAD in the HCUP NIS database. The 2804 IBD/CDAD patients had an adjusted excess LOS of 3.0 (95% CI = 2.3–3.7) days, which was similar to our findings. However, that study identified patients only by discharge diagnosis and did not have access to clinical data for multivariate severity adjustment, unlike in our investigation. Ultimately, further study is needed to quantify the effect of HO-CDAD in IBD patients, although it seems reasonable that HO-CDAD would increase the economic burden of these patients.

We note considerable variation between estimates of LOS and cost in this dataset. HO-CDAD in the age ≥65 and CAbx study groups was associated with significant increases in both LOS and costs compared to controls, but, in the renal impairment and cancer groups, significant increases were seen in LOS only. Approximately 25% of patients were missing cost data, and this was mainly from the larger hospitals, which appeared to have higher costs before multivariate adjustment. Thus, our cost results—but not our LOS results—may be biased. Costs were derived from total hospital billed charges; charges for physician services were likely not included in the total cost. Moreover, the cost per day during a hospitalization is not consistent over the entire LOS, as earlier days in a hospital stay cost more than later ones. Finally, because the nature and extent of the charges included in *Health Facts* differed by institution, no systematic adjustment was attempted. Thus, in this study, LOS likely provides a clearer picture of resource utilization, with the ability to capture the additional days of care required among all patients.

Data should be interpreted in light of some additional limitations. Use of a positive toxin test may have expanded our ability to identify study patients compared to using

diagnosis codes alone, but positive toxin results may represent colonization rather than true infection in some patients. This may be reflected by the number of patients (30%) who received no CDAD-associated antibiotic treatment. In other studies, a smaller fraction of CDAD patients remained untreated (13% of 269 cases[25], 12% of 50 cases[26]). However, inclusion of patients with colonization rather than infection would likely have resulted in an *under-estimation* of the resource utilization associated with CDAD. Another limitation related to cohort selection is the lack of available data on diarrhea symptom onset. This may have resulted in the inclusion of patients who presented with severe diarrhea with onset in the community, in whom toxin testing was delayed. Finally, as with any multivariate analysis, it is possible that unmeasured variables affected these results. Nonetheless, the number of variables we examined was quite large and generally more detailed than in prior studies.

Our study has many strengths. To our knowledge, this is the first large study to describe incremental resource burden of HO-CDAD in these patient groups. Moreover, data were obtained from multiple, geographically diverse institutions, making our results more generalizable to US hospitals than smaller, single-center studies. To avoid over-estimation of attributable outcomes, we matched patients conservatively, including assignment of a pseudo-index date for the control population to ensure more similar exposure to risk, acuity, and pre-index LOS. Furthermore, we utilized clinical and treatment characteristics in our EHR-based data source that are not available in an administrative claims-based analysis. Notably, even with this conservative approach, we found substantial differences between HO-CDAD cases and controls in almost every study group.

Conclusions

Renal impairment, advanced age, cancer/BMT, and CAbx exposure are associated with significantly higher LOS among patients with HO-CDAD compared to controls. Similarly, older patients, renally impaired patients, and those with CAbx use are associated with significantly higher total hospital costs when HO-CDAD is present, with CAbx users being the most resource intensive. Thus, we conclude that the true burden of HO-CDAD is dependent on the case-mix of those with the infection. Opportunities for future research include confirmation of these results through prospective or additional retrospective studies. Our findings suggest that prompt evaluation and treatment for patients in these risk groups are warranted. Efforts may include improved infection control practices, empiric treatment of CDAD, and conservative use of CAbx.

Transparency

Declaration of funding
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Declaration of financial/other relationships
RC, BD, and TH are employees of Cerner Corporation, which received payment for consulting services delivered to Optimer in connection with the conduct of this study and the development of this manuscript. MS and ST are employees of Optimer Pharmaceuticals. BN's company, OptiStatim, LLC, was paid a consulting fee by the Cerner Corporation. RC, BD, and TH are stockholders and employees of Cerner Corporation, which owns the Health Facts database and provides consulting services to pharmaceutical and biotechnology companies, including Optimer.

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Notice of Correction

The version of this article published in JME 2013 vol 16 issue 3 contained an error on pages 6–7.
The sentence should have read "*Moreover, C. difficile infection is recognized as a new measure of hospital-acquired infection in the Hospital Inpatient Quality Reporting Program, and will soon be subject to payment adjustments.*"
The error has been corrected for this version.

