Clostridium difficile Infection Is Associated With Increased Risk of Death and Prolonged Hospitalization in Children

Julia Shaklee Sammons,1,2 Russell Localio,2 Rui Xiao,2 Susan E. Coffin,1,2,3 and Theoklis Zaoutis1,2,4

1Division of Infectious Diseases, and Departments of 2Pediatrics and 3Biostatistics and Epidemiology, Perelman School of Medicine, University of Pennsylvania; 4Infection Prevention and Control and 5The Center for Pediatric Clinical Effectiveness Research, The Children’s Hospital of Philadelphia, Pennsylvania

(See the Editorial Commentary by El Feghaly and Tarr on pages 9–12.)

Background. Clostridium difficile infection (CDI) is associated with significant morbidity and mortality among adults. However, outcomes are poorly defined among children.

Methods. A retrospective cohort study was performed among hospitalized children at 41 children’s hospitals between January 2006 and August 2011. Patients with CDI (exposed) were matched 1:2 to patients without CDI (unexposed) based on the probability of developing CDI (propensity score derived from patient characteristics). Exposed subjects were stratified by C. difficile test date, suggestive of community-onset (CO) versus hospital-onset (HO) CDI. Outcomes were analyzed for matched subjects.

Results. We identified 5107 exposed and 693,409 unexposed subjects. Median age was 6 years (interquartile range [IQR], 2–13 years) for exposed and 8 years (IQR, 3–14 years) for unexposed subjects. Of these, 4474 exposed were successfully matched to 8821 unexposed by propensity score. In-hospital mortality differed significantly (CDI, 1.43% vs matched unexposed, 0.66%; P < .001). Mortality rates were similar between CO-CDI and matched subjects. However, mortality rates were significantly greater among HO-CDI compared with matched unexposed (odds ratio, 6.73 [95% confidence interval {CI}, 3.77–12.02]). Mean differences in length of stay (LOS) and total cost were significant: 5.55 days (95% CI, 4.54–6.56 days) and $18,900 (95% CI, $15,100–$22,700) for CO-CDI, and 21.60 days (95% CI, 19.29–23.90 days) and $93,600 (95% CI, $80,000–$107,200) for HO-CDI.

Conclusions. Pediatric CDI is associated with increased mortality, longer LOS, and higher costs. These findings underscore the importance of antibiotic stewardship and infection control programs to prevent this disease in children.

Keywords. C. difficile infection; pediatrics; outcomes; epidemiology.
outcomes of hospitalized children are limited. Historically, *C. difficile* was believed to cause less significant disease among children compared with adults; however, severe cases of CDI have been reported, and the NAP1 strain has been identified in children [15–18]. As the epidemiology of CDI has changed, additional studies evaluating associated outcomes are needed to better understand its impact among hospitalized children.

**MATERIALS AND METHODS**

**Study Design**

We performed a retrospective, multicenter cohort study to assess outcomes associated with CDI among a cohort of hospitalized children at 41 free-standing children’s hospitals. Primary outcomes were in-hospital mortality, length of stay (LOS), and total standardized cost. This study was reviewed and approved by the Institutional Review Board of the Children’s Hospital of Philadelphia.

**Data Source**

The Pediatric Health Information System (PHIS) database is a comprehensive database containing clinical and financial details of >6 million admissions from 43 Child Health Corporation of America hospitals. Member hospitals represent 17 of 20 major metropolitan areas across the United States, with one children’s hospital representing each city. Data elements include demographics, admission and discharge dates, *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* diagnosis and procedure codes, payer information, and specific financial utilization data (pharmacy, imaging, and clinical services). All patients have a primary diagnosis code plus up to 20 secondary diagnoses, coded at discharge. Pharmacy data include the date, type, and administration route of any medication ordered.

**Study Population**

Children aged 12 months to 18 years admitted to PHIS hospitals for at least 3 days between 1 January 2006 and 1 August 2011 were eligible for the study. Patients with CDI (exposed) were identified by the presence of an ICD-9-CM code for CDI (code 008.45) plus a *C. difficile* test charge, based on a validated case finding tool [19]. This ICD-9-CM code is the only code specific for CDI. For subjects with multiple CDI-related admissions, only the first admission was used. Patients without CDI (unexposed) were selected from among hospitalized children without the CDI ICD-9-CM code. Exposed subjects tested for *C. difficile* before hospital day 3 were defined as having community-onset (CO) CDI, as patients presenting with symptoms upon admission would be expected to be tested by that time [14]. Exposed subjects tested on or after hospital day 3 were defined as having hospital-onset (HO) CDI. Day of admission was defined as hospital day 0.

**Data Collection**

All data were obtained from the PHIS database. Clinical and demographic data collected included age, sex, race, comorbid diagnoses, in-hospital procedures, and medication exposure, including antimicrobial agents, proton pump inhibitors or H2 blockers, and total parenteral nutrition. The presence of comorbidities was assessed using a previously validated ICD-9-CM code–based diagnostic classification system for pediatric chronic conditions [20]. Data collected on underlying severity of illness included admission to the intensive care unit (ICU) and receipt of respiratory (supplemental oxygen or mechanical ventilation) or pressor support (dopamine, epinephrine, dobutamine, or norepinephrine).

**Data Analysis**

**Propensity Score Matching**

To balance important patient characteristics between groups, we implemented stratified and propensity score–based matching. We developed propensity scores that represented each patient’s probability of developing CDI based on baseline characteristics [21]. The propensity score was developed using measured covariates believed to impact development of CDI and to be associated with outcomes, including age, sex, race, number of comorbidities, in-hospital procedures, medication use, and underlying severity of illness, using a multivariable logistic regression model. For exposed patients, receipt of medications, procedures, and severity of illness markers were considered present if exposure occurred prior to *C. difficile* testing. Models were developed within each hospital, producing a predicted probability of infection. Exposed and unexposed subjects were then matched by their propensity score within each hospital using nearest neighbor-matching without replacement, within calipers of width 0.25 (log odds scale), and a ratio of 2:1 (unexposed to exposed). Patients without an eligible match were excluded from additional analysis in order to reduce risk of bias from nonexchangeable subjects.

Once matching was complete, balance of covariates between matched subjects was assessed within each hospital using Wilcoxon rank-sum or Pearson $\chi^2$ analysis as appropriate. Additional balance checks were performed after combining matched subjects from each hospital into the final matched cohort.

Propensity score matching was performed using R statistical software (MatchIt package) within Stata (R version 2.14.1 [2011–12-22], R Foundation for Statistical Computing). All tests were 2-tailed and $P < .05$ was considered statistically significant.
Analysis of Outcomes
In-hospital mortality was analyzed among matched subjects using Fisher exact $\chi^2$ analysis, as the matched sample represented 2 similar groups of patients; simple logistic regression was used to provide odds ratios (ORs). LOS was analyzed using a generalized linear model with a log link (log gamma model), accounting for clustering by hospitals. Covariates remaining unbalanced between groups after matching were included in the final model. Additional analysis of LOS was performed using competing risk regression, adjusted for the competing risk of death. To assess total hospital costs, hospital charges were converted into total standardized costs using standardized unit costs for a total of 20,903 Clinical Transaction Classification codes across PHIS hospitals [22]. Costs were analyzed between matched subjects using the same model as with LOS.

Subgroup Analysis
Subanalyses were performed within subgroups of patients with CO-CDI and HO-CDI. Outcomes were analyzed within subgroups as detailed above.

Sensitivity Analyses
Simulations were applied to test the impact on our observed results of the effect of a hypothetical omitted confounder at varying levels of prevalence of that confounder. In addition, as a planned analysis, and in order to address the possibility that longer LOS prior to C. difficile testing might lead to increased total LOS in patients with CDI, we repeated the analysis for LOS using the models above, but used only the LOS after C. difficile testing for the exposed group. Stata statistical software, version 12.1 (StataCorp, College Station, Texas) was used for all analyses.

RESULTS

Patient Characteristics
We identified 5107 exposed and 693,409 unexposed eligible subjects (Figure 1). Median age was 6 years (interquartile range [IQR], 2–13 years) for exposed and 8 years (IQR, 3–14 years) for unexposed subjects. Exposed and unexposed subjects differed significantly in demographic and clinical characteristics, with exposed subjects having higher numbers of comorbidities, more medication exposures, and increased severity of illness (Table 1).

After developing the propensity score, 4474 exposed were matched to 8821 unexposed subjects (Figure 1). Of the exposed subjects, 2414 (54%) underwent C. difficile testing by hospital day 3, consistent with CO-CDI. Matched subjects were similar in demographic and clinical characteristics, except for number of comorbidities, antibiotic exposure, and pressor support prior to C. difficile testing (Table 2). The direction of imbalance of these covariates between groups was toward matched unexposed subjects having more exposure to antimicrobial agents and pressors and increased numbers of comorbidities.

There were 633 exposed subjects (12%) without an eligible match (Table 3). These subjects were identified in 40 of the 41 analyzed hospitals. Compared with matched exposed subjects (n = 4474), unmatched subjects were significantly younger.
(median, 5 years [IQR, 2–12 years, \(P = .0092\)), had more ICU admissions \((P < .001\), more frequent exposures to pressors, respiratory support, and total parenteral nutrition \((P < .001\), and a higher percentage with \(\geq 3\) comorbidities \((50.7\%, \(P < .001\)).

Outcomes

A total of 3845 subjects died \((141 [2.76\%] exposed and 3704 [0.53\%] unexposed\), of whom 122 were matched by propensity score \((64 [1.43\%] matched exposed and 58 [0.66\%] matched unexposed\). In-hospital mortality differed significantly between matched exposed and unexposed subjects \((P < .001\). Median LOS among matched exposed and unexposed subjects was 10 days (IQR, 5–23 days) and 4 days (IQR, 3–7 days), respectively.

After adjusted analysis, model-based mean difference in LOS was 12.19 days (95% confidence interval [CI], 10.56–13.81). This is presented graphically using all matched subjects in Figure 2. Mean difference in total standardized cost was \$48,500 (95% CI, \$42,300–\$54,800). Of note, unmatched exposed subjects had higher rates of death \((12.16\%, \(P < .001\)) and significantly longer median LOS \((34\) days \([IQR, 17–62\) days\]; \(P < .001\) compared with matched exposed subjects.

Subgroup Analysis

After stratification of exposed subjects by \(C.\) difficile test date, outcomes were analyzed for subgroups of matched patients. Of the matched exposed subjects who died, 50 (2.43%) had HO-CDI and 14 (0.58%) had CO-CDI. Mortality rates were significantly higher among HO-CDI compared with matched subjects \((OR, 6.73 [95\% CI, 3.77–12.02]). Mortality was similar between patients with CO-CDI and matched unexposed subjects \((OR, 1.20 [95\% CI, 0.62–2.35]). Median LOS was 23 days (IQR, 12–44 days) among those with HO-CDI and 6 days (IQR, 4–13 days)
among those with CO-CDI. Mean differences in LOS and total standardized costs were 21.60 days (95% CI, 19.29–23.90 days) and $93 600 (95% CI, $80 000–$107 200) for HO-CDI and 5.55 days (95% CI, 4.54–6.56 days) and $18 900 (95% CI, $15 100–$22 700) for CO-CDI.

Of note, those with HO-CDI who underwent C. difficile testing later in the hospitalization (after 7 days) had a higher mortality rate (41 [82%] vs 9 [18%]; P < .001) and longer median LOS (32 days [IQR, 22–53 days] vs 11 days [IQR, 7–18 days]) compared with those who underwent earlier testing (days 3–7), suggesting a hospital-dose response effect. There was no significant difference in mortality rate or median LOS among those with CO-CDI who underwent early (hospital day 0 or 1) compared with late (hospital day 2) testing.

**Sensitivity Analyses**

To determine whether our results could be explained by unmeasured confounding, we performed simulations using a hypothetical omitted confounder differentially associated with death or LOS. With a relatively prevalent omitted confounder (5%), the association of that confounder and death would have to be 50 times greater among those with HO-CDI compared with matched unexposed subjects to eliminate statistical significance. The association between a similarly prevalent omitted confounder and LOS would have to be 1.6 times greater among those with CO-CDI and 10 times greater among those with HO-CDI compared with unexposed subjects to eliminate statistical significance. After repeating the analysis of LOS using LOS after C. difficile testing for exposed and total LOS for unexposed subjects, LOS remained significantly longer among exposed subjects, with model-based mean difference in LOS of 6.08 days (95% CI, 4.84–7.32 days) for all exposed subjects, 4.5 days (95%
CI, 3.5–5.5 days) for CO-CDI, and 9.57 days (95% CI, 7.78–11.35 days) for HO-CDI.

**DISCUSSION**

In this large, multicenter cohort study, we found that CDI was associated with worse outcomes among hospitalized children who are otherwise similar in important demographic and clinical characteristics, but was most pronounced among those with hospital onset disease. The presence of CDI was associated with >6-fold higher mortality rates among those with HO-CDI and resulted in significantly longer LOS and increased total hospital costs among all subjects.

Although the epidemiology of CDI has changed over the past decade, data regarding outcomes associated with CDI among children are limited. Our findings are consistent with existing data in adults, which show that CDI is associated with increased mortality and healthcare costs, particularly among the elderly, those with comorbidities, and the critically ill [14, 23, 24]. A study evaluating attributable outcomes of CDI among adult inpatients found that patients with CDI had longer LOS and higher rates of readmission and death. Patients with CDI were also more likely to be discharged to a long-term care facility or outside hospital compared with patients without CDI [9].

Although our dataset included hospitalized patients only, we hypothesized that patients with CDI and symptom onset in the community would undergo *C. difficile* testing before hospital day 3 [14]. Using *C. difficile* test date as a cutoff point, we stratified exposed subjects as having likely CO-CDI versus HO-CDI. It should be noted that the use of *C. difficile* test date as a means to stratify patients is indicative only of disease onset and should not be confused with the terms community or healthcare facility–associated disease. It is possible that patients with CO-CDI may have had additional healthcare exposures prior to admission that were not captured in our dataset, making their disease healthcare facility associated. In addition, the *C. difficile* test date represents the date the test was ordered rather than performed. Still, we would expect providers to order the test in response to symptom onset.

Using this stratification method, we found that patients with CO-CDI comprised 54% of cases. This is similar to data from the Centers for Disease Control and Prevention’s National Health Safety Network in 2010, which reported that 52% of cases of CDI were present upon admission [14]. In our study, patients with HO-CDI had significantly higher rates of death and longer LOS compared with those with CO-CDI and significantly worse outcomes compared with matched unexposed subjects. Although death did not differ between those with CO-CDI and matched unexposed subjects, these patients had significantly longer LOS and total hospital costs. This is consistent with recent data from adults suggesting that community-associated CDI is often associated with severe outcomes, including hospitalization [25]. Given the increased recognition of CDI among persons in the community [3, 6, 26–32], our findings highlight an important area for future research in children.

To our knowledge, our study is the most rigorous evaluation of outcomes associated with CDI among hospitalized children to date. We believe our study design addresses some limitations...
the only prior study to examine the impact of CDI on outcomes of hospitalized children [8]. Specifically, to account for the possibility that sicker patients may have worse outcomes regardless of the presence of CDI, we performed propensity score matching within each hospital to balance key patient characteristics between subjects. At baseline, patients with and without CDI differed significantly in patient characteristics, including number of comorbidities and severity of illness. Propensity score matching was successful in balancing these covariates between subjects. In fact, for the covariates that remained unbalanced after matching, the direction of imbalance was toward unexposed subjects having more comorbidities and increased severity of illness, which would bias our results toward the null. In addition, 12% of exposed subjects were excluded from final analysis due to lack of an eligible match among the unexposed subjects. These patients had increased numbers of comorbidities and more frequent admissions to the ICU compared with matched exposed subjects. Likewise, unmatched exposed subjects had higher rates of death and longer LOS. Thus, by excluding them, our matched analysis underestimates the difference in outcomes.

Finally, we performed sensitivity analyses to assess the degree to which an omitted confounder could explain our results. We found that our finding of >6-fold increased mortality among patients with HO-CDI compared with matched unexposed subjects persisted despite the addition of a prevalent hypothetical omitted confounder. This was also true for our analysis of LOS in patients with both CO-CDI and HO-CDI. Furthermore, to account for the possibility that longer LOS prior to C. difficile testing may be associated with longer total LOS, we excluded the time in the hospital prior to C. difficile testing for exposed subjects and found that the difference in LOS remained significantly different between groups.

To our knowledge, there is a single prior study evaluating outcomes associated with CDI among hospitalized children, but this study is limited. In the previous study, outcomes were compared between patients with and without CDI using the Kids Inpatient Database (KID) [8]. However, PHIS has important advantages over KID in the evaluation of outcomes, including the availability of treatment data as well as a validated ICD-9-CM code for identifying hospitalized children with CDI in the database [19]. Although the prior study also applied propensity score matching to compare outcomes between subjects, our study offers important methodological advantages, including a propensity score–matched analysis that accounts for hospital-level factors and a sensitivity analysis to assess the potential impact of an omitted confounder. Attention to hospital-level effects is particularly important, as variability in practice as well as differences in rates of CDI across hospitals can significantly affect outcomes between institutions and lead to confounding

by hospital. Finally, our study provides additional stratified analysis, which was not included in the prior study. This analysis revealed important differences in outcomes between patients with onset of CDI in the community versus hospital-onset disease.

Our study has limitations. Because PHIS hospitals are freestanding children’s hospitals, our results might not be generalizable to all institutions providing pediatric care. However, tertiary care centers are more likely to admit children with comorbid conditions in whom CDI occurs. In addition, PHIS hospitals represent a variety of geographic and metropolitan areas. The use of administrative data may also lead to misclassification of exposure. We recently validated the use of administrative data in identifying hospitalized children with CDI within PHIS and found that our case-finding tool was both sensitive and specific in identifying hospitalized children with CDI with a PPV of 81% [19]. Although this still leaves the potential for misclassification of exposed as unexposed, misclassification should not be differential in regard to outcomes and the direction of bias would likely be toward the null.

Our study shows that CDI dramatically impacts outcomes among hospitalized children, resulting in increased risk of death, longer LOS, and higher hospital costs. This finding reinforces the importance of CDI prevention efforts by institutions providing care to children, a group for which the impact of CDI has been underappreciated. Given that rates of CDI have been shown to decline in adult hospitals with active CDI prevention programs [14], our findings highlight the need for the combination of antibiotic stewardship and infection control programs in avoiding the acquisition and spread of this preventable disease in children.

Notes

Financial support. This work was supported by a National Institutes of Health Institutional Training Grant, Infectious Diseases Epidemiology Training Program, University of Pennsylvania School of Medicine (5T32AI-055435-08).

Potential conflicts of interest. J. S. S. reports pending research support for an investigator-initiated study supported by Merck. T. Z. reports research support from Merck; works as a consultant for Merck, Cubist, Pfizer, Astellas, and Hemocue; and has received honorarium for lectures from Merck. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References


