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Risk factors for *Clostridioides (Clostridium) difficile* infection following solid organ transplantation in children

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Abstract

Background: *Clostridioides (Clostridium) difficile* infection (CDI) in pediatric solid organ transplant (SOT) recipients is a growing problem, though CDI risk factors in this population are poorly understood. Our objective was to characterize CDI risk factors in pediatric SOT recipients.

Methods: This retrospective case-control study, performed at a single freestanding academic children's hospital, included all SOT recipients age 1–22 years who were tested for *C. difficile* by toxin B gene PCR between August 2009 and August 2017. CDI risk factors were assessed by comparing PCR-positive and PCR-negative cases by generalized linear mixed models.

Results: Between August 2009 and August 2017, 409 SOTs were performed of which 138 (33.7%), 134 (32.8%), 131 (32.0%), and 6 (1.5%) were kidney, liver, heart, and small intestine transplants, respectively. 205 SOT recipients were tested for CDI, with 723 *C. difficile* PCR tests performed among these patients. 68/205 (33%) patients developed CDI at least once during the study period. Median (interquartile range) time to diagnosis of first CDI following SOT was 8.9 (1.2, 19.6) months. CDI was independently associated with calcineurin inhibitor use at time of *C. difficile* testing (odds ratio [OR] 2.38, 95% confidence interval [CI] 1.08, 5.24, p=0.03) and systemic antibiotic exposure within 30 days of *C. difficile* testing (OR 1.74, 95% CI 1.08, 2.79, p=0.02).

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EO, LCB, SJP, WJM and LKK each substantially contributed to the conception or design of the work; the acquisition, analysis, or interpretation of data for the work; critical revision of the draft of the work for important intellectual content; and approval of the final of the version to be published. EO, LCB, SJP, WJM and LKK each agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conclusions: CDI is a common, relatively late post-transplant complication and independently associated with calcineurin inhibitor and systemic antibiotic exposure. The potential impact of specific immunosuppressive drug and antibiotic selection on CDI risk reduction requires further investigation.

Keywords

Solid organ transplantation; *Clostridioides difficile*; *Clostridium difficile*; pediatrics; immunosuppression

Introduction

Clostridioides (Clostridium) difficile is a gram-positive, spore-forming bacterium that causes a wide range of clinical conditions, including asymptomatic colonization, diarrhea, toxic megacolon, and pseudomembranous colitis. *C. difficile* infection (CDI) is the most common healthcare-associated pathogen in the United States,[1] with approximately 500,000 infections and 29,000 deaths per year.[2] The incidence and severity of CDI has increased in recent years, and the US Centers for Disease Control and Prevention classifies *C. difficile* among the most pressing antibiotic resistant public health threats.[3] Although more common in adults, CDI is an evolving problem in children with increasing prevalence,[4] particularly in children with diarrhea onset in the community.[5]

Solid organ transplant (SOT) has been identified as a risk factor for CDI in adults and children;[6,7] up to 30% of adult SOT recipients develop CDI.[8] Notably, CDI has been reported to be associated with graft loss in adult SOT recipients, suggesting *C. difficile* acquisition may have important implications in post-SOT outcomes.[9] The immunosuppressive regimens used for patients undergoing SOT, along with increased exposure to healthcare settings, put them at increased risk of infection. Pediatric SOT recipients are at higher risk of incident and recurrent CDI and may be at higher risk of severe outcomes.[10] However, risk factors contributing to CDI in pediatric SOT recipients are poorly understood. The primary objective of this case-control study was to characterize risk factors for CDI in pediatric SOT recipients.

Patients and Methods

This study was performed at the Ann & Robert H. Lurie Children's Hospital of Chicago, an academic freestanding children's hospital where approximately 50 SOTs are performed each year, including heart, liver, kidney and small intestine transplantation. Recipients of any type of transplant were included in the analysis. The Institutional Review Board at Lurie Children's approved this study with a waiver of informed consent.

This retrospective case-control study included all SOT recipients 1–22 years old tested for *C. difficile* at our facility between August 2009 (the month when our facility began PCR testing for CDI) and August 2017. Data were extracted from the electronic medical record. We identified SOT recipients and date of transplant using ICD-9/ICD-10 codes, and we then identified *C. difficile* PCR testing date in these SOT recipients through our laboratory testing database. Cases were defined as testing events where PCR was positive for *C. difficile* (i.e.,

laboratory identified CDI). Controls were defined as *C. difficile* testing events where PCR was negative. For patients with more than one *C. difficile* testing event, all events that occurred after SOT were included. Our clinical microbiology laboratory tested for toxigenic *C. difficile* by the GeneXpert *tcdB* (toxin B gene) PCR (Cepheid, Sunnyvale, California)[11,12] throughout the study period and limits *C. difficile* testing to unformed stools collected from patients at least 1 year of age who have not been tested for *C. difficile* in the past 7 days.

Demographic data, including age at *C. difficile* testing, sex, race, ethnicity, age at SOT and type of SOT, were extracted from the medical record. *C. difficile* PCR result, antibiotic use within 30 days prior to *C. difficile* testing, immunosuppressant regimen at the time of CDI testing, hospitalization within 12 weeks prior to CDI testing, presence of gastrostomy or jejunostomy tube, use of proton pump inhibitor (PPI) medication within 7 days prior to CDI testing, and time from SOT to CDI test were also collected. A convenience sample of *C. difficile* molecular epidemiology data for 12 CDI cases in SOT recipients was obtained as part of a larger study of CDI at our pediatric medical center in 2012–2013. Anaerobic stool culture and restriction endonuclease analysis typing data were performed as previously described.[12]

Descriptive statistics summarized all demographic and clinical variables of interest. Primary analyses employed a series of generalized linear mixed models, with logit link, to assess the association between each patient-level or test-level predictor of interest and the presence of a positive CDI test, in turn. Specifically, models included a fixed effect for the predictor of interest and a random patient effect to account for correlation of multiple tests from the same patient. Predictors deemed significant in univariable models with an alpha of 0.15 were included in a multivariable model. Backward elimination was implemented to arrive at the final multivariable model. All hypothesis tests considered a two-sided type one error rate of 0.05, unless otherwise specified, and no corrections were made for multiple testing. The software used to perform the analysis was SAS v9.4.

Results

Between August 2009 and August 2017, 409 SOTs were performed at our center, of which 138 (33.7%), 134 (32.8%), 131 (32.0%), and 6 (1.5%) were kidney, liver, heart, and small intestine transplants, respectively. During this time period at our center, 205 SOT recipients age 1–22 years were tested for CDI. In total, 723 *C. difficile* PCR tests were performed among these 205 patients (median two tests per patient during the study period). There were 132 positive tests (18.3%) and 591 negative tests (81.7%). Among the 205 patients included in this study, 68 (33.2%) developed CDI at least once during the study period. Median (interquartile range) time to diagnosis of first CDI episode following SOT was 8.9 (1.2, 19.6) months. Patient characteristics are listed in Table 1.

Antibiotic exposure within 30 days prior to *C. difficile* testing occurred in 486 (67.2%) of the testing events. Third/fourth-generation cephalosporins were the most frequently used antibiotic (n=124, 17.2%); clindamycin (n=10, 1.4%) and fluoroquinolone (n=18, 2.5%) exposure was uncommon. Among the 486 testing events with preceding antibiotic exposure,

214 (44.0%) received two or more distinct classes of antibiotics. Calcineurin inhibitors were the most frequently used immunosuppressant (n=634, 87.7%) at the time of *C. difficile* testing events; 484/634 (76.3%) of patients receiving a calcineurin inhibitor also received mycophenolate. Medication exposures prior to *C. difficile* testing events are summarized in Table 2.

Independent risk factors for CDI after SOT were identified by generalized linear mixed models (Table 3). In the final multivariable model, CDI was significantly associated with both calcineurin inhibitor use at the time of *C. difficile* testing (odds ratio [OR] 2.38, 95% confidence interval [CI] 1.08, 5.24, p=0.03) and systemic antibiotic exposure within 30 days of *C. difficile* testing (OR 1.74 95% CI 1.08, 2.79, p=0.02). Among those receiving any systemic antibiotics, receipt of 2 or more antibiotic classes was not associated with a significant increase in odds of CDI, compared to those receiving only 1 antibiotic class (OR 0.82, 95% CI 0.51, 1.32, p=0.41). As a *post hoc* analysis, we assessed the association between blood tacrolimus levels and the likelihood of *C. difficile* positivity. We extracted the median blood tacrolimus level measured between 48 hours prior and up to 30 days prior to *C. difficile* testing for patients on calcineurin inhibitors at the time of *C. difficile* testing. There were 557 *C. difficile* testing events with blood tacrolimus levels measured within the past 30 days, and among these, 104 (18.7%) and 453 (81.3%) were *C. difficile* positive and negative, respectively. Median tacrolimus level was log transformed in a generalized linear mixed effect model to improve model fit. There was no significant association between log tacrolimus level and odds of CDI (OR 0.88, 95% CI 0.55, 1.41, p=0.61). Further, we assessed likelihood of *C. difficile* positivity when mycophenolate was used in addition to a calcineurin inhibitor. Compared to those who received only a calcineurin inhibitor, the odds for CDI in those additionally receiving mycophenolate did not differ (OR 0.72, 95% CI 0.40, 1.32, p=0.29).

C. difficile restriction endonuclease analysis typing data were available from a convenience sample of 12 CDI cases. The restriction endonuclease analysis groups identified in this convenience sample were: DH (n=4), Y (n=2), AL (n=1), CF (n=1), D (n=1), and non-specific (i.e., uncharacterized) restriction endonuclease analysis groups (n=3).

Discussion

In our single-center cohort, CDI was a common post-transplant complication, occurring in approximately one-third of children post-SOT. Furthermore, CDI was a relatively late post-transplant infectious complication; CDI occurred at least 9 and 20 months after SOT in 50% and 25% of patients, respectively. We identified calcineurin inhibitor use at the time of *C. difficile* testing and systemic antibiotic exposure within 30 days of CDI testing as independent risk factors for CDI following SOT. Median blood level of tacrolimus in the prior 30 days was not associated with likelihood of CDI. Among those on calcineurin inhibitors, the addition of mycophenolate was not associated with increased odds of CDI. Furthermore, among those receiving systemic antibiotics, receipt of two or more classes of systemic antibiotics within 30 days of *C. difficile* testing did not significantly increase odds of CDI compared to those who only received one class.

Compared to a prior study in pediatric SOT recipients,[13] the proportion of children developing CDI was nearly three-fold higher in our cohort (33% vs. 12%) and occurred later in the post-SOT course (9 months vs. 2 months post-SOT). Children in our cohort also developed CDI later than adult patients in whom CDI most commonly occurred within 90 days post-SOT.[8] The reasons for differences in CDI incidence are not clear, but differences in *C. difficile* testing methodologies between institutions may have contributed to this difference. Our study identified CDI cases using the highly sensitive Cepheid GeneXpert *tcdB* PCR test. The prior study in pediatric SOT recipients[13] utilized toxin enzyme immunoassay for the first half of the study and the Illumigene loop-mediated isothermal amplification test during the second half of the study; both tests are less sensitive than our PCR test.[14] Differences in antibiotic and immunosuppressive medication use between institutions may also play a role. The observation of CDI as a later post-SOT complication in our population may be related to differences in risk of hospital exposure to *C. difficile* in the immediate post-SOT period. We have previously reported substantially greater numbers of community-onset CDIs than hospital-onset CDIs in our single-center pediatric population,[12] and intra-hospital *C. difficile* transmission between children at our medical center is very uncommon.[15]

We identified an independent association between CDI with both calcineurin inhibitor use and recent antibiotic exposure, neither of which were identified as risk factors for CDI post-SOT in a pediatric study similarly performed in a large academic free-standing children's hospital.[13] However, CDI risk factors previously identified in the general pediatric population, including PPI use[16,17] and presence of a gastrostomy or jejunostomy tube,[7,18] were not independent risk factors in our pediatric SOT population. The mechanism by which calcineurin inhibitors increase risk of CDI is unknown. In a murine model, immunosuppressive drugs disrupt gut microbiota and permit expansion of uropathogenic *E. coli* in the gut, but this was not unique to calcineurin inhibitors.[19] In human kidney transplant recipients, the use of an mTOR inhibitor versus tacrolimus resulted in similar levels of gut microbiome alpha diversity, though differences emerged in microbiota gene expression patterns.[20] Although we did not distinguish between tacrolimus and cyclosporine in the present study, prior work has suggested that risk of CDI post-lung transplant is similar between these two calcineurin inhibitors.[21] Regarding other immunosuppressants, in mice mycophenolate was associated with loss of GI microbiome diversity, expansion of *Proteobacteria*, and enrichment of lipopolysaccharide biosynthesis.[22] Although antimicrobial stewardship is a well-accepted CDI risk reduction strategy in SOT recipients,[23] the impact of modifying immunosuppression regimens to reduce CDI risk is unexplored. The mechanism by which calcineurin inhibitors increase risk of CDI and potential impact of selection of immunosuppressive drugs on CDI risk both require further investigation.

Although the number of typed *C. difficile* isolates in this study was relatively limited, we identified restriction endonuclease analysis groups DH and Y (which correspond to PCR ribotypes 106 and 014/020, respectively)[24] as the most common *C. difficile* strains in our pediatric SOT cohort. These molecular epidemiologic findings are consistent with recent national data indicating that ribotypes 106 and 014/020 are among the most common strain types causing CDI in adults in the US.[25] Importantly, there were no children in our pediatric

SOT cohort who developed CDI caused by the epidemic, multi-drug resistant, and potentially hypervirulent BI/NAP1/027 strain.[26]

There are several limitations of this study. Our study was a single-center retrospective chart review, thus its generalizability may be somewhat limited. Our center performs heart, liver, kidney, and small intestinal SOT. Thus, CDI following lung and other types of SOT could not be assessed. Although our microbiology laboratory restricts CDI testing by toxin B gene PCR to unformed stools, we cannot rule out that some patients were misdiagnosed with CDI and instead had an alternative cause for their diarrheal illness with concomitant *C. difficile* colonization. To lessen the likelihood of this occurrence, we omitted children less than one-year old who were tested for *C. difficile* given the exceedingly low likelihood of CDI in this young patient population as supported by recent CDI testing guidelines.[27] While we did not assess for frequency of severe CDI and its complications, our prior research has indicated that severe and complicated CDI is very uncommon in our single-center pediatric population and the accurate identification of which is precluded by patient comorbidities and concomitant medications.[28]

In summary, in our pediatric SOT population, we identified calcineurin inhibitor and antibiotic exposure as independent risk factors for CDI, which was a late post-SOT infectious complication in our cohort. The potential impact of specific immunosuppressive drug and antibiotic selection on CDI risk reduction requires further investigation.

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Table 1.

Patient Characteristics (n=205)

Characteristic	N (%)
Sex	
Female	85 (41.5)
Male	120 (58.5)
Race	
White	98 (47.8)
Black	27 (13.2)
Other	77 (37.6)
Missing/Declined	3 (1.5)
Ethnicity	
Hispanic/Latino	70 (34.2)
Non-Hispanic/Latino	128 (62.4)
Missing/Declined	7 (3.4)
Transplant type	
Heart	71 (34.6)
Kidney	59 (28.8)
Liver	71 (34.6)
Small Bowel	4 (2.0)
Median (interquartile range) age at transplant	4.1 (1.3, 12.5)
Positive C. difficile test during study period	
Yes	68 (33.2)
No	137 (66.8)

Table 2.

Medication exposures prior to *C. difficile* testing events (n=723)

Medication	N (%)
Antibiotic exposure (prior 30d)	
Any systemic antibiotic	486 (67.2)
Third/fourth-generation cephalosporins	124 (17.2)
Clindamycin	10 (1.4)
Fluoroquinolones	18 (2.5)
Immunosuppressant use at time of C. difficile testing	
Calcineurin inhibitors	634 (87.7)
Tacrolimus	605 (83.7)
Cyclosporine	45 (6.2)
Mycophenolate mofetil	539 (74.6)
Sirolimus	117 (16.2)
Corticosteroids	78 (10.8)
Azathioprine	84 (11.6)
Proton-pump inhibitor exposure (prior 7d)	124 (17.2)

d- days

Table 3.

Risk Factors for CDI from Generalized Linear Mixed Models*

Predictor	Unadjusted Models		Final Adjusted Model	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Sex				
Female	Ref			
Male	1.13 (0.69, 1.87)	0.63		
Age at transplant (years)	0.98 (0.94, 1.02)	0.37		
Race				
White	Ref	0.92		
Black	0.87 (0.39, 1.97)			
Other	0.92 (0.54, 1.56)			
Ethnicity				
Hispanic	Ref	0.21		
Non-Hispanic	0.72 (0.42, 1.21)			
Transplant type				
Heart	Ref	0.41		
Kidney	0.69 (0.36, 1.34)			
Liver	1.05 (0.59, 1.86)			
Small Bowel	0.41 (0.09, 1.88)			
Recent hospitalization (prior 12 weeks)	0.93 (0.58, 1.49)	0.75		
Gastrostomy or jejunostomy tube	1.45 (0.79, 2.66)	0.24		
Time from transplant to *C. difficile* testing event	0.99 (0.98, 1.00)	0.08		
Antibiotic exposure (prior 30d)				
Any systemic antibiotic	1.62 (1.01, 2.59)	0.04	**1.74 (1.08, 2.79)**	**0.02**
Third/fourth-generation cephalosporins	0.80 (0.45, 1.44)	0.46		
Clindamycin	0.98 (0.19, 5.00)	0.98		
Fluoroquinolones	0.23 (0.03, 1.80)	0.16		
Immunosuppressant use at time of C. difficile testing				
Calcineurin inhibitors	2.12 (0.97, 4.64)	0.06	**2.38 (1.08 5.24)**	**0.03**
Mycophenolate mofetil	0.79 (0.45, 1.37)	0.40		
Sirolimus	1.35 (0.76, 2.40)	0.30		
Corticosteroids	1.10 (0.58, 2.11)	0.77		
Azathioprine	1.17 (0.56, 2.46)	0.68		
Proton-pump inhibitor exposure (prior 7d)	0.84 (0.48, 1.48)	0.54		

*Mixed models included a fixed effect for the predictor of interest and a random patient effect to account for correlation of multiple tests from the same patient

Ref- reference group; d- days; OR- odds ratio; CI- confidence interval. Bolded values indicate statistical significance.