Successful use of early, repeat fecal microbiota transplantation for initial treatment of severe, refractory *Clostridioides difficile* colitis

Catherine M. Cappetto, BS/BS, PharmD, RPh, BCPS, Department of Pharmacy, Cleveland Clinic Fairview Hospital, Cleveland, OH, and Northeast Ohio Medical University College of Pharmacy, Rootstown, OH, USA

Purpose. There is a paucity of literature surrounding the use of early fecal microbiota transplantation (FMT) for patients presenting with an initial episode of severe, refractory *Clostridioides difficile* infection (CDI). Information on optimal antibiotic dosing and therapy duration surrounding FMT during an acute, initial episode of CDI is also limited. Described here is a case of successful treatment of CDI after 4 FMTs during an acute, initial episode of severe, refractory *Clostridioides difficile* colitis.

Summary. A 69-year-old community-dwelling, Caucasian male presented after 48 hours of vomiting and diarrhea. A stool sample was collected and resulted positive for *Clostridioides difficile* by both polymerase chain reaction (PCR) and enzyme-linked immunosorbent assay (ELISA). The patient was treated with several days of oral and rectal vancomycin therapy in addition to intravenous metronidazole, but those treatments failed. His clinical and nutrition status deteriorated over the course of several days until salvage therapy was ordered, with administration of 1 inpatient nasogastric FMT and 1 inpatient colonoscopic FMT followed by outpatient colonoscopic FMTs on 2 consecutive days within 2 weeks of hospital discharge.

Conclusion. This case suggests a role for early, repeat FMT during an initial presentation of a severe *Clostridioides difficile* colitis episode refractory to pharmacologic antimicrobial therapy. It also adds to emerging literature regarding the timing of antibiotic cessation surrounding FMT.

Keywords: *Cdiff, Clostridioides difficile, Clostridium difficile,* fecal microbiota transplantation, fecal microbiota transplant, FMT

Address correspondence to Dr. Cappetto (cappetc2@ccf.org)

*C*lostridioides difficile infection (CDI) is caused by a spore-forming, gram-positive anaerobic bacillus that produces exotoxins A and B.[1] These toxins are responsible for causing gastrointestinal mucosal injury, inflammation, and harmful systemic effects in addition to toxic megacolon, which may be fatal.[1] Based on expert opinion, a severe initial episode of CDI can be defined as leukocytosis with a white blood cell (WBC) count of ≥15,000 cells/μL or a serum creatinine concentration of >1.5 mg/dL. Fulminant infections may also include the presence of hypotension, shock, ileus, or toxic megacolon.[2] In the United States, *C. difficile* causes approximately 500,000 infections and is linked to around 30,000 fatalities annually.[3] CDI is the most common cause of healthcare-associated diarrhea in adult patients and has also become a prevalent pathogen in the community.[4,5] CDI not only impacts the individual patient but poses significant costs to the healthcare system, nearly $4.8 billion annually.[2] Exposure to antibiotics is a modifiable risk factor for CDI.[3,4] Antimicrobial stewardship is important in order to limit exposure to broad-spectrum antibiotics and antibiotic classes that have been associated with a high risk of CDI, such as clindamycin, fluoroquinolones, extended-spectrum cephalosporins, and carbapenems.[4,5]

Infectious Diseases Society of America (IDSA) and Society for

Healthcare Epidemiology of America (SHEA) guidelines strongly recommend, on the basis of high-quality evidence, that first-line therapy for an initial episode of severe CDI should begin with oral vancomycin or fidaxomicin for 10 days.[5] The IDSA/SHEA guidelines recommend fecal microbiota transplantation (FMT) for patients who have recurrent CDI (rCDI), defined as having an episode of symptom onset and positive assay result following an episode with positive assay result in the previous 2 to 8 weeks.[2] Early FMT for rCDI has demonstrated success rates of 77% to 100%, with success rates of 75% to 90% demonstrated with repeat FMTs.[2,6,7] For patients refractory to guideline-directed CDI antimicrobial therapy, defined as failure of standard therapy including but not limited to vancomycin and metronidazole without resolution of diarrhea by day 7 or failure of maximum medical therapy, no clear guidelines exist.[8] Alternative pharmacologic strategies such as intravenous (IV) immune globulins, fecal bacteriotherapy, probiotics, vaccinations, anion-binding resins, rifaximin, tigecycline, nitazoxanide, teicoplanin, tiacumicin, and ramoplanin, which are not all readily available, have been described for cases of relapsed rather than refractory CDI.[8] The European Consensus Guidelines on FMT recommend use of FMT for both mild and severe rCDI and as a consideration in refractory CDI.[6] At this time, there are limited options for and a lack of consensus on guideline-directed treatment strategies. This complicates clinical decision-making for healthcare providers when patients present acutely with severe, refractory (rather than recurrent) CDI as an initial episode. The objective of this case report is to describe the success of early, repeat FMT as a treatment strategy for an initial episode of severe, refractory CDI and discuss timing of antimicrobial cessation surrounding repeat FMT.

Case report

A 69-year-old community-dwelling, Caucasian male with a past medical history significant for coronary artery

KEY POINTS

- Accurate and timely antimicrobial stewardship is warranted to clarify patients' medication allergies and associated reactions, avoid unnecessary antibiotics, and de-escalate broad-spectrum therapy to decrease exposure and risk of *Clostridioides difficile* infection (CDI).

- Optimal timing of antimicrobial cessation surrounding initial and repeat fecal microbiota transplantations (FMTs) for CDI is unknown, but treatment with repeat FMTs while holding antibiotics for up to 24 hours prior to and indefinitely post FMT, as clinically tolerated, can be considered.

- Early, repeat FMTs may be a viable option for initial treatment of severe, refractory CDI after failure of antibiotic therapy.
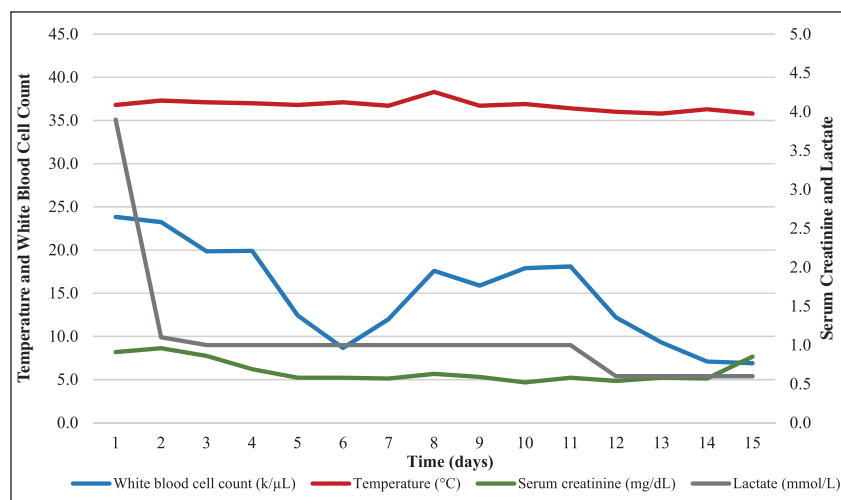
disease, hyperlipidemia, hypothyroidism, and chronic pain presented to a 500-bed community teaching hospital with complaints of vomiting and diarrhea for the past 48 hours. His gastrointestinal symptoms had begun 1 week prior to admission and subsided after 48 hours without clinical or pharmacologic intervention. Upon resurgence of the vomiting and diarrhea 3 days later and persistence of those symptoms for the next 2 days, the patient arrived to the emergency department (ED). The patient became incontinent of stool, with more than 10 loose, watery bowel movements per day. He had difficulty maintaining fluid and nutrition status due to persistent nausea and emesis (more than 12 times per day consistently for 48 hours). The patient also reported generalized weakness and fatigue. He had an extensive dental cavity and reported that he had scheduled an appointment for tooth extraction for

the following week. With regard to the single dental caries, the patient noted that 2 months previously he had completed a prophylactic 10-day course of clindamycin 300 mg 3 times daily (ordered due to a possible penicillin allergy, with questionable localized swelling; the patient reported no history of prior cephalosporin use). He reported that he had experienced no adverse effects during that clindamycin course.

In the ED a stool sample was obtained, vital signs were assessed, and fluid samples were collected for laboratory testing; results are summarized in Figure 1. Upon physical examination, the patient was alert and oriented to person, place, and time, with dry buccal mucosa and diffuse abdominal tenderness, distention, and guarding in all quadrants. The review of symptoms was negative for chest pain, syncope, shortness of breath, cough, flank pain, hematuria, and constipation. Fluid resuscitation and empiric antibiotics were initiated (a treatment timeline is provided in Table 1). A computed tomography scan of the abdomen demonstrated extensive wall thickening and hyperemia of the rectosigmoid colon and descending colon, which was concerning as suggestive of acute infectious, inflammatory, or ischemic colitis. An abdominal x-ray demonstrated several prominent, mildly dilated loops of small bowel within the midabdomen suggestive of an ileus. A colorectal surgery consult was obtained, and the patient was transferred to the medical intensive care unit (MICU) for hypotension and worsening abdominal distention, which was complicated by anemia and a hemoccult-positive stool sample.

While the patient was in the MICU, polymerase chain reaction and enzyme-linked immunosorbent assays resulted positive for *C. difficile* toxin. An infectious diseases consult was ordered, and the patient remained in intensive care for 3 days before being transferred to the medical step-down unit for 3 additional days prior to his transfer to another hospital. Before the interhospital transfer, the patient

Figure 1. Selected laboratory values and measured temperatures during patient's inpatient care.

Upon arrival to the medical center, the patient was admitted by the gastroenterology service, with subsequent consultation of the infectious diseases, colorectal surgery, and pharmacy services. The antibiotics continued at this time included oral and rectal vancomycin and IV metronidazole, as noted in Table 1. On hospitalization day 7, the WBC was 12,000 cells/µL, and that evening the patient had an initially low-grade fever (38.8°C) and again developed worsening abdominal pain and distention with continued frequent loose stools, indicating progression of CDI. Due to the patient's worsening clinical presentation, he received the first nasogastric (NG) FMT on hospitalization day 8. No bowel preparation was administered prior to the FMT due to the acuity of the situation and the continuation of loose, unformed stool production. In contrast to the usual practice of cessation of antimicrobial therapy 12 to 72 hours prior to FMT, based on the unstable clinical course of the patient and high risk of sepsis and rapid deterioration, cautious antimicrobial de-escalation was exercised, as noted in Table 1.[6,10]

Vancomycin enemas were discontinued 7 hours and IV metronidazole was discontinued 5 hours prior to the initial FMT on day 8, and the oral vancomycin dosage was decreased the following evening (post FMT) to 125 mg every 8 hours in an attempt to allow persistence of newly established gut flora. Two tablets of atropine/diphenoxylate (0.025 mg/2.5 mg) were administered orally 1 hour before and 3 hours after the FMT to enhance the retention of the newly instilled donor stool. With the head of the bed at a 50-degree angle, the patient's NG tube was instilled with 30 mL of thawed Microbiome FMP30 (OpenBiome, Cambridge, MA) donor stool preparation over 2 minutes, then the NG tube was flushed with 30 mL of tap water and 20 minutes later was removed. Following the procedure, the patient experienced a temporary reduction in symptoms and a minimal decrease in WBC count (from 17,600 cells/µL to 15,900 cells/µL). These

received IV metronidazole and varying doses of oral and rectal vancomycin, as outlined in Table 1; vancomycin dosing, which varied from guideline-directed doses, is reported as a range in Table 1 to reflect variable dosing due to differences in clinical severity classification by the consultant teams. Several dose changes to antimicrobial orders occurred due to recommendations from multiple services, including the critical care team. In accordance with pharmacist recommendations, intensivists ordered vancomycin 125 mg orally 4 times daily based on classification of the patient's CDI as severe.[2] This order was in contrast to the order of an infectious diseases provider, who had empirically increased the vancomycin dosage to 250 mg orally 4 times daily. Although higher vancomycin dosages, ranging from 250 mg to 500 mg 4 times daily, are occasionally recommended for severe rather than fulminant CDI, there is limited clinical evidence to support such dosing.[9] The surgical team added metronidazole 500 mg IV every 8 hours and enema infusion (500 mg/100 mL) per rectum every 6 hours, which was reflective of dosing for fulminant CDI, since there was concern for shock with the presence of hypotension (responsive to fluids), the presence of an ileus, and the risk of the development of toxic megacolon. The lack of consensus on

the severity classification may have accounted for the omission of oral vancomycin dose escalation to 500 mg 4 times daily.

During the MICU stay, the patient's emesis resolved but he continued having 7 to 10 liquid, blood-streaked, mucosal bowel movements per day and had developed significant abdominal distention in addition to abdominal, scrotal, and lower-extremity edema. His WBC counts remained elevated, with a slow downward trend towards normal limits, but again spiked (reaching a high of 17,600 cells/µL) prior to the first FMT (Figure 1). The patient continued to be unable to consume a full liquid diet without experiencing significant abdominal pain and tenderness. He was assessed for total parenteral nutrition (TPN), and a peripherally inserted central catheter (PICC) line was placed on day 6. Since the patient was not responding to antibiotics, was unable to sustain enteral nutrition, and was at high risk for abdominal perforation and sepsis, the gastroenterology service was consulted. The gastroenterology service determined on day 6 that the patient had severe, refractory CDI with antibiotic failure and recommended urgent FMT. On day 6 of the hospitalization, the patient was transferred to a 1,000-bed, FMT-capable academic medical center to undergo inpatient FMT.

Table 1. Timeline of Patient's Treatment

Setting and Day	Treatment
Inpatient (institution A)	
1	Four 1-L 0.9% NaCl IV boluses and empiric therapy: ciprofloxacin 400 mg IV once, metronidazole 500 mg IV once, vancomycin 1,500 mg IV once
2	Vancomycin oral solution (125-250 mg q 6 h), vancomycin 500 mg in 0.9% NaCl 100 mL solution rectal enema q 6 h (retained ~20 min), metronidazole 500 mg IV q 8 h
3	Day 2 dosing continued
4	Day 2 vancomycin oral solution only continued
5	Day 2 dosing continued
6	Day 2 dosing continued
Inpatient (institution B)	
7	Vancomycin 250 mg orally q 6 h, vancomycin enema 500 mg q 6 h, metronidazole 500 mg IV q 8 h
8	Day 7 dosing continued until vancomycin enema and IV metronidazole discontinued 5 and 7 hours prior to FMT, respectively Retention agent: 2 tablets of atropine/diphenoxylate (0.025 mg/2.5 mg) orally 1 hour before and 3 hours after FMT Inpatient nasogastric FMT: 30 mL donor stool
9	Vancomycin 250 mg orally q 6 h (3 doses) decreased to 125 mg q 8 h (1 dose)
10	Vancomycin 125 mg orally q 8 h (2 doses) increased to 250 mg q 6 h (2 doses)
11	Last dose of oral vancomycin 250 mg at midnight, then all antibiotics discontinued 10 hours prior to FMT Retention agent: 2 tablets of atropine/diphenoxylate (0.025 mg/2.5 mg) orally 2.5 hours before and 1 tablet 1.5 hours after FMT Inpatient colonoscopic FMT: 240 mL of donor stool
12–15	No antibiotics (inpatient day 12 through postdischarge period)
Outpatient (postdischarge day)	
1–9	Probiotic: *Lactobacillus, Streptococcus,* and *Bifidobacterium* (25 billion active cultures per 97 mg) 1 capsule orally daily; dicyclomine 10 mg orally 4 times daily before meals, as needed for abdominal cramping; calcium polycarbophil 625 mg orally daily; and methylcellulose powder 2 g in 240 mL of water orally once daily
10	Probiotic and dicyclomine continued (see days 1–9 dosing) Bowel preparation: bisacodyl 10 mg orally 21 hours prior to FMT and oral polyethylene glycol 238 g 19 hours prior to FMT
11	Probiotic and dicyclomine continued (see days 1–9 dosing) Bowel preparation: magnesium citrate 5.2 g/90 mL orally 4 hours prior to FMT Retention agent: loperamide 4 mg orally 30 minutes pre and post FMT 1st outpatient colonoscopic FMT: 450 mL emulsified donor stool
12	Probiotic and dicyclomine continued (see days 1–9 dosing) Bowel preparation and retention agent: none 2nd outpatient colonoscopic FMT: 500 mL emulsified donor stool

Abbreviations: FMT, fecal microbiota transplant; IV, intravenous; NaCl, sodium hydrochloride.

developments were followed by a moderate improvement in the abdominal exam findings on day 9 before gastrointestinal symptoms and pain again worsened on day 10, with an increase in the WBC count from 15,900 cells/μL to 17,900 cells/μL (Figure 1). A kidney, ureter, and bladder x-ray was negative for obstruction or perforation at that time. On hospitalization day 10, TPN was initiated because the patient was still unable to tolerate a clear liquid diet.

By late morning on hospitalization day 11, the patient had not received antibiotics for 10 hours, having last received an oral dose of vancomycin at midnight on day 11. Also on day 11, the WBC count had increased to 18,100

cells/μL, with a significant amount of worsening of abdominal pain and cramping again reported by the patient. A repeat FMT was then conducted via colonoscopy on day 11. Again, due to the patient's acuity and continued loose bowel movements, no bowel preparation was administered prior to the FMT. Two tablets of atropine/diphenoxylate (0.025 mg/2.5 mg) were administered orally 2.5 hours before and 1 tablet was administered 1.5 hours after the FMT to enhance the retention of the newly instilled donor stool. During the colonoscopic FMT, 240 mL of emulsified donor stool that had been frozen and thawed was instilled into the transverse colon.[11] The colonoscopy results demonstrated erythema, congestion, and erosion likely secondary to ischemic colitis. After the second FMT the WBC counts decreased from 18,100 cells/ μL to 12,200 cells /μL within 24 hours on day 12, and the abdominal pain and distention significantly declined. Bowel movements slowly progressed to slightly more formed stools and their frequency decreased from 7 to 4 per day. The patient continued to receive TPN during days 10 through 14 while still having difficulty tolerating and advancing his diet. On days 13 through 15 the WBC counts continued trending downward to normal limits (Figure 1). On day 15 the patient was afebrile and able to tolerate a full liquid diet, and solid foods had been reintroduced; therefore, TPN was discontinued. The patient's abdominal pain and distention were not yet absent, but on day 16 those symptoms had significantly lessened and the patient was discharged home without antibiotics in stable condition.

Within 1 week of discharge the patient experienced a recurrence of abdominal cramping and distention, as well as increased stool frequency and diarrhea. The patient contacted the outpatient gastroenterology service and was scheduled for outpatient colonoscopic FMTs on days 11 and 12 post discharge. Repeat FMT is typically performed in the event of recurrent diarrhea for 1 week post FMT.[10]

The patient was instructed to adhere to a clear liquid diet from the day prior to FMT up until 5 hours prior to the procedure. He completed bowel preparation the day prior to the initial outpatient FMT with bisacodyl 10 mg by mouth taken 21 hours prior to the FMT and polyethylene glycol 238 g taken by mouth 19 hours prior to the FMT, as outlined in Table 1. The morning of the FMT, the patient consumed magnesium citrate solution (5.2 g/90 mL). Thirty minutes before the procedure, the patient took loperamide 4 mg orally, and following the procedure 4 mg of loperamide was administered in the office to enhance the retention of the newly instilled stool.

The initial outpatient FMT was performed using 450 mL of emulsified donor stool preparation, which was instilled via colonoscopy into the patient's cecum. The colonoscopy results demonstrated altered vasculature, erythema, erosions, congestion, inflammation, plaques with contact bleeding, and pseudomembranous mucosa in the rectum, sigmoid colon, and descending colon. The patient was determined to still have moderate to severe active *C. difficile* colitis and therefore was scheduled for a repeat FMT the following day. Given the severity of illness and high morbidity and mortality rates associated with the presence of pseudomembranous colitis, as visualized during the first outpatient colonoscopic FMT, the decision was made to repeat the FMT the following day with the aim of inducing clinical remission, as recommended by the European consensus guidelines.[6] No bowel preparation was completed prior to the second outpatient FMT, since the patient's gut contained newly implanted donor stool. For the second outpatient colonoscopic FMT, 500 mL of emulsified donor stool preparation was instilled into the patient's cecum. Post FMT, the patient was advised to avoid unnecessary antibiotics, follow a high-fiber diet (with the addition of methylcellulose 2 g in 240 mL of water up to 3 times daily for fiber supplementation), take dicyclomine 10 mg

4 times daily before meals as needed for abdominal cramping, and take a once-daily oral probiotic supplement. Although probiotic use is not recommended in the current IDSA/SHEA guidelines and most randomized controlled studies of its use were not adequately powered, based on available data showing trends of reduced CDI recurrence with use of probiotics for secondary prevention, the consulted gastroenterologist advised that the benefits of administration of an oral daily probiotic supplement indefinitely would outweigh the risks.[12-14]

At the time of writing, the patient had been followed for 2 years from the date of initial presentation with severe, refractory CDI. The patient had been continued on the daily probiotic supplement along with dietary and pharmacologic fiber supplementation with calcium polycarbophil 625 mg orally daily and methylcellulose powder 2 g in 240 mL of water orally once daily. He had attended routine follow-up visits with his primary care provider, had returned to his routine activities of daily living, and had avoided antibiotic usage. He was delabeled as having penicillin allergy in the electronic medical record, and he had remained clinically stable without experiencing a recurrence of CDI. As of the time of writing, the patient was deemed to have experienced a clinical cure on the basis of the resolution of diarrhea and gastrointestinal symptoms without the need for additional antimicrobial treatment or repeat FMTs.

Discussion

FMT has been primarily studied as a treatment for rCDI. Recurrent CDI is more often severe compared to initial episodes and is associated with higher mortality.[15,16] Treatment with FMT versus vancomycin may be more effective for rCDI.[17] In contrast, literature regarding early FMT for acute infections during initial episodes of severe, refractory CDI is sparse and mainly includes retrospective or observational reports.[18,19] The indications for and

selection and timing of pre- and post-FMT antimicrobials, bowel preparation protocols, and repeat FMTs, in addition to long-term outcomes of FMT in this population, are not well defined. Also, the burden of treatment failure is significant. Prior literature has revealed that rates of initial CDI antibiotic treatment failure range from 14% to 22% and continue to increase with recurrences.[20] Prior studies have also demonstrated a risk of CDI both during and up to 3 months after antibiotic usage due to disruption of the native gut microbiota.[3] There is an up to 10-fold increase in the risk of CDI occurring within the first month following antimicrobial therapy.[3] Unnecessary exposure, exposure to multiple offending antimicrobials, and prolonged use of antibiotics are known to increase the risk of CDI.[3]

Therefore, optimal and timely treatment strategies are needed, but there are several hurdles to overcome. Inpatient formulary restrictions due to cost constraints, guideline recommendations, stewardship initiatives, and pharmacy and therapeutics committee decisions significantly limit the availability of alternative pharmacologic therapies such as fidaxomicin, immune globulin, and bezlotoxumab. These were considered last-line options for the patient described in this report, to be used only if treatment with the preferred formulary agents (vancomycin and metronidazole) failed and if inpatient FMTs were unsuccessful at stabilizing CDI symptoms. For treatment of a potential future recurrence of CDI, fidaxomicin was recommended by the infectious diseases service as an alternative outpatient therapy (instead of oral vancomycin) in order to circumvent inpatient formulary restrictions and incorporate an alternative mechanism of action in addition to providing a first-line IDSA/SHEA guideline–directed treatment strategy.[2]

FMT may be a highly effective, cost-reducing alternative to pharmacotherapy alone for CDI for many institutions. Literature suggests that cure rates with administration of FMTs for severe CDI refractory to antibiotics range from 50% to 91%.[21-27] A single FMT may provide transient clinical improvement rather than sustained cure for patients with pseudomembranous colitis, and repeat infusions may be required to sustain cure if it is achieved.[23-26] The presence of pseudomembranes reflects increased disease severity and a lower likelihood of response to a single FMT.[24] For severe and/or complicated CDI with pseudomembranes, a single FMT might not result in complete resolution of CDI symptoms but could decrease the CDI symptom burden, enabling a response to anti-CDI therapy.[24] For patients with pseudomembranes, a 100% cure rate may be attainable by continuing repeat FMTs until the disappearance of the pseudomembranes.[28] In previous studies a high rate of success was achieved when pseudomembranous colitis was treated with repeat FMTs at 3- to 5-day intervals until the colitis had resolved.[22,24] Additional data indicates that patients with pseudomembranous colitis who receive an average of 4 FMTs (range, 3–6 FMTs) can achieve significantly higher cure rates than those treated with a single FMT.[29] The rationale for repeat FMTs for the patient described in this report was to reduce symptoms, disease burden, and morbidity and mortality associated with CDI and to restore the gut microbiota involved in the pathogen's persistence and colonization.[18,30,31] Therefore, based on the deteriorating clinical presentation combined with a worsening of the patient's laboratory markers and vital signs (Figure 1), gastrointestinal symptoms including persistent diarrhea, and uncontrolled pain on day 11, the decision was made to perform repeat FMT while he was still in the hospital. Upon visualization of pseudomembranous colitis during colonoscopic FMT, the severity and resistance of the active, refractory CDI was evident.

Although the US Food and Drug Administration (FDA) has issued a statement about the risk of serious and life-threatening adverse events related to FMT, with the transmission of multidrug-resistant pathogens (enteropathogenic and Shigatoxin-producing *Escherichia coli*) detected in donor stool samples used for investigational FMT,[32-34] early repeat FMT with cautious antimicrobial de-escalation and cessation significantly improved the clinical outcome in the case described here. Initial administration of antibiotics may have reduced the efficacy of the FMTs by disrupting the healthy microbiome. Guidance developed at the 2016 European consensus conference on FMT in clinical practice strongly recommends treatment with oral vancomycin or fidaxomicin at least 3 days prior to FMT, with treatment discontinued 12 to 48 hours prior to FMT for rCDI.[6] Additional literature regarding severe, refractory CDI (as opposed to rCDI) recommends discontinuation of antibiotics 12 to 72 hours before FMT to prevent an antibiotic effect on the transplanted fecal microbiota.[6,10,35] De-escalating antibiotics in a stepwise approach by discontinuing metronidazole 48 hours prior to FMT and vancomycin 12 to 24 hours prior to FMT has also been demonstrated to promote resolution of severe CDI following FMT.[25] Alternative strategies for antibiotic cessation include treating with oral vancomycin for 5 days, suspending therapy for 12 to 24 hours prior to FMT (unless clinical deterioration is evident), then implementing FMT and, based on FMT response, resuming oral vancomycin 24 to 48 hours post FMT for a minimum of 5 days. This strategy alternates oral vancomycin and FMT every 5 days if pseudomembranes persist and involves withholding vancomycin for 12 to 24 hours prior to FMT. If symptoms resolve, FMT is stopped; if pseudomembranes are absent, vancomycin is also discontinued.[24]

Restoring the microbiome is challenging while an active infection is present and is further complicated by the severity of illness requiring antibiotics. Therefore, the decision was made to conservatively de-escalate the vancomycin enema and IV metronidazole regimen 5 to 7 hours prior to the first inpatient NG tube FMT on hospitalization day 8 but continue vancomycin orally

due to the clinical instability and the high probability of rapid deterioration of the patient's clinical status. The day after the initial FMT (hospitalization day 9), oral vancomycin was resumed but dosing was reduced from 250 mg every 6 hours to 125 mg every 8 hours over for approximately 24 hours with the aim of promoting anti-CDI therapy efficacy while the CDI burden was decreased during the post-FMT period (Table 1). However, due to only transient clinical improvement within 48 hours of the initial FMT (on day 10), vancomycin dosing was increased back to 250 mg every 6 hours (Table 1). Because CDI symptoms persisted, all antibiotics were discontinued (with close monitoring) 10 hours prior to the second FMT on day 11, and the method of fecal microbiota delivery was changed to the colonoscopic route (Table 1). Clinical stability was achieved within hours after the second inpatient colonoscopic FMT, so all antibiotics remained on hold at discharge. When gastrointestinal symptoms recurred at 1 week post discharge, consecutive repeat FMTs were completed on days 11 and 12 in the outpatient setting. This treatment approach was based on the patient's clinical deterioration after discharge and the presence of pseudomembranes visualized during colonoscopic FMT. After 2 outpatient FMTs, the patient's symptoms resolved to baseline over the following weeks. His diet was advanced to solid food, his appetite returned, and abdominal cramping, pain, and distention dissipated.

More studies investigating the ideal timing of initiation and discontinuation of CDI-directed antimicrobial therapy surrounding FMT, ideal timing and formulations of bowel preparations for FMT, optimal formulation and route of FMT, timing and number of early and repetitive FMTs, and the role of early FMT in therapy for severe, refractory CDI are needed. Studies to elucidate the long-term implications of transplanting foreign gut microbiota are still warranted, but the use of early, repeat FMT resulted in extraordinary clinical improvement and sustained clinical cure in the case reported here. This case report describes novel timing of antimicrobial dosing and de-escalation surrounding FMT and the utility of early, repeat FMT during the initial presentation of severe *C. difficile* colitis refractory to antimicrobial therapy.

Conclusion

FMT is a promising option for initial treatment in cases of severe, refractory *C. difficile* colitis after failure of guideline-directed antimicrobial therapy. For patients with clinical instability and increased disease burden, it may be appropriate to perform early FMT without suspending antibiotics or shortening the duration of antibiotic cessation prior to FMT. It may also be advisable to attempt indefinite antimicrobial cessation following FMT and repeat FMT as the patient's clinical status necessitates. Although not without risk, FMT for initial treatment in the setting of severe, refractory CDI may provide a viable, life-saving option for patients with *C. difficile* colitis.

Disclosures

The author has declared no potential conflicts of interest.

References

1. Centers for Disease Control and Prevention. FAQs for clinicians about *C. diff.* Published March 27, 2020. Accessed April 12, 2020. https://www.cdc.gov/cdiff/clinicians/faq.html

2. 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.* 2018;66(7):e1-e48. doi:10.1093/cid/cix1085

3. American Society of Health-System Pharmacists. Clinical updates focusing on prevention, treatment and recurrence of *Clostridium difficile* infection. ASHP Advantage. Published 2019. Accessed May 24, 2019. https://www.ashpadvantage.com/cdiff/enewsletter.php

4. Deshpande A, Pasupuleti V, Thota P, et al. Community-associated *Clostridium difficile* infection and antibiotics: a meta-analysis. *J Antimicrob Chemother.* 2013;68(9):1951-1961. doi:10.1093/jac/dkt129

5. Brown KA, Khanafer N, Daneman N, Fisman D. Meta-analysis of antibiotics and the risk of community-associated *Clostridium difficile* infection. *J Antimicrob Chemother.* 2013;57:2326. doi:10.1128/AAC.02176-12

6. Cammarota G, Ianiro G, Tilg H, et al; European FMT Working Group. European consensus conference on faecal microbiota transplantation in clinical practice. *Gut.* 2017;66:569-580. doi:10.1136/gutnl-2016–313017

7. Rao K, Young V. Fecal microbiota transplantation for the management of *Clostridium difficile* infection. *Infect Dis Clin North Am.* 2015;29(1):109-122. doi:10.1016/j.idc.2014.11.009

8. Kapoor S. Treatment of *Clostridium difficile* disease in patients not responding to metronidazole. *J Infect.* 2008;56:394-395. doi:10.1086/599224

9. Gonzales M, Pepin J, Frost EH, et al. Faecal pharmacokinetics of orally administered vancomycin in patients with suspected *Clostridium difficile* infection. *BMC Infect Dis.* 2010;10:363. doi:10.1186/1471-2334-10-363

10. Tauxe WM, Dhere T, Ward A, et al. Fecal microbiota transplant protocol for *Clostridium difficile* infection. *Lab Med.* 2015;46(1):e19-e23. doi:10.1309/LMCI95M0TWPDZKOD

11. OpenBiome. FMT preparations. Accessed February 27, 2020. https://www.openbiome.org/cr-fmt-preparations

12. Crow J, Davis S, Chaykosky D, et al. Probiotics and fecal microbiota transplant for primary and secondary prevention of *Clostridium difficile* infection. *Pharmacotherapy.* 2015;35(11):1016-1025). doi:10.1002/phar.1644

13. Na X, Kelly C. Probiotics in *Clostridium difficile* infection. *J Clin Gastroenterol.* 2011;45(suppl):S154-S158. doi:10.1097/MCG.0b013e31822ec787

14. Johnson S, Maziade P, McFarland L, et al. Is primary prevention of *Clostridium difficile* infection possible with specific probiotics? *Int J Infect Dis.* 2012;16:e786-e792. doi:10.1016/j.ijid.2012.06.005

15. Lagier JC, Delord M, Million M, et al. Dramatic reduction in *Clostridium difficile* ribotype 027-associated mortality with early fecal transplantation by the nasogastric route: a preliminary report. *Eur J Clin Microbiol Infect Dis.* 2015;34(8):1597-1601. doi:10.1007/s10096-015-2394-x.

16. Olsen MA, Yan Y, Reske KA, et al. Recurrent *Clostridium difficile* infection is associated with increased mortality. *Clin Microbiol Infect.* 2015;21(2):164-170. doi:10.1016/j.cmi.2014.08.017

17. Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile. N Engl J Med*. 2013;368:407-415. doi:10.1056/NEJMoa1205037

18. Hocquart M, Lagier JC, Cassir N, et al. Early fecal microbiota transplantation improves survival in severe *Clostridium difficile* infections. *Clin Infect Dis*. 2018;66(5):645-650. doi:10.1093/cid/cix762

19. Tixier EN, Verheyen E, Ungaro RC, Grinspan AM. Faecal microbiota transplant decreases mortality in severe and fulminant *Clostridioides difficile* infection in critically ill patients. *Aliment Pharmacol Ther*. 2019;50:1094-1099. doi:10.1111/apt.15526

20. Vardakas KZ, Polyzos KA, Patouni K, et al. Treatment failure and recurrence of *Clostridium difficile* infection following treatment with vancomycin or metronidazole: a systematic review of the evidence. *Int J Antimicrob Agents*. 2012;40:1-8. doi:10.1016/j.ijantimicag.2012.01.004

21. Agrawal M, Aroniadis OC, Brandt LJ, et al. The long-term efficacy and safety of fecal microbiota transplant for recurrent, severe, and complicated *Clostridium difficile* infection in 146 elderly individuals. *J Clin Gastroenterol*. 2016;50:403-407. doi:10.1097/MCG.0000000000000410

22. Cammarota G, Ianiro G, Magalini S, Gasbarrini A, Gui D. Decrease in surgery for *Clostridium difficile* infection after starting a program to transplant fecal microbiota. *Ann Intern Med*. 2015;163:487-488. doi:10.7326/L15-5139

23. Ianiro G, Valerio L, Masucci L, et al. Predictors of failure after single faecal microbiota transplantation in patients with recurrent *Clostridium difficile* infection: results from a 3-year, single centre cohort study. *Clin Microbiol Infect*. 2017;23:337.e1-337.e3. doi:10.1016/j.cmi.2016.12.025

24. Fischer M, Sipe BW, Rogers NA, et al. Faecal microbiota transplantation plus selected use of vancomycin for severe-complicated *Clostridium difficile* infection: description of a protocol with high success rate. *Aliment Pharmacol Ther*. 2015;42:470-476.doi:10.1111/apt.13290

25. Weingarden AR, Hamilton MJ, Sadowsky MJ, Khoruts A. Resolution of severe *Clostridium difficile* infection following sequential fecal microbiota transplantation. *J Clin Gastroenterol*. 2013;47:735-737. doi:10.1097/MCG.0b013e31829004ae

26. Fischer M, Sipe BW, Cheng YW, et al. Fecal microbiota transplant in severe and severe-complicated *Clostridium difficile*: a promising treatment approach. *Gut Microbes*. 2017;8:289-302. doi:10.1080/19490976.2016.1273998

27. Eiseman B, Silen W, Bascom GS, Kauvar AJ. Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis. *Surgery*. 1958;44:854-859. PMID:13592638.

28. Cammarota G, Masucci L, Ianiro G, et al. Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent *Clostridium difficile* infection. *Aliment Pharmacol Ther*. 2015;41:835-843. doi:10.1111/apt.13144

29. Ianiro G, Masucci L, Quaranta G, et al. Randomised clinical trial: faecal microbiota transplantation by colonoscopy plus vancomycin for the treatment of severe refractory *Clostridium difficile* infection—single versus multiple infusions. *Aliment Pharmacol Ther*. 2018;48:152-159. doi:10.1111/apt.14816

30. Brandt LJ, Borody TJ, Campbell JB. Endoscopic fecal microbiota transplantation: "first-line" treatment for severe *Clostridium difficile* infection? *J Clin Gastroenterol*. 2011;45(8):655-657. doi:10.1097/MCG.0b013e3182257d4f

31. Borody TJ, Warren E, Leis S, et al. Bacteriotherapy using fecal flora: toying with human motions. *J Clin Gastroenterol*. 2004;38:475-483. doi:10.1097/01.mcg.0000128988.13808.dc

32. US Food and Drug Administration. FDA In brief: FDA warns about potential risk of serious infections caused by multi-drug resistant organisms related to the investigational use of fecal microbiota for transplantation. Published June 13, 2019. Accessed April 12, 2020. http://www.fda.gov/news-events/fda-brief/fda-brief-fda-warns-about-potential-risk-serious-infections-cuased-multi-drug-resistant-organisms

33. US Food and Drug Administration. Fecal microbiota for transplantation: safety alert – risk of serious adverse events likely due to transmission of pathogenic organisms. Published March 12, 2020. Accessed April 11, 2020. https://www.fda.gov/safety/medical-product-safety-information/fecal-microbiota-transplantation-safety-alert-risk-serious-adverse-events-likely-due-transmission

34. Center for Biologics Evaluation and Research, US Food and Drug Administration. Guidance for industry enforcement policy regarding investigational new drug requirements for use of fecal microbiota for transplantation to treat *Clostridium difficile* infection not responsive to standard therapies. Published July 2013. Accessed April 11, 2020. https://www.fda.gov/media/86440/download

35. Jang M, Hwan J, Jung S, Park K. Refractory *Clostridium difficile* infection cured with fecal microbiota transplantation in vancomycin-resistant *Enterococcus* colonized patient. *Intest Res*. 2015;13(1):80-84. doi:10.5217/ir.2015.13.1.80