Response to Fecal Microbiota Transplant (FMT) in Refractory *Clostridioides difficile* Infection (CDI) is Modest Compared to Recurrent CDI in Hospitalized Patients.

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Background

There are limited treatment options for *Clostridioides difficile* infection (CDI) refractory to c onventional antibiotic therapy (metronidazole, vancomycin, or fidaxomicin). Fecal microbi ota transplant (FMT) is considered a safe and effective treatment for recurrent CDI but ha s not been widely utilized for refractory CDI due to concerns about safety. Even when incl uded in studies, refractory CDI has not been analyzed separately from recurrent CDI. We reviewed cases of FMT performed in the inpatient setting for CDI to evaluate its safety an d efficacy for refractory CDI.

Methods

Patient population

University of Virginia (UVA) Medical Center is a 619-bed tertiary care hospital in central Virginia. There were two types of patients who received FMT while admitted to UVA Medical Center: 1) Patients with three or more recurrent CDI episodes and 2) Patients with CDI refractory to conventional treatment, including metronidazole, vancomycin, and/or colectomy/ileostomy. These patients were referred to Infectious Diseases, Gastroenterology, or Surgery for consultation regarding potential FMT. FMT was performed if there was consensus among the specialists that benefits outweighed the risks of the FMT. Patients signed informed consent acknowledging the fact that the procedures were considered investigational use in CDI not responding to standard treatment as per 2014 FDA guidance.

Study design

We performed a retrospective chart review of patients who underwent FMT from July 2014 to December 2019 to evaluate the safety and efficacy of FMT in the inpatient setting for refractory CDI as part of the efforts by the Antimicrobial Stewardship Program and the Antibiotic Utilization Committee. We reviewed the electronic medical record of each patient to collect patient demographics, CDI history, laboratory tests results, and clinical data from encounter notes.

FMT procedure

FMT procedure was performed from universal donor specimens which were prescreened and purchased from OpenBiome (Boston, MA USA). FMT was mainly performed through colonoscopy, but if the patient had special circumstances other routes were utilized, such as ileoscopy or upper gastrointestinal feeding tube in patients with ileostomy or colectomy. If pseudomembranes were visualized on colonoscopy during FMT, repeat FMTs were performed until there were no pseudomembranes seen on colonoscopy. After FMT, there were no set protocol regarding treatment with *C. difficile* active antibiotics and decision to resume antibiotics was left to the discretion of the physician treating the patient.

Study outcomes

The patient's clinical progression was followed by reviewing the electronic medical record of the patient's concurrent hospitalization. Outcomes were noted as resolved, recurrence, deaths, or *C. difficile*-negative persistent diarrhea. The recurrence, deaths, and persistent diarrheas were documented if they occurred within 90 days of the first FMT.

Statistical analysis

Student's t test or Mann-Whitney U test were used for analysis. A 2-tailed P value of 0.05 was considered statistically significant (GraphPad Prism (La Jolla, CA)).

Results

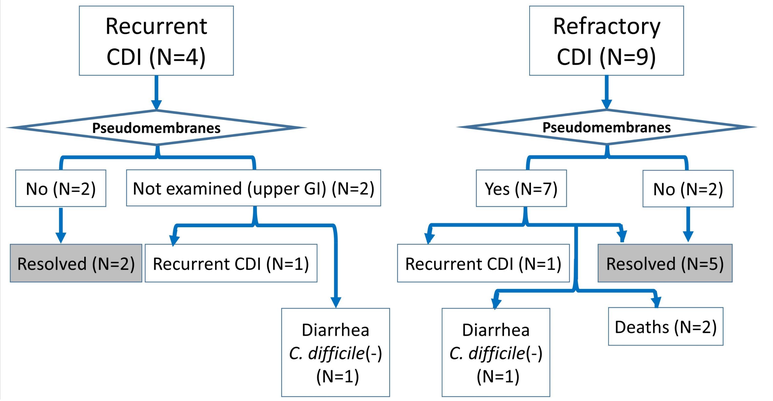

Figure 1. Outcomes of patients who received FMT for recurrent or refractory CDI.

Refractory CDI

Among the nine patients who received FMT for refractory or fulminant CDI, seven (78%) patients had pseudomembranes visualized on colonoscopy **(Figure 2).** The average number of FMTs performed was 2.15 (range 1-3). Among the seven patients with pseudomembranes, three patients received three FMTs following protocol, and had resolution of diarrhea. Two patients with pseudomembranes received two FMTs,with one resulting in recurrent CDI and one with persistent *C. difficile*-negative diarrhea. One patient had severe sepsis at the time of FMT and died soon after. One patient withdrew care after 1 FMT for unrelated reasons and died. Overall, there were three failures: one recurrence and two deaths (regardless of causes), leading to a 33.3% failure rate, or 66.7% success rate for FMT performed for refractory cases.

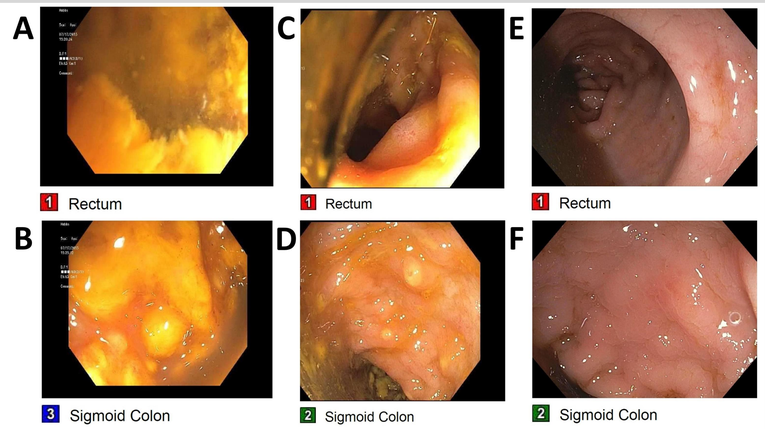

Figure 2. Colonscopic changes after FMT in patients with pseudomembranes. Colonoscopic findings from one patient shows yellow pseudomembranes covering both the rectum (A) and the sigmoid colon (B) during the first FMT. There is some improvement on the second FMT in the rectum (C) and the sigmoid colon (D). On the patient's third FMT, both the rectum (E) and the sigmoid colon (F) exhibited resolution of pseudomembranes and healthy intestinal epithelium.

References

1.van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, et al. Duodenal Infusion of Donor Feces for Recurrent Clostridium difficile. New England Journal of Medicine. 2013 Jan 31;368(5):407–15.
2.Quraishi MN, Widlak M, Bhala N, Moore D, Price M, Sharma 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 Sep;46(5):479–93.
3.Cheng Y-W, Phelps E, Ganapini V, Khan N, Ouyang F, Xu H, et al. Fecal microbiota transplantation for the treatment of recurrent and severe Clostridium difficile infection in solid organ transplant recipients: A multicenter experience. American Journal of Transplantation. 2019 Feb;19(2):501–11.

Results

Blood counts and biochemistry after FMT

WBC count in the refractory CDI group was higher (25.25 ± 15.84) than the recurrent CDI group (5.523 ± 3.353) at the time of diagnosis, but without statistical significance (**Figure 3**). The WBC count did not change significantly with FMT, but there was a trend towards decreasing with FMT in the refractory CDI group. Neutrophil count in refractory CDI (13.64 ± 3.262) was higher at the time of diagnosis than in the recurrent group (3.403 ± 2.312) ($p<0.05$). The change with FMT was not statistically significant, but there was a trend toward decrease in neutrophil count with FMT in refractory or fulminant group while a trend toward increase in neutrophil count in the recurrent group was seen, which may suggest an immunomodulatory role for FMT in CDI. CRP levels were checked in only 4 patients. Lactic acid level difference was not statistically significant but there was a trend toward a higher level in refractory CDI (3.017 ± 0090) than recurrent CDI (1.250 ± 0.2121) at the time of diagnosis. Albumin and creatinine levels were not different between refractory and recurrent CDI and there were not significant changes with FMT.

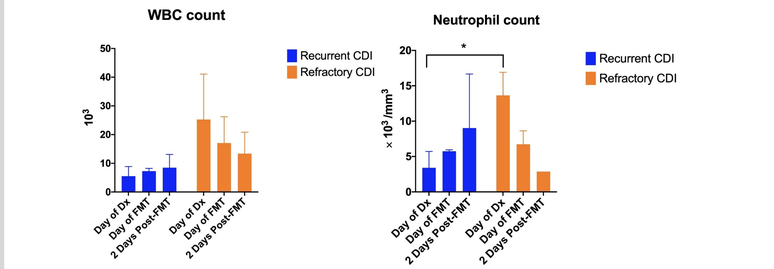

Figure 3. Leukocyte response to CDI and FMT.

Discussion

For recurrent CDI, FMT has become one of the most effective treatments, with a cure rate around 80-90%[1]. Treatment of refractory CDI using FMT has also been studied, but have not been evaluated separately from recurrent CDI in most studies[2].

In our study, we were able to separate the cases by the indication for FMT. There were 6 out of 9 (66.7%) patients with refractory disease who responded to FMT, which is a promising result and warrants further investigation at a larger scale. This is moderate compared to the cure rate in recurrent CDI which is in the 80-90% range, but in light of the fact that refractory CDI as defined in our study does not respond to treatment with metronidazole, vancomycin, or fidaxomicin, and there are very few therapeutic options with little evidence for use, this is a promising finding.

Regarding the safety of the procedure, two deaths occurred within 90 days of the procedure in the patients who underwent FMT. One death was attributed to renal failure which predated the CDI. One patient died from potential sepsis, without clear admission diagnosis, patient having presented with unexplained eosinophilia pointing to a potential parasite infection, DRESS, or hematologic malignancy. One notable issue with the patient was the CMV viremia. Patient had elevated CMV viral load after FMT and was treated with IV ganciclovir prior to patient's death.

FMT should be considered an alternative option when treating refractory CDI. With CMV reactivation reported in association with FMT reported in solid organ transplants[3], further evaluation of a role for CMV reactivation in FMT is needed