The Effect of Hospital-Acquired *Clostridium difficile* Infection on In-Hospital Mortality

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**Background:** The effects of hospital-acquired *Clostridium difficile* infection (CDI) on patient outcomes are incompletely understood. We conducted this study to determine the independent impact of hospital-acquired CDI on in-hospital mortality after adjusting for the time-varying nature of CDI and baseline mortality risk at hospital admission.

**Methods:** This retrospective observational study used data from the Ottawa Hospital (Ottawa, Ontario, Canada) data warehouse. Inpatient admissions with a start date after July 1, 2002, and a discharge date before March 31, 2009, were included. Stratified analyses and a Cox multivariate proportional hazards regression model were used to determine if hospital-acquired CDI was associated with time to in-hospital death.

**Results:** A total of 136,877 admissions were included. Hospital-acquired CDI was identified in 1393 admissions (overall risk per admission, 1.02%; 95% confidence interval [CI], 0.97%-1.06%). The risk of hospital-acquired CDI significantly increased as the baseline mortality risk increased: from 0.2% to 2.6% in the lowest to highest deciles of baseline risk. Hospital-acquired CDI significantly increased the absolute risk of in-hospital death across all deciles of baseline risk (pooled absolute increase, 11%; 95% CI, 9%-13%). Cox regression analysis revealed an average 3-fold increase in the hazard of death associated with hospital-acquired CDI (95% CI, 2.4-3.7); this hazard ratio decreased with increasing baseline mortality risk.

**Conclusions:** Hospital-acquired CDI was independently associated with an increased risk of in-hospital death. Across all baseline risk strata, for every 10 patients acquiring the infection, 1 person died.

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tional information systems of The Ottawa Hospital. These systems include the patient registration system, the clinical data repository (containing laboratory, pharmacy, radiology, and clinical notes), and the discharge abstract database (which summarizes demographic, diagnostic, and procedural information for each inpatient admission). This study was approved by the Ottawa Hospital research ethics board.

STUDY ELIGIBILITY CRITERIA

We included inpatient admissions at The Ottawa Hospital with a start date after July 1, 2002, and a discharge date before March 31, 2009. The study start date was selected to ensure that we had laboratory data for all admissions; the study end date represented the most complete admissions from the discharge abstract database at the time of analysis.

We excluded inpatient admissions where the length of stay was less than 3 days because hospital-acquired CDI requires a positive test result no earlier than 3 days into the admission.14 We also excluded admissions for patients younger than 15 years and those admitted to an obstetrical service because the baseline risk prediction method for in-hospital mortality that we used in this study was not validated in these populations.

For all included admissions, we abstracted the following information from the data warehouse: age, sex, admission and discharge dates, admitting hospital service, diagnoses coded using International Statistical Classification of Diseases, 10th Revision (ICD-10), and all laboratory test results. For each admission, we measured health care utilization in the year prior to the admission by calculating the number of inpatient admissions and emergency department visits to The Ottawa Hospital and the total number of inpatient days in The Ottawa Hospital.

DETERMINING HOSPITAL-ACQUIRED CDI STATUS

A hospital-acquired CDI case was defined as laboratory confirmation of a positive C difficile toxin assay from liquid stool obtained at least 72 hours after admission. Positive toxin assays that occurred within 2 months of a previous positive test result were not included. In other words, the 2 positive samples were counted as 1 case with the date of the first positive test result used. These criteria are mandated by the Ontario Provincial Infectious Diseases Advisory Committee.14 If 2 positive test results occurred during a single admission and were more than 2 months apart, only the first positive test result was included in our analysis.

We used electronic laboratory reports of C difficile toxin assays, instead of ICD-10 diagnostic codes, to determine hospital-acquired CDI status. The accuracy of the ICD-10 code for CDI is poor, with sensitivity and specificity of 70% and 99%, respectively.15,16 We applied text searching techniques to the electronic laboratory reports to identify all reports of positive test results for the included admissions. We then compared the date and time of the positive toxin assay with the admission date and time to determine if the positive C difficile toxin assay indicated a hospital-acquired case. We validated the results from our electronic algorithm by comparing with reports of positive test results manually classified by infection control staff. Compared with a gold standard classification by our hospital’s Department of Infection Control, our algorithm had a sensitivity and specificity of 100%.

MAIN OUTCOME MEASURE

The primary outcome was time to in-hospital death. This outcome was determined using the discharge abstract database housed within the data warehouse. Richards et al17 validated the coding of this outcome in the discharge abstract database by reabstracting data from 1936 randomly selected medical charts from 18 hospitals across Canada; no discrepancy was found between the discharge abstract database and the medical chart review.

STATISTICAL ANALYSIS

We summarized characteristics of included admissions by hospital-acquired CDI status. An important characteristic that we examined was baseline mortality risk.

We calculated the baseline mortality risk for each admission using a regression model developed by Escobar et al18 and validated in our hospital’s population.19 This model calculates a patient’s risk of dying in-hospital using data available at the time of admission. This feature of the model is important because it ensures that the baseline mortality risk is not confounded by complications arising during the admission. The model includes age, sex, comorbidities (measured with the Charlson comorbidity score20 using weights from Schnellweiss et al21), acuity of admission, admitting hospital service, and severity of acute disease (summarized using the Laboratory-based Acute Physiology Score [LAPS]19).

To investigate the association between baseline mortality risk and hospital-acquired CDI, we divided the population into deciles of baseline mortality risk and calculated the proportion of admissions within each decile that were classified as a hospital-acquired CDI case. We used the Cochran-Armitage test22 to determine if there was a significant trend in the risk of infection by baseline mortality risk.

We calculated the unadjusted association between hospital-acquired CDI and in-hospital mortality using an odds ratio. The adjusted association between hospital-acquired CDI and in-hospital mortality was assessed using 2 methods. First, we performed a stratified analysis in which we divided the population into deciles of baseline mortality risk and calculated the absolute and relative risk of mortality associated with hospital-acquired CDI within each stratum. For both absolute and relative risk, we created a forest plot and estimated the overall risk using a fixed-effects model. Second, we used a Cox multivariate proportional hazards regression model23 with patient observation starting at admission and being censored at discharge. This approach was selected to accommodate the time-varying nature of hospital-acquired CDI. Baseline mortality risk, hospital-acquired CDI (expressed as a time-dependent covariate24), and the interaction between these 2 variables were the primary predictors forced into the model. We included the interaction term to evaluate the presence of effect modification. We also included other covariates that were available within the data warehouse for evaluation as possible predictors of mortality. These covariates were number of admissions to our hospital in the previous year, number of emergency department visits to our hospital in the previous year, total number of inpatient days in our hospital in the previous year, and year of admission (to account for trends over time). Because inclusion of these covariates was considered exploratory and not based on specific clinical hypotheses, they were subjected to stepwise backward elimination from the model. We chose an α level of .10 for retention in the model because the consequences of retaining an unimportant variable in our model were considered less severe than those of excluding an important variable, given our large sample size.25 We used fractional polynomial functions to determine the best linear or nonlinear form for continuous covariates.26,27 Covariates were centered about their means to reduce the risk of multicollinearity.28 We accounted for clustering due to multiple hospitalizations of the same patient within the study period using a marginal approach with
robust sandwich estimates for the covariance matrix. The estimated regression coefficients and covariance parameters from the model were used to generate a plot of the adjusted hazard ratio (HR) and 95% confidence intervals (CIs) associated with hospital-acquired CDI as a function of baseline mortality risk. We used SAS statistical software (version 9.1.3; SAS Inc, Cary, North Carolina) for all analyses.

RESULTS

DESCRIPTION OF STUDY COHORT

A total of 136,877 admissions were included (Table) from 89,086 unique patients (29.8% with repeated admissions). Approximately half of the admissions were female patients, and their mean age was 63 years. Chronic diseases were common in the cohort with a mean Charlson score of 2.4; only 37% of admissions had a Charlson score of 0. Three-quarters of patients were admitted urgently. Thirty-five percent of patients had 1 or more admission to The Ottawa Hospital in the year prior to their study admission. The median baseline mortality risk was 1.8% (interquartile range [IQR], 0.4%-7.6%).

RISK OF HOSPITAL-ACQUIRED CDI

Hospital-acquired CDI was identified in 1393 admissions for an overall risk of 1.02% per admission (95% CI, 0.97%-1.06%). Only 27 patients (0.03%) had repeated hospital-acquired CDI across their multiple admissions. Compared with uninfected patients, patients with hospital-acquired CDI were older, had more comorbidities, inpatient admissions, and emergency department visits in the previous year, and were more likely to be admitted urgently (Table). In addition, patients with hospital-acquired CDI were more acutely ill at admission (having a higher LAPS) and had a higher median baseline mortality risk (8.0% vs 1.8%).

The risk of hospital-acquired CDI significantly increased as the baseline mortality risk increased (χ² value=15,679.6; P < .001) (Figure 1). Overall, the absolute risk of hospital-acquired CDI was low. Approximately 2.6% of the admissions in the decile with the highest baseline mortality risk acquired CDI, compared with only 0.2% of the admissions in the decile with the lowest risk.

TIMING OF HOSPITAL-ACQUIRED CDI

Most cases of hospital-acquired CDI (75%) were identified on or after the seventh day of the admission. Only 2.8% and 5.5% of CDI cases were detected on the third and fourth day of the encounter, respectively. The median number of days from admission to CDI case detection was 12 days (IQR, 7-24 days). For patients with hos-
pital-acquired CDI who died, the median number of days from CDI detection to death was 14 days (IQR, 5.5-31.0 days).

**IN-HOSPITAL MORTALITY**

The unadjusted association between hospital-acquired CDI and in-hospital death was OR, 4.62 (95% CI, 4.06-5.25). The stratified analysis showed that hospital-acquired CDI was significantly associated with an increased risk of in-hospital death, regardless of the baseline mortality risk. The absolute risk difference (Figure 2A) ranged from a minimum of 4% (95% CI, -4% to 11%) in the second risk decile to a maximum of 17% (95% CI, 11%-23%) in the eighth risk decile. There was moderate heterogeneity across the deciles (tests for heterogeneity: χ² value, 15.89; P=.07; I²=43%). The pooled absolute risk difference estimate was 11% (95% CI, 9%-13%). The relative risk of death (Figure 2B) was also significantly increased regardless of the baseline mortality risk, although the relative risk decreased from the lowest to the highest baseline mortality risk deciles. Within the lowest-risk decile, the relative risk of death associated with hospital-acquired CDI was 45.70 (95% CI, 11.35-183.98), while in the highest-risk decile it was 1.29 (95% CI, 1.11-1.50). There was considerable heterogeneity across the deciles (χ² value, 153.31; P<.001; I²=94%). The pooled relative risk estimate was 1.99 (95% CI, 1.81-2.19).

The results of the Cox model show that baseline mortality risk (HR, 1.07; 95% CI, 1.06-1.07), hospital-acquired CDI (HR, 2.98; 95% CI, 2.42-3.65), and the interaction between these 2 variables (HR, 0.67; 95% CI, 0.61-0.73) was significant (P<.001). Regression coefficients associated with baseline mortality risk were transformed so that the HRs represent the effect associated with an approximately 10% relative increase in baseline mortality risk. Other covariates retained in the model were year of admission (HR, 0.96; 95% CI, 0.95-0.97), as well as transformations of the number of admissions to our hospital in the previous year (HR, 1.15; 95% CI, 1.05-1.26) and the total number of inpatient days in our hospital in the previous year (HR, 1.03; 95% CI, 1.00-1.05). The only variable that was offered to the model and excluded was the number of emergency department visits to our hospital in the previous year. This variable was excluded because it was collinear with the number of admissions to our hospital in the previous year.

The regression coefficient associated with hospital-acquired CDI suggests that, for an “average” patient (a patient with covariate values set at mean levels), hospital-acquired CDI increased the hazard of dying 3-fold (95% 1.29, 1.11-1.50).
CI, 2.42-3.65). Moreover, the interaction term of baseline mortality risk and hospital-acquired CDI suggests that the HR associated with hospital-acquired CDI decreased with increasing baseline mortality risk; in particular, the HR decreased by approximately 4% with each 10% relative increase in baseline mortality risk. Thus, hospital-acquired CDI had a greater relative impact on death for patients with a lower baseline mortality risk (Figure 3).

**COMMENT**

Our study has several important findings. Overall, the risk of acquiring CDI during a nonobstetrical hospital admission is 1 in 100. This risk is lower in patients who have a low baseline mortality risk. For patients with a baseline mortality risk at or below the median of 1.8%, the risk of acquiring CDI ranges from 1 in 120 to 1 in 775. In contrast to the low risk of acquiring CDI inhospital, we found that the clinical impact of CDI is significant. There was a statistically significant and independent association of CDI with the risk of death in-hospital. Using a simple stratified analysis, we found that across deciles of baseline mortality risk, hospital-acquired CDI increased the absolute risk of death by approximately 10%. This means that across all baseline risk strata, for every 10 patients acquiring the infection, 1 person died. Our model-based approach, accounting for hospital-acquired CDI acquisition as a time-varying covariate and adjusting for year of admission and number of inpatient admissions and hospital days in the previous year, found an average 3-fold increase in the hazard of death associated with CDI acquisition.

We found the relative impact of hospital-acquired CDI on in-hospital mortality to decrease with increasing baseline mortality risk. We speculate that this occurs because patients with a high baseline mortality risk already have many factors that predispose them to a poor outcome. Acquiring CDI, in this context, will have a small relative impact on a patient’s overall sickness. In contrast, a healthy patient who acquires CDI will experience a larger relative impact.

Taken together, these findings highlight the need for and the challenge of overcoming an important barrier to sustaining efforts to minimize the spread of CDI. Our findings have important implications for health care providers, investigators, and hospital managers responsible for reducing the incidence of CDI. Health care providers need to work diligently to minimize the spread of CDI despite the absence of any immediate clinical feedback to guide their actions. Careful selection of antibiotic usage and hand hygiene are 2 practices in which physicians are notoriously noncompliant with guidelines. Health care providers must also be aware of the high level of risk that hospital-acquired CDI poses to ill patients as well as to comparatively healthy patients. Given the low risk of hospital-acquired CDI, investigators should assess the impact of interventions by measuring clinical outcomes for sufficiently large patient populations. Finally, hospital managers should focus their interventions specifically toward patients at the highest risk of dying because these patients have the highest risk for hospital-acquired CDI. In addition, managers must work to minimize the role of environmental contamination in the spread of infection.

Figure 3. Model-based hazard ratio (HR) of death associated with hospital-acquired *Clostridium difficile*-associated disease (CDAD) as a function of baseline mortality risk. The solid line represents model-based HR; the dashed lines represent 95% confidence intervals.
Our results are, in many ways, consistent with those of previous studies that have examined the association between hospital-acquired CDI and mortality.6-13 We believe we have quantified the impact in a valid manner given our analytical methods, the clinical data we had available, and the size of our cohort. An important strength of our approach was its ability to account for the time-varying nature of CDI. To our knowledge, this had not been done by any of the previous studies. Failing to account for the time in hospital before CDI acquisition may lead to an inflated estimate of its impact on mortality.33 Another strength of our study was its ability to explore the risks of hospital-acquired CDI while accounting for baseline mortality risk using clinical data. It is also noteworthy that nearly all of the previous studies had been case-control designs. These factors may have led to some nuanced differences between our study and prior investigations.

There are limitations to our work. First, we may not have identified all CDI cases. Our institution uses an enzyme immunofluorescence assay to detect *Clostridium difficile* toxin on submitted stool samples. The sensitivity of this test is estimated to be 70% to 90%.34,35 We may also have missed cases that were diagnosed following discharge or detected solely by colonoscopy or sigmoidoscopy. It is also possible that community-acquired cases of CDI may have been misclassified as hospital-acquired. Because misclassification was likely to be nondifferential across our entire cohort, we do not expect that it resulted in a biased estimate of hospital-acquired CDI impact, which was the main objective of the study. Second, we did not evaluate the impact of treatments for CDI. It is possible that the sicker patients may have been treated more aggressively for their CDI and, therefore, not had the same sequelae. We feel this to be unlikely, but we will analyze the impact of CDI treatment in future investigations. Third, we did not account for CDI strain in our analysis. Our hospital does perform surveillance for the NAP1 strain, which has been shown to be associated with CDI severity. Our surveillance data show that NAP1 strains account for approximately 20% of isolates, and this proportion seems to be gradually increasing over time. While we are not certain whether it was NAP1 isolates that were disproportionately attributable for deaths, we did include year in our model to account for the evolving pattern of isolates and did not find a significant direct association.

In summary, we have demonstrated that hospital-acquired CDI has a major impact on patients, with an average 3-fold increase in the hazard of death despite its low absolute infection rate. We recommend further research to better understand the modifiable factors predicting who will acquire CDI in-hospital and who will do poorly when such an event occurs. This proposed research will guide institutions and health care providers to select the most appropriate strategy for reducing the infection and its impact.

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REFERENCES


Correction

Error in Opioid Dose. In the editorial “Long-term Opioid Treatment of Nonmalignant Pain: A Believer Loses His Faith” published in the September 13 issue of the Archives (2010;170[16]:1422-1424), median opioid doses were incorrectly cited from the original investigation by Braden et al.1 appearing in the same issue, for patients without a malignant neoplasm who were not in hospice programs and who had used opioids continuously for at least 90 days. The correct median doses in morphine equivalents were 35 mg in the Arkansas sample and 32 mg in the HealthCore sample.