Current challenges in the treatment of severe *Clostridium difficile* infection: early treatment potential of fecal microbiota transplantation

Ther Adv Gastroenterol
2017, Vol. 10(4) 373–381
DOI: 10.1177/1756283X17690480

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Abstract
Fecal microbiota transplantation (FMT) is a very effective treatment for recurrent *Clostridium difficile* infection (CDI). Less is known about the application of FMT as a curative treatment of severe or complicated CDI. In this review, we present and discuss evidence supporting the curative use of FMT in severe or complicated CDI. We performed a literature search in PubMed and Embase for studies on the curative use of FMT in severe or complicated CDI. In addition, we describe a patient with severe CDI not responding to initial antibiotic treatment, who was successfully treated with curative FMT. We found 23 reports (12 case reports; 11 case series) about FMT as treatment for severe or complicated CDI. The patients described all had severe or complicated CDI, did not respond to conventional CDI antibiotic treatment and received FMT as last resort treatment. Patients were treated with (sequential) FMT, whether or not followed by additional antibiotic treatment for CDI. FMT, with or without additional antibiotic CDI treatment, appears to be a promising curative treatment option in patients with severe and complicated CDI, or only complicated CDI, who do not respond sufficiently to conventional antibiotic treatment. Treatment with FMT should be considered in these patients before proceeding to emergency bowel surgery.

Keywords: colectomy, fecal microbiota transplantation (FMT), gut microbiota, severe and complicated *Clostridium difficile* infection (CDI), treatment

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Introduction

Since the early 2000s, the incidence and severity of *Clostridium difficile* infection (CDI) has increased dramatically, in part due to the emergence of the more virulent B1/NAP1/027 strain, but also due to host factors. The infection related mortality and all-cause mortality associated with CDI is 5% and 15–20% respectively [Feuerstadt *et al.* 2014; Lofgren *et al.* 2014; Van Beurden *et al.* 2016a]. Disruption of the normal intestinal microbiota (mostly by the use of antibiotics) is a key factor in the pathogenesis of CDI, leading to a decrease in diversity, which enhances *C. difficile* overgrowth and subsequent infection [Chang *et al.* 2008; Song *et al.* 2013]. Even antibiotics used for treatment of CDI are able to influence the balance of the gut microbiota [Louie *et al.* 2009; Bassis *et al.* 2014]. A decrease in the diversity of the intestinal microbiota is detectable within days of the start of antibiotics.

A major challenge in the management of CDI is the high recurrence rate. After an initial episode of CDI, 20–25% of patients develop a recurrent infection [Johnson, 2009]. Treatment of recurrent

CDI can effectively be achieved by the instillation of stools from a healthy donor, after initial antibiotic treatment of CDI [Van Nood *et al.* 2013]. This so called fecal microbiota transplantation (FMT) restores the disrupted intestinal microbiota, resulting in colonization resistance, which prevents germination of residual spores of *C. difficile*. The observation that the gut microbiota of the recipient resembles that of the donor indicates that the donors' microorganisms are capable of restoring the structure and function of the gut microbiota of the patient [Khoruts *et al.* 2010].

Originally, FMT was conceived as a curative treatment modality by Eiseman and colleagues in 1958, who first reported successful FMT via enema in four patients with severe pseudomembranous colitis (PMC) due to CDI [Eiseman *et al.* 1958]. However, to date, FMT is mainly used as a treatment strategy to avoid another recurrence of CDI after primary antibiotic therapy. Less is known about the application of FMT as curative treatment in the case of poorly controlled refractory CDI, with ongoing colitis and systemic inflammatory response. Yet, the curative potential of FMT in such a setting has high clinical relevance, because 3–10% of patients with CDI develop severe life-threatening disease requiring colectomy in up to 30% of patients [Neal *et al.* 2011]. A feared complication of severe CDI is the occurrence of a toxic megacolon, with a reported mortality rate between 30% and 80% [Johal *et al.* 2004; Berman *et al.* 2008; Earhart, 2008; Hall and Berger, 2008]. Recently, Cammarota and colleagues showed that the frequency of surgery in patients with CDI decreased rapidly after the introduction of FMT as treatment for those patients with severe CDI [Cammarota *et al.* 2015a]. In this review, we present and discuss evidence supporting the curative use of FMT in severe or complicated CDI, to modify clinical course and prevent colectomy.

Methods

Source of data

We describe a patient with severe CDI, not responding to initial antibiotic treatment, who was successfully treated with curative FMT. In addition, we performed a literature search in PubMed and Embase for studies on the curative use of FMT in severe or complicated CDI. Only completed studies were included. Search terms, both free text and medical subject headings (MeSH), included: *Clostridium difficile* (infection/associated diarrhea), CDI, CDAD, fecal microbiota transplant, FMT, stool, infusion, installation, microbiota, bacteriotherapy, severe or fulminant or complicated/complication, pseudomembranous colitis, PMC. Variations of root words were searched alone or in combination.

Definitions

Severe CDI is defined by the appearance of a serum albumin <3 g/dl, plus either a white blood count $\geqslant$ 15,000 cells/mm^3 or abdominal tenderness [Surawicz *et al.* 2013]. Complicated CDI is defined as any of the following events attributable to CDI: intensive care unit (ICU) admission, hypotension, temperature $\geqslant$ 38.5°C, ileus, significant abdominal distension, alteration of mental status, white blood count $\geqslant$ 35,000 cells/mm^3 or $<$2000 cells/mm^3, serum lactate level $>$2.2 mmol/l, and end organ failure [Surawicz *et al.* 2013]. Refractory CDI is defined as CDI not responding to conventional treatment.

Results

Case description

A 69-year-old male was admitted to our intensive care unit from the emergency department, where he had presented with septic shock and bloody diarrhea for the last three weeks. His medical history included hypertension, cardiomyopathy, chronic obstructive pulmonary disease and a recently diagnosed laryngeal carcinoma (T3N0) for which curative treatment was planned. Until admission, he had lived independently at home. Two months before admission, he had used amoxicillin/clavulanic acid as treatment for laryngitis. On admission, he had a confused mental state, hypotension of 77/28 mmHg, a temperature of 35.6°C and diffuse abdominal tenderness on physical examination. Laboratory tests showed increased inflammation parameters (leucocytes 38.9 $\times$ 10^9/l; C-reactive protein 318 mg/l), renal insufficiency (creatinine 534 umol/l), a low albumin (23 g/l) and a normal lactate (1.6 mmol/l). Upon admission, treatment was started with broad-spectrum antibiotics. An abdominal CT-scan showed diffuse colonic wall thickening with a mucosal enhancement pattern and infiltration, suspect for colitis. *C. difficile* was isolated

from a stool sample (PCR-ribotype 001). With a diagnosis of severe CDI, antibiotic treatment was switched to oral vancomycin in combination with metronidazole intravenously. This did not result in clinical improvement and after nine days of therapy, the patient was still dependent of vasopressor support, and developed progressive abdominal distension, delirium and metabolic acidosis. A surgical consultation followed to explore the possibility of colectomy. At the same time, the curative potential of FMT was considered. After weighing the options, a decision was made to treat the patient with FMT, which was delivered through a nasoduodenal tube, 12 days after admission. One day before FMT, both vancomycin and metronidazole were stopped. However, because of his poor clinical condition and the ensuing risk of not treating his severe CDI with antibiotics on the day before FMT, the decision was made to continue antibiotic treatment with oral fidaxomicin, starting the day before FMT, and to continue this treatment during and after FMT. From the fourth day after FMT, the patient started to improve clinically, with a marked decrease in abdominal distension. Feces polymerase chain reactions were negative for *C. difficile* on days three and 12 after FMT. Fidaxomicin was continued until nine days after FMT. The patient could be discharged from the ICU 14 days after FMT. He did not develop recurrent CDI, despite several antibiotic treatments post FMT for various indications.

Literature review

The initial search strategy for FMT in severe or complicated CDI yielded 792 publications. Of those, 762 were excluded after screening titles and abstracts. Subsequently, 30 papers were retrieved in full text and of these, 23 studies met our eligibility criteria.

We found 12 case reports and 11 case series about FMT as treatment for severe or complicated CDI (Table 1).

Case reports

Twelve case reports have been published where fulminant colitis was treated with FMT via enema, colonoscopy or a nasoduodenal/nasojejunal tube (Table 1). The patients described all had severe or complicated CDI, and received FMT as a last resort treatment. Prior to FMT, nine cases had been refractory to conventional antibiotic treatment with vancomycin (orally or via enema) and metronidazole (orally or intravenously) or either vancomycin or metronidazole by themselves; one case had not responded to intravenous fluids and oral *Lactobacillus* [Fenton *et al.* 1974]; one case had not responded to treatments with either metronidazole, vancomycin, fidaxomicin, tigecycline, rifaximin or immunoglobulins [Neemann *et al.* 2012]; and one case had not responded to metronidazole, vancomycin, rifaximin, ceftriaxone or probiotics [Berro *et al.* 2016]. In 11 of the 12 described case reports, resolution of diarrhea and cure of CDI was achieved after FMT. In three patients, antibiotic CDI therapy was continued after FMT [Trubiano *et al.* 2013; Pecere *et al.* 2015; Jeon *et al.* 2016]. One patient developed a recurrence 47 days after FMT, which was successfully treated with vancomycin [Marcos *et al.* 2015].

Case series

Eiseman and colleagues first reported successful FMT via enema in four patients with severe PMC due to CDI [Eiseman *et al.* 1958]. All patients were refractory to conventional antibiotic CDI therapy. More than 50 years later, Yoon and colleagues treated 12 patients with refractory CDI with FMT. Pretreatment regimens included metronidazole and vancomycin in all patients, and nitazoxanide ($n = 3$), rifaximin ($n = 4$), cholestyramine ($n = 4$), *Lactobacilli* ($n = 4$) or *Saccharomyces boulardii* ($n = 7$) in a subset of patients. CDI therapy was stopped before FMT. All patients experienced a durable clinical response to FMT (follow-up three weeks to eight years). Information on mortality was missing [Yoon *et al.* 2010].

Weingarden and colleagues treated four patients with FMT for severe CDI that was refractory to antibiotic therapy. PMC was present in all cases. In the first two patients, CDI treatment with antibiotics was stopped before FMT. They showed an impressive but unsustained improvement after a single FMT: one patient underwent subtotal colectomy five days post FMT because of the return of symptoms and signs of CDI, and one patient developed a post-FMT recurrence and was retreated with vancomycin followed by a second FMT. Because of their experience with the first two patients, they (successfully) treated a third patient with FMT, followed by 12 days of

Table 1. Studies about curative fecal microbiota transplantation in patients with severe or complicated *Clostridium difficile* infection.

Study	Indication	Number of patients	Delivery route	Cure rate
[Eiseman *et al.* 1958]	PMC	4	Enema	100%
[Fenton *et al.* 1974]	PMC	1	Enema	100%
[Bowden *et al.* 1981]	PMC	16	Enema ($n = 15$); enteric tube ($n = 1$)	81%
[You *et al.* 2008]	Fulminant CDI	1	Enema	100%
[Yoon *et al.* 2010]	rCDI	12 PMC in 3 patients	Colonoscopy	100%
[Gallegos-Orozco *et al.* 2012]	PMC	1	Colonoscopy	100%
[Neemann *et al.* 2012]	sCDI	1	Nasojejunal tube	100%
[Trubiano *et al.* 2013]	sCDI	1	Gastroscopy	100%
[Weingarden *et al.* 2013]	sCDI, PMC	4	Colonoscopy	50%
[Fischer *et al.* 2015]	sCDI and/or cCDI	sCDI: 10 sCDI/cCDI: 19 PMC in 21 patients	Sequential FMT via colonoscopy with the need for repeat FMT and continued vancomycin guided by clinical response and pseudomembranes at colonoscopy	sCDI: 1 FMT: 70% 2 FMTs: 30% Overall cure rate: 100% cCDI 1 FMT: 47% 2 FMT: 42% 3 FMT: 11% Overall cure rate: 89%
[Marcos *et al.* 2015]	sCDI	1	Nasoduodenal tube	Recurrence 47 days post-FMT (toxin test positive, no symptoms). Successful treatment with vancomycin.
[Pecere *et al.* 2015]	sCDI, PMC	1	Sequential fecal infusions (3 times) via colonoscopy in combination with fidaxomicin until the last FMT	100%
[Wang *et al.* 2015]	Severe PMC in a 13 month old boy	1	Nasojejunal tube	100%
[Zainah *et al.* 2015]	sCDI	14	Nasogastric tube	79%
[Agrawal *et al.* 2015]	sCDI and cCDI	sCDI: 45 cCDI: 12	Varied across institutions: duodenoscopy ($n = 13$), push enteroscopy ($n = 3$), colonoscopy ($n = 118$), sigmoidoscopy ($n = 9$), enema ($n = 3$)	sCDI: 91% cCDI: 66%
[Aroniadis *et al.* 2015]	sCDI and/or cCDI	17	Varied among institutions: nasoduodenal tube, enema, sigmoidoscopy, colonoscopy	88.2%
[Cammarota *et al.* 2015b]	PMC	7	Repeated fecal infusions via colonoscopy every 3 days until resolution colitis	Single FMT ($n = 2$): 0% Repeated FMT ($n = 5$): 100%
[Asonuma *et al.* 2016]	PMC	1	Colonoscopy	100%
[Berro *et al.* 2016]	PMC	1	Gastroscopy	100%

Table 1. (Continued)

Study	Indication	Number of patients	Delivery route	Cure rate
[Gweon *et al.* 2016]	rCDI or sCDI, PMC	rCDI: 5 sCDI: 2 PMC in 5 patients	Upper GI tract route	71%
[Jeon *et al.* 2016]	sCDI, PMC	1	Nasoenteric tube	100%
[Shin *et al.* 2016]	PMC	1	FMT via colonoscopy, followed by tapered regimen of vancomycin for one month	100%
[Fischer *et al.* 2016]	sCDI and/or cCDI	sCDI: 25 sCDI/cCDI: 17	Single FMT via nasogastric tube, sigmoidoscopy, or colonoscopy.	sCDI: 28% sCDI/cCDI: 47%

PMC: pseudomembranous colitis.
FMT: Fecal Microbiota Transplantation.
rCDI: refractory *Clostridium difficile* infection.
sCDI: severe *Clostridium difficile* infection.
cCDI: complicated *Clostridium difficile* infection.

fidaxomicin, followed by a second FMT. The fourth patient was also treated with FMT, followed by fidaxomicin. However, this patient refused second FMT, developed fulminant CDI, and elected comfort care in a hospice [Weingarden *et al.* 2013].

Fisher and colleagues found that especially patients with severe CDI accompanied with PMC tended to respond poorly to single FMT. They developed a protocol for treatment of severe and complicated CDI consisting of FMT, followed by vancomycin therapy for patients with pseudomembranes at the time of FMT, followed by a second FMT for patients without clinical response during vancomycin treatment. If pseudomembranes were still present at the time of the second FMT, treatment with vancomycin was continued. Following this protocol, 29 patients with severe CDI unresponsive to antimicrobial therapy (oral vancomycin, fidaxomicin, rectal vancomycin in patients with ileus, in combination with or without metronidazole intravenously) were treated, achieving an overall positive treatment response of 93% [Fischer *et al.* 2015].

In a retrospective study, Zainah and colleagues reported the outcome of 14 patients treated with FMT via nasogastric tube for severe CDI refractory to conventional treatment (metronidazole and vancomycin). PMC was present in 7% of the patients. Antibiotic CDI therapy was stopped before FMT in all patients. Ten of 14 patients (79%) were cured by FMT, the other 4 patients (29%) died within 30 days after FMT. None of the deaths were related to CDI or FMT (Hodgkin's lymphoma, uterine carcinoma, ovarian cancer and glioblastoma multiforme, respectively). In a randomized clinical trial by Cammarota and colleagues, comparing FMT with vancomycin for CDI, seven patients were diagnosed with PMC [Cammarota *et al.* 2015b]. The first two patients with PMC were treated with single FMT. However, they developed a recurrence within a week after FMT. Because of their experience with the first two patients, the authors changed their protocol, offering multiple FMTs (until resolution of colitis, without additional antibiotic treatment) to those patients with PMC. Following this protocol, five consecutive patients with PMC were successfully treated. All patients received three days of pretreatment with vancomycin and full bowel lavage.

With regard to FMT treatment in severe or complicated CDI, Agrawal and colleagues recently published the largest multicenter retrospective case series to date, comprising patients with recurrent (n = 89), severe (n = 45) or complicated CDI (n = 12), treated with FMT [Agrawal *et al.* 2015]. At the time of FMT, all patients were unresponsive to conventional therapy with vancomycin, metronidazole,

fidaxomicin and probiotics. Information on the presence of pseudomembranes was not reported. They found a cure rate of 41 out of 45 (91%) in patients with severe CDI, and 8 out of 12 (66%) in patients with complicated CDI. Ten patients died between 19 days and 7 months after FMT as a result of unrelated causes, including cancer ($n = 3$), stroke ($n = 1$), pneumonia ($n = 1$), advanced Alzheimer disease ($n = 1$) and decompensated heart failure ($n = 4$). With regard to mortality, the authors did not differentiate between patients treated for recurrent, severe or complicated CDI.

Aroniadis and colleagues performed a multicenter follow up study on the use of FMT for severe CDI, complicated CDI, or both. In their total cohort of 17 patients, two had severe CDI, two had complicated CDI, and 13 had severe and complicated CDI. At the time of FMT, all patients were unresponsive to conventional treatment with vancomycin and metronidazole. In addition, fidaxomicin was attempted in three patients, tigecycline in two patients and rifaximin in one patient. Fifteen patients were cured after a single FMT, yielding a primary cure rate of 88.2%. Four patients received antibiotics for CDI after FMT, two immediately after FMT (one patient vancomycin, one patient fidaxomicin), and the other two at a later date, because of *C. difficile* negative diarrhea. These two patients received a second FMT, which was successful in one patient, yielding a secondary cure rate of 94.1%. Gweon and colleagues described their experience with FMT in seven elderly patients in poor medical condition with refractory ($n = 5$) or severe complicated ($n = 2$) CDI. PMC was observed in five patients. CDI antibiotic treatment was stopped before FMT in all patients. Two patients developed a recurrent infection 90 and 130 days post-FMT, respectively, which was successfully treated with a second FMT. Another recent study by Fischer and colleagues aimed to identify risk factors associated with FMT failure [Fischer *et al.* 2016]. In total, the authors treated 328 CDI patients with FMT, of whom 42 patients had been diagnosed with severe, or complicated CDI. Of these 42 patients, only 15 were cured, yielding a primary cure rate of 36%. They identified the severity of CDI as an independent predictor of early FMT failure. Information on pretreatment, mortality, or additional treatment with antibiotics was missing.

Discussion

Based on this literature review, FMT with or without additional antibiotic CDI treatment, seems to be a promising curative treatment option in patients with severe, or complicated CDI, who do not respond to conventional antibiotic treatment. In addition, FMT could and perhaps should be considered before proceeding to surgery.

Current treatment guidelines suggest metronidazole for mild to moderate CDI, and oral vancomycin (or, in case of ileus, rectal vancomycin) with or without metronidazole intravenously for severe, or complicated disease [Cohen *et al.* 2010]. When antibiotic treatment is not sufficient in severe or complicated CDI, a subtotal colectomy is indicated. An effective surgical alternative may be a diverting loop ileostomy in combination with colonic lavage, followed by antegrade intracolonic treatment with vancomycin [Neal *et al.* 2011]. However, studies show that surgical treatment for fulminant CDI is associated with a mortality rate ranging from 11% to 57%, indicating that this treatment is far from perfect [Dallal *et al.* 2002; Koss *et al.* 2006; Butala and Divino, 2010; Neal *et al.* 2011].

All described patients in this review were unresponsive to conventional CDI therapy with antibiotics, probiotics or a combination of the two at the time of FMT. Surgery was considered in a large number of patients because of the severity of CDI. Although data on mortality were not available in all studies, the existing case data suggest that FMT decreases the mortality rate associated with severe CDI, and that FMT could be considered in patients with severe CDI unresponsive to conventional antibiotic treatment, before proceeding to surgery. This is supported by data showing that the frequency of surgical intervention in patients with severe CDI decreased rapidly after the introduction of FMT [Cammarota *et al.* 2015a]. Recently, research has shown that patients with severe CDI at diagnosis had a lower fecal microbiota diversity compared with those without severe disease, which supports the role of FMT in the treatment of severe or complicated CDI [Seekatz *et al.* 2016]. Although the available data suggest that FMT is a safe treatment in severe CDI, we should be aware that FMT needs to be performed cautiously because of the patient's serious medical condition. In every patient the ideal route of delivery should be

assessed. Although administration through colonoscopy has the advantage of visibility of relevant pathology, this delivery method carries the risk of perforation, especially in patients with severe or complicated CDI [Patel *et al.* 2013; Potakamuri *et al.* 2013]. On the other hand, regurgitation of donor feces with subsequent aspiration pneumonia has been described in patients treated with FMT via a nasoduodenal tube [Gweon *et al.* 2016; Van Beurden *et al.* 2016b].

Interestingly, it has been suggested that additional antibiotic CDI treatment after FMT, followed by a second FMT, may improve outcomes in patients with severe CDI [Borody and Khoruts, 2012; Weingarden *et al.* 2013; Fischer *et al.* 2015]. Using this protocol, Fischer and colleagues achieved a cure rate of 93%, which is higher than after treatment with single FMT. Our patient with refractory CDI was also successfully treated with FMT, followed by fidaxomicin. We had a preference for the narrow antibiotic spectrum of fidaxomicin, which has been shown to result in less negative influence on the precarious balance of the gut microbiota compared with vancomycin [Louie *et al.* 2010]. However, in most case reports and case series, the cases responded to single FMT without additional antibiotic treatment, suggesting that a combined treatment is not necessary in all patients. More research is needed to determine the additional value of sequential FMTs followed by antibiotic treatment, especially in relation to the presence or absence of PMC.

An important barrier of FMT includes the limited time window to recruit and screen a suitable donor and prepare the material. Public stool banks like OpenBiome®, and the Netherlands Donor Feces Bank (NDFB) greatly simplify the logistics of FMT, which is key for urgent FMTs for severe or complicated CDI.

In conclusion, this review shows that (sequential) FMT whether or not followed by additional antibiotic treatment for CDI, does have the potential to eradicate infection with *C. difficile* and avoid bowel surgery in uncontrolled (pseudomembranous) colitis. Further research should focus on microbiome profiling to navigate mechanistic insights, especially the impact of additional antibiotic treatment after FMT. In addition, data on mortality rates of FMT for severe or complicated CDI should be compared with those after surgery.

In the meantime, in case of severe or complicated CDI unresponsive to conventional treatment, a practical approach would be to actively consider FMT, and to weigh the decision whether or not to continue antibiotic CDI treatment on an individual basis, depending on the clinical condition of the patient.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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