Treatment of recurrent Clostridioides difficile infections with faecal microbiota transplantation: peri-procedural methods in a consecutive case series

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Abstract

***Background*: Faecal microbiota transplantation (FMT) has high efficacy against recurrent Clostridioides difficile infection (CDI). Despite the increasing use of this therapy, the delay between diagnosis and treatment is excessive. Furthermore, donor selection is an important and time-consuming process.**

***Methods*: We reviewed patients who underwent FMT for recurrent CDI at the CHU Charleroi Hospital between 2015 and 2022. The general context, type of administration, adverse events, and donor selection were reported. FMT was conducted using gastroduodenoscopy, colonoscopy, and enema with either fresh or frozen material.**

***Results*: Ten patients with multiple comorbidities were treated by FMT. Seven patients were cured after one procedure. One patient was successfully cured after a change to an unrelated donor, and preliminary efficacy was established.**

***Conclusions*: FMT is an effective treatment that should be considered during the earlier phases of treatment. Stool donors should be thoroughly screened for infectious diseases and other criteria related to microbiota composition.** (Acta gastroenterol. belg., **2023,** 86, **486-489**).

Keywords: Faecal microbiota transplantation, Clostridium difficile, microbiota

Introduction

Recurrent *Clostridioides difficile* infection (rCDI) is a burdensome disease, defined as the recurrence of symptoms within 8 weeks after treatment completion (1,2). Guidelines recommend the use of faecal microbiota transplantation (FMT) after three episodes of *Clostridioides difficile* infection (CDI) (3). FMT is a highly effective treatment option for managing rCDI, as confirmed in a recent meta-analysis. The protocol for donor screening is based on age, pre-existing comorbidities, and microbiological analysis (4). Stool banks and registries of FMT are recommended to ease and improve the safety of the procedure; however, these measures have not yet been implemented in Belgium.

Methods

Conventional treatments for CDI failed in all patients, and all of them presented recurrent symptoms corresponding to an rCDI diagnosis. CDI was detected either by an enzymatic immunoassay (EIA) targeting *C. difficile* toxin or by polymerase chain reaction (PCR) for *C. difficile* toxin gene.

Donors were selected from among the patients' relatives who were under 65 years and had to fill out a self-screening questionnaire on behaviours associated with potentially transmissible infections and dysbiosis. Donor candidates were excluded if they had received antibiotics or travelled outside Europe 3 months before donation. The microbiological analysis performed in the donor screening is described in Table 1. Additional analyses were performed in the recipient patients to establish the serological immune status concerning Epstein-Barr virus and Cytomegalovirus. On the donation day, the donor was again questioned about the issues related to exclusion criteria.

Given the procedure's negative connotation, psychological consultation was suggested.

Written informed consent was obtained from the patients or their relatives (if the patient could not sign) and from the donor.

A practitioner prepared the suspension for FMT within 6 hours of stool donation. The faecal material was mixed in a blender with NaCl 0.9% isotonic solution to reach an appropriate consistency for administration. The mixture was filtered, and an additional isotonic solution was added if necessary. The FMT suspension was transferred to a ready-to-use 60 ml syringe, in which 10% glycerol was added for freeze storing at -80 °C .

When the upper route was chosen for FMT administration, 40 mg of omeprazole was administered the evening before the procedure, and prokinetics were administered on the day of the procedure. All antibiotics were stopped 2 days before the procedure, and the patients were clinically examined. The route of administration was discussed with the endoscopy team that considered the risk of adverse events and the will of the patient. For the upper route, a gastrointestinal endoscopy was performed under general anaesthesia. FMT preparation was delivered through the scope, as far as possible in the

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Table 1

Pathogen screening of donor		
Blood	Stool	Swab
Treponema pallidum antibodies (VDRL), Hepatitis A IgM Hepatitis B (HBsAg and HBcAb) Hepatitis C antibody HIV-1 and HIV-2 antibodies Ebstein Barr virus IgM and IgG Cytomegalovirus IgM and IgG *Strongyloides stercoralis* IgG	*Clostridioides Difficile* PCR Enteropathogenic bacteria by standard stool culture and/or PCR Parasites Blood *Helicobacter Pylori* faecal antigen (if FMT by upper way)	Multi-drug resistant bacteria (MRSA, CPE and ESBL) COVID-19 PCR considering the pandemic situation

duodenum or after the Treitz angle. After the procedure, the patient was positioned upright at 45° until the end of the procedure to minimize the risk of aspiration. For the lower gastrointestinal route, the patient received a bowel preparation as for a standard colonoscopy.

Patients were observed for 6 hours after the procedure. Loperamide 2 mg was used on the day of the procedure and the day after to prolong the retention of the faecal suspension in the colon. The resolution of rCDI was acknowledged based on the absence of diarrhoea for 8 weeks. The clinical state of the patient was monitored at 3 and 6 months.

The entire procedure was performed according to the guidelines of the Superior Health Council of Belgium (4).

Results

In our case series, 10 patients were treated with FMT between 2015 and 2022. Clinical data of treated patients and the FMT procedure details are described in Table 2. The median number of CDI episodes treated before FMT was 3 [range: 3–4], and the median number of months between the diagnosis of CDI and FMT administration was 5 [range: 4–6.75]. Seven patients were cured after one FMT, two after two FMT, and one after four FMT. We observed a complete recovery after the first FMT in 70% of the patients. Follow-up showed no recurrence at 6 months post-FMT, and no significant adverse events were reported.

Two patients are described below to define a strategy after an eventual therapeutic failure:

The first was a 51-year-old woman with no significant disease except anxiodepression. She developed CDI after a single course of ciprofloxacin. Seven episodes of CDI were unsuccessfully treated with metronidazole and vancomycin. She was referred to us for FMT 11 months after the first CDI episode. She had no family members eligible for stool donation. One of her friends fulfilled the inclusion criteria and accepted to participate in the procedure. After only one administration conducted through the upper gastrointestinal tract, the patient recovered from CDI. During follow-up, we observed the disappearance of diarrhoea but the persistence of occasional crampoid abdominal pain.

The second patient was a 60-year-old man displaying neurological symptoms after a haemorrhagic stroke. He was treated with several antibiotics for urinary and pulmonary infections during a 7-month hospitalization. After the fourth episode of CDI, an FMT was discussed, and his son-in-law was selected for the donation. Considering the patient's clinical status, two first FMTs were conducted by enema. Following another relapse, FMT was performed via gastroscopy, but the situation did not improve, and a fourth recurrence was discovered. We sought out another donor after consulting with an FMT reference centre. The donor of 'patient number 3' was contacted, and they agreed to provide material for this unrelated patient. The tests were repeated, considering the delay between the procedures. After only one procedure, performed using an enema, the symptoms of CDI disappeared.

Discussion

FMT is generally considered a treatment option only after two episodes of CDI. However, the procedure could have been initiated earlier in three cases reported in this study. The apparent cause of this delay could be attributed to ignorance or fear of the procedure among care providers. However, in our series, none of the patients or their families objected to the procedure, mainly because of the clinical distress induced by rCDI. Notably, the median delay between the first episode of CDI and FMT treatment was 5 months, which is a relatively long delay. Therefore, training healthcare professionals and extending communication with other institutions that perform FMT are encouraged (6).

The upper route was preferred for FMT administration (8/10). This choice was based on the randomized, controlled trial of FMT conducted by van Nood et al. in 2013 (6). In our case series, the primary clinical success was 70%, concurrent with the first FMT performed through the upper way (7).

Looking for an appropriate donor does not seem to be limited by safety concerns. Two patients were treated in our series with the same donor, and both responded well. The method of administration could explain the initial non-response in the 60-year-old male patient. It is possible that a fourth administration with the same donor would have resolved the situation. However, despite an upper procedure with the same donor, CDI symptoms did not improve. Another explanation for the failure to

Table 2.

Case	Age-Years	Sex	Underlying illness	Antimicrobial agents used before C.difficile infection	Atlas score	No of CDI episodes treated before FMT	Duration of CDI, in months from initial diagnosis to first FMT	Relationship to the recipient (Age)	Type of FMT	Location	Resolution (number of FMT)	Follow up at 6 months
1	92	M	Cardiopathy, dementia	Amox	6	3	4	Daughter (57)	GD	H	Complete (1)	Death from unrelated cause
2	81	M	Gastrectomy, IRC	Cefta, Amp, mero, Vm	2	3	4	Son (42)	GD	A	Complete (1)	Weight regain
3	51	F	Anxiodepression	Cpfx	0	7	11	friend* (51)	GD	A	Complete (1)	Episodic abdominal pain
4	89	F	Ischemic stroke	Amp, Pip-taz	2	3	6	Granddaughter (46)	GD	H	Complete (1)	Constipation
5	60	F	Turner syndrome, epilepsy, ss dural hematoma	Amp, Pip-taz	2	3	7	Sister (60)	GD	H	Complete (2)	Appetite regain
6	65	F	Hemodialysis Multiple myeloma	Cefta	1	3	6	Son (42)	GD	A	Complete (2)	Death from unrelated cause
7	60	M	Hemorragic stroke	Pip-taz, Amp, cefu, Cpfx	4	4	7	Son-in-law (33) volontary donor*(at 4th FMT)	Enema (1th and 2nd) GD(3th) Enema (4th)	H	Non responder (1, 2, 3th) Complete after the 4th FMT(1)	Appetite regain
8	65	M	Cardiac insufficiency, Marfan, BPCO	None	3	3	2	Son (46)	CS	H	Complete (1)	Appetite regain
9	48	F	Multiple sclerosis, RCUH	Amox, cefu, Cpfx	3	3	4	Sister (51)	GD	H	Complete (1)	Weight regain
10	77	F	stroke	None	2	4	4	Granddaughter in law (56)	GD	H	Complete (1)	Episodic abdominal pain

Abbreviations : Amox, amoxicillin ; Amp, ampicillin ; CDI, Clostridium disease infection ; Cefta, ceftazidim ; cefu, cefuroxim ; Cpfx, ciprofloxacin ; FMT, fecal microbiota transplant; Mero, meropenem ; Pip-taz, piperacillin-tazobactam; Vm, vancomycin ; CD Clostridioides Difficile ; FMT Fecal microbiota transplantation ; GD gastroduodenoscopy; CS colonoscopy; H Hospitalisation; A Ambulatory. *Same donor

respond to the first FMTs is the severity of CDI and the fact that the patient was hospitalized (8). The medical situation of the patient directed our team to a change in strategy, which is consistent with the concept of super donors mentioned in the literature (9). Some authors have even used pooled faeces samples after a failure of conventional FMT, justifying this approach as a form of 'extended' microbiota diversity (10).

In the future, analyses other than pathogen exclusion should be considered to overcome the failure of FMT treatment in the context of burdensome and costly diseases like rCDI. Concerning different FMT strategies, all variables, such as the route of administration, the medical situation of the patient, or the choice of donor, should be discussed collegially, and a precise record of these data should be noted in the corresponding medical file or a registry. Despite our limited experience, we encourage the earlier consideration of FMT as a treatment option to minimize patient suffering and hospitalization costs. We also recommend that a stool bank be established.

Conflicts of Interest

The authors declare no conflict of interest.

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