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Fecal microbiota transplant for *Clostridium difficile* infection in older adults

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Abstract

Background: The objective of this study was to describe the safety of fecal microbiota transplant (FMT) for *Clostridium difficile* infection (CDI) among older adults.

Methods: We performed a case review of all FMT recipients aged 65 or older treated at Emory University Hospital, a tertiary care and referral center for Georgia and surrounding states.

Results: CDI resolved in 27 (87%) of 31 respondents, including three individuals who received multiple FMTs. Among four whose CDI was not resolved at follow up, three respondents did well initially before CDI recurred, and one individual never eradicated his CDI despite repeating FMT. During the study, five deaths and eight serious adverse events requiring hospitalization were reported within the study group during the follow-up period. Fecal transplant was not a causative factor in these events. The most common adverse event reported in 4 (13%) of 31 respondents was subjective worsening of arthritis.

Conclusion: FMT is a generally safe and effective treatment option for older adults with CDI.

Keywords: *Clostridium difficile*, fecal transplant, microbiota, older adults

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Introduction

Clostridium difficile infection (CDI) is a diarrheal disease with a high burden of morbidity and mortality in the United States [Elixhauser *et al.* 2006]. *C. difficile* is Gram-positive spore-forming bacteria sometimes present in small numbers in the healthy human gut [Khan and Elzouki, 2014]. When the intestinal ecosystem is disrupted by exposure to antibiotics or other factors, *C. difficile* can proliferate [Brown *et al.* 2014]. Pathogenic *C. difficile* produces entero- and cytotoxins, which cause an acute inflammatory diarrhea; in severe cases, pseudomembranous colitis can also result [Khan and Elzouki, 2014]. *C. difficile* is a frequent cause of nosocomial diarrhea, can add significant time and cost to a hospital stay [Elixhauser *et al.* 2006; Lucado *et al.* 2006], and can lead to readmission [Elixhauser *et al.* 2006]. Although traditionally treated with antibiotics, such as metronidazole or vancomycin, some individuals remain vulnerable to CDI recurrence. Continuous therapy with vancomycin is effective in controlling the symptoms of recurrent CDI, but it is expensive and not without side effects [Nelson *et al.* 2011; Vrieze *et al.* 2014].

Being over 65 years old is a risk factor for developing CDI [Bignardi, 1998]. Two-thirds of the patients hospitalized for CDI in the United States are 65 years of age or older [Elixhauser *et al.* 2006]. Compared with younger adults, older adults suffer increased morbidity and mortality from CDI [Pepin *et al.* 2005], as well as increased rates of CDI recurrence and antibiotic treatment failure [Louie *et al.* 2013]. Those over 80 years of age are particularly vulnerable to CDI; death rates from CDI among hospitalized members of this age group may exceed 20% [Cober and Malani, 2009].

Fecal microbiota transplantation (FMT) is an emerging therapy for CDI that offers the potential for a rapid and lasting elimination of CDI by restoration of healthy microbiota [Khoruts *et al.* 2010; Khoruts and Sadowsky, 2011]. FMT entails cessation of antibiotics followed by an infusion of feces from a healthy donor into the recipient's gastrointestinal (GI) tract [Friedman-Moraco *et al.* 2014].

The efficacy and safety of FMT for CDI in the general population has been previously described

[Brandt *et al.* 2012; Guo *et al.* 2012; Kelly *et al.* 2012; Van Nood *et al.* 2013; Cammarota *et al.* 2014, 2015; Moore *et al.* 2014; Drekonja *et al.* 2015]. FMT as an effective treatment of CDI began after a randomized control trial by van Nood and colleagues was stopped at interim analysis because of the superiority of FMT *versus* standard antibiotic therapy, and was subsequently published in 2013 [Van Nood *et al.* 2013]. Although FMT had been performed prior to 2013, it lacked randomized trials showing its efficacy. An additional, open-label randomized control trial was published this year with 90% resolution in CDI [Cammarota *et al.* 2015]. Studies have documented the successful use of FMT in children [Walia *et al.* 2014], those who are immunocompromised [Kelly *et al.* 2014], and solid organ transplant recipients [Friedman-Moraco *et al.* 2014]. Studies have also documented high cure rates using FMT *via* oral frozen preparation [Youngster *et al.* 2014a, 2014b]. While many prior FMT studies have had older patient populations [Garborg *et al.* 2010; Van Nood *et al.* 2013; Cammarota *et al.* 2015], none of the studies have specifically focused on safety and efficacy of FMT in older adults. A recent multisite, retrospective follow-up study was published that collected outcome measures from 146 patients aged 65 or older, with a published cure rate of 95.9% after FMT [Agrawal *et al.* 2015]. However, the multiple sites included in the study differed in infusion protocol and did not include data from nasogastric (NG), nasoduodenal (ND), nasojejunal (NJ), or percutaneous endoscopic gastrostomy (PEG) tube routes. We thus decided to describe our experience treating older adults with FMT for CDI at a single tertiary care facility that included such data.

Materials and methods

A follow-up study was performed of all FMT recipients 65 years of age or older who were treated for CDI since our institution began offering FMT in 2012. Our FMT protocol has been approved at Emory Healthcare by the Medical Practices, Infection Control, Antibiotic Utilization and the Pharmacy and Therapeutics Committees since July 2012. This retrospective analysis was approved by the Emory Institutional Review Board. Our site performed FMT for CDI in both inpatient and outpatient settings using a variety of infusion methods. Informed consents for FMT were obtained from all patients or their medical decision makers. A data collection form was used to elicit and record demographic and historical facts as well as pre-, peri-, and post-FMT information. We reviewed the clinical records, including laboratory testing and discharge summaries, and collected follow-up data from speaking with patients or their caregivers.

The primary outcomes measured during the follow-up period were resolution of CDI, adverse events (AEs), significant adverse advents (SAEs), and death. Resolution was defined as the absence of significant diarrhea (diarrhea as defined by at least three episodes per day) or a marked reduction in diarrhea not requiring antibiotic therapy. This definition of resolution is consistent with other recent studies [Louie *et al.* 2011; Kelly *et al.* 2014] and practice guidelines [Cohen *et al.* 2010; Surawicz *et al.* 2013]. Any patient requiring repeat FMT was recorded as a nonresolution. When uncertainty existed, laboratory results were considered definitive. AEs were defined as any untoward health events occurring after receiving FMT. SAEs were defined as events requiring prolonged hospitalization.

Results

Between July 2012 and April 2014, 64 patients with recurrent CDI received FMTs. Thirty-one of these recipients were 65 years of age or older at the time of FMT (Table 1). All 31 were included in our study; none were lost to follow up. Ages within this group ranged from 65 to 96 years, with a mean age at time of FMT of 77 years. All had a history of multiple CDI episodes (mean = 5, range= 3–10). The mean time of follow up after FMT was 9 months (range 2–24 months). The most common comorbidities observed in this group were hypertension, dyslipidemia, cancer, and diabetes (Table 2). All but one had been treated with vancomycin prior to FMT; the remaining patient had received metronidazole, clindamycin, and fidaxomicin without CDI resolution.

Thirty-six FMT procedures were performed on the 31 patients (Table 3). Four patients in the study group received multiple FMTs, including two who received two FMTs from our service, one who received three FMTs from our service, and one who had previously received FMT as an inpatient at another center and subsequently relapsed.

Twenty-four (77%) of 31 patients experienced lasting resolution of CDI after a single FMT. Three others reported resolution of diarrhea after

Table 1. Study demographics.

Total number of study patients	*N* = 31
Female	18 (58%)
White	25 (80%)
African American	6 (20%)
Mean age (years)	77 (range 65–96)
Median age (years)	76
Mean follow up (months)	9 (range 2–24)
Mean prior episodes of CDI	5 (range 3–10)
Antibiotics received prior to FMT*	Reported by 31 (100%)
Vancomycin	30 (97%)
Metronidazole	23 (74%)
Fidoxamicin	14 (44%)
Ciprofloxacin	3 (10%)
Rifaximin	2 (6%)
Levofloxacin	2 (6%)
Total FMTs performed	*N* = 36
Colonoscopy	25 (66%)
Nasogastric tube	3 (8%)
Nasoduodenal tube	3 (8%)
Nasojejunal tube	3 (8%)
Gastrostomy tube	2 (6%)

*Dosing regimens varied.
FMT, fecal microbiota transplant.

repeated FMTs, increasing the overall CDI resolution rate to 27 (87%) of 31 respondents. Nine patients with resolution reported taking antibiotics for incidental reasons after FMT; none of them experienced a recurrence of CDI.

Four (13%) of 31 continued to experience CDI. One patient did not improve despite receiving two FMTs *via* NJ and NG approaches, and three patients showed initial resolution after FMT but later developed CDI recurrence.

Twenty-five patients received FMT *via* outpatient colonoscopy; 24 (96%) of 25 had resolution of diarrhea. The sole treatment failure in this group occurred in an 81-year-old woman who was symptom free for 2 months following FMT. She experienced CDI recurrence as she was moving across the country and was unable to repeat FMT with our service.

Nine patients received FMT *via* an upper GI approach (i.e. PEG/NG/ND/NJ). Only three of these procedures (33%) resulted in a lasting resolution of diarrhea associated with CDI. Two patients did well initially, but experienced CDI relapses at 1 week and at 8 months, respectively. The four remaining patients of this group continued to experience CDI and opted to repeat FMT: three *via* colonoscopy (all resulting in resolution) and one *via* NG tube (resulting in continued CDI).

Patients who received the upper route of administration were those who were inpatients and too ill to tolerate colonoscopy. Related donors were used for the first seven FMTs in our program, but standard donors have been used exclusively since then, given the preference of the patients. Vancomycin was continued up until the FMT in patients who were being actively treated for *C. difficile*.

Weight and body mass index data from clinic visits before and after FMT were available for 24 of 31 patients. Fifteen (62.5%) of 24 patients gained weight following FMT, while 9 (37.5%) of 24 lost weight. Individuals gained a mean of 2.0 kg during the follow-up period; the standard deviation was 3.2 kg.

Five individuals in the cohort died during the follow-up period, with a mean survival of 128 days (range 14–270 days) after receiving FMT (Table 4). None of the deaths were attributed to FMT.

A 72-year-old woman had recurrent CDI despite receiving two inpatient upper GI FMTs. She required intensive care for hypotension before suffering a pulmonary flare of her pre-existing Churg–Strauss syndrome. Rather than repeating FMT a third time, she opted for a continuous vancomycin regimen (which was effective in suppressing CDI) and subsequently died in a hospice.

A 96-year-old man had 8 months free of CDI following FMT; he then developed recurrence requiring three hospitalizations for dehydration. At this time it became evident that his pre-existing prostate cancer had advanced. At that point, the patient opted for a continuous vancomycin regimen and hospice care rather than repeating FMT.

A 95-year-old man received FMT *via* NJ tube during an admission for acute CDI and was discharged to a subacute nursing facility. After 1 week, he experienced recurrence, requiring hospitalization due to hypotension, diarrhea, and *C.*

Table 2. Comorbidities prior to FMT in 31 older adults.

Category	Disease	Number of total patients affected
Cardiology	Hypertension	16 (52%)
	Dyslipidemia	11 (35%)
	Atrial fibrillation	6 (19%)
	Past cerebrovascular accident	6 (19%)
	Coronary artery disease	6 (19%)
	Congestive heart failure	4 (13%)
	Pacemaker/defibrillator placement	4 (13%)
	Past myocardial infarction	3 (10%)
Endocrinology	Diabetes mellitus	8 (26%)
	Osteoporosis	3 (10%)
	Osteomyelitis	1 (3%)
	Dysphosphatemia	1 (3%)
Gastroenterology	Gastroesophageal reflux disorder	7 (23%)
	Past diverticulitis episode	5 (16%)
	Past gastrointestinal bleed	4 (13%)
	Esophageal stricture	2 (7%)
	Cirrhosis	2 (7%)
	CMV colitis	1 (3%)
	Ulcerative colitis	1 (3%)
	Autoimmune hepatitis	1 (3%)
	Gastroparesis	1 (3%)
Hematology	Anemia	6 (19%)
	Past thrombotic event (DVT/PE)	5 (16%)
	IVC filter placement	2 (7%)
Nephrology	Severe UTI	6 (19%)
	Chronic kidney disease	6 (19%)
	Kidney transplant recipient	1 (3%)
Neurology	Spinal stenosis	1 (3%)
Oncology	Malignancy	8 (26%)
Psychiatry	Dementia	5 (16%)
	Major depressive disorder	3 (10%)
Pulmonology	Recent pneumonia	4 (13%)
	Chronic obstructive pulmonary disease	2 (7%)
	Past bilateral lung transplant	1 (3%)
Rheumatology	Rheumatoid arthritis	1 (3%)
	Churg–Strauss syndrome	1 (3%)
	Pseudogout arthritis	1 (3%)
Surgery	Past fundoplication	1 (3%)
	Past hysterectomy	8/18* (44%)
	Past arthroplasty	6 (19%)
	Cholecystectomy	7 (23%)
	Past appendectomy	3 (10%)
	Past bowel resection	2 (7%)

*of 18 women in study.
CMV, cytomegalovirus; DVT, deep venous thrombosis; FMT, fecal microbiota transplant; IVC, inferior vena cava; PE, pulmonary embolism; UTI, urinary tract infection.

difficile colitis. He was found to be in septic shock and subsequently died 2 days later. He suffered from multiple comorbidities prior to FMT, including prostate cancer, stroke, dementia, recent pulmonary empyema requiring resection, and recent pulmonary embolus requiring inferior

Table 3. CDI outcomes at follow up.

Patient characteristics		Total FMTs	CDI resolution*	Nonresolution$	*p* value
All patients ($n = 31$)		36	27 (75%)	9 (25%)	–
Race	African American ($n = 6$)	8	5 (63%)	3 (37%)	0.662
	White ($n = 25$)	28	22 (79%)	6 (21%)	0.775
Age	65–79 ($n = 19$)	22	18 (82%)	4 (18%)	0.747
	80⩽ ($n = 12$)	14	9 (64%)	5 (36%)	0.496
Sex	Female ($n = 18$)	21	16 (76%)	5 (24%)	NS
	Male ($n = 13$)	16	11 (69%)	5 (31%)	0.738
Donor type	Standard donor 1	14	11 (79%)	3 (21%)	NS
	Standard donor 2	7	6 (86%)	1 (24%)	NS
	Standard donor 3	5	4 (80%)	1 (20%)	NS
	Related donors ($n = 7$)	9	5 (56%)	2 (44%)	NS
Infusion type	Postpyloric	10	3 (30%)	7 (70%)	0.02‡
	Colonoscopic	26	24 (92%)	2 (8%)	0.10
Setting	Inpatient	12	5 (42%)	7 (58%)	0.073
	Outpatient	34	32 (94%)	2 (6%)	0.046‡
Post FMT antibiotic usage§	Received	9	9 (100%)	0 (0%)	0.17
	Did not receive	22	18 (82%)	4 (18%)	0.747

Discordance between 'All patients' and 'Total FMTs' represents multiple FMTs per person. Fisher exact test used to calculate *p* values with comparison to 'All patients'.
*Defined as absence of CDI at time of follow up.
$Defined as continued CDI after FMT as well as later relapses. Includes all FMTs that were later repeated.
‡Signifies significance at $p = 0.05$.
§For non-CDI indications; includes vancomycin, metronidazole, ciprofloxacin, amoxicillin/clavulanate, and doxycycline.
CDI, *Clostridium difficile* infection; FMT, fecal microbiota transplant; NS, not significant.

vena cava filter placement. As CDI was his underlying disease, his death was not attributed to FMT.

A 65-year-old man experienced a complete remission of CDI after FMT but died 2 months later from complications of pre-existing malignancy.

A 78-year-old man experienced a complete remission of CDI after FMT but was later hospitalized for a severe urinary tract infection (UTI), lower extremity gangrene, as well as a lower GI bleed. He died of fluid overload from renal failure during that admission after becoming unable to tolerate dialysis.

Among the 26 surviving patients, eight experienced major health events after receiving FMT, which necessitated or complicated hospitalization. A 73-year-old woman suffered a cerebrovascular accident following FMT *via* colonoscopy [Friedman-Moraco *et al.* 2014], and subsequently recovered fully. An 80-year-old man experienced an indirect benefit of FMT *via* colonoscopy when a suspicious lesion was observed and biopsied during the procedure. Pathological findings were consistent with a tubulovillous adenoma with high-grade dysplasia. After making a complete recovery from CDI following FMT, the patient underwent laparoscopic resection. Ten inches of sigmoid colon were removed without complication and found to contain colonic adenocarcinoma *in situ* with clear margins.

Six other individuals in the study experienced major health events during the follow-up period unrelated to FMT. An 81-year-old woman suffered relapse of CDI 2 months after FMT *via* colonoscopy and required hospitalization. A 66-year-old woman with bilateral lung transplant was hospitalized for diverticulitis and UTI 8 months after receiving FMT *via* colonoscopy. During these episodes, she was treated with antibiotics but did not suffer a relapse of CDI. An 82-year-old woman suffered two episodes of aspiration pneumonia, at 2 and at 6 months, respectively, after receiving a curative FMT *via* PEG tube. She was treated successfully without CDI

Table 4. Adverse events following FMT.

Adverse event	Incidents reported in 31 FMT recipients
Deaths	5 (16% of 31)
Churg–Strauss flare	1
Previously diagnosed cancer	2
Renal failure	1
Clostridium difficile sepsis	1
Major health events	Reported by 11 (35%)
Cerebrovascular accident	1
Partial colectomy	1
Hospitalized for CDI	1
Diverticulitis	1
Severe urinary tract infection	2
Aspiration pneumonia	2
Myocardial infarction	1
Vascular transplant	1
Lysis of adhesions	1
Minor health events	Reported by 15 (48%)
Worsened arthritis	4
Constipation	3
Diarrhea	3
Urinary tract infection	2
Urolithiasis	1
Root canal	1
Rib fracture	1
Insomnia	1
Chronic asymptomatic bacteriuria	1
Nausea	1
Foul smelling urine	1

CDI, *Clostridium difficile* infection; FMT, fecal microbiota transplant.

relapse. A 79-year-old man developed a severe UTI requiring hospitalization 4 months after successful FMT *via* colonoscopy. His UTI was successfully treated with amoxicillin/clavulanate without a relapse of CDI. An 80-year-old man with pre-existing coronary artery disease was hospitalized following his third myocardial infarction. A 67-year-old man with multiple pre-existing comorbidities underwent a peripheral vascular transplant and surgery for lysis of adhesions.

Data were also collected on adverse health events not requiring hospitalization reported by patients after receiving FMT (Table 4). Four patients (13%) reported a worsening of their pre-existing arthritis. Three patients (10%) complained of constipation, which responded to over-the-counter (OTC) treatments; another three patients (10%) complained of diarrhea also controllable with OTC treatments. Two patients (6%) developed UTIs since receiving FMT. Single individuals (3% each) reported new complaints after receiving FMT, including urolithiasis, foul-smelling urine, chronic asymptomatic bacteriuria, dental abscess, fall with rib fracture, insomnia, and nausea.

Discussion

This case series presents evidence that FMT is a safe and effective treatment for CDI in older adults.

The most common reported AE was worsening of pre-existing joint disease. This finding contrasts with a previous report [Brandt *et al.* 2012] of two adults whose arthritis improved following FMT. There is emerging evidence that the presence of organisms such as parvovirus [Caliskan *et al.* 2005; Tello-Winniczuk *et al.* 2011] or gut bacteria [Wu *et al.* 2010; Gomez *et al.* 2012; Scher *et al.* 2013] may contribute to joint disease. The relatively high level of pre-existing joint disease in older adults may contribute to our finding.

One incident was concerning for the safety of FMT in our study. This occurred in a 95-year-old man who received FMT *via* NJ tube while hospitalized for CDI. His case is similar to one recently reported by Solari and colleagues of a 68-year-old man who received FMT *via* PEG tube while hospitalized for CDI [Solari *et al.* 2014]. Both patients' conditions were stable on a continuous vancomycin regimen, which was discontinued before FMT. Both tolerated FMT well, but developed septic shock and died within 1 week of FMT. While FMT may have been a contributing factor in these individuals' deaths, there is no direct evidence of a causal association.

In previous studies of patients with recurrent CDI, treatment with antibiotics was found to trigger recurrences more than 60% of the time [Drekonja *et al.* 2011; Zilberberg *et al.* 2014]. We did not observe CDI recurrences in the nine patients who took antibiotics for incidental reasons after FMT.

Our study was unique in its use of NG, ND, NJ, and PEG tubes in patients too ill to receive

infusion *via* colonoscopy. Among the nine patients receiving upper GI infusion, only three (33%) achieved lasting remission of CDI. Our rates of resolution of CDI *via* upper GI infusion are lower than those from other studies [Van Nood *et al.* 2013]. However, these data are confounded by the pre-existing conditions that prevented the FMT to be performed *via* colonoscopy; these conditions may have affected CDI resolution. Likewise, patients receiving FMT in an outpatient setting were much more likely to achieve CDI resolution compared with patients receiving it in an inpatient setting (94% resolution *versus* 42% resolution), but these data are confounded by the comorbidities that caused the patients to be hospitalized. While the patients receiving FMT in an inpatient setting were sicker, other factors may be at play, including increased exposure to *C. difficile*.

There are additional benefits to FMT *via* colonoscopy other than CDI resolution. A larger amount of stool infusate can be instilled when performed using colonoscopy than through other methods. Furthermore, colonoscopy allows for the endoscopist to examine the colon for additional findings prior to infusion. In one the study patients, a suspicious lesion was noticed prior to infusion and was biopsied. Histologic examination was significant for adenocarcinoma *in situ*, and the patient subsequently received a partial sigmoidectomy. Outside of the study, our center has diagnosed FMT recipients with microscopic colitis and collagenous colitis (data not shown) based on suspicious findings during colonoscopy.

An additional issue that needs to be taken into account is the projected life expectancy of an FMT recipient. For our 95-year-old patient who died 9 days after FMT due to CDI recurrence, one can speculate that the cessation of vancomycin prior to FMT may have put the patient at risk for recurrence in CDI and continued vancomycin in lieu of FMT may have prolonged his life. Although we have insufficient data to suggest a treatment policy, we believe that lifelong vancomycin suppression is an option in patients who may not survive a relapse.

Based on our data, we recommend FMT as an effective treatment for older adults with recurrent CDI who meet criteria for colonoscopy in the outpatient setting. Colonoscopy is a safe and effective procedure and FMT infusion performed in this manner produces excellent outcomes with low risk.

Limitations to our study include small sample size and low ethnic and geographic variety of our study population due to our reliance on a single center. These hinder the applicability of our findings to broader populations. Furthermore, the follow-up time varied from patient to patient. Despite these limitations, this study provides good evidence for the safety and effectiveness of FMT in older adults with recurrent CDI.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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