Fecal microbiota transplantation in refractory or recurrent *Clostridium difficile* infection: a real-life experience in a non-academic center

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ABSTRACT

Aim: this study aimed to describe the efficacy and safety of fecal microbiota transplantation (FMT) for the treatment of refractory and recurrent *Clostridium difficile* infection (CDI).

Methods: this was an observational study of patients with refractory or recurrent CDI treated with FMT between June 2014 and January 2017. Primary and secondary outcomes were the resolution of diarrhea without CDI recurrence within two months after one or more FMT. A descriptive analysis was performed.

Results: thirty-four FMT were performed in 28 patients, 88.2% (n = 30) using an upper route with a gastroscopy and 11.8% (n = 4) with colonoscopy; 50% (n = 17) of FMT were due to recurrent CDI and 50% (n = 17) were due to refractory CDI. The overall cure rate of upper FMT was 87.5% (21/24) and 100% (4/4) when colonoscopy was performed. A cure was achieved after one FMT in 88% (22/25) of cases and after two or more FMT in 8% (2/25) of cases, resulting in an overall cure rate of 96% (24/25). No severe adverse events were reported.

Conclusion: FMT constitutes an effective and safe approach for the management of refractory and recurrent CDI, with an overall cure rate of 96% and no reported severe adverse events.

Key words: *Clostridium difficile* infection. Fecal microbiota transplantation. Gut microbiota. Endoscopy. Antibiotics.

INTRODUCTION

*Clostridium difficile* infection (CDI) is a leading nosocomial infection and the prevalence, severity and mortality have increased over the past years due to the emergence of more virulent strains of this pathogen (1). Moreover, it is apparent that young and healthy individuals with no previous exposure to antibiotics or hospitals can also develop CDI (2,3). The standard approach for CDI is antibiotic treatment with vancomycin or metronidazole, resulting in an initial clinical response in more than 80% of patients (1,4-6). Nevertheless, recurrence rates range from 15 to 30% and these episodes are further treated with additional cycles of antibiotics. However, up to 45% and 65% will suffer a second and a third CDI recurrence, respectively (4). Antibiotics may result in intestinal dysbiosis allowing the growth of toxigenic *Clostridium difficile* strains and therefore, perpetuate CDI (1).

Fecal microbiota transplantation (FMT) appears to be a safe, highly effective and relatively inexpensive approach for refractory and recurrent CDI and is currently being tested for applications other than CDI (6). The procedure consists of an infusion of a liquid suspension of stool from a healthy individual into the gastrointestinal tract of a receptor with the aim to cure a specific pathology (4,7-9). FMT aims to restore the normal microbiota of the recipient, inducing a balance in the colonic flora and facilitating the host defense against CDI by preventing the growth of toxigenic *Clostridium difficile* strains (10-12).

The study aimed to describe the efficacy and safety of FMT for the treatment of refractory and recurrent CDI.
MATERIAL AND METHODS

A retrospective analysis was performed of a prospective database that included all patients with refractory and recurrent CDI that underwent FMT between June 2014 and January 2017 in our department. An institutional protocol was developed in order to standardize the criteria of recipients, donors and the procedure itself (13). The transplant protocol was approved by the hospital’s Ethical Committee and all patients or their legal substitutes gave written informed consent for the procedure.

Donors were unrelated volunteers selected and screened based on medical history and laboratory testing. Exclusion criteria included known or recent exposure to HIV, hepatitis B or C; high-risk sexual behavior; the use of illicit drugs; tattoo or body piercing within six months; known current communicable disease; travel within the last six months to areas with endemic diarrheal illnesses; personal history of inflammatory bowel disease, irritable bowel syndrome, idiopathic chronic constipation or chronic diarrhea, gastrointestinal malignancy or known polyposis, major gastrointestinal surgery, morbid obesity, metabolic syndrome, atopy and multiple sclerosis; antibiotics within the preceding three months and major immunosuppressive medications. Donor blood tests included syphilis, HIV, hepatitis A, B and C, and donor stool tests included Clostridium difficile toxin, bacterial culture for enteric pathogens, ova and parasites, Giardia antigen and cryptosporidium antigen (13). Patients older than 18 years with recurrent or refractory CDI and no immunosuppressive conditions were considered for FMT (13). Recurrent CDI was defined as at least three episodes of mild-moderate CDI and failure of a 6-8 week taper with vancomycin or without an alternative antibiotic, or at least two episodes of severe CDI resulting in hospitalization and associated with a significant morbidity. Refractory CDI was defined as a moderate episode that did not respond to vancomycin for at least a week or a severe episode with no response to vancomycin after 48 hours (4,13). Mild-moderate disease was defined as the presence of diarrhea without any criteria of severe or complicated CDI. Severe disease was defined as a CDI infection accompanied by hypoaalbuminemia (serum albumin < 3 g/dl) with a white blood cell count of ≥ 15,000 cells/mm³ or abdominal tenderness (14).

All patients maintained the antibiotic prescription for CDI until the day before the FMT and underwent bowel preparation with 4 l of polyethylene glycol the night before the procedure. Proton-pump inhibitor was given to the recipient the evening before and the morning of the procedure if a gastroscopy was performed. When the FMT was performed during colonoscopy, loperamide was previously administered to promote retention of the FMT (13).

FMT was initially performed using an upper route to the distal duodenum with a gastroscope, and 50 cc of a processed suspension of fresh stool from an unrelated donor collected between six to 24 hours before the procedure was instilled during the procedure. In the case of a failure of the upper route for FMT, a second FMT via a lower route was performed. In these cases, colonoscopy was performed with instillation of seven 50 cc syringes with 50 ml of a liquid suspension of stool throughout the terminal ileum and colon (cecum, ascending colon, transverse colon, descending colon and sigmoid colon), sparing the rectum to avoid fecal urgency. Cure was defined as the resolution of diarrhea attributable to CDI. The primary outcome was defined as resolution of diarrhea (cure) without recurrence of CDI within two months after only one FMT. The secondary outcome was defined as the resolution of diarrhea (cure) without recurrence of CDI within two months after two or more FMT. Recurrence was defined as a relapse of CDI symptoms after an initial resolution of diarrhea within two months after FMT. Patients with less than two months of follow-up after FMT or patients who were given antibiotics for infectious conditions other than CDI within two months after FMT were excluded from the analysis. All patients were included in a prospective database and followed-up in the outpatient clinic.

Patients were followed-up in order to monitor mild adverse events that were possibly related to FMT including abdominal pain, flatulence, vomiting, constipation, diarrhea and transient fever. The existence of other previously reported conditions that could be related to FMT were also studied, including septicemia, pneumonia, peritonitis, peripheral neuropathy, Sjogren’s disease, idiopathic thrombocytopenic purpura, rheumatoid arthritis, and inflammatory bowel disease flares.

A descriptive analysis was performed using medians, ranges and percentages. Discrete variables were compared using the Chi-squared test. The SPSS statistical package (version 20.0; IBM Corp., Armonk, New York, USA) was used for data entry and data analysis. Inferential analysis using the Wilson method was used to calculate the confidence intervals (CI) of proportions (15,16).

RESULTS

Thirty-four FMT were performed in 28 patients during the study period, 88.2% (n = 30) using an upper route with a gastroscopy and 11.8% (n = 4) with colonoscopy. The median age of the recipients was 79 years of age (interquartile range 69.3-84) and 67.9% (n = 19) were female. The characteristics of the patients are summarized in table 1.

With regard to the indications for each FMT, 41.2% (n = 14) were due to severe recurrent CDI; 8.8% (n = 3), due to mild-to-moderate recurrent CDI; 20.6% (n = 7), to severe refractory CDI; and 29.4% (n = 10), due to mild-to-moderate refractory CDI (Table 2). Of all 34 procedures, three upper FMT were excluded from the analysis due to loss of follow-up during the first two months after FMT. In addition, there was recurrence of diarrhea during the two months after FMT related to antibiotic treatment for urinary/respi-

| Table 1. Characteristics of patients who underwent FMT |
|---------------------|-----------|
| Gender (female)     | 19 (67.9) |
| Age (years, median) | 79 (69.3-84) |
| Previous ATB        | 27 (96.4) |
| Chronic PPI         | 15 (53.6) |
| NGT Feeding         | 8 (28.6) |
| ATB: antibiotics; NGT: nasogastric tube; PPI: proton-pump inhibitor. |
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The primary cure rate was 88% (22/25 of patients) and the secondary cure rate represented another 8% (2/25) in the remaining 28 patients. This resulted in an overall cure rate of 96% (24/25) with 95% CI of 0.805-0.993 (95% CI with continuity correction 0.777-0.998). One cycle of fidaxomicin was given with a subsequent resolution of diarrhea in the only patient who was not cured after several FMT. With regard to the primary outcome, cure was achieved in 11 of 12 (91.7%) patients transplanted for refractory CDI compared to 11 of 13 (84.6%) transplanted for recurrent CDI (p = 0.6). The median time to resolution of diarrhea after FMT was one day, ranging from one to two days. No adverse events were reported immediately after FMT and during follow-up.

**DISCUSSION**

In our series, FMT achieved a primary cure rate in 88% (22/25) of patients and a secondary cure rate in 8% (2/25). This resulted in an overall cure rate of 96% (24/25) for refractory and recurrent CDI. These results were similar to our previously reported data of primary, secondary and overall cure rates of 83.3% (5/6), 16.7% (1/6) and 100% (6/6), respectively (13). Our results are in line with previous reports, as well as several systematic reviews and meta-analysis showing that FMT resulted in resolution rates ranging between 81-100% for recurrent CDI and 55% for refractory CDI (1,6-8,10,17-21). Moreover, a systematic review concluded that 92% of patients had a resolution of symptoms of CDI.

**Table 2. Characteristics of FMT and CDI episodes in which FMT was performed**

<table>
<thead>
<tr>
<th></th>
<th>n (%/IQR)</th>
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<tbody>
<tr>
<td>Number of previous CDI episodes</td>
<td>0.5 (0.0-2.0)</td>
</tr>
<tr>
<td>Time from CDI to FMT (days)</td>
<td>31.5 (20.8-83.3)</td>
</tr>
<tr>
<td>Leucocytes (/μl)</td>
<td>14,555 (10,655-22,870)</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.87 (0.68-1.32)</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>2.4 (2.1-3.0)</td>
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**Indication for FMT**

- Mild-to-moderate recurrent CDI: 3 (8.8)
- Severe recurrent CDI: 14 (41.2)
- Mild-to-moderate refractory CDI: 10 (29.4)
- Severe refractory CDI: 7 (20.6)

**FMT route:**

- Upper route (gastroscopy): 30 (88.2)
- Lower route (colonoscopy): 4 (11.4)

**Cure of CDI (procedure):**

- Upper route (gastroscopy): 21 (87.5)*
- Lower route (colonoscopy): 4 (100%)

**Cure of CDI (patients):**

- 1 FMT: 24 (88%)*
- > 1 FMT: 2 (8%)

**Time from FMT to resolution of diarrhea (days):**

- 1.0 (1.0-2.0)

**Adverse events:**

- 0

CDI: *Clostridium difficile* infection; FMT: fecal microbiota transplantation. *Six patients were excluded due to a lack of follow-up or subsequent antibiotic treatment.*

**Fig. 1.** Flowchart of all FMT performed in the series of 28 patients. In the first FMT, there were 29 procedures as one patient had recurrent CDI that was successfully treated with FMT and six months later had a refractory CDI and underwent FMT again. Three patients had a follow-up of less than two months after FMT. ATB: patients with recurrence of CDI after antibiotic treatment for infections other than CDI.
89% after a single treatment and 5% after retreatment due to failure or relapse (21). Therefore, a recent European consensus on FMT advocates this procedure as a treatment option for both mild and severe recurrent CDI and also recommends this as a treatment option for refractory CDI (7). In our study, the efficacy of FMT in refractory CDI was comparable to that achieved in recurrent CDI (primary cure rate: 84.6% and 91.7%, p = 0.6). Nevertheless, the adequate time to perform FMT in recurrent CDI remains to be determined as different gastrointestinal societies have different opinions (6,14,18,22). American guidelines recommend FMT for the treatment of a third episode of CDI after failure of a pulsed/tapered vancomycin regimen (6,14,17). On the other hand, European guidelines recommend the use of FMT for a second episode of CDI (6,18,22).

Although the optimal route for the delivery of fecal microbiota remains to be determined, FMT may be performed using an upper gastrointestinal route which includes a nasogastric or nasojunal tube, upper gastrointestinal endoscopy, or using a lower gastrointestinal route with colonoscopy or retention enema (3,4,10,12,23). In our study, the overall cure rate of FMT was 87.5% when upper gastrointestinal endoscopy was used, and 100% when a lower route with colonoscopy was used. This is similar to our initial study with rates of 83.3% and 100%, respectively (13). Many systematic reviews have reported a slightly superior efficacy of FMT administered via colonoscopy, although this was not statistically significant (7,10). On the other hand, a recent systematic review reported a significantly (p = 0.015) higher cure rate for a lower gastrointestinal route (93.2%) compared to an upper gastrointestinal route (81.9%) (17). Nevertheless, a recent European consensus on FMT strongly recommended the use of FMT via colonoscopy or the upper gastrointestinal tract (7). Upper gastrointestinal endoscopy-guided FMT was the preferred route in our protocol, regardless of the severity of CDI. This was due to its simplicity compared to colonoscopy, which was reserved for patients in which upper endoscopy guided-TMF was not successful (13).

No adverse events were reported during the follow-up period in our study. FMT seemed to be safe and well tolerated with few adverse events (6). The most frequent immediate adverse events reported after FMT included abdominal pain, flatulence, vomiting, constipation, diarrhea and transient fever (6,7,9,23). Some of these symptoms are probably related to the gastric administration of the fecal microbiota. The lack of adverse events in our series may be related to the duodenal infusion. These symptoms are usually moderate and self-limited (6,17). Other reported adverse events include septicemia, pneumonia, peritonitis, peripheral neuropathy, Sjogren’s disease, idiopathic thrombocytopenic purpura, rheumatoid arthritis, and inflammatory bowel disease flares (3,17). Long-term follow-up after FMT is required in order to evaluate its safety with regard to the risk of the onset of latent infections or other diseases or conditions related to gut microbiota. These include obesity, diabetes, atherosclerosis, inflammatory bowel disease, colon cancer, irritable bowel syndrome, asthma and autism (6).

The current European consensus on FMT have defined recommendations regarding the use of large-volume bowel lavage of recipients before FMT, the appropriate time frame for the cessation of antibiotic treatment for CDI, appropriate type of stool and the relationship of the donor and the recipient (7). Our institutional protocol is in line with current recommendations even though it was developed before the European consensus. All recipients remained on the antibiotics prescribed for CDI until the day before FMT and received a large-volume bowel lavage before FMT (13). Moreover, fresh stools of unrelated donors were used in our study, which is in line with recent recommendations that acknowledge the comparable cure rates of FMT with related or unrelated donors and fresh stool or frozen stool (4,6-8,17,23).

In conclusion, FMT constitutes an effective and safe approach for the management of refractory and recurrent CDI, with an overall cure rate of 96% and with no reported severe adverse events.

The efficacy and safety of FMT in CDI has resulted in a widening of the range of possible indications of FMT for other disorders where gut microbiota dysfunction may play a role. These include inflammatory bowel disease, irritable bowel syndrome, metabolic syndrome, autoimmune and allergic diseases and neurodevelopmental disorders (3,4,24). Nevertheless, the only currently accepted indication for FMT is CDI infection (4,7). In addition, the development of other forms of FMT delivery such as capsulized frozen FMT inoculate, which can be administered orally, will obviate the need for invasive administration procedures, decreasing costs and risks related to the procedure itself (25).
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