Revista de Gastroenterología de México 89 (2024) 513–520

REVISTA DE GASTROENTEROLOGÍA DE MÉXICO
www.elsevier.es/rgmx

ORIGINAL ARTICLE

Fecal microbiota transplantation through colonoscopy in the treatment of recurrent *Clostridioides difficile*: Experience at a university center

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Received 15 February 2024; accepted 21 March 2024
Available online 10 October 2024

KEYWORDS
Clostridioides difficile;
Fecal microbiota transplantation;
Colonoscopy;
Third age;
Pregnancy

Abstract
Introduction: The majority of cases of *Clostridioides difficile* infection (CDI) respond to antibiotic treatment. Fecal microbiota transplantation (FMT) has been accepted as an effective treatment in cases of recurrent CDI.
Aim: Our aim was to describe the clinical results of FMT performed for the treatment of recurrent CDI.
Material and methods: The study was conducted on patients with recurrent CDI treated with FMT through colonoscopy, within the time frame of January 2021 and December 2023. Demographic and clinical data were collected, including pre-FMT treatment data, the FMT success rate, and clinical progression during follow-up. Telephone surveys were carried out to evaluate satisfaction.
Results: Thirteen patients with a mean age of 55 years underwent FMT (including 7 patients above 65 years of age and one pregnant woman). Patients presented with a median of 3 previous episodes of CDI (range 2-4). The median time interval from first episode of CDI to FMT was 4 months (range 3-10). The effectiveness of a single FMT session was 100%. During post-FMT follow-up (median of 11 months, range 3-32), 3 patients have presented with a new CDI episode, and a successful second FMT was performed on 2 of them. No adverse events were registered, and all patients had a positive perception of FMT.

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Conclusions: In the present study, despite its small size, FMT through colonoscopy was shown to be a safe, effective, and lasting therapy in cases of recurrent CDI, concurring with results from larger studies.
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PALABRAS CLAVE
Clostridioides difficile;
Trasplante de microbiota fecal;
Colonoscopia;
Tercera edad;
Embarazo

Trasplante de microbiota fecal mediante colonoscopia en el tratamiento de la infección por *Clostridioides difficile* recurrente: experiencia de un Centro Universitario

Resumen
Introducción: La mayoría de los casos de infección por *Clostridioides difficile* (ICD) responden tratamiento antibiótico. El trasplante de microbiota fecal (TMF) ha sido aceptado como un tratamiento efectivo en casos de ICD recurrente.
Objetivo: Describir resultados clínicos del TMF realizado para el tratamiento de la ICD recurrente.
Material y métodos: Pacientes con ICD recurrente tratados con TMF mediante colonoscopia entre enero 2021 y diciembre 2023. Se recopilaron datos demográficos y clínicos, incluyendo detalles del tratamiento previo al TMF, la tasa de éxito del TMF y la evolución clínica durante el periodo de seguimiento. Se realizaron encuestas telefónicas para evaluar la satisfacción.
Resultados: Fueron sometidos a TMF 13 pacientes (siete pacientes mayores de 65 años y una mujer embarazada) con una mediana de edad de 55 años. Los pacientes presentaron una mediana de tres episodios previos de ICD (rango 2-4). La mediana de la duración desde el primer episodio de ICD hasta el TMF fue de cuatro meses (rango 3-10). La efectividad con una sesión de TMF fue de 100%. Durante el periodo de seguimiento pos-TMF (mediana de 11 meses, rango 3-32), tres pacientes han presentado un nuevo episodio de ICD, y en dos casos se llevó a cabo con éxito un segundo TMF. No se registraron eventos adversos. Todos los pacientes tuvieron una percepción positiva del TMF.
Conclusiones: El TMF mediante colonoscopia, si bien es una serie pequeña, concuerda con estudios de mayor envergadura, como una terapia segura, efectiva y duradera en casos de ICD recurrente.
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Introduction and aims

Clostridioides difficile infection (CDI) was first described in 1978,[1] and since then, has been shown to be the primary cause of nosocomial diarrhea and the main identifiable cause of antimicrobial-associated diarrhea.[2] There has been an increase in the incidence of CDI in recent decades, associated with elevated morbidity and mortality and considerable use of healthcare resources.[3] A retrospective study showed a 43% increase in the annual incidence of CDI, between 2001 and 2012, and during that same period of time, cases of recurrent CDI increased by 188%.[4] According to the latest advisory of the Health Ministry of Chile (period 2013-2018), 1,687 cases of *Clostridioides difficile* (*C. difficile*) were diagnosed more frequently in 2015 and less frequently in 2017,[5] corroborating the reality of CDI in Chile.

Conventional treatment of CDI is based on suspending the causal antibiotic and employing enteral antibiotics, such as vancomycin, fidaxomicin, metronidazole, or rifaximin.[6,7] Despite those strategies, CDI is characterized by a high recurrence rate, at 20% after the first infection and up to 65% after the second recurrence.[8] In the setting of a second recurrence ($\geq$ 3 episodes), fecal microbiota transplantation (FMT) has been suggested, based on the alteration of the intestinal bacterial diversity in persons with recurrent CDI.[9,10] FMT consists of the administration of fecal material from a selected healthy individual into the patient with CDI, to restore the protective intestinal microbiota.[11] Studies have shown that FMT is an effective (defined as the absence of a new episode of CDI for eight weeks, post-FMT) and safe (evaluated through the presence of mild, moderate, severe, and serious adverse events) strategy. A meta-analysis that included 1,973 persons with recurrent and refractory CDI showed that FMT was more effective than treatment with vancomycin (RR: 0.23 95% CI 0.07-0.80), with clinical resolution in 92% of patients.[9] To the best of our knowledge, there is little information in Latin America about the long-term clinical results of this therapeutic strategy and its effectiveness in ''third age'' patients and pregnant women. The

aim of our study was to describe the clinical results of FMT performed through colonoscopy on adult patients with CDI, determining the percentage of success of this therapeutic strategy and the percentage of adverse events secondary to FMT carried out through colonoscopy at our university center.

Material and methods

A retrospective descriptive case series was conducted, in which the clinical records of all patients with recurrent CDI, treated with FMT through colonoscopy at the *Clínica Universidad de los Andes* between January 2021 and December 2023, were reviewed. The STROBE checklist for retrospective studies was employed. All the transplants were carried out by three of the authors (R. Quera, P. Nuñez, and C. von Muhlenbrock) at the endoscopy center of our institution, in accordance with the regulations and protocol of the gastroenterology section of the *Clínica Universidad de los Andes*.

Patients were included, according to the following criteria: a) CDI diagnosis based on the clinical presentation and confirmation of the presence of *C. difficile*, through the polymerase chain reaction (PCR) technique for toxin A and B; b) a history of two or more demonstrated episodes of recurrent CDI treated with the standard antibiotic regimen;[7] and c) clinical follow-up of at least three months, post-FMT. CDI severity was evaluated through the Hines index.[12] Post-FMT follow-up was carried out through the evaluation of the clinical records and a telephone satisfaction survey. FMT success was defined as the absence of a new episode of CDI during the eight weeks after the procedure.

Adverse events secondary to FMT were classified according to severity, into mild (no interference in daily routine: fatigue, nausea, flatulence, diarrhea, constipation, abdominal pain, bloating), moderate (effects limited to daily routine: maintained fatigue, fever, and abdominal pain), severe (bacteriemia, respiratory insufficiency, bleeding, microperforation), and serious (hospitalization, incapacity or intervention needed to prevent permanent damage and death).

FMT protocol: Each potential donor was evaluated by a gastroenterologist (R. Quera, P. Nuñez, or C. von Muhlenbrock) or infectologist (R. Espinoza), who carried out an adequate anamnesis and physical examination. The donors that met the clinical criteria underwent blood and stool analyses, as indicated by the suggestions in international guidelines.[10] The details of the exams for each donor can be seen in supplementary material No. 1. Each patient suspended treatment with oral vancomycin 24-48 hours prior to transplantation and underwent colonoscopy preparation with polyethylene glycol without electrolytes (3-4 liters). FMT was performed with a fresh stool sample from the donor (30 to 100 g), which was collected no more than 6 hours prior to transplant. To obtain the microbiota solution, the donor stools were solubilized in physiologic serum (NaCl 0.9%, 300 mL) with a blender used exclusively for FMT. Once the solution was homogeneous, it was filtered, and the supernatant was collected in 60 mL syringes. During colonoscopy, upon reaching the ileum, the solution was instilled through the working channel of the colonoscope, following a withdrawal regimen: 100 mL in the ileum, 100 mL in the cecum and ascending colon, 75 mL in the transverse colon, and the remaining 25 mL in the proximal descending colon. Before beginning the colonoscopy, and once the procedure was completed and the patient recovered from the sedation, 2 mg of loperamide were indicated, to retain the transplanted solution the longest amount of time possible. Fig. 1 summarizes the procedure.

Statistical analysis

Measures of central tendency were used for the continuous variables (age, height, weight, number of stools), according to data distribution, using the Shapiro-Wilk test. The categorical variables were described through absolute and relative frequency percentages (%). The therapeutic success of FMT was analyzed through the number of positive results, with respect to the procedures performed on the study sample. The Stata 12 statistics program was employed.

Ethical considerations

This study was approved by the Ethics Committee of the institution and the *Universidad de los Andes* (Folio CEC 2023046) and meets the ethics guidelines of the 1975 Declaration of Helsinki. All patients included in this study signed statements of informed consent for the performance of this procedure and authorized the publication of the data. The authors declare that this article contains no personal information that could identify the patients.

Results

Within the study time frame of January 2021 and December 2023, 15 FMTs were performed on 13 patients, 9 of whom were men. Median patient age was 55 years (range 21-82) at the time of FMT. Fourteen of the FMTs were carried out after two or more recurrences of CDI. The other FMT was performed after the first recurrence of CDI, as requested by the patient and his family. In 14 procedures, the patients contracted CDI after using antibiotics and in seven cases there was a history of proton pump inhibitor use during the first episode of CDI.

In 13 of the FMTs, the patients had received at least two 2-week treatment courses with metronidazole or vancomycin and at least one regimen of long-lasting vancomycin in decreasing doses or pulses. In one patient, fidaxomicin was used as treatment for a CDI episode. There was no association with rifaximin or a probiotic in any patient.

The median of CDI episodes prior to FMT was 3 (range 2-4). In two patients, CDI was severe, requiring hospitalization, and in 3 cases it was moderate. The median time interval from the first CDI episode and the performance of FMT was four months (range 3-10). The donor was a direct relative in 10 procedures. The median stool volume utilized in the transplantations was 85 g (range 35-100). Findings during colonoscopy included colonic erosions in the patient with Crohn's disease and diverticula in three other patients. No pseudomembranes were found in any of the procedures. Effectiveness after FMT was 100% and all patients had a clin-

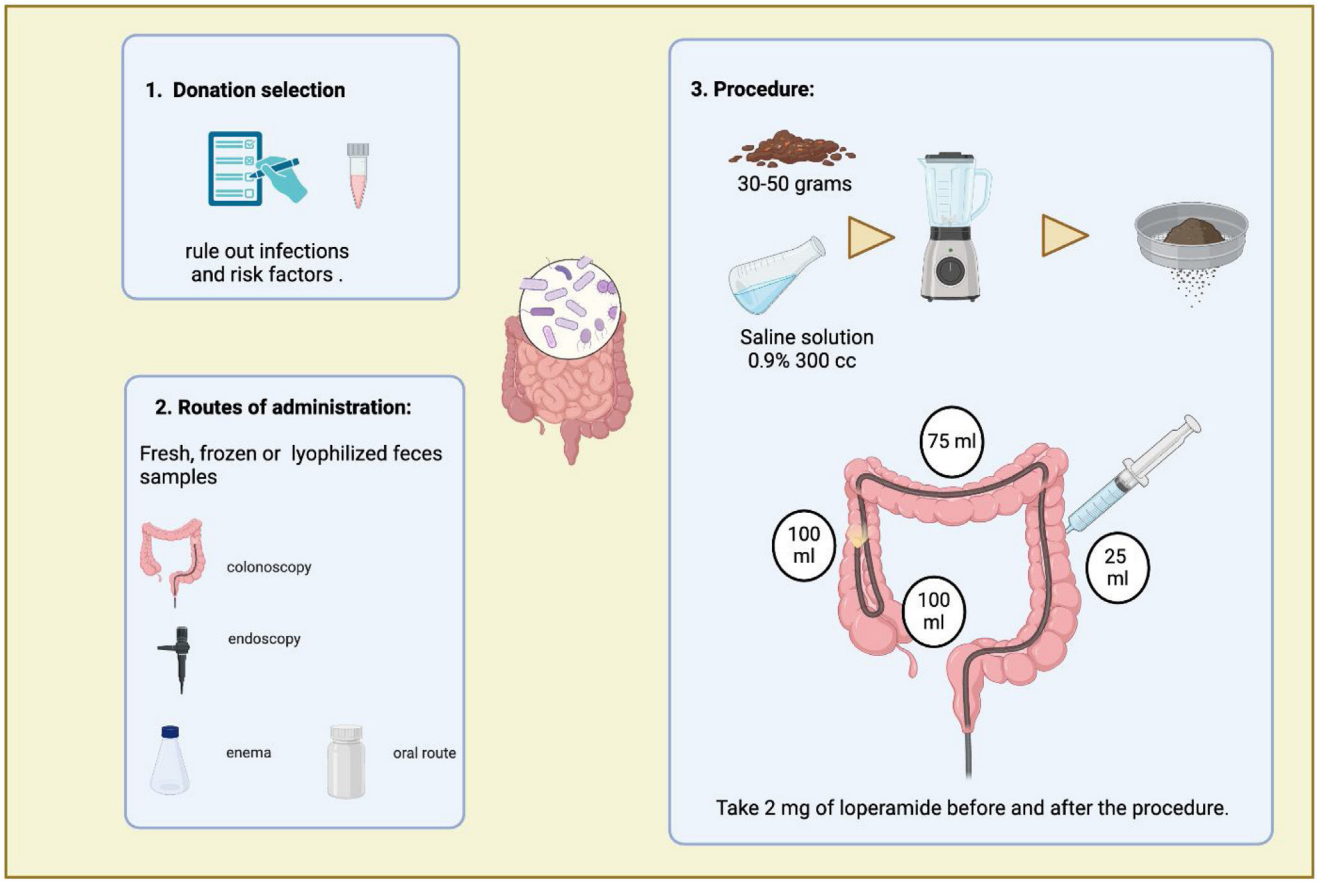

Figure 1 Fecal microbiota transplant process. Prior to the procedure, potential donors undergo an interview and physical examination to identify risk factors, comorbidities, and family history, which are subsequently evaluated according to the local protocol of our center, ruling out various potentially transmissible infectious diseases. The image shows the standardized procedure at our center, where 30 to 50 g of donor feces are diluted in 300 mL of saline solution and then processed and administered via colonoscopy, with 100 mL distributed in the terminal ileum, 100 mL in the right colon, 75 mL in the transverse colon, and 25 mL in the left colon. Prior to and following the procedure, loperamide is administered to reduce intestinal transit time.

ical response with formed stools within one week (Bristol Scale 3 or 4). One FMT was performed in a woman in the tenth week of pregnancy, with no complications during the pregnancy. She gave birth at week 37 (+ 4) and the neonate weighed 3.2 kg and measured 40 cm in length.

During the median follow-up of 11 months (range 3-32), three patients presented with a new CDI more that 10 months after the FMT. One of those patients was treated with vancomycin and had treatment response, whereas the other two cases underwent a second FMT. Table 1 describes the histories of each procedure. No patient presented with an adverse event due to colonoscopy and only one patient reported the presence of abdominal bloating and meteorism after FMT. All patients stated they would undergo this strategy again, if necessary.

Discussion and conclusions

Recurrent CDI is a significant health problem due to its frequency, increased incidence, elevated costs, hospital readmission rate, and potential risk of death.[4,13–17] Conventional treatment with prolonged antibiotic use not only has a high failure rate, reaching 40%, but also contributes to the maintenance and increase of intestinal dysbiosis.[18,19] Thus, different guidelines have recommended the use of FMT after $\geq$ 2 recurrences of CDI,[6,7,20,21] with effectiveness that varies from 55 to 100%.[9,22] Our study supports those results, given that all our patients responded positively to FMT. One of the patients was treated with fidaxomicin, an expensive antibiotic that is not available in Chile. A meta-analysis that included 37 randomized controlled trials and 30 case series, with 1,973 patients with recurrent and refractory CDI, showed that FMT was more effective than treatment with vancomycin (RR: 0.23 95% CI 0.07-0.80), with clinical resolution in 92% of cases.[9]

Different risk factors are associated with the development of recurrent CDI, among which are age $\geq$ 65 years and the concomitant use of proton pump inhibitors during CDI.[11] Regarding age, physiologic factors, such as immunosenescence and the decrease in gut microbiota diversity, predispose the older adult to episodes of CDI.[23,24] Compared with the younger population, patients over 65 years of age have an 8-times higher CDI rate and a 3.5 to 10-times higher recurrence rate.[25] That age group also has a higher mortality rate, with every 11 patients with medical care-associated

Table 1 Demographic characteristics and clinical course of patients that underwent fecal microbiota transplantation.

Sex, age	Comorbidity	AB pre-FMT	CDI severity	Number of recurrences	CDI treatment	Donor	Quantity (mg/ml)	Post-FMT time (months)	Post-FMT CDI (months; treatment)
M, 75	Gastrostomy, traumatic brain injury	Cephalosporin	Severe	2	Vancomycin, fidaxomicin	Son	100/300	32	No
F, 42	IBS	Quinolone	Mild	3	Vancomycin	NR	35/225	30	No
*M, 48	IBS, neurogenic bladder, UTI	Clindamycin	Mild	2	Metronidazole, vancomycin	NR	85/300	19	Yes (19; vancomycin/FMT)
M, 55	Acute pancreatitis, diabetes	Cephalosporin	Moderate	2	Vancomycin	Nephew	85/300	18	No
F, 32	Pregnancy 10 weeks	Cephalosporin	Mild	2	Metronidazole, vancomycin	Brother	35/300	15	Yes (vancomycin)
M, 78	DM2, DHC	Amoxicillin/Clavulanic acid; Clarithromycin	Moderate	2	Vancomycin	Son	100/300	14	No
F, 43	DM2	Quinolones	Severe	2	Vancomycin	NR	100/300	14	No
M, 74	DM2	Quinolones, metronidazole	Mild	3	Metronidazole, vancomycin	NR	43/300	11	No
**M, 75	COPD, pneumonia	Quinolones	Mild	2	Metronidazole, vancomycin	Nephew	92/300	10	Yes (10; vancomycin/FMT)
M, 38	No	Quinolones, metronidazole	Mild	3	Metronidazole, Vancomycin	NR	100/300	10	No
M, 71	DM2	Quinolones	Mild	2	Vancomycin	Daughter	100/300	8	No
*M, 48	IBS, neurogenic bladder, UTI	Quinolones, cephalosporin	Mild	2	Vancomycin	Daughter	100/300	6	No
M, 21	Crohn's disease	No	Mild	2	Metronidazole vancomycin	Brother	55/300	5	No
F, 82	HBP	Ceftriaxone, ertapenem	Moderate	2	Vancomycin	Grandson	79/300	4	No
**M, 76	COPD, pneumonia	Quinolones	Mild	1	Vancomycin	Nephew	77/300	3	No

AB: antibiotic; CDI: *Clostridioides difficile* infection; COPD: chronic obstructive pulmonary disease; DM2: type 2 diabetes mellitus; F: female; FMT: fecal microbiota transplantation; HBP: high blood pressure; IBS: irritable bowel syndrome; M: male; NR: not a relative; UTI: urinary tract infection.

* The same retransplanted patient.

** The same retransplanted patient.

CDI dying within 30 days after diagnosis.[26] Studies have confirmed that FMT can be used in patients above 65 years of age, maintaining adequate response rates.[27–29] A recent study that included 19 patients above 80 years of age showed the effectiveness of FMT at 86.9%, compared with 94.3% in the group of 18-79 years of age ($p = 0.44$).[29] In our study, seven of the 15 FMTs were performed on patients $\geq$ 65 years of age and were effective in all of them.

On the other hand, studies have indicated that the use of proton pump inhibitors during CDI increases the risk of recurrence.[30–32] A study that included 3,250 episodes of recurrent CDI showed that the use of proton pump inhibitors during CDI significantly increased the risk of recurrence, when compared with the group that did not use them (OR 1.17; 95% CI 1.07-1.15).31 In our study, there was a history of proton pump inhibitor use during the first CDI episode in seven of the patients that underwent FMT.

An increase in the incidence of CDI in pregnant women has also been observed.[33,34] A retrospective study that included 31 pregnant women showed that CDI during pregnancy could be associated with higher failure rates regarding antibacterial treatment and a greater probability of adverse results at the end of pregnancy, compared with pregnant women without CDI.[35] There is little information on the effectiveness of FMT during pregnancy and only clinical cases have been published.[36] In our case series, one FMT was performed on a woman in her tenth month of pregnancy, showing that the procedure could be a safe and efficacious strategy in the management of recurrent CDI during pregnancy. Maintaining oral vancomycin during pregnancy has been suggested for pregnant women with recurrent CDI.[37] Our patient was only in her ninth month of pregnancy at the time of her third CDI episode, and she had not had a favorable response to vancomycin since her first CDI episode.

Given the importance of the type of microbiota, the identification of a healthy donor is the essential first step for having a successful FMT. In addition, the donor should be thoroughly studied, ruling out risk factors and infectious diseases. In our case series, the recommendations described in different publications were followed.[10,38]

Although frozen or lyophilized fecal content is not available in Chile, studies have suggested that their use can reach identical effectiveness percentages as those of FMTs performed with fresh stools,[39,40] maintaining the transplanted microbiota for a prolonged period.[41]

Guidelines recommend the use of a minimum of 30-50 g of donor stool, which occurred in all our procedures.[9,38] Several FMT administration routes have been described, including endoscopy, nasogastric, nasoduodenal, or nasojejunal tubes, enema, and colonoscopy.[9,42] However, the technique through colonoscopy has been shown to be more effective than through endoscopy (92-97% vs 82-94%, $p = 0,02$),[9] the former being the one suggested by guidelines and the technique we used in the 15 procedures of our case series. We began solution instillation in the terminal ileum in all our procedures. Weingarden et al. recently showed that instillation at the terminal ileum could increase FMT effectiveness (OR 4.83, 95% CI 1.359-17.167).[43]

Regarding the presence of adverse events, the majority are mild, self-limited, and gastrointestinal.[44] Although severe complications have been reported, the majority have been described in isolated case reports.[45] In our study, no patient presented with an adverse event due to colonoscopy, and only one patient referred to the presence of abdominal bloating and meteorism after FMT.

Lastly, in our case series, all patients stated they would undergo this strategy again, if necessary. In fact, two patients decided to have a new FMT as soon as they presented with CDI recurrence secondary to the use of a new course of antibiotics. Studies have shown favorable perception of FMT in patients.[46]

Even though our study has limitations, such as reduced sample size, a retrospective design, and experience from a single center, we believe it contributes valuable information, especially by including patients $\geq$ 65 years of age and a pregnant patient, two groups in which FMT has been less analyzed and that need a higher number of patients to be able to make recommendations. On the other hand, we feel our study also has strengths. First, all the cases were discussed at the gastroenterology meeting of our center, prior to FMT performance, and a consensus was reached for proceeding with the intervention. Second, all the procedures carried out followed the regulations and protocol of the gastroenterology section of our center. Said practices contribute to the quality and coherence of our study results.

In conclusion, in our experience, FMT via colonoscopy could be a simple, safe, and effective strategy in the treatment of recurrent CDI that is possible to generalize and is available at a low cost in a large number of centers.

Financial disclosure

No financial support was received in relation to this study/article.

Conflict of interest

The authors declare that there is no conflict of interest.

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