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Fecal Microbiota Transplantation Is Effective for Postcolectomy Recurrent *Clostridioides difficile* Infection

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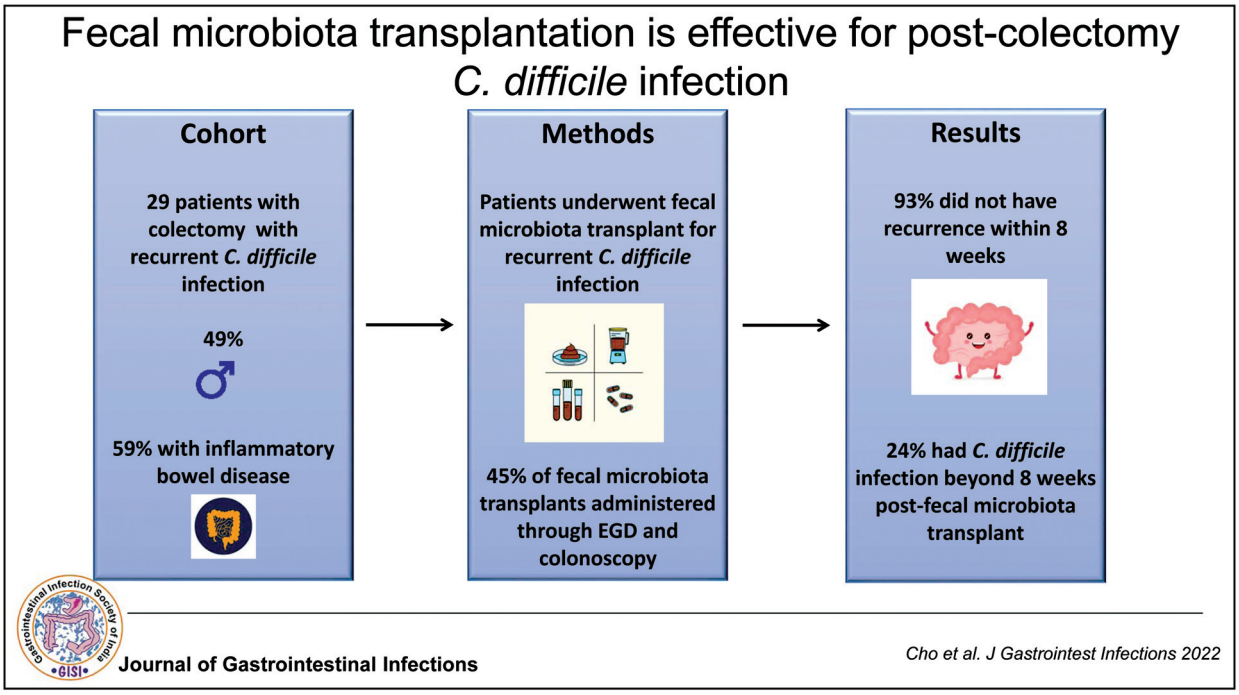

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Abstract

Background The outcomes from fecal microbiota transplantation (FMT) for recurrent *Clostridioides difficile* infection (rCDI) in patients after complete or partial colectomy are not well-defined.

Objectives We sought to report our experience with FMT for rCDI in patients who have undergone colectomy.

Methods Descriptive analyses of FMT outcomes from 2014 to 2020 were performed in patients who previously had undergone complete or partial colectomy.

Results Twenty-nine patients with prior colectomy for inflammatory bowel disease, malignancy, slow-transit constipation refractory to medical therapy, or fulminant CDI underwent FMT for rCDI. Two patients (6.9%) had rCDI within 8 weeks post-FMT. Seven had CDI beyond 8 weeks (median 10 months) with 71% related to antibiotic exposure post-FMT, suggesting a 69% overall success.

Conclusion FMT resolves rCDI in most patients after colectomy with subsequent antibiotic exposure predicting CDI after FMT.

Keywords

- *Clostridioides difficile* infection
- colectomy
- fecal microbiota transplantation

Introduction

Fecal microbiota transplantation (FMT) is a highly effective tool for the management of recurrent and refractory *Clostridioides difficile* infection (CDI).[1,2] Studies of FMT for recurrent CDI in patients who have had complete or partial colectomy are limited.[3–7] We report our institutional outcomes of FMT for recurrent CDI in patients who developed recurrent CDI and had undergone prior complete or partial colectomy.

Methods

We identified patients with prior history of colectomy including proctocolectomy with either ileostomy or ileal pouch-anal anastomosis (IPAA), ileorectal anastomosis, and ileosigmoid anastomosis who had undergone an FMT. This search was done from the Mayo Clinic FMT database to identify these patients who received FMT between 2014 and 2020. We extracted demographics, operative reports, medical history, CDI management, and FMT outcomes. Clinical outcomes that were studied post-FMT were need for hospitalization after FMT, mortality, recurrence of CDI after FMT, length of time between FMT and recurrent CDI, number of repeat FMTs after the initial FMT, and treatment of rCDI after FMT. This study was approved by the Institutional Review Board (IRB# 20–006845).

Recurrent CDI prior to FMT was defined as recurrence of watery and loose stools more than the patient's baseline after symptom improvement or resolution within 8 weeks of index CDI. The routes of FMT included esophagogastroduodenoscopy (EGD), EGD and flexible sigmoidoscopy, EGD and pouchoscopy, enteroscopy and pouchoscopy, and instillation through an ileostomy catheter. This retrospective study included all three medical centers under our enterprise located in Arizona, Minnesota, and Florida. Standard donors provided stool for FMT except for one center who also utilized OpenBiome starting in 2019. Our standardized donor protocol for FMT has been previously published.[8]

One dose of FMT is 50 g of stool in 250 cc of diluent (90% normal saline and 10% glycerol). For these procedures, approximately 150 cc of emulsified donor stool was instilled during the EGD and 100 cc instilled during the flexible sigmoidoscopy or pouchoscopy. CDI recurrence after FMT was defined as a return of diarrhea within 8 weeks of FMT with a positive *C. difficile* stool assay.

Descriptive statistical analysis was performed to summarize the data collected from the electronic medical record.

Results

Between 2014 and 2020, we identified 29 patients with a history of colectomy prior to FMT. Seventeen patients (59%) underwent colectomy for inflammatory bowel disease (IBD) and the median interval time between IBD diagnosis and colectomy was 14 years (range: 0–33 years). The median age at IBD diagnosis was 25 years. Of the patients with IBD, seven (41%) patients had Crohn's disease and ten had ulcerative colitis (59%). Of the patients with Crohn's disease, three had IPAA, two had ileorectal anastomoses, and two had ileosigmoid anastomoses. Of the patients with ulcerative colitis, seven had IPAA, two had ileorectal anastomoses, and one had an end ileostomy.

Other indications included familial adenomatous polyposis ($n = 2$, 7%), malignancy ($n = 1$, 3%), slow-transit constipation refractory to medical therapy ($n = 7$, 24%), and fulminant CDI ($n = 2$, 7%). Overall, 13 patients had an ileorectal anastomosis (45%), 10 had IPAA (34%), 4 had ileosigmoid anastomosis (14%), and 2 had an end ileostomy (6%).

Eight patients (28%) had a history of CDI prior to colectomy, ranging from 1 to 5 episodes, which were treated with vancomycin with one patient being treated with both vancomycin and intravenous metronidazole. Of these patients, six had underwent colectomy for IBD (50% had ulcerative colitis), one for fulminant CDI, and one for slow-transit

constipation. The median interval between colectomy and CDI was 4 years (►**Table 1**). Twenty-four patients (83%) were on proton pump inhibitor therapy prior to FMT.

Thirteen patients underwent FMT by a combined EGD and flexible sigmoidoscopy (45%) and eight patients (28%) underwent EGD and pouchoscopy. The rest of the patients had EGD, flexible sigmoidoscopy, enteroscopy and pouchoscopy, or infusion with ileostomy catheter (►**Table 2**). Patients who underwent flexible sigmoidoscopy had a colectomy with either an ileosigmoid anastomosis or ileorectal anastomosis.

Table 1 Clinical characteristics of patients who underwent FMT after colectomy

Characteristics	Total patients ($n = 29$)
Male, *n* (%)	14 (49%)
Ethnicity, *n* (%)	
Caucasian	28 (97%)
Hispanic or Latino	1 (3%)
Age at FMT, years	
Median	51
Range	21–81
Weight at FMT, kg	
Median	69.8
Range	55.5 ± 133
BMI at FMT, kg/m^2	
Median	26.6
Range	19.6 ± 52.3
BMI category, *n* (%)	
Normal, 18.5–24.9	12 (41%)
Overweight, 25–29.9	11 (38%)
Obese, >30	6 (21%)
Smoking history, *n* (%)	
Never	18 (62%)
Current	4 (14%)
Former	7 (24%)
Reason for colectomy, *n* (%)	
Inflammatory bowel disease	17 (59%)
Familial adenomatous polyposis	2 (7%)
Constipation	7 (24%)
Malignancy	1 (3%)
Fulminant *C. difficile* infection	2 (7%)
Age at colectomy, years	
Median	45
Range	17–75
Age at IBD diagnosis, years, $n = 17$	
Median	25
Range	10–52
Time between IBD diagnosis to colectomy, years	
Median	14
Range	0–33
Surgery classification, *n* (%)	
Ileal pouch-anal anastomosis	10 (34%)
Ileosigmoid anastomosis	4 (14%)
Ileorectal anastomosis	13 (45%)
End ileostomy	1 (3%)
Loop ileostomy	1 (3%)
PSC, *n* (%)	5 (17%)
Preoperative biologic use, *n* (%)	9 (31%)
Crohn's involvement of pouch, *n* (%)	2 (7%)
Prior CDI history before colectomy, *n* (%)	8 (28%)
Duration from colectomy to CDI, years	
Median	4
Range	0–25
FMT route, *n* (%)	
EGD	3 (10%)
Flexible sigmoidoscopy	3 (10%)
EGD and flexible sigmoidoscopy	13 (45%)
EGD and pouchoscopy	8 (28%)
Enteroscopy and pouchoscopy	1 (3%)
Ileostomy catheter	1 (3%)

Abbreviations: BMI, body mass index; CDI, *Clostridioides difficile* infection; EGD, esophagogastroduodenoscopy; FMT, fecal microbiota transplantation; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis.

Two patients (7%) had rCDI within 8 weeks post-FMT (one at 1 week and the other at 3 weeks) and seven patients (24%) had subsequent CDI (beyond 8 weeks) after FMT. Both patients with rCDI shortly after FMT had ileorectal anastomoses and had undergone FMT via EGD and flexible sigmoidoscopy. Neither had a history of IBD or had antibiotic exposure between FMT and recurrence. One patient was treated with vancomycin and the other was treated with rifaximin for their rCDI after FMT with no repeat FMTs.

Two patients were hospitalized after FMT (7%), one for abdominal pain, nausea, and diarrhea 48 hours post-FMT and the other for nausea and vomiting immediately following FMT. Both patients were discharged within 36 hours of admission. There were no deaths reported after FMT.

Among those that had CDI more than 8 weeks after FMT ($n = 7$, 24%), the median time from FMT to subsequent CDI was 10 months, 71% had exposure to antibiotics within 3 months prior to developing a subsequent episode of CDI.

Table 2 FMT clinical outcomes

Outcomes	Total patients ($n = 29$)
Recurrence within 8 weeks after FMT, *n* (%)	2 (7%)
Subsequent CDI after FMT (beyond 8 weeks), *n* (%)	7 (24%)
Duration from FMT to CDI ($n = 7$), months	
Median	10
Range	5–25
Antibiotic use for pouchitis after FMT, *n*	3
Repeat FMT, *n* (%)	5 (17%)
Number of repeat FMT, *n*	
Median	0
Range	0–2
Duration between first and second FMT, months	
Median	16
Range	12–27
Hospitalization after FMT, *n* (%)	2 (7%)
Hospitalized at time of FMT, *n* (%)	1 (3%)
Death after FMT, *n* (%)	0 (0%)

Abbreviations: CDI, *Clostridioides difficile* infection; FMT, fecal microbiota transplantation.

Five of these patients (71%) had repeat FMT with a median interval of 16 months between the first and second FMT. One patient required two additional FMTs for symptom resolution. The other two patients were managed with antibiotics alone with CDI resolution.

Discussion

In our cohort of 29 patients who had undergone colectomy and were treated with FMT for rCDI, CDI recurrence within 8 weeks of FMT was uncommon at 7%. For those who had subsequent CDI (beyond 8 weeks) after the initial FMT, five patients underwent a second FMT. Complications from FMT were rare with two patients needing hospitalization after the procedure but discharged promptly.

CDI is an infection that most commonly affects the colon but several reports in the literature have demonstrated small intestinal involvement.[3–7] FMT has been shown to be an effective treatment to prevent rCDI in patients with two or more episodes of rCDI.[9] A recent systematic review suggested that repeat FMTs may be more efficacious than vancomycin treatment in rCDI.[10] There is also rising evidence that FMT can be effective in severe and fulminant CDI and should be given in patients with refractory CDI as salvage therapy.[11,12] The majority of our patient population underwent colectomy for IBD, and previous studies have shown that FMT in IBD patients were effective in treating rCDI and did not result in serious adverse events.[13,14] We demonstrated in our study that FMT is safe to perform in patients who have undergone partial or total colectomy with low rates of CDI recurrence post-FMT.

In patients with an intact colon, the route of FMT is typically through a colonoscopy and the donor stool is instilled into the cecum to allow longer time for the donor stool microbiota to engraft. To maximize the amount of time the donor fecal material stays in the recipient's intestines, a dual approach with upper and lower endoscopy was mostly utilized. Ninety-three percent of patients did not have recurrence within 8 weeks of FMT, but 24% of patients did develop a subsequent episode of CDI with majority of these patients being exposed to antibiotics prior to development of CDI.

This report is limited by its retrospective nature conducted at a referral center. As such, follow-up of patients may not be complete, and results may not be generalizable to the general population. Some cases may have been missed and patients with colectomy who had rCDI may not have consented to FMT. There was also significant heterogeneity in our cohort as the extent of colectomy and underlying disease leading up to colectomy was variable. There have been other reports of patients who have undergone FMT postcolectomy[15,16] including one with 13 patients.[3] The strength of our study is that it represents one of the largest cohort of patients with a history of colectomy and subsequent FMT and was able to describe outcomes from this procedure in this specific cohort. Future studies could include comparing patients with prior history of colectomy and rCDI who undergo medical therapy only versus FMT and evaluate if there are differences in clinical outcomes.

In conclusion, CDI recurrence in postcolectomy patients was low at 7% within 8 weeks of FMT but 24% of patients developed a subsequent episode of CDI after FMT with five patients undergoing repeat FMT. However, 71% of these patients were exposed to antibiotics, a known CDI risk factor, prior to their subsequent CDI episode. FMT appears to be safe in postcolectomy patients with rare hospitalizations and no mortality associated with the procedure.

Ethical Statement

The protocol for this study was approved by Mayo Clinic Institutional Review Board. The manuscript has not been submitted or accepted elsewhere. All authors fulfill the criteria for authorship and have approved the revised version of the manuscript. This was a retrospective study and a waiver for informed consent was approved by the IRB.

Author Contributions

The authors confirm contribution to the paper as follows: Study conception and design: J.C., S.K., D.S.P.; data collection: J.C.; analysis and interpretation of results: J.C., S.K., and D.S.P.; draft manuscript preparation: J.C., S.K.; manuscript editing: J.C., M.V.R., R.O., E.V.L. Jr, J.D., D.S.P., S.K. All authors reviewed the results and approved the final version of the manuscript.

Data Availability Statement
The data can be obtained from the corresponding author on a reasonable request.

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Conflict of Interest
None declared.

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