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Clostridioides difficile Infection Is Associated with Adverse Outcomes among Hospitalized Pediatric Patients with Acute Pancreatitis

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ABSTRACT

Purpose: Studies in adults have shown an increasing incidence of *Clostridioides difficile* infection (CDI) in patients hospitalized with acute pancreatitis (AP). There is lack of epidemiological data on CDI and its impact on hospitalized pediatric patients with AP.
Methods: We analyzed the National Inpatient Sample and Kids' Inpatient Database between the years 2003 and 2016 and included all patients (age <21 years) with a primary diagnosis of AP using specific International Classification of Diseases codes. We compared clinical outcomes between children with CDI and those without CDI. Our primary outcome was severe AP and secondary outcomes included length of stay and hospital charges.
Results: A total of 123,240 hospitalizations related to AP were analyzed and CDI was noted in 0.6% of the hospital. The prevalence rate of CDI doubled from 0.4% (2003) to 0.8% (2016), p=0.03. AP patients with CDI had increased comorbidities, and also underwent more invasive surgical procedures, p<0.05. AP patients with CDI had a higher in-hospital mortality rate and increased prevalence of severe AP, p<0.001. Multivariate regression models showed that CDI was associated with 2.4 times (confidence interval [CI]: 1.91 to 3.01, p<0.001) increased odds of severe AP. CDI patients had 7.24 (CI: 6.81 to 7.67, p<0.001) additional hospital days while incurring $59,032 (CI: 54,050 to 64,014, p<0.001) additional hospitalization charges.
Conclusion: CDI in pediatric patients with AP is associated with adverse clinical outcomes and increased healthcare resource utilization. Further studies are needed to elucidate this association to prevent the development of CDI and to improve outcomes.

Keywords: *Clostridioides difficile*; Pancreatitis; Mortality; Length of stay; Hospital charges; Child

INTRODUCTION

Clostridioides (formerly known as *Clostridium*) *difficile* infection (CDI) is one of the leading causes of gastrointestinal (GI) mortality in adults after GI tract malignancies, cirrhosis, alcoholic liver disease and vascular disorders of the intestine [1,2]. Overall, the CDI-related

Conflict of Interest
The authors have no financial conflicts of interest.

hospitalizations had increased substantially by 237% since 2000 leading to significant morbidity and decreased quality of life [1]. Similarly, an increasing incidence of CDI among the pediatric population has been noted in prior epidemiological studies [3,4]. Further, CDI is associated with increased risk of mortality among the pediatric population and causes significant morbidity including increased need for colectomy and prolonged hospital stay [4]. A recent single-center study in adults showed that patients with pancreatic diseases are at increased risk of CDI compared to patients with other comorbidities such as hepatobiliary disease, malignancies, and renal disease [5]. Studies in adults have shown that CDI was associated with adverse hospital outcomes such as the increased risk of mortality and prolonged hospital stay while incurring higher hospitalization charges among patients with acute pancreatitis (AP) [6-8]. In adults with pancreatic disorders, the use of antibiotics and the presence of multiple comorbidities have been associated with a significantly increased risk of CDI [6,8]. The incidence of CDI has been particularly higher among patients with necrotizing pancreatitis where the use of antibiotics is significantly higher and often has a complicated clinical course due to the severity of disease [9]. Despite recommendations from the American Pancreatic Association and the North American Society of Pediatric Gastroenterology Hepatology and Nutrition (NASPGHAN) recommending against the routine use of antibiotics, a recent systematic review showed that 31% to 82% of the patients with AP were started on antibiotics worldwide [10-12]. Similar to rising CDI, various studies have shown that the incidence of AP-related hospitalizations is also increasing among the pediatric population [13-15]. However, there is paucity of data regarding the burden of CDI and its impact on hospital outcomes among pediatric patients with AP. With the increasing incidence of AP in the pediatric population, we sought to investigate the burden of CDI among patients with AP and its impact on hospital outcomes.

MATERIALS AND METHODS

Nonoverlapping years of Kids Inpatient Database (KID) and National Inpatient Sample (NIS) databases between the years 2003 and 2016 were included for analysis. Both KID and NIS databases are part of the Health Care and Utilization Project (HCUP), a publicly available database containing de-identified data of patients across the United States (US). KID database is the largest available pediatric all-payer database containing information on patients up to 20 years of age. KID is released almost every three years and each dataset contains information on approximately 7 million patients. Pediatric data are sampled at a rate of 80% from 4,200 hospitals in the US. NIS database includes data on both adult and pediatric patients and are released annually. Each dataset contains stratified sampled (rate of 20%) data on about 7 million patients from various community hospitals in the US, excluding long-term and rehabilitation services. For this study, we included non-overlapping years of KID and NIS from 2003 to 2016.

Variable selection

All patients with a primary diagnosis of AP using specific International Classification of Diseases (ICD) 9 (577.0) and ICD 10 (K85) CM codes. Race/ethnicity was categorized into Caucasians, African Americans, Hispanics, and others. We categorized insurance as public (Medicaid/Medicare insurance), private (commercial/work), and others (including self-pay, no charges, uninsured, others). Further using the ICD 9 and 10 codes, we analyzed various etiological factors and comorbid conditions among patients with AP, such as biliary disease including cholangitis, cholelithiasis, diabetic ketoacidosis, hypertriglyceridemia,

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hypercalcemia, anomalies of the pancreas, abdominal trauma, systemic lupus erythematosus, inflammatory bowel disease (IBD), cystic fibrosis, solid organ transplants, alcohol-related pancreatitis and common childhood malignancies including lymphoma/leukemia, central nervous system tumors, retinoblastoma, hepatoblastoma, neuroblastoma, and osteosarcoma.

The primary outcome of the study was the development of severe AP (based on 2017 NASPGHAN pancreas committee criteria for AP severity) and secondary outcomes included healthcare resource utilization (length of stay and total hospital costs) [16]. The outcome of severe AP was defined as the presence of end-organ damage, which is either use of mechanical ventilation or a diagnosis of at least one of the following: pulmonary insufficiency, acute kidney injury (AKI), systemic inflammatory response syndrome (SIRS) with end-organ dysfunction or use of vasopressors [16]. We also analyzed the healthcare resource utilization, including the length of hospital stay and the difference in total hospitalization costs between the two groups.

We also evaluated other outcome measures, including complications such as sepsis, thrombotic complications (deep vein thrombosis [DVT]/pulmonary embolism [PE]), pseudocyst of the pancreas, and mortality between the groups. We compared various surgical procedures such as central venous catheter (CVC) placement, cholecystectomy, endoscopic retrograde cholangiopancreatography (ERCP), percutaneous/open biliary procedures, and pancreatectomy between those with and without CDI. As per the data user agreement of HCUP, any column with less than 10 patients was not reported. ICD codes of all the variables are provided in **Supplementary Table 1**.

Statistical analysis

Categorical variables were reported as proportions and percentages while continuous variables were reported as median and interquartile ranges. Categorical variables were compared using the chi-square test and continuous variables using the Student *t*-test. A *p*-value of <0.05 was considered statistically significant. Separate multiple logistic regression models were constructed to analyze the impact of CDI on severe AP as the clinical outcome. Multiple linear regression models were constructed to analyze the impact of nutritional status on length of hospital stay and total hospitalization charges.

RESULTS

We analyzed a total of 123,240 pediatric AP hospitalizations and CDI was noted in 789 hospital admissions (0.6%). The prevalence rate of CDI doubled during the study period from 0.4% in 2003 to 0.8% in 2016, p=0.03. AP patients with CDI were younger (13.7 vs. 15.1 years), had more public insurance (48.3% vs. 42.1%), and were hospitalized often in urban teaching hospitals (82.4% vs. 60.0%). AP patients with CDI had more associated comorbid conditions including IBD, malignancies, solid organ transplants, and morbid obesity, p<0.05 (**Table 1**).

Clinical outcomes

AP patients with CDI had increased illness severity compared to the control population. The prevalence rate of severe AP was significantly higher among AP patients with CDI (16.2% vs. 3.8%), p<0.001 (**Table 2**). Overall, the mortality rate of patients with AP is 0.15% (180 deaths). CDI patients had an increased mortality rate of 1.4% compared to 0.1%, p<0.001.

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Table 1. Univariate analysis comparing demographics, hospital factors, associated disorders, and etiologies between acute pancreatitis in patients with and without *Clostridioides difficile* infection

Parameter	AP without CDI (n=122,451, 99.4%)	AP with CDI (n=789, 0.6%)	*p*-value
Demographics			
Age (y)	15.1±4.7	13.7±5.5	<0.001
Sex			0.08
Male	51,197 (42.1)	356 (45.1)	
Female	70,347 (57.9)	433 (54.9)	
Race			<0.01
Caucasians	55,109 (45.0)	355 (44.9)	
African Americans	11,956 (9.8)	50 (6.3)	
Hispanics	27,964 (22.8)	197 (24.9)	
Others	27,421 (22.4)	188 (23.8)	
Insurance			<0.001
Public	51,068 (42.1)	381 (48.3)	
Private	54,985 (44.9)	353 (44.7)	
Self-pay/other/uninsured	15,858 (13.0)	55 (7.0)	
Bed size of hospital			0.13
Small	16,689 (13.8)	94 (12.1)	
Medium	31,967 (26.4)	227 (29.2)	
Large	72,298 (59.8)	457 (58.7)	
Location/teaching status			<0.001
Rural	12,981 (10.7)	13 (1.7)	
Urban non-teaching	35,390 (29.3)	124 (15.9)	
Urban teaching	72,583 (60.0)	641 (82.4)	
Hospitalization			0.15
Elective	7,866 (6.4)	41 (5.2)	
Non-elective	114,091 (93.6)	748 (94.8)	
Associated etiologies and conditions			
Cholelithiasis	26,673 (21.8)	102 (12.9)	<0.001
Other biliary diseases	4,062 (3.3)	50 (6.3)	<0.001
Hypertriglyceridemia	3,790 (3.1)	34 (4.3)	0.05
Hypercalcemia	328 (0.3)	11 (1.3)	<0.001
Cystic fibrosis	1,446 (1.2)	13 (1.6)	0.22
IBD	2,811 (2.3)	74 (9.4)	<0.001
Malignancies	2,960 (2.4)	126 (16.0)	<0.001
Solid organ transplants	777 (0.6)	11 (1.4)	0.008
Alcohol-related	5,875 (4.8)	21 (2.7)	0.002
Morbid obesity	3,939 (3.2)	37 (4.7)	0.02

Values are presented as mean±standard deviation or number (%).
AP: acute pancreatitis, CDI: *Clostridioides difficile* infection, IBD: inflammatory bowel disease.

Univariate analysis demonstrated 9.2 times (95% confidence interval [CI]: 4.8 to 17.6, $p<0.001$) increased risk of mortality among AP patients with CDI. Further, AP patients with CDI had an increased prevalence of respiratory failure, AKI, and severe sepsis (10.4% vs. 1.1%), $p<0.001$. AP patients with CDI had more complications such as increased rates of PE, DVT, and pseudocyst formation, $p<0.001$ (**Table 2**). They also had more interventions such as CVC placement (24.5% vs. 6.0%), invasive mechanical ventilation, and abdominal procedures including open biliary procedures (1.4% vs. 0.3%), and pancreatectomy (3.9% vs. 0.6%), $p<0.001$. Multivariate logistic regression analysis showed that CDI was associated with 2.4 times (CI: 1.91 to 3.01, $p<0.001$) increased odds of severe AP among the pediatric population (**Table 3**).

AP patients with CDI had significantly increased mean duration of hospital stay compared to AP patients without CDI (16±0.6 vs. 5±0.01 days), $p<0.001$. Consequently, patients with CDI had higher mean total hospitalization charges compared to control population (115,228±6,124 vs. 30,683±201 USD), $p<0.001$. Multivariate regression analysis demonstrated

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Table 2. Univariate analysis comparing surgical interventions and clinical outcome measures between acute pancreatitis in patients with and without *Clostridium difficile* infection

Parameter	AP without CDI (n=35,423, 96.5%)	AP with CDI (n=1,275, 3.5%)	*p*-value
Outcomes			
Severe acute pancreatitis	4,641 (3.8)	128 (16.2)	<0.001
Length of stay (d)*	5±0.01	16±0.6	<0.001
Total hospital charges (USD)*	115,228±6,124	30,683±201	<0.001
Mortality	169 (0.1)	11 (1.4)	<0.001
AKI	1,777 (1.5)	48 (6.1)	<0.001
Respiratory failure	2,764 (2.3)	87 (11.0)	<0.001
Invasive mechanical ventilation	1,268 (1.0)	53 (6.7)	<0.001
CVC placement	7,299 (6.0)	193 (24.5)	<0.001
Sepsis	1,356 (1.1)	82 (10.4)	<0.001
PE	120 (0.1)	14 (1.8)	<0.001
DVT	156 (0.1)	16 (2.0)	<0.001
Pseudocyst	4,030 (3.3)	107 (13.6)	<0.001
Cholecystectomy	17,124 (14.0)	68 (8.6)	<0.001
ERCP done for any reason	8,872 (7.2)	50 (6.3)	0.32
Open biliary procedures	315 (0.3)	11 (1.4)	<0.001
Pancreatectomy	692 (0.6)	31 (3.9)	<0.001

Values are presented as number (%) or *mean±standard error.
AP: acute pancreatitis, CDI: *Clostridioides difficile* infection, USD: United States Dollar, AKI: acute kidney injury, CVC: central venous catheter, PE: pulmonary embolism, DVT: deep vein thrombosis, ERCP: endoscopic retrograde cholangiopancreatography.

Table 3. Multivariate logistic regression analysis for the primary outcome of severe acute pancreatitis

Parameter	Odds ratio	95% confidence interval	*p*-value
Clostridioides difficile infection	2.39	1.91 to 3.01	<0.001
Age (y)	1.017	1.01 to 1.02	<0.001
Male vs. female (Reference)	0.77	0.72 to 0.82	<0.001
Race			
Caucasians	Reference	Reference	Reference
African Americans	1.09	0.99 to 1.21	0.07
Hispanics	0.83	0.77 to 0.91	<0.001
Others	1.01	0.93 to 1.09	0.72
Insurance			
Public	Reference	Reference	Reference
Private	0.90	0.84 to 0.96	0.004
Self-pay/others/uninsured	0.85	0.76 to 0.94	0.002
Bed size of the hospital			
Small	Reference	Reference	Reference
Medium	1.04	0.93 to 1.16	0.42
Large	1.11	1.009 to 1.22	0.03
Location/teaching status			
Rural	Reference	Reference	Reference
Urban nonteaching	1.52	1.32 to 1.75	<0.001
Urban teaching	2.17	1.90 to 2.48	<0.001
Elective vs. non-elective admission	0.93	0.81 to 1.06	0.28
Cholelithiasis	1.13	1.04 to 1.23	0.002
Other biliary diseases	1.02	0.86 to 1.20	0.79
Hypertriglyceridemia	2.94	2.61 to 3.30	<0.001
Hypercalcemia	13.50	2.51 to 4.88	<0.001
Pseudocyst	3.58	3.24 to 3.95	<0.001
Inflammatory bowel disease	0.56	0.43 to 0.72	<0.001
Malignancies	1.83	1.59 to 2.11	<0.001
Solid organ transplant status	2.89	2.28 to 3.66	<0.001
Alcohol-related	0.98	0.84 to 1.14	0.85
Morbid obesity	1.98	1.75 to 2.25	<0.001

that in patients with AP, CDI was independently associated with 7.24 (CI: 6.81 to 7.67, $p<0.001$) additional days of hospitalization and incurred 59,032 USD (CI: 54,050 to 64,014,

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Table 4. Multivariate analysis evaluating the impact of *Clostridioides difficile* infection on the outcomes of severe AP, length of stay and total hospitalization charges among all patients with AP

Outcome	Odds ratio	95% CI	*p*-value
Severe AP	2.39	1.91 to 3.006	<0.001
	Average difference	95% CI	*p*-value
Length of stay (d)	7.24	6.81 to 7.67	<0.001
Total hospitalization charges (USD)	59,032	54,050 to 64,014	<0.001

AP: acute pancreatitis, CI: confidence interval, USD: United States Dollar.

p<0.001) of additional hospitalization charges (**Table 4**). The full model of multivariate analysis is provided in **Supplementary Table 2**.

DISCUSSION

In this population-based study using nationally representative databases, we demonstrated the significant association between CDI and adverse clinical outcomes among patients with AP. CDI are associated with significant chronic comorbid conditions and are associated with worse clinical outcomes and complications. The risk of associated severe AP was almost 2.4 times increased for patients with CDI. Albeit low overall mortality rates among pediatric AP, the risk of mortality is particularly higher among patients with CDI.

We report a CDI rate of 0.6% among pediatric patients with AP. Adult studies have shown similar rates between 0.5% to 0.9% [6,8]. In our study, the prevalence of CDI doubled between 2003 and 2016 which is consistent with various studies in adults demonstrating an increasing trend of CDI among the general population as well in patients with AP [1,6]. In another adult study, the incidence rate of CDI was reported as 10% among patients with necrotizing pancreatitis [9]. Here, antibiotic usage and organ failure increased the risk of CDI in necrotizing pancreatitis, and patients with CDI had increased morbidity, readmission, and disease duration [9].

CDI in AP could be attributed to various reasons such as gut barrier dysfunction, and indiscriminate use of antibiotics [17-19]. Although guidelines in adults recommend against the routine use of prophylactic use of antibiotics in AP patients, a recent audit of clinical practice showed the use of antibiotics in about 58% of all AP patients [19]. In this cohort, 44% of the patients with mild AP and 100% of severe AP also received antibiotics reiterating its overuse [19]. Similar to adult guidelines, NASPGHAN recommends antibiotics only for AP patients with infectious complications and also in hospitalized patients with necrotizing pancreatitis who fail to improve without antibiotics [11]. Routine use of antibiotics is not recommended even in children with severe AP in the absence of the above-mentioned indications [11]. Leukocytosis, elevated CRP, high amylase and lipase levels often may prompt clinicians to start antibiotics in these patients [19]. Despite these guidelines, pediatric subspecialists often encounter the difficult task of distinguishing SIRS secondary to the surge of inflammatory mediators from the AP from the evolving infection [19]. Often this clinical dilemma prompts clinicians to take a more conservative approach of starting antibiotics despite lack of clear indications.

We found that patients who underwent invasive surgical procedures (open bile duct exploration & pancreatectomy) had more associated CDI than patients with relatively less invasive procedures like ERCP (**Table 2**). This might be related to increased disease severity and operative interventions mandating the use of antibiotics to prevent post-operative infection.

We compared our results with a study in adults which utilized the HCUP database and similar methodology [6]. Despite lower overall mortality rate (0.15%) in our cohort with AP compared to adult AP patients (0.83%), the pediatric patients with CDI in our cohort had more than 9 times increased risk of inpatient mortality compared to 3 times (CI: 2.78 to 3.57, $p<0.001$) increased mortality risk among adults [6]. Pediatric AP patients also had an increased prevalence of organ dysfunction which is consistent with the findings in the adult population [9]. CDI was associated with almost 2.4 times increased odds of severe AP among the pediatric population. A similar population-based study among adults showed that CDI was associated with 1.39 times (CI: 1.23 to 1.58, $p<0.001$) of associated severe AP [20]. Although pediatric AP patients had improved outcomes than adults, the presence of CDI is associated with increased morbidity and mortality compared to adults.

In our study, CDI was associated with 7 additional days of hospitalization and in adult studies, CDI was associated with 5 to 8 more days of hospital stay [6,20]. After adjusting for various comorbid conditions, CDI contributed to higher inflation-adjusted hospitalization charges by 59,032 USD. Similar studies have shown increased expenditure among adult AP patients by almost 46,098 USD (CI: 40,598 to 51,597, $p<0.001$) [6].

Our study has various limitations including the retrospective nature of the large database analysis. We rely on coding accuracy to analyze various diagnoses and so errors due to manual coding should be taken into account during the interpretation of results. Information regarding the use of antibiotics during hospitalization is not available. Although we have taken sepsis into account as one of the variables, there will be instances in which patients might have received antibiotics based on critical clinical conditions without culture-proven evidence and/or might not have coded with a specific sepsis diagnosis. Similarly, data on known risk factors for CDI such as the use of antibiotics, proton pump inhibitors, feeding tubes were not available for analysis. Each record is a hospitalization encounter and we do not have data on readmissions or outpatient follow-up visits. Further, we were not able to distinguish between nosocomial and community-acquired CDI in our study population.

Despite these limitations, we have several strengths to our study including the analysis of a large number of pediatric patient encounters using two large databases to provide national estimates. Both AP and CDI have specific ICD 9 and 10 codes thus we are certain about identifying the patients with reasonable accuracy. Our large size cohort allowed us to control for multiple factors associated with hospital outcomes which are otherwise difficult to analyze in small sample studies due to the relatively low prevalence of CDI in AP patients.

In conclusion, CDI was independently associated with increased severity of disease in patients with AP and contributed to higher hospitalization charges and prolonged hospital stay. With the rising prevalence of CDI in pediatric patients hospitalized for AP, further studies are needed to elucidate this association to prevent the development of CDI and to improve outcomes.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

ICD codes

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Supplementary Table 2

Multivariate linear regression demonstrating the impact of various factors affecting the length of stay and total hospitalization charges related to acute pancreatitis

Click here to view

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