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The impact of hospital-onset *Clostridium Difficile* infection on outcomes of hospitalized patients with sepsis

Tara Lagu, MD, MPH^{1,2,3}, Mihaela S. Stefan, MD^{1,2,3}, Sarah Haessler, MD^{3,4}, Thomas L. Higgins, MD, MBA^{2,3,5}, Michael B. Rothberg, MD, MPH⁶, Brian H. Nathanson, PhD⁷, Nicholas S. Hannon¹, Jay S. Steingrub, MD^{1,3,5}, and Peter K. Lindenauer, MD, MSc^{1,3}

¹Center for Quality of Care Research, Baystate Medical Center, Springfield, MA

²Division of General Medicine, Baystate Medical Center, Springfield, MA

³Tufts University School of Medicine, Boston, MA

⁴Division of Infectious Diseases, Baystate Medical Center, Springfield, MA

⁵Division of Pulmonary and Critical Care, Baystate Medical Center, Springfield, MA

⁶Department of Medicine, Medicine Institute, Cleveland Clinic, Cleveland, OH

⁷OptiStatim LLC, Longmeadow, MA

Abstract

Objective—To examine the impact of hospital-onset *C. Difficile* infections (HOCDI) on the outcomes of patients with sepsis.

Background—Most prior studies that have addressed this issue lacked adequate matching to controls, suffered from small sample size, or failed to consider time-to-infection.

Design—Retrospective cohort study.

Setting & Patients—We identified adults with a principal or secondary diagnosis of sepsis who received care at one of the institutions that participated in a large multi-hospital database between July 1, 2004, and December 31, 2010. Among eligible patients with sepsis, we identified patients who developed HOCDI during their hospital stay.

Measurements—We used propensity matching and date of diagnosis to match cases to patients without CDI and compared outcomes between the two groups.

Main Results—Of 218,915 sepsis patients, 2,368 (1.08%) developed HOCDI. Unadjusted in-hospital mortality was significantly higher in HOCDI patients than controls (25% vs. 10%, $p<0.001$). After multivariate adjustment, in-hospital mortality rate was 24% in cases vs. 15% in controls. In an analysis limited to survivors, adjusted length of stay (LOS) among cases with CDI

Corresponding Author: Dr. Tara Lagu, Center for Quality of Care Research, Baystate Medical Center, 280 Chestnut St., 3rd Floor, Springfield, MA 01199, Phone: 413-505-9173, Fax: 413-794-8866, lagutc@gmail.com.

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was 5.1 days longer than controls (95% CI: 4.4, 5.8) and the median-adjusted cost increase was \$4,916 ($p<0.001$).

Conclusions—After rigorous adjustment for time to diagnosis and presenting severity, hospital-acquired CDI was associated with increased mortality, LOS, and cost. Our results can be used to assess the cost-effectiveness of prevention programs and suggest that efforts directed towards high-risk patient populations are needed.

Keywords

clostridium difficile; sepsis; hospital-acquired infections; attributing outcomes

INTRODUCTION

There are approximately 3 million cases of *Clostridium difficile* infection (CDI) per year in the United States.¹⁻⁴ Of these, 10% result in a hospitalization or occur as a consequence of the exposures and treatments associated with hospitalization.¹⁻⁴ Some patients with CDI experience mild diarrhea that is responsive to therapy; but other patients experience severe, life-threatening disease that is refractory to treatment, leading to pseudomembranous colitis, toxic megacolon, and sepsis with a 60-day mortality rate that exceeds 12%.⁵⁻¹⁴

Hospital-onset CDI (HOCDI), defined as *Clostridium difficile*-associated diarrhea and related symptoms with onset more than 48 hours after admission to a health care facility,¹⁵ represents a unique marriage of CDI risk factors.⁵ A vulnerable patient is introduced into an environment that contains both exposure to *Clostridium difficile* (through other patients or health care workers) and treatment with antibacterial agents that may diminish normal flora. Consequently, CDI is common among hospitalized patients.¹⁶⁻¹⁸ A particularly important group for understanding the burden of disease is patients who initially present to the hospital with sepsis and subsequently develop HOCDI. Sepsis patients are often critically ill and are universally treated with antibiotics.

Determining the incremental cost and mortality risk attributable to HOCDI is methodologically challenging. Because HOCDI is associated with presenting severity, the sickest patients are also the most likely to contract the disease. HOCDI is also associated with time of exposure or length of stay (LOS). Because LOS is a risk factor, comparing LOS between those with and without HOCDI will overestimate the impact if the time to diagnosis is not taken into account.^{16,17,19,20} We aimed to examine the impact of HOCDI in hospitalized patients with sepsis using a large, multi-hospital database with statistical methods that took presenting severity and time to diagnosis into account.

METHODS

Data Source and Subjects

Permission to conduct this study was obtained from the Institutional Review Board at Baystate Medical Center. We used the Premier Healthcare Informatics database, a voluntary, fee-supported database created to measure quality and health care utilization which has been used extensively in health services research.²¹⁻²³ In addition to the elements found in

hospital claims derived from the uniform billing 04 (UB-04) form, Premier data include an itemized, date-stamped log of all items and services charged to the patient or their insurer, including medications, laboratory tests, and diagnostic and therapeutic services. Approximately 75% of hospitals that submit data also provide information on actual hospital costs, taken from internal cost accounting systems. The rest provide cost estimates based on Medicare cost-to-charge ratios. Participating hospitals are similar to the composition of acute care hospitals nationwide, although they are more commonly small- to mid-sized non-teaching facilities and are more likely to be located in the southern US.

We included medical (non-surgical) adult patients with sepsis who were admitted to a participating hospital between July 1, 2004, and December 31, 2010. Because we sought to focus on the care of patients who present to the hospital with sepsis, we defined sepsis as the presence of a diagnosis of sepsis plus evidence of both blood cultures and antibiotic treatment within the first two days of hospitalization; we used the first two days of hospitalization rather than just the first day because, in administrative datasets, the duration of the first hospital day includes partial days that can vary in length. We excluded patients who died or were discharged prior to day 3 because HOCDI is defined as onset after 48 hours in a health care facility.¹⁵ We also excluded surviving patients who received less than three consecutive days of antibiotics, and patients who were transferred from or to another acute care facility; the latter exclusion criterion was used because we could not accurately determine the onset or subsequent course of their illness.

Identification of Patients at Risk for and Diagnosed with Hospital-Onset CDI

Among eligible patients with sepsis, we aimed to identify a cohort at risk for developing CDI during the hospital stay. We excluded patients: 1.) with a diagnosis indicating that diarrhea was present on admission; 2.) with a diagnosis of CDI that was indicated to be present on admission; 3.) who were tested for CDI on the first or second hospital day; and 4.) who received an antibiotic that could be consistent with treatment for CDI (oral or intravenous [IV] metronidazole or oral vancomycin) on hospital days 1 or 2.

Next, we aimed to identify sepsis patients at risk for HOCDI who developed HOCDI during their hospital stay. Among eligible patients described above, we considered a patient to have “HOCDI” if they had an ICD-9-CM (*International Classification of Diseases, Ninth Revision, Clinical Modification*) diagnosis of CDI (primary or secondary but not present on admission) plus evidence of testing for CDI after hospital day 2 and treatment with oral vancomycin or oral or IV metronidazole that was started after hospital day 2 and within 2 days of the C. Difficile test and evidence of treatment for CDI for at least 3 days unless the patient was discharged or died.

Patient Information

We recorded patient age, gender, marital status, insurance status, race, and ethnicity. Using software provided by the Healthcare Costs and Utilization Project of the Agency for Healthcare Research and Quality, we categorized information on thirty comorbid conditions. We also created a single numerical comorbidity score based on a previously published and validated combined comorbidity score that predicts 1-year mortality.²⁴ Based on a

previously described algorithm,²⁵ we used diagnosis codes to assess the source (lung, abdomen, urinary tract, blood, other) and type of sepsis (gram positive, gram negative, mixed, anaerobic, fungal). Because patients can have more than one potential source of sepsis (e.g., pneumonia and urinary tract infection) and more than one organism causing infection (e.g., urine with gram negative rods and blood culture with gram positive cocci), these categories are not mutually exclusive (Online Table). We used billing codes to identify the use of therapies, monitoring devices, and pharmacologic treatments to characterize both initial severity of illness and severity at the time of CDI diagnosis. These therapies are included in a validated sepsis mortality prediction model (designed for administrative datasets) with similar discrimination and calibration to clinical ICU risk-adjustment models such as the MPM₀-III.^{26,27}

Outcomes

Our primary outcome of interest was in-hospital mortality. Secondary outcomes included LOS and costs for survivors only and for all patients.

Statistical Methods

We calculated patient-level summary statistics for all patients using frequencies for binary variables and medians and interquartile percentiles for continuous variables. P-values <0.05 were considered statistically significant.

To account for presenting severity and time to diagnosis, we used methods that have been described elsewhere.^{12,13,18,20,28} First, we identified patients who were eligible to develop HOCDI. Second, for all eligible patients, we identified a date of disease onset, or “index date.” For patients who met criteria for HOCDI, this was the date on which the patient was tested for CDI. For eligible patients without disease, this was a date randomly assigned to any time during the hospital stay.²⁹ Next, we developed a non-parsimonious propensity score model that included all patient characteristics (demographics, comorbidities, sepsis source, and severity of illness on presentation and on the index date; all variables listed in Table 1 were included in the propensity model). Some of the variables for this model (e.g., mechanical ventilation and vasopressors) were derived from a validated severity model.²⁶ We adjusted for correlation within hospital when creating the propensity score using Huber-White robust standard error estimators clustered at the hospital level.³⁰ We then created matched pairs with the same length of stay prior to the index date and similar propensity for developing CDI. We first matched on index date and then, within each index-date-matched subset, matched patients with and without HOCDI by their propensity score using a 5 to 1 Greedy Match algorithm.³¹ We used the differences in length of stay between the cases and controls after the index date to calculate the additional attributable LOS estimates; we also separately estimated the impact on cost and LOS in a group limited to those who survived after discharge because of concerns that death could shorten length of stay and reduce costs.

Analysis Across Clinical Subgroups

In a secondary analysis, we examined heterogeneity in the association between HOCDI and outcomes within subsets of patients defined by age, combined comorbidity score, and admission to ICU by Day 2. We created separate propensity scores using the same

covariates in the primary analysis, but limited matches to within these subsets. For each group, we examined how the covariates in the HOCDI and control groups differed after matching with inference tests that took the paired nature of the data into account. All analyses were carried out using STATA/SE 11.1 (StataCorp, College Station, TX).

RESULTS

We identified 486,943 adult sepsis admissions to a Premier hospital between July 1, 2004, and December 31, 2010. After applying all exclusion criteria, we had a final sample of 218,915 admissions with sepsis (from 400 hospitals) at risk for HOCDI (Figure 1). Of these, 2,368 (1.08%) met criteria for diagnosis of CDI after hospital day 2 and were matched to controls using index date and propensity score.

Patient and Hospital Factors

After matching, the median age was 71 years in cases and 70 years in controls (Table 1). Less than half (46%) of the population was male. Most cases (61%) and controls (58%) were white. Heart failure, hypertension, chronic lung disease, renal failure, and weight loss were the most common comorbid conditions. Our propensity model, which had a c statistic of 0.75, identified patients whose risk varied from a mean of 0.1% in the first decile to a mean of 3.8% in the 10th decile. Before matching, 40% of cases and 29% of controls were treated in the ICU by hospital day 2; after matching, 40% of both cases and controls were treated in the ICU by hospital day 2.

Distribution by Length of Stay, Index Day, and Risk for Mortality

The unadjusted and unmatched length of stay was longer for cases than controls (19 days versus 8 days, Online Figure 1 and Table 2). Approximately 90% of the patients had an index day of 14 or less (Figure 2). Among patients both with and without CDI, the unadjusted mortality risk increased as the index day (and thus the total LOS) increased.

Adjusted Results

Compared to patients without disease, HOCDI patients had an increased unadjusted mortality (24% versus 10%, $p<0.001$). This translates into a relative risk of 2.4 (95% CI: 2.2, 2.5). In the matched cohort, the difference in the mortality rates was attenuated, but still significantly higher in the HOCDI patients (24% versus 15%, $p<0.001$, an absolute difference of 9%; 95% CI 6.4, 10.8). The adjusted relative risk of mortality for HOCDI was 1.6 (95% CI: 1.4, 1.8; Table 2). After matching, patients with CDI had a LOS of 19.2 days versus 14.2 days in matched controls (difference of 5.1 days; 95% CI: 4.4, 5.7; $p<0.001$). When the LOS analysis was limited to survivors only, this difference of 5 days remained ($p<0.001$). In an analysis limited to survivors only, the difference in median costs between cases and controls was \$4,916 (95% CI: \$4,088, \$5,768; $p<0.001$). In a secondary analysis examining heterogeneity between HOCDI and outcomes across clinical subgroups, the absolute difference in mortality and costs between cases and controls varied across demographics, comorbidity, and ICU admission, but the relative risks were similar (Figure 3 and Online Figure 3).

DISCUSSION

In this large cohort of patients with sepsis, we found that approximately 1 in 100 patients with sepsis developed HOCDI. Even after matching with controls based on the date of symptom onset and propensity score, patients who developed HOCDI were more than 1.6 times more likely to die in the hospital. HOCDI also added 5 days to the average hospitalization for patients with sepsis and increased median costs by approximately \$5,000. These findings suggest that a hospital that prevents one case of HOCDI per month in sepsis patients could avoid 1 death and 60 inpatient days annually, achieving an approximate yearly savings of \$60,000.

Until now, the incremental cost and mortality attributable to HOCDI in sepsis patients have been poorly understood. Attributing outcomes can be methodologically challenging because patients who are at greatest risk for poor outcomes are the most likely to contract the disease and are at risk for longer periods of time. Therefore, it is necessary to take into account differences in severity of illness and time at risk between diseased and non-diseased populations and to ensure that outcomes attributed to the disease occur after disease onset.^{28,32} The majority of prior studies examining the impact of CDI on hospitalized patients have been limited by a lack of adequate matching to controls, small sample size, or failure to take into account time-to-infection.^{16,17,19,20}

A few studies have taken into account severity, time-to infection, or both in estimating the impact of HOCDI. Using a time-dependent Cox model that accounted for time to infection, Micek et al. found no difference in mortality but a longer LOS in mechanically ventilated patients (not limited to sepsis) with CDI.³³ However, their study was conducted at only 3 centers, did not take into account severity at the time of diagnosis, and did not clearly distinguish between community-onset-CDI and HOCDI. Oake et al. and Forster et al. examined the impact of CDI on patients hospitalized in a two-hospital health system in Canada.^{12,13} Using the baseline mortality estimate in a Cox multivariate proportional hazards regression model that accounted for the time-varying nature of CDI, they found that HOCDI increased absolute risk of death by approximately 10%. Also, notably similar to our study was their findings that HOCDI occurred in approximately 1 in 100 patients and that the attributable median increase in LOS due to hospital-onset CDI was 6 days. Although methodologically rigorous, these two small studies did not assess the impact of CDI on costs of care, were not focused on sepsis patients or even patients who received antibiotics, and also did not clearly distinguish between community-onset CDI and HOCDI.

Our study therefore has important strengths. It is the first to examine the impact of HOCDI, including costs, on the outcomes of patients hospitalized with sepsis. The fact that we took into account both time to diagnosis and severity at the time of diagnosis (by using an index date for both cases and controls and determining severity on that date) prevented us from overestimating the impact of HOCDI on outcomes. The large differences in outcomes we observed in unadjusted and unmatched data were tempered after multivariate adjustment (e.g., difference in LOS from 10.6 days to 5.1 additional days; costs from \$14,620 to \$4,916 additional costs after adjustment). Our patient sample was derived from a large, multi-hospital database that contains actual hospital costs as derived from internal accounting

systems. The fact that our study used data from hundreds of hospitals means that our estimates of cost, LOS, and mortality may be more generalizable than the work of Micek, Oake, and Forster.

This work also has important implications. First, hospital administrators, clinicians, and researchers can use our results to evaluate the cost-effectiveness of HOCDI prevention measures (e.g., hand hygiene programs, antibiotic stewardship). By quantifying the cost per case in sepsis patients, we allow administrators and researchers to compare the incremental costs of HOCDI prevention programs to the dollars and lives saved due to prevention efforts. Second, we found that our propensity model identified patients whose risk varied greatly. This suggests that an opportunity exists to identify subgroups of patients that are at highest risk. Identifying high-risk subgroups will allow for targeted risk reduction interventions and the opportunity to reduce transmission (e.g., by placing high-risk patients in a private room). Finally, we have reaffirmed that time to diagnosis and presenting severity need to be rigorously addressed prior to making estimates of the impact of CDI burden and other hospital-acquired conditions and injuries.

There are limitations to this study as well. We did not have access to microbiological data. However, we required a diagnosis code of CDI, evidence of testing, and treatment after the date of testing in order to confirm a diagnosis. We also adopted detailed exclusion criteria to ensure that CDI that was not present on admission and that controls did not have CDI. These stringent inclusion and exclusion criteria strengthened the internal validity of our estimates of disease impact. We used administrative claims data, which limited our ability to adjust for severity. However, the detailed nature of the database allowed us to use treatments, such as vasopressors and antibiotics, to identify cases; treatments were also used as a validated indicator of severity,²⁶ which may have helped to reduce some of this potential bias. While our propensity model included many predictors of CDI, such as use of proton pump inhibitors and factors associated with mortality, not every confounder was completely balanced after propensity matching, although the statistical differences may have been related to our large sample size and therefore might not be clinically significant. We also may have failed to include all possible predictors of CDI in the propensity model.

In a large, diverse cohort of hospitalized patients with sepsis, we found that HOCDI lengthened hospital stay by approximately five days, increased risk of in-hospital mortality by 9%, and increased hospital cost by approximately \$5,000 per patient. These findings highlight the importance of identifying effective prevention measures and of determining the patient populations at greatest risk for hospital-onset CDI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Lindenauer had full access to all of the data in the study; they take responsibility for the integrity of the data and the accuracy of the data analysis. Drs. Lagu, Lindenauer, Steingrub, Higgins, Stefan, Haessler, and Rothberg conceived of the study. Dr. Lindenauer acquired the data. Drs. Lagu, Lindenauer, Rothberg, Steingrub, Nathanson, Stefan, Haessler, Higgins, and Mr. Hannon analyzed and interpreted the data. Dr. Lagu drafted the manuscript. Drs. Lagu, Lindenauer, Rothberg, Steingrub, Nathanson, Stefan, Haessler, Higgins, and Mr. Hannon critically reviewed the manuscript for important intellectual content. Dr. Nathanson carried out the statistical analyses. Dr. Nathanson, through his company OptiStatim LLC, was paid by the investigators with funding from the Department of Medicine at Baystate Medical Center to assist in conducting the statistical analyses in this study.

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Figure 1.
Derivation of patients with sepsis who were at risk for HOCDI

Figure 2.
Unadjusted mortality by index day among patients with and without HOCDI

Figure 3.
Adjusted In-hospital mortality across patient subgroups among patients with and without HOCDI

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	Before Matching			After Matching		
	HOCDI n = 2,368 %	No CDI n = 216,547 %	p	HOCDI n = 2,368 %	No CDI n = 2,368 %	p
Fungal	17.5	7.5	<0.01	17.5	18.3	0.44
Most Common Comorbid Conditions						
Congestive Heart Failure	35.1	24.6	<0.01	35.1	37.5	0.06
Chronic Lung Disease	31.6	27.6	<0.01	31.6	32.1	0.71
Hypertension	31.5	37.7	<0.01	31.5	29.7	0.16
Renal Failure	29.7	23.8	<0.01	29.7	31.2	0.28
Weight Loss	27.7	13.3	<0.01	27.7	29.4	0.17
Treatments by Day 2						
ICU Admission	40.0	29.5	<0.01	40.0	40.7	0.64
Use of Bicarbonate	12.2	7.1	<0.01	12.2	13.6	0.15
Fresh Frozen Plasma	1.4	1.0	0.03	1.4	1.1	0.36
Inotropes	1.4	0.9	0.01	1.4	2.2	0.04
Hydrocortisone	6.7	4.7	<0.01	6.7	7.4	0.33
Thiamine	4.2	3.3	0.01	4.2	4.1	0.83
Psychotropics (e.g., Haldol for delirium)	10.0	9.2	0.21	10.0	10.8	0.36
Restraints (e.g., for delirium)	2.0	1.5	0.05	2.0	2.5	0.29
Angiotensin-Converting-Enzyme Inhibitors	12.1	13.2	0.12	12.1	10.9	0.20
Statins	18.8	21.1	0.01	18.8	16.9	0.09
Drotrecogin alfa	0.6	0.3	0.00	0.6	0.6	0.85
Foley Catheter	19.2	19.8	0.50	19.2	22.0	0.02
Diuretics	28.5	25.4	0.01	28.5	29.6	0.42
Red Blood Cells	15.5	10.6	<0.01	15.5	15.8	0.81
Calcium Channel Blockers	19.3	16.8	0.01	19.3	19.1	0.82
Beta Blockers	32.7	29.6	0.01	32.7	30.6	0.12
Proton Pump Inhibitors	59.6	53.1	<0.01	59.6	61.0	0.31

Table 2

Comparison of length of stay, mortality, and costs for propensity-matched patients with and without Hospital-Onset *Clostridium Difficile* (HOCDI)

Outcome	HOCDI	No HOCDI	Difference (95% CI)	p
Length of Stay, days				
Raw Results	19.2	8.3	8.4 (8.4, 8.5)	<0.01
Raw Results for Survivors only	18.6	8.0	10.6 (10.3, 11.0)	<0.01
Matched Results	19.2	14.2	5.1 (4.4, 5.7)	<0.01
Matched Results for Survivors only	18.6	13.6	5.1 (4.4, 5.8)	<0.01
Mortality, %				
Raw Results	24.0	10.1	13.9 (12.6, 15.1) RR = 2.4 (2.2, 2.5)	<0.01
Matched Results	24.0	15.4	8.6 (6.4, 10.9) RR = 1.6 (1.4, 1.8)	<0.01
Costs, US \$				
Raw Results Median Costs, and Interquartile Range in brackets	\$26,187 [15117, 46273]	\$9,988 [6296, 17351]	\$16,190 (15826, 16555)	<0.01
Raw Results for Survivors Only	\$24,038 [14169, 41654]	\$9,429 [6070, 15875]	\$14,620 (14246, 14996)	<0.01
Matched Results	\$26,187 [15117, 46273]	\$19,160 [12392, 33777]	\$5,308 (4521, 6108)	
Matched Results for Survivors Only	\$24,038 [14169, 41654]	\$17,811 [11614, 29298]	\$4,916 (4088, 5768)	<0.01