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Fecal Microbiota Transplantation in a toddler after heart transplant was a safe and effective treatment for recurrent *Clostridioides difficile* infection: A case report

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Abstract

Pediatric recipients of solid organ transplant (SOT) have a significantly increased risk of *Clostridioides* (formerly *Clostridium*) *difficile* infection (CDI), which is associated with adverse outcomes after SOT. Alterations to the intestinal microbiota community structure increase the risk of CDI. Fecal microbiota transplantation (FMT) is a safe and effective treatment for recurrent CDI (rCDI) in immunocompetent children and adults. While there are increasing data that FMT in immunosuppressed patients is safe and effective without increased risk of infection, data regarding safety and efficacy of FMT in children after SOT are limited. To our knowledge, we report the youngest immunocompromised patient to undergo FMT, and the third overall case of FMT in a child after heart transplant. Our patient presented with 5 episodes of rCDI in 6 months, and *16S rRNA* genetic analysis revealed significant loss of overall microbiota community structure and

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Supporting Information

Supporting information includes a supplement which gives a detailed description of microbiota community analysis.

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diversity prior to FMT compared with a donor and a healthy, age-matched control. After FMT, marked and prolonged (at least 16 months) shifts in the recipient microbiota community structure and diversity were evident, approaching that of donor and healthy, age-matched control. FMT was well-tolerated, restored microbial diversity without any graft or transplant complications, and prevented further rCDI episodes after more than 4 years of follow up.

Keywords

Pediatric Heart Transplant; Fecal Microbiota Transplant; *Clostridium difficile*

Introduction

Alterations to the intestinal microbiome increase the risk of *Clostridioides* (formerly *Clostridium*) *difficile* infection (CDI).¹ Pediatric and adult solid organ transplant (SOT) recipients have a significantly increased risk of CDI.^{2–5} There is an over 8-fold increased risk of CDI in children after SOT compared to other pediatric patients, and CDI is more likely to recur in patients after SOT.⁶ CDI is independently associated with increased mortality, length of hospital stay, hospital charges, and complications in the transplanted organ.^{5,7–10} Due to the increased incidence, recurrence, morbidity, and mortality of CDI after SOT, effective and durable treatment for CDI after SOT is of great importance.^{8,9}

Fecal microbiota transplantation (FMT) is a safe and effective treatment in immunocompetent children and adults for recurrent CDI (rCDI).^{4,11–13} Increasing data on FMT in immunosuppressed patients support the feasibility of FMT in this high risk population without an increased risk of infection.^{4,8,14–16} However, data in immunosuppressed children are limited. There are 2 reported cases of FMT in a pediatric patient after heart transplant (HTx).^{17,18} We present a successful case of FMT in a 2-year-old pediatric patient with rCDI after HTx. FMT was well-tolerated, restored microbial diversity without any graft or transplant complications, and prevented further rCDI episodes after more than 4 years of follow up. This is an important addition to the literature because this is the youngest immunosuppressed SOT patient to undergo FMT, and we include detailed pre- and post-FMT microbiota community analysis with comparison to a healthy, age-matched control.

2. Clinical Report

A 2-year-old female presented after 5 episodes of rCDI in 6 months. She had previously undergone HTx (CMV donor positive/recipient negative; EBV donor negative/recipient negative; crossmatch negative) at 5 months of age following failed single ventricle palliation of hypoplastic left heart syndrome. Her immediate post-transplant course was unremarkable. However, she began having episodes of CDI 9 months post-HTx. Her first episode occurred at 15 months of age and was diagnosed by *Clostridioides difficile* toxin PCR testing. The first episode resolved with 14 days of oral metronidazole, but CDI recurred 3 weeks later. CDI resolved with 14 days of oral vancomycin but recurred 2 weeks later, and extensive testing for other infectious (including multiple specimens tested for stool culture, stool O&P, Giardia/Cryptosporidium antigen, rotavirus, viral culture and viral particles, and quantitative

adenovirus, enterovirus, and cytomegalovirus PCR) and chronic causes of diarrhea was negative. She started an 84-day oral vancomycin taper, but CDI recurred prior to completion of treatment. Diarrhea (defined as > 3 unformed stools in over 24 hours) only resolved after restarting 4 times daily vancomycin plus 2 weeks of oral nitazoxanide. Another oral vancomycin taper was initiated, but she developed recurrent symptoms within a month and failed yet another oral vancomycin taper. This rCDI course was associated with a significant failure to thrive and a weight below the 1st percentile for age. She was ultimately referred for FMT.

Informed consent was obtained and FMT was carried out under a protocol approved by the Institutional Review Board at Baylor College of Medicine. Her morning immunosuppression was withheld on the day of FMT, but otherwise she was maintained on her stable immunosuppressive regimen of tacrolimus (goal trough level 8–10 ng/mL) and mycophenolate (60 mg PO BID). She underwent colonoscopy (normal findings) that included delivery of screened, filtered, and frozen donor stool FMT (80 cc screened, frozen-thawed, father-donated sample [from 50g of stool, filtered and diluted with normal saline and 10% glycerol] to the terminal ileum and 170 cc to the cecum). There were no procedural complications, and she experienced complete resolution of symptoms within 2 days. However, CDI recurred 8 weeks later after she received 1 week of oral amoxicillin for a respiratory infection. She underwent repeat FMT without procedural complications (60 cc via nasogastric tube; same donor preparation) with complete resolution of symptoms within 2 days. At 4 years of follow up, she has not experienced any CDI recurrences or infectious diarrhea despite receiving oral antibiotics twice per year for ear and sinus infections. She has also demonstrated good weight gain; her weight-for-length increased from below the 1st percentile to the 10th percentile. She has not experienced any episodes of rejection or other transplant-related adverse events or complications, including coronary allograft vasculopathy (CAV), and she has normal graft function.

Fecal microbiota community analysis was performed prior to FMT and at 4- and 16-month follow-up after the second FMT (see supplement for 16S rDNA methodology). A significant loss in overall microbiota diversity (alpha diversity measured by the Shannon diversity index and beta diversity [Bray-Curtis dissimilarity]; Figures 1A & 1B) was evident in the pre-FMT stool sample when compared to a healthy, age-matched control sample and to the donor sample. The pre-FMT stool sample was characterized by a different overall composition at the bacterial phylum (Figure 2A) and genus (Figure 2B) levels compared to control and donor samples. After FMT, there were marked recipient microbiota shifts (Figure 1B) with alpha-diversity approaching fecal control and donor levels (Figure 1A). The disease-free 4-month post-FMT sample composition remained distinct from the pre-FMT sample (Figures 2A & 2B), with microbiota community composition developing further by 16 months post-FMT where it more closely resembled donor and healthy control microbiota communities (Figures 2A & 2B), most notably at the phylum level.

3. Discussion

There is a paucity of data on the safety and efficacy of FMT for rCDI in the pediatric SOT population. There is also no consensus on pre-FMT immunosuppressive management

despite the concern for increased risk of post-FMT adverse events for patients taking major immunosuppressive agents.¹⁹ To our knowledge, we report the third case of FMT in a pediatric patient after HTx and the youngest immunocompromised SOT patient to undergo FMT. We are currently unaware of any specific protocols for pre-FMT immunosuppressive management. We elected to withhold all immunosuppressive treatment on the day of the procedure as the patient was NPO and had stable goal therapeutic levels, and we wanted to avoid augmented immunosuppression around the time of FMT in the event of any complication or diarrhea that could lead to supratherapeutic drug levels. FMT was well tolerated without any adverse events and was effective in preventing rCDI or infectious diarrhea up to 4 years post-FMT. Importantly, our patient has not experienced any episodes of cellular or antibody-mediated rejection (AMR), there is no evidence of CAV or graft dysfunction, and the patient's growth has improved significantly.

Barfuss et al. reported a case of CAV 2 months after FMT. However, this patient previously developed *de novo* donor specific antibodies 2 years before FMT and had 2 prior episodes of AMR prior to CAV diagnosis. While CAV was found shortly after FMT, potentially suggesting a temporal correlation, the authors do correctly point out that many factors could have contributed to severe rejection with CAV, and that "identifying a causal factor from a single case is clearly impossible".¹⁸ Furthermore, no microbiota community analysis (pre- or post-FMT) was performed, and there were no other indications that FMT played a role. In fact, FMT has proven safe without any episodes of rejection in over 80 cases of FMT in SOT recipients.^{4,8,20} Furthermore, a randomized controlled trial of FMT in adults undergoing hematopoietic stem cell transplant (HSCT) was well-tolerated and partly restored fecal microbiota diversity.²¹

A unique aspect of this case is the pre- and sequential post-FMT microbiota community analysis, which included comparison to the adult donor and a healthy, age-matched control. There are limited data on the fecal microbiota community dynamics in the pediatric SOT population. We detected a significantly altered fecal microbiota community structure with low diversity at the time of recurrent CDI, most likely attributed to extensive vancomycin administration. There is a strong association between perturbation of the intestinal microbiota community structure and susceptibility to CDI, and the clinical success of FMT presents some of the strongest support for modulation of CDI susceptibility by the microbiota.¹ FMT increased microbiota diversity, and the resulting community dynamics were distinct from both pre-FMT and donor samples. After the first FMT, the recipient microbiota remained more vulnerable to antibiotic induced CDI (there was recurrence of CDI after antibiotic treatment within 8 weeks of FMT), but a repeat FMT resulted in sustained resilience; there have been no subsequent episodes of CDI or infectious diarrhea despite antibiotic usage. Therefore, our case highlights that serial FMT may be necessary for treatment of rCDI in SOT recipients, which has also been suggested by Flannigan et al.¹⁷ Friedman-Moraco et al. described two SOT patients who both required serial FMT for resolution of rCDI,⁸ and the reported initial success rate for FMT in immunocompetent patients is 91% compared to 78% for immunocompromised patients.^{17,20,22} This may be due to the fact that SOT recipients have a more severely altered intestinal microbiota community than immunocompetent patients with rCDI, and sequential FMT may be necessary to be efficacious. The recent largest retrospective cohort study on pediatric FMT for rCDI

indicated that FMT is less efficacious with increasing number of CDI episodes.¹³ The 5 recurrences in our patient may have contributed to our patient requiring repeated FMT as well. This case also highlights that FMT can still be safe and effective when delivered less invasively via a nasogastric tube, which is consistent with reports by Kronman *et al.* and Brumbaugh *et al.*^{11,23}

This case also suggests that alterations to the intestinal microbiota community structure may have clinical implications in children after SOT, such as in adults after HSCT and in adults after kidney transplant.^{24–27} Specifically, a lack of fecal microbiota diversity at engraftment is an independent predictor of mortality in adults after HSCT.²⁴ Conversely, changes in microbiota community structure may also reflect deteriorating health in the patient. If a lack of microbiota diversity is a modifiable risk factor that adversely affects health outcomes of children after SOT, intestinal microbiota community analysis and restoration could play a significant role in the pursuit to improve the outcomes of children after SOT.

4. Conclusion

Our report examines the youngest reported patient with SOT to undergo FMT for rCDI with a follow-up period of over 4 years. Serial FMT was safe, well tolerated, without infectious or other complications, and effective in this 2-year-old child after HTx. She continues to have stable graft function and improved growth parameters without infectious disease complications, coronary allograft vasculopathy, or any episodes of cellular or antibody-mediated rejection 4 years after FMT. This case report adds to the growing body of literature that suggests the intestinal microbiota plays a significant role in the health and outcomes of immunocompromised patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

(AMR)	antibody-mediated rejection
(CDI)	<i>Clostridioides difficile</i> infection
(CAV)	coronary allograft vasculopathy
(FMT)	fecal microbiota transplantation
(HTx)	heart transplant
(HSCT)	hematopoietic stem cell transplant

(rCDI)	recurrent CDI
(SOT)	solid organ transplant

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Figure 1. Alpha and Beta Diversity Responses.

1A: Changes in Alpha Diversity Before and After Fecal Microbiota Transplant (FMT). Microbiome *16S rRNA* genetic analysis revealed less alpha diversity in the pre-FMT sample (middle) compared to Donor and Healthy Control. Alpha diversity was maintained in both the post-FMT1 and post-FMT2 samples. **1B:** Changes in Beta Diversity Before and After FMT. The pre-FMT sample was distinct from Donor and Healthy Control samples. Both the post-FMT1 and post-FMT2 samples remained distinct from the pre-FMT sample.

Figure 2. Relative Bacterial Abundance.

2A: Phylum Level. Microbiome *16S rRNA* genetic analysis revealed that the pre-FMT sample had a different overall bacterial composition at the phylum level compared to the Donor and Healthy Control samples. The 4-month post-FMT sample composition remained distinct from the pre-FMT sample with microbiota community composition developing further by 16 months post-FMT, where it more closely resembled donor and healthy control microbiota communities. **2B:** Genus Level. Microbiome *16S rRNA* analysis revealed that the pre-FMT sample had a different overall community composition at the genus level compared to the Donor and Healthy Control samples. The 4-month post-FMT sample composition remained distinct from the pre-FMT sample with microbiota community composition developing further by 16 months post-FMT, where it more closely resembled donor and healthy control microbiota communities.