ORIGINAL ARTICLE

Fecal Microbiota Transplantation for *Clostridium difficile*-associated Diarrhea in Hematopoietic Stem Cell Transplant Recipients: A Single-center Experience from a Tertiary Center in India

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Abstract

Objectives: Fecal microbiota transplantation (FMT) is an emerging option for recurrent or refractory *Clostridium difficile*-associated diarrhea (CDAD). We describe a single-center experience of FMT in hematopoietic stem cell transplant (HSCT) recipients with CDAD in India.

Methods: A prospective observational study of HSCT recipients with CDAD who received FMT in our center.

Results: A total of 13 patients were included. All the patients were allogenic HSCT recipients; FMT was performed in seven patients due to refractory CDAD, in five patients due to the presence of both CDAD and graft vs host disease (GVHD), and in 1 patient due to recurrent CDAD. The approach to FMT was colonoscopic in 10 (77%) patients. Only one patient reported bacteremia and one patient had candidemia, both of which were unrelated to FMT. Of the 10 patients who had complete resolution of CDAD, only one patient presented with a recurrence of CDAD within 8 weeks post-FMT.

Conclusion: This is the first study from India using FMT as a therapeutic modality for CDAD in the setting of HSCT. Here we demonstrate that FMT in India is an effective option, especially when patients have refractory CDAD, recurrent CDAD, or both GVHD and CDAD. Further studies should explore the efficacy and feasibility of FMT in India.

Keywords: *Clostridium difficile*, *Clostridium difficile*-associated diarrhea, Fecal microbiota transplantation, Hematopoietic stem cell transplantation.

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Highlights

- First study from India using fecal microbiota transplantation (FMT) as a therapeutic modality for *Clostridium difficile*-associated diarrhea (CDAD).
- Fecal microbiota transplantation is effective in refractory CDAD, recurrent CDAD, or both graft vs host disease (GVHD) and CDAD.
- Fecal microbiota transplantation protocols need to be established in India to overcome logistic difficulties.

Introduction

Clostridium difficile infection (CDI) is among the leading causes of antibiotic-associated diarrhea (AAD). The prevalence of CDI in India is reported to be between 1.2 and 29% according to recent studies.[1,2] *Clostridium difficile*-associated diarrhea is an increasing problem, especially in immunocompromised patients. Patients undergoing hematopoietic stem cell transplantation (HSCT) are at an increased risk for CDAD. Some studies have reported that CDAD rates in HSCT recipients can be as high as 25%, with higher rates found in allogeneic HSCT recipients than autologous HSCT recipients.[3,4] Prior receipt of chemotherapies and antimicrobial agents, considerable healthcare exposures, higher rates of colonization with *C. difficile* and the underlying immunosuppressive state are factors that predispose HSCT recipients to CDAD.

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Table 1: Criteria for donor screening used in our center

Criteria for donor screening used in our center
• Off immunosuppressive therapy, chemotherapy, antimicrobial agents, or proton pump inhibitors in the preceding 3 months
• No personal or family history of chronic gastrointestinal diseases
• No history of HIV, syphilis, hepatitis B or hepatitis C viral infections
• No personal history of cancer, including gastrointestinal cancers or polyposis syndrome, and first-degree family history of premature colon cancer
• Previous tissue or organ transplant recipients are excluded
Laboratory evaluation of the donor in our setting
• Hemogram, liver function tests, CRP, and ESR
• HIV and VDRL
• Hepatitis C antibody
• Hepatitis A IgM antibody
• Hepatitis B surface antigen
• Routine stool examination
• Stool bacterial culture
• Modified ZN staining for cryptosporidium, isospora, and microsporidia
• *Clostridium difficile* assay

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; VDRL, venereal disease research laboratory test (for syphilis); ZN, Ziehl Neelsen

There is evidence to suggest that CDAD may increase the risk of GVHD in HSCT recipients, but this has not been universally demonstrated.[5] Intestinal dysbiosis and disruption of the gut microbiota are factors common to both GVHD and CDAD, but studies have not established a definitive association between these clinical entities.

Fecal microbiota transplantation refers to a process by which the stool specimens collected from healthy donors are instilled into the gastrointestinal tract of a recipient. Currently, FMT is offered to patients with recurrent CDAD and those with refractory CDAD. A meta-analysis published in 2017 which included 37 studies, seven randomized controlled trials, and 30 case series, found that FMT was more effective than oral vancomycin therapy for patients with recurrent or refractory CDAD.[6] Serious adverse events were reported to be rare.[6] Although limited, there is growing literature on the use of FMT in patients who have undergone HSCT. Webb et al.[7] reported seven HSCT recipients who underwent FMT for recurrent CDAD. Six of these did not show any signs of relapse. Moss et al.[8] delivered FMT to eight patients with recurrent CDAD. Resolution was seen in all patients at 8 weeks, while one had a recurrence at a later time.[8]

Fecal microbiota transplantation is also being explored as a potential therapy for GVHD. In a study of 55 patients with grade IV steroid–refractory gastrointestinal GVHD, FMT was associated with a longer median survival time.[9] Fecal microbiota transplantation is not available in the majority of the centers in India, and there is limited data regarding the use of FMT in CDAD or in patients undergoing HSCT in India. Fecal microbiota transplantation in India can be challenging. Gut colonization with antibiotic-resistant bacteria remains a concern. There is an urgent need to generate local data regarding the efficacy and safety of FMT in our patients and to establish this therapeutic modality. We describe a single-center experience of FMT in HSCT recipients with CDAD in India and describe the process, indications, and outcomes of performing this procedure in HSCT recipients in our settings.

Methods

This was a prospective observational study of HSCT recipients with CDAD who received FMT in our center, during a 12-month period from January 2022 to December 2022.

Inclusion and Exclusion Criteria

Patients who underwent FMT after HSCT were included. The indications for FMT included the following: (A) Refractory CDAD, (B) recurrence of CDAD, and (C) presence of both CDAD and GVHD. Patients were excluded from receiving FMT if (A) they were neutropenic (B) had active sepsis, or (C) toxic megacolon. Recipients who had to be administered antimicrobial agents within 48 hours after FMT were excluded. Only those patients who underwent FMT as a part of routine care, as deemed appropriate by the treating clinicians, were included in the analysis.

Definitions

"Refractory CDAD" was defined as patients who did not respond to 4 days of the appropriate antimicrobial therapy for CDAD (response was defined as at least a 50% reduction in the stool volume).[10]

"Recurrence" was defined as a recurrence of diarrhea confirmed by repeat *Clostridium difficile* testing within 8 weeks from the previous episode of CDAD, provided the initial episode completely resolved.

Resolution of CDAD after FMT was defined as complete cessation of diarrhea without administration of any anti-CDAD therapy or antimotility agents for at least 48 hours.

Diagnosis of *Clostridium difficile*-associated Diarrhea and Graft vs Host Disease

- *Clostridium difficile*-associated diarrhea: Only those patients who had both glutamate dehydrogenase (GDH) antigen and toxin (A and/or B) positive were included in the study.
- Graft vs host disease: All patients included in the study had biopsy-proven gastrointestinal GVHD.

Process of Fecal Microbiota Transplantation

Table 1 shows the criteria used for donor screening in our center. Based on these criteria, the appropriate donor was selected for the procedure.

Details of the Procedure of Fecal Microbiota Transplantation

The donor was selected by the Department of Infectious Diseases and Microbiology (common consensus) based on the above criteria,

Table 2: Characteristics of patients who underwent FMT

Patient characteristics	*Number (%)*
Age	Median: 39, range: 4–56
Gender	Males: 5/13 (38.5%)
	Females: 8/13 (61.5%)
Type of HSCT	
Allogenic	13/13 (100)
Indication for FMT	
• Refractory CDAD	7/13 (53.8)
• Two or more recurrences of CDAD	1/13 (7.7)
• Presence of both CDAD and GVHD	5/13 (38.5)
Underlying malignancy	
• Acute myeloid leukemia (AML)	11/13 (84.6)
• Fanconi's anemia	1/13 (7.7)
• Thalassemia major	1/13 (7.7)
Details of therapy given to patients with refractory CDAD before FMT	
• Patient 1	Oral vancomycin for 7 days, oral teicoplanin for 3 days
• Patient 2	Oral vancomycin for 9 days
• Patient 3	Oral vancomycin for 5 days, oral teicoplanin for 3 days
• Patient 4	Oral vancomycin for 10 days
• Patient 5	Oral vancomycin for 7 days, nitazoxanide for 5 days
• Patient 6	Oral vancomycin for 12 days
• Patient 7	Oral vancomycin and IV metronidazole for 7 days
Details of therapy given to patients with GVHD before FMT	
• Patient 1	Methylprednisolone for 6 days
• Patient 2	Methylprednisolone for 9 days, ruxolitinib for 3 days
• Patient 3	Methylprednisolone for 10 days
• Patient 4	Methylprednisolone for 7 days, ruxolitinib for 4 days
• Patient 5	Methylprednisolone for 5 days

after careful clinical and laboratory evaluation. Around 50 gm of stool specimens were submitted by the donor on the day of the transplant in a sterile container. Using a sterile wooden spatula, around 50 gm of stool was emulsified in 250 mL of nonbuffered sterile saline (autoclaved in a screw-capped glass bottle and cooled). The emulsion was sieved through a triple-layered sterile gauze to filter out coarse particles (>1–2 mm). The resultant filtrate was collected in a sterile flask and transferred to the endoscopy suite with an airtight seal. The FMT solution was infused within 6 hours of donor voiding. Either a nasojejunal or a colonoscopy approach was used. If there was no improvement in symptoms after 4 days, patients were administered another installation between days 5 and 9 from the first installation. Patients were off all antimicrobial agents beginning from 48 hours before the FMT to 48 hours after the FMT.

Data was collected using the hospital's electronic health records. The Institutional Ethics Committee approved the study before its commencement.

Results

Patient Characteristics

The analysis included 13 patients in total. Table 2 describes the characteristics of patients who underwent FMT. The median age of the patients was 39 years (range, 4–56 years). All the patients had undergone an allogeneic HSCT.

Details of Fecal Microbiota Transplantation

Table 3 describes the details of the FMT procedure, including the number of installations, the approach used in FMT, and outcomes at the end of 3 months. The median day on which the FMT was performed post-HSCT was 57 (range, 17–107). All the patients received two installations of FMT. A total of 10 (77%) patients received FMT *via* the colonoscopic approach.

Outcomes after Fecal Microbiota Transplantation

Table 4 describes the outcomes and complications in patients undergoing FMT. Bacteremia was reported in only one patient within the 2 weeks following FMT, while one patient reported candidemia in the same period. These were unrelated to the FMT. One patient succumbed within 2 weeks after FMT. There was resolution of CDAD in 10 (83%) of the remaining 12 patients by the end of 2 weeks post-FMT.

Discussion

Clostridium difficile-associated diarrhea can be a condition associated with significant morbidity and mortality in HSCT recipients. Lack of uniform availability of testing methods, lack of availability of fidaxomicin, and financial constraints make it particularly challenging to manage such patients effectively in the Indian settings. Loss of intestinal microbial diversity is a factor common to both GVHD and CDAD. When patients have both CDAD and GVHD in the setting of allogeneic transplantation, management can be even more challenging, as these patients need to be given potent immunosuppressants. In these highly immunosuppressed patients, prolonged diarrhea can often lead to secondary complications such as bacteremia and candidemia, which can be due to multidrug-resistant pathogens in our settings. This further complicates the management of such patients.

Table 3: Details of FMT

FMT details	*Number (%)*
Number of donors screened for each patient	Median: 3, range: 1–5
Day post-HSCT on which FMT was performed	Median: 57, range: 17–107
Number of patients who underwent two installations of FMT	13/13 (100)
Number of patients in the intensive care unit (ICU) in the periprocedural period	7/13
Approach to FMT	
• Nasojejunal	3/13 (23)
• Colonoscopic	10/13 (77)

Table 4: Outcomes and complications after FMT

Outcomes and complications	*Number (%)*
Bacteremia in the first 2 weeks following FMT	1/13 (7.7) (One patient had central line related *Klebsiella pneumoniae* bacteremia)
Candidemia in the first 2 weeks following FMT	1/13 (7.7) (One patient had central line related *Candida auris* candidemia)
Other infections in the first 2 weeks following FMT	1/13 (7.7) (One patient had reactivation of CMV viremia)
Number of patients who had resolution of CDAD by the end of 2 weeks following FMT	10/12 (83.3) (One patient succumbed due to noninfectious complications within 2 weeks after FMT; hence, excluded. This patient had a sudden respiratory arrest)
Number of patients who had recurrence of CDAD at the end of 8 weeks (out of the 10 patients who had resolution of CDAD after FMT)	1/10 (10)
Day 14 mortality	1/13 (7.7)
Day 28 mortality	1/13 (7.7)

Fecal microbiota transplantation has emerged as a promising option for recurrent and refractory CDAD, and also in the setting of refractory gastrointestinal GVHD. In India, fidaxomicin is not available, and hence, the options for treating CDAD, especially when refractory to vancomycin are limited. Hence, FMT can emerge as a useful modality. However, there is no data from India regarding the feasibility, efficacy, and complications of FMT in patients undergoing HSCT. There is sparse data from India regarding FMT in any setting.

In this study, FMT was used as an effective modality for CDAD patients undergoing HSCT. As shown in Table 2, the commonest indication for FMT in our patients was refractory CDAD. In India, due to the lack of availability of fidaxomicin, oral vancomycin often remains the backbone of therapy. However, resistance to vancomycin is emerging. In a study published in 2022, 67 and 85% of the stool samples from a university hospital in Kenya harbored vancomycin and metronidazole-resistant strains of *Clostridium difficile*, respectively.[11] Although there is limited data from India, refractory CDAD can be a concern in our settings. In these patients, as shown in the study here, FMT can be a promising option. The remaining patients in our study underwent FMT either for recurrent CDAD or for the combined indication of CDAD and gastrointestinal GVHD, indications for which the literature is growing.[6,9] Patients with combined CDAD and GVHD are difficult to manage in our settings as these patients need intense immunosuppression and when this is given in the presence of CDAD it can create a complex scenario. As shown in our current study, FMT can be considered in this situation.

The procedure can be a challenge in our settings, given the lack of availability of stool capsules and stool banks, and the absence of well-established protocols in most centers across the country. A median of 3 donors had to be screened in our center, and this further illustrates the challenges faced in our setting. Colonization of the donor stool with resistant organisms can be a particular concern in our settings. As an example, one of the potential donors who were asymptomatic was found to have carbapenem-resistant *Escherichia coli* in the stool and had to be excluded, while another was found to have GDH Antigen positive. These examples highlight the complexities involved in donor screening in India, and hence, FMT becomes challenging. Thus, the donor screening needs to be intense, as shown in our protocol. This has to be balanced with the financial constraints in our settings. All patients included in this study underwent two installations of FMT. In a trial of 232 patients who were administered FMT, those with suboptimal response at day 4 were administered a repeat FMT, and those with two installations had higher response rates.[12] In our institute, we routinely administer two installations given the higher response rates associated with two installations. Studies have shown that the efficacy of the colonoscopy approach may be slightly higher than that of the upper gastrointestinal approach.[6] In our institute, though the preferred approach, sometimes individual circumstances including patient and physician preferences may impact this decision. In this study, both approaches seemed to have comparable success. Most importantly we demonstrate that FMT is doable in India, despite the challenges and the paucity of well-established protocols.

A significant proportion of patients showed a robust clinical response. The response was durable, and a majority of these patients remained symptom-free 8 weeks after the procedure.

A significant proportion of patients in our current study showed a robust clinical response. The response was durable, and a majority of these patients remained symptom-free 8 weeks after the procedure. One patient developed bacteremia with *K. pneumoniae* within 2 weeks. This was deemed to be related to the central line,

as evidenced by the differential time to positivity. Bacteremia in the recipient needs careful evaluation, as bacteremia has been reported in relation to FMT.[13] Another patient developed candidemia while one patient developed cytomegalovirus (CMV) viremia, both of which were thought to be unrelated to FMT. Overall FMT was well tolerated in most patients.

Limitations

Our study has certain limitations. Microbiome analysis was not carried out before and after transplantation, and hence, an objective measure of the changes in the gut flora could not be proven. Further studies are needed to establish the safety and efficacy of FMT in the setting of HSCT in the Indian setting.

Conclusion

In conclusion, this is the first study from India using FMT as a therapeutic modality for CDAD in the setting of HSCT. This study shows that FMT in India is doable, and can be an effective option, especially when patients have refractory CDAD, recurrent CDAD, or both GVHD and CDAD. Further studies should explore the efficacy and feasibility of FMT in India, which will pave the way for establishing stringent protocols and making this modality available to clinicians across the country.

Ethical Approval

An Institutional Ethics Committee approval was obtained prior to the commencement of this study.

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