

Higher Mortality Rates Associated with *Clostridioides difficile* Infection in Hospitalized Children with Cystic Fibrosis

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Abstract

Objective(s): To determine the impact of *Clostridioides difficile* **Infection (CDI)** among pediatric Cystic Fibrosis (CF) hospitalizations using a large nationally representative pediatric hospital database. **Study design:** We identified Cystic Fibrosis-related hospitalizations during the years 1997 to 2016 in the Kids' Inpatient Database [KID] and compared in-hospital mortality, Length of Stay [LOS], and hospital charges among hospitalizations with and without a coexisting diagnosis of *C. difficile* using logistic regression models for mortality and general linear models with gamma distribution and logarithmic transformation for LOS and hospital charges. We also evaluated temporal trends in the proportion of CF hospitalizations with concomitant CDI using data published triennially **Results:** We analyzed 21, 616 pediatric CF hospitalizations between the years 1997 to 2016 and found a total of 240 (1.1%) hospitalizations with concurrent CDI diagnosis. Adjusted analyses demonstrated an association of CDI with increased mortality (OR 5.2, 95% CI 2.5-10.7), longer LOS (46.5% increment, 95% CI 36.0-57.1), and higher charges (65.8% increment, 95% CI 53.5-78.1) for all comparisons. The proportion of CF hospitalizations with CDI increased over time from 0.64% in 1997 to 1.73% in 2016 (p<0.001). **Conclusion(s):** As CDI is associated with excess mortality, LOS, and cost in children hospitalized for CF, efforts to reduce infection rates and aggressive diagnosis and treatment of active infections should be prioritized to improve hospital outcomes among children with CF.

Higher Mortality Rates Associated with *Clostridioides difficile* Infection in Hospitalized Children with Cystic Fibrosis

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Abbreviations and Acronyms:

CDAD- *Clostridioides difficile* – Associated Disease

CDI – *Clostridioides difficile* Infection

CF – Cystic Fibrosis

HCUP - Healthcare Cost and Utilization Project

ICD-9, CM- International Classification of Diseases, 9th Edition, Clinical Modification

ICD-10, CM- International Classification of Diseases, 10th Edition, Clinical Modification

KID - Kids' Inpatient Database

LOS- Length of Stay

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Results:

We analyzed 21, 616 pediatric CF hospitalizations between the years 1997 to 2016 and found a total of 240 (1.1%) hospitalizations with concurrent CDI diagnosis. Adjusted analyses demonstrated an association of CDI with increased mortality (OR 5.2, 95% CI 2.5-10.7), longer LOS (46.5% increment, 95% CI 36.0-57.1), and higher charges (65.8% increment, 95% CI 53.5-78.1) for all comparisons. The proportion of CF hospitalizations with CDI increased over time from 0.64% in 1997 to 1.73% in 2016 (p<0.001).

Conclusion(s):

As CDI is associated with excess mortality, LOS, and cost in children hospitalized for CF, efforts to reduce infection rates and aggressive diagnosis and treatment of active infections should be prioritized to improve hospital outcomes among children with CF.

Introduction

C. difficile infection (CDI) is the most common pathogen causing health care-associated infections (HCAI) in the United States, accounting for 15% of all such infections. In the adult population, the incidence of CDI and number and severity of hospitalizations has been increasing in conjunction with the description of hypervirulent strains of *C. difficile* between 2001 and 2012. More recent reports, including nationwide studies, have also shown that CDI has become an emerging problem in hospitalized children.

In children with Cystic Fibrosis (CF), several risk factors for *C. difficile* colonization exists, such as frequent hospitalizations and exposure to a broad array of antibiotics. Despite these risk factors, the occurrence of CDI in CF is reported to be rare. In recent years however, there has been a few case reports and small case series that have described severe complicated CDI in children with CF. Furthermore, an adult study indicated that patients with CF have a three-fold risk of developing CDI as compared to non-CF controls and CF patients with CDI have higher mortality, colectomy rates, length of stay, and hospital charges. Less is known about the impact of CDI on outcomes of CF hospitalizations.

We sought to compare the in-hospital mortality, Length of Stay (LOS) and healthcare charges between pediatric CF hospitalizations with and without CDI using a large, nationally representative database and explore time trends in the proportion of CF hospitalizations with concomitant CDI between 1997 to 2016.

Materials and Methods

Data Source

We analyzed data from the Kids' Inpatient Database (KID) to conduct a cross sectional analysis of hospital outcomes including mortality, length of stay and health care expenditure among pediatric CF hospitalizations. The KID is published triennially beginning in 1997 and is a nationally representative sample of pediatric hospitalizations from the Healthcare Cost and Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality. KID is the largest, all-payer hospitalization database in the United States and contains data from 22–46 states (depending on the year), and two to three million discharges.

The database contains 25 International Classification of Diseases, Ninth Revision (ICD-9) and up to 30 ICD, Tenth Revision (ICD-10) codes per discharge. It contains more than 75 clinical and nonclinical variables, clinical modification diagnostic and procedure codes, hospital characteristics, and out-comes. HCUP-KID assigns an individual-level population weight that allows an estimation of national case rates and trends. KID has been used in published studies of pediatric CF.

Study Sample

We identified all hospitalized children with a diagnosis code for Cystic Fibrosis in any position (International Classification of Diseases, 9th ed., clinical modification [ICD-9 &10-CM] codes 277.00, 277.09 and E84.8, E84.9). Children younger than 1 year were excluded because of uncertainty about the true morbidity of *C. difficile* in infants. *C. difficile* could be both a normal commensal flora and non-pathogenic in infants younger than 1 year.

Primary Exposure of Interest

We identified co-existing diagnoses of CDI utilizing the following diagnosis codes in any position, ICD-9-CM 008.45, a code that was described and validated to study *C. difficile* -associated disease (CDAD) rates previously and ICD-10-CM A04.71

Outcomes

Our primary outcomes of interest were in-hospital mortality (crude and adjusted ratio), median length of stay (LOS) and median healthcare expenditure across all years from 1997 to 2016 among CF patients with CDI and without CDI (Tables 1.2 and 1.3).

Covariates

Information on age, gender, race, geographic region, insurance status, hospital location and bed size were obtained from the KID.

Statistical Analysis

We summarized the demographic data among CF hospitalizations by age, sex, race, geographic region, payer, hospital location and bed size and compared those with and without a co-occurring diagnosis of CDI. Continuous variables were summarized using means and standard deviations while categorical variables were expressed in proportions. We then compared demographic and clinical characteristics between patient admissions for CF with and without CDI using non-parametric bivariate tests as appropriate.

Next, we summarized outcomes of in-hospital mortality, LOS, and healthcare expenditures overall and by presence or absence of CDI using bivariate statistics. We then fit multivariate models to determine the independent associations between CDI and study outcomes, adjusting for variables associated with CDI at $p < 0.1$ on bivariate analyses (calendar year, sex, payer and hospital location/teaching status). For mortality, we fit logistic regression models to estimate odds ratios and 95% confidence intervals. To accommodate the skewed distributions for outcomes of LOS and hospital charges, we used general linear models with gamma distribution and logarithmic transformation. We reported on the percentage change from the referent along with 95% confidence interval.

We next evaluated trends in the proportion of CF hospitalizations with co-existing *C. difficile* over time between the years 1997 to 2016 using the chi-square test of trend.

All analyses were conducted using SAS 9.4 (Cary, North Carolina).

Results

Patient and Hospital Characteristics of CF Hospitalizations

Table 1.1 presents the demographic characteristics of hospital discharges for patients with CF overall and stratified by CDI status. The median age (13 years, $p=0.33$) of the sample was similar in both groups. Whites and southern geographic region constituted the greatest proportion of CF hospitalizations in both groups. Private insurance composed the largest proportion of insurance overall (51%). Patients were mostly seen at urban teaching hospitals (84%) with large bed size (59%).

Outcomes of CF Hospitalizations with and without co-existing diagnosis of *C. difficile*

In-Hospital Mortality

The overall mortality among CF hospitalizations with CDI was 3% compared to <1% among CF hospitalizations without CDI ($P < 0.001$) (Table 1.2). Upon multivariate analysis, the odds of mortality among CF hospitalizations with *C. difficile* infection was 5.2 times that of pediatric CF hospitalizations without *C. difficile* (95% CI: 2.5-10.7)(Table 1.3).

Length of Admission

Overall median length of stay was 10 days among CF hospitalizations with CDI compared to 7 days among CF hospitalizations without CDI ($p < 0.001$) (Table 1.2). After adjustment, the length of stay for CF hospitalizations with CDI was 46.5% longer than CF hospitalizations without CDI (95% CI: 36.0-57.1) (Table 1.3).

Health Care Expenditure

Overall median hospital charges (in USD) were 41,842 among pediatric CF *C. difficile* hospitalizations compared to 23,806 among non-*C. difficile* hospitalizations ($P < 0.001$) (Table 1.2). After adjustment, hospital charges among *C. difficile* CF hospitalization were 65.8% more than the for non-*C. difficile* hospitalizations (95% CI: 53.5-78.1)(Table 1.3).

Temporal Trends in CF Hospitalizations with coexisting diagnosis of *C. difficile*

We analyzed a total of 21, 616 pediatric hospitalizations between the years 1997 to 2016, of which 1.1% (240) of hospitalizations had concurrent code for CDI. The proportions of *C. difficile* diagnosis among all hospitalizations during the seven time points between 1997 and 2016 showed an overall increasing trend at 0.64%, 0.60%, 0.96%, 1.77%, 1.42%, 1.43% and 1.73%, respectively ($P < 0.001$ for trend). (Figure 1)

Discussion:

In a nationally representative sample of pediatric CF hospitalizations, we found that concomitant CDI is associated with higher mortality, length of stay, and hospital charges. Furthermore, we observed an increasing proportion of CF hospitalizations complicated by CDI over time between 1997 and 2016. Taken together, these data highlight the need for heightened awareness, early identification, and aggressive management of CF hospitalizations complicated by CDI.

Prior studies have reported the rare occurrence of CDI in CF, despite high colonization rates (47% to 50% of CF patients) with *C. difficile*. In contrast, our study adds support to the more recent case reports and small case series describing the severe, life threatening impact of *C. difficile* infection in CF patients, creating an urgent need for interventions to improve hospital outcomes among CF children with CDI.

Increasing CDI among children with CF could be due to several factors, including increased survival rates and thus more time at risk for acquiring nosocomial CDI, exposure to newer antimicrobial agents in the treatment of CF exacerbations, and the dissemination of a more-virulent epidemic strain of *C. difficile*, such as North American pulsed-field gel electrophoresis type 1 (NAP1). Alternative explanations include the possibility of more frequent testing and/or documentation and coding for CDI during inpatient admissions for CF. Our findings may also be partially explained by greater detection of asymptomatic carriage of *C. difficile*. Indeed, patients with CF and infants less than 1 year of age are the only populations reported in which *C. difficile* cytotoxin is frequently recovered from asymptomatic individuals. Early exposure to *C. difficile* with induction of an immunological response that offers protection against the effects of toxin(s) but not against colonization, epithelial cell associated factors that prevent the binding of cytotoxin, altered intestinal environment unfavorable for *C. difficile* to exert its virulence have been proposed. As such, increasing awareness of *C. difficile* emergence overall and testing in hospitalized children may contribute to the rising trend, which may not necessarily reflect true infection with *C. difficile* in the CF population. In addition, in the late 2000s, the introduction of more sensitive *C. difficile* assays, such as nucleic acid amplification tests (NAATs), could have probably led to potential overdiagnosis of CDI, since this test detects the gene encoding the toxin rather than the actual toxin. The relative contribution of each of these factors in the CF population has not been defined.

Nevertheless, the excess in-hospital mortality in *C. difficile*-CF was striking and persisted after multivariate analysis after adjusting for underlying patient and hospital characteristics. Clinicians caring for CF patients should be aware of this risk, particularly as CDI may have an atypical presentation with lack of diarrhea in CF patients. Given this excess mortality along with longer LOS and higher hospital charges, improved diagnosis and treatment will be needed to help mitigate the increased virulence of *C. difficile* that has been associated with greater morbidity and/or resistance to standard treatment in the general population..

Strengths:

Our study had multiples strengths, including the use of HCUP KID data, which is a nationally representative sample of pediatric CF hospitalizations across geographic regions, hospital characteristics, and health insurance payers. This represents the breadth of hospital-level care provided to pediatric CF patients. The large sample size of the database allows adequate precision and power for our primary analyses. In addition,

our use of multivariable regression analysis allowed for control of potential confounding factors including calendar year, sex, payer and hospital location/teaching status in studying the association between co-existing *C. difficile* diagnosis and outcomes.

Limitations:

We acknowledge several limitations in our study. Administrative data sources may contain miscoded or inaccurate information. For example, the use of ICD-9 code to study CDAD may potentially misclassify CDAD if physicians or hospital coders did not code for this diagnosis or if test results were not back at the time of hospital discharge. However, the ICD-9 code (ICD-9-CM 008.45) for *C. difficile* has been described and validated previously with 78% sensitivity and 99.7% specificity for correctly identifying and classifying admissions.

An administrative definition of *C. difficile* may also include some patients who had colonization rather than true disease; however, patients in our study were ill enough to require hospitalization, and so this proportion may likely be smaller. In addition, it is a well-established fact that CF patients have high rates of colonization, and therefore testing may be limited to cases where there is only a high index of suspicion. On the other hand, given CDI's atypical presentation in CF with lack of diarrhea, there are chances that this diagnosis may either have been overlooked, or a formed stool sample may have been rejected by the lab, causing an underestimate of the disease burden.

Administrative databases also offer limited ability to adjust for the severity of underlying CF disease or use of concomitant medications (immunosuppressive drugs, antibiotics, CFTR modulators, mucolytics). We recognize the possibility of detection bias, with patients with more severe disease being more likely to be tested for *C. difficile*. The possibility of this bias (i.e., more frequent testing for *C. difficile* among those hospitalized patients with more severe disease) playing a role in our results cannot be completely ruled out as an explanation for the increasing disparity in outcomes of hospitalized CF patients with and without *C. difficile* infection. We are also not able to determine time of onset of *C. difficile* infection relative to the hospitalization.

Significance:

There are several implications of our findings. To our knowledge, this is the first study describing temporal changes in characteristics and outcomes of pediatric *C. difficile* -CF patients from a nationwide sample. The higher mortality among CF hospitalizations with concomitant CDI raises concern for delayed diagnosis given its atypical presentation, lack of provider awareness, high virulence, and inadequate effectiveness of treatment on a national scale.

Conclusion:

In conclusion, our findings demonstrate an excess burden of CDI among hospitalized pediatric patients with CF and an increasing proportion of hospitalizations with co-occurring CDI and CF over time. Taken together, these findings suggest the need for heightened awareness of this potentially lethal comorbidity and appropriate efforts to facilitate the early diagnosis and aggressive treatment of CDI among pediatric patients with CF.

References:

Figure Legend:

Figure 1: Temporal trends in Pediatric CF Hospitalizations Stratified by CDI analyzed in the 1997-2016 KID Database

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Figure 1 (1).docx available at <https://authorea.com/users/474608/articles/564365-higher-mortality-rates-associated-with-clostridioides-difficile-infection-in-hospitalized-children-with-cystic-fibrosis>

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