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FECAL MICROBIOTA TRANSPLANTATION FOR *CLOSTRIDIOIDES DIFFICILE* INFECTION IN IMMUNOCOMPROMISED PEDIATRIC PATIENTS

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The authors of no relevant conflicts of interest.

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Abstract

Objectives—We sought to evaluate the safety and effectiveness of fecal microbiota transplantation (FMT) for recurrent *Clostridioides difficile* infection (CDI) in pediatric immunocompromised (IC) patients.

Methods—This is a multi-center retrospective cohort study of pediatric participants who underwent FMT between March 2013 and April 2020 with 12-week follow-up. Pediatric patients were included if they met the definition of IC and were treated with FMT for an indication of recurrent CDI. We excluded patients over 18 years of age, those with incomplete records, insufficient follow up, or not meeting study definition of IC. We also excluded those treated for *Clostridioides difficile* recurrence without meeting the study definition and those with inflammatory bowel disease without another immunocompromising condition.

Results—Of 59 pediatric patients identified at nine centers, there were 42 who met inclusion and no exclusion criteria. Included patients had a median age of 6.7 years. Etiology of IC included: solid organ transplantation (18, 43%), malignancy (12, 28%), primary immunodeficiency (10, 24%), or other chronic conditions (2, 5%). Success rate was 79% after first FMT and 86% after one or more FMT. There were no statistically significant differences in patient characteristics or procedural components when patients with a failed FMT were compared to those with a successful FMT. There were 15 total serious adverse events (SAEs) in 13 out of 42 (31%) patients that occurred during the follow-up period; four (9.5%) of which were likely treatment-related. There were no deaths or infections with multi-drug resistant organisms during follow-up and all patients with a serious adverse event fully recovered.

Conclusions—The success rate of FMT for recurrent CDI in this pediatric IC cohort is high and mirrors data for IC adults and immunocompetent children. FMT-related SAEs do occur (9.5%) and highlight the need for careful consideration of risk and benefit.

Keywords

infection; children; serious adverse events; malignancy

Introduction

Fecal microbiota transplantation (FMT) is used for the treatment of *Clostridioides* (formerly *Clostridium*) *difficile* infection (CDI), with an evolving body of literature in both children and adults. Despite its effectiveness, it is not an approved therapy and is classified as an investigational agent by the United States Food and Drug administration (FDA).[1,2] Initial adult randomized control trials (RCTs) on FMT excluded immunocompromised (IC) patients due to the theoretical risk of infectious complications.[3,4] Since that time, several case series and a systematic review demonstrated safety and efficacy of FMT in IC adults comparable to their immunocompetent counterparts.[5–7]

New safety concerns arose in 2019, following the development of extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli (E. coli)* bacteremia following FMT in two IC patients, one of whom died.[8] Clonality of *E. coli* from the blood cultures of both patients and the donor stool was established. In response to these events, the FDA released a safety alert recommending that FMT donors be screened for risk factors for colonization with multi-drug resistant organisms (MDROs) and the exclusion of MDRO positive donor stool during the investigational use of FMT.[9]

Currently, data on the use of FMT for CDI in IC children is limited to case reports and small case series.[10–14] Such studies are important since these children have increased risk for CDI, higher rates of recurrent CDI (rCDI), and an increased risk of negative *C. difficile*-associated outcomes.[7,15] Since children differ from their adult counterparts in predictors of FMT success and adverse event profiles, and in light of the new safety concerns, analyzing data of IC children independently from adults is prudent.[1] We sought to evaluate the safety and effectiveness of FMT for treatment of CDI in pediatric IC patients through a multicenter retrospective cohort.

Methods

In this multicenter retrospective cohort study, we included pediatric IC patients who underwent FMT for a diagnosis of CDI at nine pediatric centers across the United States between March 2013 and April 2020. We recruited centers through the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) FMT Special Interest Group. A 76-item form based on expert opinion was created using Research Electronic Data Capture (REDCap) hosted at Vanderbilt University Medical Center.[16] Data on demographics, CDI characteristics, FMT technique, and details surrounding IC status were collected. The institutional review boards (IRB) of each institution approved the study. Practitioners from the individual institutions reviewed patients' clinical records and imported data into REDCap.[16]

The primary aims of this study included (i) determining the success rate of FMT in pediatric IC patients and (ii) assessing serious adverse events (SAEs) during the 12-week follow-up period. Data on non-serious adverse events were also collected. A successful FMT required no recurrence of CDI within 12 weeks post-procedure.[18] Recurrence (or FMT failure) required both a return of diarrhea (defined as non-formed stools) and concomitant positive

C. difficile test (e.g. nucleic acid amplification test alone or part of a two-step algorithm including stool toxin test).

We defined IC as patients (i) with an inherited or acquired primary immunodeficiency or (ii) on immunosuppressive medications (antimetabolites, calcineurin inhibitors, or antineoplastic agents) at the time, or within three months, of FMT. All patients underwent FMT for an indication of rCDI; meaning that they had more than one episode of CDI with an episode of CDI occurring within eight weeks of a previous infection per standard definitions.[17] CDI diagnostic testing was performed based on institutional preference.

We excluded patients with inflammatory bowel disease (IBD) on standard immunosuppressive therapy unless they had an additional reason for IC, such as solid organ transplantation requiring immunosuppression, as IBD patients are suspected to have differences in clinical response to FMT.[19] We also excluded those who (i) were over 18 years of age, (ii) had incomplete records, (iii) had treatment for rCDI during the follow-up period without meeting the study definition of recurrence, (iv) did not meet criteria for IC, or (v) did not have at least 12 weeks of follow-up.

FMT donor screening (including for MDROs) and donor stool preparation was not standardized and was at the discretion of the treating physician using donor-directed or stool bank protocol. Local stool banks and patient-selected donors underwent screening per published guidelines (Supplementary Table 1) which did not include MDRO screening.[20,21] All commercial stool bank samples were provided by OpenBiome (Cambridge, MA) and screened for ESBL-producing organisms, carbapenem-resistant enterobacteriaceae (CRE), methicillin-resistant Staphylococcus aureus (MRSA), and Vancomycin-resistant enterococci (VRE), including prior to the FDA safety alert in 2019.

Death, life-threatening or important medical events, or hospitalizations qualified as serious adverse events (SAEs). Adverse events (AEs) were defined as undesirable experiences in a patient post-FMT that were obtainable through the medical record on chart extraction. FMT relation to SAEs was based on the consensus of three independent reviewers (MRN, LKK, and RK).

We calculated the success rate for FMT as percentages after one and more than one FMT. AEs and SAEs are reported as total number of events and as percentages of the IC cohort (given that some subjects encountered more than one SAE). Patients with and without a failed FMT were compared using Fisher's Exact test and analyzed using Stata (StataCorp, College Station, TX).

Results

Study patient characteristics

We identified 59 patients in the database, 42 of whom met inclusion criteria. Reasons for exclusion included: (i) six having IBD without another IC condition, (ii) five not meeting study definition for IC, (iii) two with insufficient follow up, (iv) two treated for rCDI after FMT without meeting the study definition for recurrence (tested positive for *C. difficile*

following FMT but did not have diarrheal symptoms), (v) one over 18 years old, and (vi) one with incomplete records. For our 42 subjects, the mean age was 6.7 years (range of 18 months to 18 years), and males comprised 71% of the cohort (Table 1).

The cause of IC included 10 (24%) with a primary immunodeficiency and 32 (76%) with a comorbidity associated with immunosuppressive medication use. These comorbidities included solid organ transplantation (18, 43%), malignancy (12, 28%), and other chronic conditions (2, 5%), which included nephropathy and chronic heart and lung disease. Two subjects with malignancy had previously undergone stem cell transplantation. Two subjects had IBD in addition to X-linked agammaglobulinemia and solid organ transplantation, respectively, and one had short gut syndrome in addition to multivisceral transplantation. The cohort characteristics are detailed in Table 1.

CDI and FMT characteristics

All patients received FMT for a primary indication of rCDI. Nearly half (19, 46%) of the subjects were hospitalized for reasons related to CDI prior to undergoing FMT, although none had FMT performed for a primary indication of severe, fulminant or complicated CDI. The median number of CDI episodes prior to FMT was four [interquartile range (IQR) 3–5], and patients experienced a median of 11 months (IQR 6–20) of symptoms before FMT. At minimum, all patients failed a standard course of vancomycin plus one other antibiotic therapy prior to FMT. The most common route of administration was via colonoscopy (23, 55%), followed by gastric (11, 26%), duodenal/jejunal (6, 14%) and capsule (2, 5%). Additional FMT-related variables are detailed in Table 2.

Outcomes

In this pediatric IC cohort, 33/42 (79%) had a successful first FMT. In the nine patients where first FMT failed, five had FMT repeated of which three were successful for an aggregate success of 86% for one or more FMT. Five (56%) of the nine failures were patients with history of solid organ transplantation, two (22%) had a primary immune deficiency and two (22%) had a hematologic malignancy. There were no statistically significant differences in patient characteristics or procedural components when patients with a failed FMT were compared to those with a successful FMT (Table 3).

Table 4 details SAEs for this cohort. There were no deaths. Fifteen total SAEs occurred in 13 out of 42 (31%) patients during the 12-week follow-up; these included 14 hospitalizations involving 12 out of 42 (29%) patients. Four hospitalizations involving four out of 42 (9.5%) patients were deemed to be related or likely-related to FMT based on expert review; these included (i) one patient with cecal perforation during colonoscopic FMT, (ii) one child with aspiration pneumonitis following EGD-guided FMT instillation, (iii) one child with fever immediately post-FMT (Day 0) admitted on empiric antibiotics who underwent a negative sepsis evaluation, and (iv) one patient with intractable diarrhea post-FMT (day zero) admitted for observation with negative *C. difficile* testing. Two of these four hospitalizations occurred in patients with primary immunodeficiency, one in a patient with solid organ transplantation and one with malignancy. Three of the four received stool frozen from a stool bank and one received patient-selected, fresh stool. Two of four

had FMT administered via colonoscopy, one administered via the gastric route and one via jejunal route.

The only non-hospitalization SAE involved the development of adrenal insufficiency in a patient with cancer and was deemed unrelated to FMT. All patients with an SAE fully recovered and none were diagnosed with an infection caused by a multi-drug resistant organism. There were no deaths reported.

More common, non-serious AEs included diarrhea (8, 19%), emesis (3, 7%), abdominal pain (2, 5%), constipation (1, 2%), blood in stool (1, 2%), and fever without hospitalization (1, 2%). Half (8, 50%) of these were reported within the first three days after FMT and all were self-limited.

Discussion

The burden of CDI in IC patients is significant with higher rates of both primary disease and rCDI in this population.[22–25] Exposure to antibiotics and immunosuppressants are associated with increased CDI risk in these vulnerable patients and multiple studies have confirmed a diagnosis of cancer to be an independent risk factor for recurrence of CDI.[15,24–27] In addition, children with cancer and a diagnosis of CDI have higher rates of morbidity and mortality. In a study of 1736 admissions in children with cancer, those with an admission complicated by healthcare facility-associated CDI had an increased length of stay by 23 days and more than double the risk of death than those without CDI.[15]

Despite a high disease burden, there has been a historical hesitance to use FMT in IC hosts due to heightened safety concerns. These patients were excluded from early clinical trials until retrospective adult data began to demonstrate efficacy and safety of FMT in IC hosts.[5–7,22,23] Notably, an important FDA safety alert was released in 2019 when two FMT trial patients, who received FMT for a non-CDI indication, developed bloodstream infections with resistant bacterial organisms that were traced back to the donor stool using genomic sequencing.[8] These cases demonstrate the significant difficulties with using a poorly standardized therapeutic agent in an evolving infectious disease landscape.[28] Case studies have reported the use of FMT in pediatric IC patients, but given the emerging literature surrounding the practice in IC adults, there is a need for more robust data in this unique pediatric population.

In our cohort of 42 pediatric IC patients, the success rate following first FMT was 79%. The aggregate success rate of 86% after one or more FMT. This is comparable, although slightly lower, to data from adult IC patients with a systematic review of 234 IC patients demonstrating 88% and 94% cure rates after first and second FMT, respectively[5] and similar to prior pediatric data with an inclusive cohort of 335 pediatric patients demonstrating a cure rate of 87% after second FMT.[1] Our study identified no differences in IC patient characteristics or FMT procedures in patients with a successful versus failed FMT. However, it was limited by small sample size and therefore less likely to identify differences if they did exist. In adult studies, predictors of FMT failure in IC patients include inpatient status,

severe and fulminant CDI, presence of pseudomembranous colitis, and use of non-CDI antibiotics at the time of FMT.[22]

Safety concerns are a major cause of hesitancy involving the use of FMT in the IC host. In our cohort, there were 15 total SAEs occurring in 13 (31%) patients during the 12-week follow-up period, with no deaths and all fully recovering. Four of the SAEs were deemed FMT-related or likely-related, occurring in four (9.5%) patients. There were no infections related to MDROs in our pediatric IC cohort identified through clinical care, although judicious screening was not done. Patients with a history of malignancy had a higher rate of SAEs, with half of those patients experiencing an SAE during follow-up. However, only one of these was deemed related to FMT, and this likely speaks to the medical complexity and frequent hospitalization at baseline for this complex population. A comparable adult IC cohort (n=80) undergoing FMT for CDI had an SAE rate of 15% during 12-week follow-up with 7.5% related or possibly related to FMT.[7] This included two deaths, one of which was related to aspiration during the FMT procedure and the other was felt to be non-related to FMT. There were no infectious complications definitely-related to FMT.[7] This SAE rate is similar to non-IC adults.[5] Our prior published cohort study reporting FMT effectiveness for CDI in children reported an overall SAE rate of 4.7%, comprised of ten hospitalizations with no deaths.[1]

Thus, this study demonstrates a higher rate of FMT-related SAEs in IC children when compared to the broader pediatric population and IC adults, although sample size and retrospective nature of this analysis limits additional conclusions. The comparably higher rate of SAEs in our cohort may be attributable to the patients' level of medical complexity, with seventy-two percent requiring hospitalization for any cause within the year preceding FMT. In addition, nearly half of our cohort had a CDI-related hospitalization prior to FMT; a point that requires careful consideration when evaluating risk versus benefit in this vulnerable population.

Traditionally, concern with administering FMT to IC patients surrounded the theoretical risk of bacterial translocation and bacteremia, especially with MDROs. However, it is important to consider that patients with rCDI have expansion of invasive bacterial species including members of the genus *Enterobacteriaceae* .[29,30] Additionally, a recent study showed that pediatric patients with CDI had a significant decrease in antimicrobial resistance genes and a sustained decrease in multidrug resistance genes in their intestinal microbiome following FMT.[31] Notably, though, tetracycline resistance genes increased after FMT, and low levels of potential pathogens were identified in donor stool.[31]

IC patients would benefit greatly from a highly refined and regulated microbial therapeutic product for the safe treatment of CDI. Currently, many microbial therapeutics products are being studied in phase III trials in adults, but remain unstudied in children.[32,33] In addition, these are often capsule or enema products which are logistically difficult to administer to children. Urgent and careful consideration of how to safely and effectively perform manipulation of the intestinal microbiome, through FMT or alternative microbial therapeutics, in pediatric IC patients is warranted.

Limitations

This study was limited by its retrospective nature as all data was obtained through the medical record. Reports of adverse events required patient report and were not actively solicited during the follow-up period. Thus, AEs were likely underreported. Although the largest study of its kind, our small sample size made it difficult to elicit statistical significance for factors, including magnitude of immunosuppression and mode of FMT delivery, which may have contributed to the likelihood of both FMT success and SAEs. Notably, no pediatric IC patients had FMT performed for a primary indication of severe or fulminant FMT, so assessments on the efficacy and safety in IC patients with severe disease cannot be made and warrant additional study. We were also limited by our 12-week follow-up period in studying additional long-term SAEs in pediatric IC patients following FMT; an important consideration when performing FMT in pediatric patients. These limitations would be better addressed through a prospective placebo-controlled trial with extended follow-up.

Conclusion

In conclusion, pediatric IC patients undergoing FMT for the treatment of rCDI have high rates of success following one or more FMT, although the complexity of this patient population and the rate of SAEs (9.5%) warrants careful assessment of risk versus benefit when considering treatment with FMT. Continued study into the safe administration of FMT, or the use of alternative microbial therapeutics, in pediatric IC patients is necessary.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Nicholson MR, Mitchell PD, Alexander E, et al. Efficacy of Fecal Microbiota Transplantation for Clostridium difficile Infection in Children. Clin Gastroenterol Hepatol. 2020;18(3):612–619.e1. doi:10.1016/j.cgh.2019.04.037 [PubMed: 31009795]
2. Quraishi MN, Widlak M, Bhala N, et al. Systematic review with meta-analysis: the efficacy of faecal microbiota transplantation for the treatment of recurrent and refractory *Clostridium difficile* infection. Aliment Pharmacol Ther. 2017;46(5):479–493. doi:10.1111/apt.14201 [PubMed: 28707337]
3. Bakken JS, Borody T, Brandt LJ, et al. Treating Clostridium difficile Infection With Fecal Microbiota Transplantation. Clin Gastroenterol Hepatol. 2011;9(12):1044–1049. doi:10.1016/j.cgh.2011.08.014 [PubMed: 21871249]
4. Kelly CR, Khoruts A, Staley C, et al. Effect of Fecal Microbiota Transplantation on Recurrence in Multiply Recurrent *Clostridium difficile* Infection: A Randomized Trial. Ann Intern Med. 2016;165(9):609. doi:10.7326/M16-0271 [PubMed: 27547925]

5. Shogbesan O, Poudel DR, Victor S, et al. A Systematic Review of the Efficacy and Safety of Fecal Microbiota Transplant for Clostridium difficile Infection in Immunocompromised Patients. Can J Gastroenterol Hepatol. 2018;2018:1–10. doi:10.1155/2018/1394379
6. Abu-Sbeih H, Ali FS, Wang Y. Clinical Review on the Utility of Fecal Microbiota Transplantation in Immunocompromised Patients. Curr Gastroenterol Rep. 2019;21(3):8. doi:10.1007/s11894-019-0677-6 [PubMed: 30815766]
7. Kelly CR, Ihunnah C, Fischer M, et al. Fecal Microbiota Transplant for Treatment of Clostridium difficile Infection in Immunocompromised Patients: Am J Gastroenterol. 2014;109(7):1065–1071. doi:10.1038/ajg.2014.133 [PubMed: 24890442]
8. DeFilipp Z, Bloom PP, Torres Soto M, et al. Drug-Resistant E. coli Bacteremia Transmitted by Fecal Microbiota Transplant. N Engl J Med. 2019;381(21):2043–2050. doi:10.1056/NEJMoa1910437 [PubMed: 31665575]
9. Drug Administration F and. Important safety alert regarding use of fecal microbiota for transplantation and risk of serious adverse reactions due to transmission of multi-drug resistant organisms. Published June 13, 2019. Accessed March 20, 2020. https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/important-safety-alert-regarding-use-fecal-microbiota-transplantation-and-risk-serious-adverse
10. Barfuss S, Knackstedt ED, Jensen K, Molina K, Lal A. Cardiac allograft vasculopathy following fecal microbiota transplantation for recurrent *C. difficile* infection. Transpl Infect Dis. 2018;20(6):e12983. doi:10.1111/tid.12983 [PubMed: 30155958]
11. Bluestone H, Kronman MP, Suskind DL. Fecal Microbiota Transplantation for Recurrent Clostridium difficile Infections in Pediatric Hematopoietic Stem Cell Transplant Recipients. J Pediatr Infect Dis Soc. 2018;7(1):e6–e8. doi:10.1093/jpids/pix076
12. Flannigan KL, Rajbar T, Moffat A, et al. Changes in Composition of the Gut Bacterial Microbiome after Fecal Microbiota Transplantation for Recurrent Clostridium difficile Infection in a Pediatric Heart Transplant Patient. Front Cardiovasc Med. 2017;4. doi:10.3389/fcvm.2017.00017
13. Kronman MP, Nielson HJ, Adler AL, et al. Fecal Microbiota Transplantation Via Nasogastric Tube for Recurrent Clostridium difficile Infection in Pediatric Patients: J Pediatr Gastroenterol Nutr. 2015;60(1):23–26. doi:10.1097/MPG.0000000000000545 [PubMed: 25162365]
14. Spinner JA, Bocchini CE, Luna RA, et al. Fecal microbiota transplantation in a toddler after heart transplant was a safe and effective treatment for recurrent Clostridiodes difficile infection: A case report. Pediatr Transplant. 2020;24(1). doi:10.1111/petr.13598
15. de Blank P, Zaoutis T, Fisher B, Troxel A, Kim J, Aplenc R. Trends in Clostridium difficile Infection and Risk Factors for Hospital Acquisition of Clostridium difficile among Children with Cancer. J Pediatr. 2013;163(3):699–705.e1. doi:10.1016/j.jpeds.2013.01.062 [PubMed: 23477996]
16. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377–381. doi:10.1016/j.jbi.2008.08.010 [PubMed: 18929686]
17. McDonald LC, Gerding DN, Johnson S, et al. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis Off Publ Infect Dis Soc Am. 2018;66(7):e1–e48. doi:10.1093/cid/cix1085
18. van Beurden YH, Nieuwdorp M, van de Berg PJEJ, Mulder CJJ, Goorhuis A. Current challenges in the treatment of severe Clostridium difficile infection: early treatment potential of fecal microbiota transplantation. Ther Adv Gastroenterol. 2017;10(4):373–381. doi:10.1177/1756283X17690480
19. Khoruts A, Rank KM, Newman KM, et al. Inflammatory Bowel Disease Affects the Outcome of Fecal Microbiota Transplantation for Recurrent Clostridium difficile Infection. Clin Gastroenterol Hepatol. 2016;14(10):1433–1438. doi:10.1016/j.cgh.2016.02.018 [PubMed: 26905904]
20. Bakken JS, Borody T, Brandt LJ, et al. Treating Clostridium difficile Infection With Fecal Microbiota Transplantation. Clin Gastroenterol Hepatol. 2011;9(12):1044–1049. doi:10.1016/j.cgh.2011.08.014 [PubMed: 21871249]

21. Mehta N, Wang T, Friedman-Moraco RJ, et al. Fecal Microbiota Transplantation Donor Screening Updates and Research Gaps for Solid Organ Transplant Recipients. J Clin Microbiol. Published online June 16, 2021. doi:10.1128/JCM.00161-21
22. Cheng YW, Phelps E, Ganapini V, et al. Fecal microbiota transplantation for the treatment of recurrent and severe *Clostridium difficile* infection in solid organ transplant recipients: A multicenter experience. Am J Transplant. 2019;19(2):501–511. doi:10.1111/ajt.15058 [PubMed: 30085388]
23. Di Bella S, Gouliouris T, Petrosillo N. Fecal microbiota transplantation (FMT) for Clostridium difficile infection: Focus on immunocompromised patients. J Infect Chemother. 2015;21(4):230–237. doi:10.1016/j.jiac.2015.01.011 [PubMed: 25703532]
24. Kociolek LK, Palac HL, Patel SJ, Shulman ST, Gerding DN. Risk Factors for Recurrent Clostridium difficile Infection in Children: A Nested Case-Control Study. J Pediatr. 2015;167(2):384–389. doi:10.1016/j.jpeds.2015.04.052 [PubMed: 26001313]
25. Nicholson MR, Thomsen IP, Slaughter JC, Creech CB, Edwards KM. Novel Risk Factors for Recurrent Clostridium difficile Infection in Children. J Pediatr Gastroenterol Nutr. 2015;60(1):18–22. doi:10.1097/MPG.0000000000000553 [PubMed: 25199038]
26. Nicholson MR, Osgood CL, Acra SA, Edwards KM. Clostridium difficile infection in the pediatric transplant patient. Pediatr Transplant. 2015;19(7):792–798. doi:10.1111/petr.12578 [PubMed: 26403484]
27. Ochfeld E, Balmert LC, Patel SJ, Muller WJ, Kociolek LK. Risk factors for Clostridioides (Clostridium) difficile infection following solid organ transplantation in children. Transpl Infect Dis Off J Transplant Soc. 2019;21(5):e13149. doi:10.1111/tid.13149
28. Gupta S, Mullish BH, Allegretti JR. Fecal Microbiota Transplantation: The Evolving Risk Landscape. Am J Gastroenterol. Published online February 5, 2021. doi:10.14309/ajg.0000000000001075
29. Chang JY, Antonopoulos DA, Kalra A, et al. Decreased diversity of the fecal Microbiome in recurrent Clostridium difficile-associated diarrhea. J Infect Dis. 2008;197(3):435–438. doi:10.1086/525047 [PubMed: 18199029]
30. Kump PK, Gröchenig HP, Lackner S, et al. Alteration of intestinal dysbiosis by fecal microbiota transplantation does not induce remission in patients with chronic active ulcerative colitis. Inflamm Bowel Dis. 2013;19(10):2155–2165. doi:10.1097/MIB.0b013e31829ea325 [PubMed: 23899544]
31. Hourigan SK, Ahn M, Gibson KM, et al. Fecal Transplant in Children With Clostridioides difficile Gives Sustained Reduction in Antimicrobial Resistance and Potential Pathogen Burden. Open Forum Infect Dis. 2019;6(10):ofz379. doi:10.1093/ofid/ofz379
32. Kao D, Roach B, Silva M, et al. Effect of Oral Capsule- vs Colonoscopy-Delivered Fecal Microbiota Transplantation on Recurrent Clostridium difficile Infection: A Randomized Clinical Trial. JAMA. 2017;318(20):1985–1993. doi:10.1001/jama.2017.17077 [PubMed: 29183074]
33. Youngster I, Mahabamunuge J, Systrom HK, et al. Oral, frozen fecal microbiota transplant (FMT) capsules for recurrent Clostridium difficile infection. BMC Med. 2016;14(1):134. doi:10.1186/s12916-016-0680-9 [PubMed: 27609178]

What is Known

- Immunocompromised children suffer from high rates of *C. difficile* infection (CDI) and worse outcomes.
- Fecal microbiota transplantation (FMT) is used for the treatment of refractory and recurrent CDI with limited data on its safety and efficacy in immunocompromised children.
- There have been safety alerts concerning invasive infections in FMT-treated immunocompromised adults.

What is New

- FMT is effective for the treatment of CDI in immunocompromised children.
- FMT-related serious adverse events can occur in immunocompromised children and careful discussion of risk and benefit is warranted.

Table 1.

Characteristics of Pediatric IC Patients Undergoing FMT for rCDI (n=42)[a]

Age, years	6.7 (1.5–18)
Sex, male	30 (71)
Race	
White	35 (83)
Black	2 (5)
Other/Unknown	5 (12)
Ethnicity	
Non-Hispanic/Latino	34 (81)
Hispanic/Latino	7 (17)
Unknown	1 (2)
Reason for IC	
Solid organ transplantation	18 (43)
Kidney	7 (17)
Liver	5 (12)
Heart	4 (10)
Intestinal	1 (2)
Multi-organ	1 (2)
Malignancy	12 (28%)
Solid tumor	8 (19)
Hematologic	4 (10)
Primary immunodeficiency	10 (24)
Hypogammaglobulinemia	7 (17)
Acquired common variable immunodeficiency	3 (7)
Other	2 (5)
Nephropathy	1 (2)
Chronic lung disease	1 (2)
Immunosuppressants used[b] (N=35)	35 (83)
Antineoplastic agents	17 (35)
Calcineurin inhibitors	10 (24)
Antimetabolites	11 (26)
Hospitalization	
Within 1 year prior to FMT	21 (72)
Related to CDI	19 (46)

IC, immunocompromised; FMT, fecal microbiota transplantation; rCDI, recurrent *Clostridioides difficile* infection

[a] N=42 unless otherwise specified.

[b] Within 3 months of FMT

Data are presented as mean (range) or n (%)

Table 2.

Characteristics of CDI and FMT in Pediatric IC Patients[a]

Number of CDI episodes before FMT	4 (3–5)
Time from initial CDI diagnosis to FMT, months	11 (6–20)
Antibiotics used prior to FMT[b]	
Vancomycin, standard course[c]	42 (100)
Vancomycin, taper[c]	38 (90)
Metronidazole	29 (69)
Fidaxomicin	9 (21)
Nitazoxanide	6 (14)
Rifaximin	2 (5)
Location FMT performed	
Outpatient	38 (90)
Inpatient	4 (10)
Donor stool	
Fresh	11 (26)
Thawed, previously frozen	31 (74)
Donor stool selection	
Commercial stool bank	21 (50)
Local stool bank	10 (24)
Patient-selected	11 (26)
Route of administration	
Colonoscopy	23 (55)
Nasogastric/ gastric tube	11 (26)
Nasoduodenal/nasojejunal/duodenal/jejunal tube	6 (14)
Capsule	2 (5)
Volume of FMT solution, ml (N=39)	125 (30–240)
Loperamide used post-FMT	9 (21)

CDI, *Clostridioides difficile* infection; FMT, fecal microbiota transplantation; IC, immunocompromised

[a] N=42 unless otherwise specified; data are presented as median (interquartile range) or n (%)

[b] Patients may have data in more than one category; percentages may not sum to 100%

[c] Standard course of vancomycin is 10 mg/kg (maximum 125 mg/dose) four times daily for 10 days; vancomycin taper is 10 mg/kg (maximum 125 mg/dose) four times daily for 10–14 days, twice daily for 7 days, once daily for 7 days, every other day for 7 days, then every 3 days for 2–8 weeks

Table 3.

Comparison of clinical predictors of response to FMT for CDI among IC children[a]

Group	No Response (N=9)	Response (N=33)	P-value
Age at FMT, median (IQR)	5 (2–9)	4 (3–12)	0.43
Female sex	3 (33%)	9 (27%)	0.72
FMT Location			0.14
Outpatient	7 (78%)	31 (94%)	
Inpatient	2 (22%)	2 (6%)	
Donor Stool			0.16
Fresh	4 (44%)	7 (21%)	
Frozen	5 (56%)	26 (79%)	
Donor sample type			0.39
Patient-identified	4 (45%)	8 (24%)	
Local stool bank	2 (22%)	6 (18%)	
Commercial stool bank	3 (33%)	19 (58%)	
Route of administration			0.77
Colonoscopy	5 (56%)	18 (55%)	
Nasogastric/gastric tube	2 (22%)	4 (12%)	
Nasoduodenal/nasojejunal/duodenal/jejunal tube	2 (22%)	9 (27%)	
Capsule	0	2 (6%)	
Type of Immunocompromise			0.77
Primary immunodeficiency	2 (22%)	8 (24%)	
Solid Organ Transplantation	5 (56%)	13 (39%)	
Malignancy	2 (22%)	10 (30%)	
Other	0	2 (6%)	
Antineoplastic agent use[b]	0	10 (30%)	0.06
Calcineurin inhibitor use[b]	4 (36%)	13 (39%)	0.78
Antimetabolite use[b]	3 (33%)	8 (24%)	0.58
Recent non-*C.difficile* infection (N=37)[b]	0	6 (21%)	0.16
Recent ANC[c] (N=30) cells/uL	2935 (2295–3883)	2830 (1680–4570)	0.69
Non-*C. difficile* antibiotic use at time of FMT (N=41)	3 (33%)	7 (22%)	0.48

FMT, fecal microbiota transplantation; CDI, *Clostridioides difficile* infection; IC, immunocompromised; IQR, interquartile range; ANC, absolute neutrophil count

[a] N= 42 unless otherwise specified

[b] Within 3 months of FMT

[c] In 30 days prior to FMT

Table 4.

Serious adverse events following FMT for CDI among IC children

Serious adverse events[a]	Number of patients	Etiology of IC	Days post-FMT	Route of FMT	Related/ Likely related to FMT
Hospitalizations	14[b]				
Cecal perforation	1	SOT	0	Colonoscopic	Yes
Diarrhea	1	PID	0	Colonoscopic	Yes
Aspiration pneumonitis[c]	1	Malignancy	0	Duodenal/Jejunal	Yes
Fever[d]	1	PID	0	Gastric	Yes
Recurrent CDI	1	SOT	4	Duodenal/Jejunal	No
Pneumocystis jiroveci pneumonia	1	Malignancy	7	Colonoscopic	No
Recurrent CDI	1	SOT	9	Duodenal/Jejunal	No
Febrile neutropenia[c,d]	1	Malignancy	18	Duodenal/Jejunal	No
Pneumomediastinum	1	Malignancy	19	Colonoscopic	No
Escherichia coli, enterococcus CLABSI[c]	1	Chronic heart and lung disease	22	Colonoscopic	No
Fever, lethargy[d]	1	Malignancy	30	Duodenal/Jejunal	No
Respiratory failure[c]	1	Chronic heart/ lung disease	38	Colonoscopic	No
Vomiting, dehydration, staph aureus + blood culture	1	Malignancy	42	Colonoscopic	No
Fever, cough[d]	1	PID	76	Colonoscopic	No
Adrenal crisis	1	Malignancy	12	Gastric	No

IC, immunocompromise; FMT, fecal microbiota transplantation; SOT, solid organ transplantation; PID, primary immunodeficiency, CDI, *Clostridioides difficile* infection; CLABSI, central line associated blood stream infection

[a] Serious adverse events: death, hospitalization, disability, life threatening event

[b] 14 hospitalizations, 12 patients

[c] Two patients with two separate hospitalizations

[d] Fever is defined as temperature >38°C