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Original article

# Faecal Microbiota Transplantation is a simple, effective and safe treatment in the management of *C. difficile* infection in daily clinical practice

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ABSTRACT

*Introduction:* Faecal microbiota transplantation (FMT) is a treatment supported by wide scientific evidence and proved to be very effective in the management of *Clostridioides difficile* infection (CDI). The objective of this study is to analyze its effectiveness and safety in a real clinical practice setting.
*Methods:* Retrospective, single-center and descriptive observational study in which all FMT performed between May 2016 and December 2020 were included. Technical success was defined as the successful administration of the faecal preparation in the patient's gastrointestinal tract and clinical success the disappearance of diarrhoea in the first 72 h after the procedure with no relapse within the following 8 weeks after the therapy was started.
*Results:* 15 FMT were performed in 13 patients. Median age was 79 years (range: 40–98 years); being 60% women and 33.3% depedent persons. The indication for FMT was recurrent CDI in 84.6%. All FMTs were performed by colonoscopy and from related donors. With a first procedure, the FMT was effective in 11 of 13 patients (84.61%; 95% CI; 54.55–98.07). Time until resolution of symptoms was less than 48 h in all cases. Post-transplant follow-up was 25.66 ± 17.5 months. No significant short or long-term complications were recorded at follow-up.
*Conclusion:* TMF is a simple, effective and safe procedure in CD infection, even in elderly patients or those with great comorbidities.

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## El Trasplante de Microbiota Fecal es un tratamiento sencillo, efectivo y seguro en el manejo de la infección por C. *difficile* en la práctica clínica diaria

*Palabras clave:*
Trasplante Microbiota Fecal
*Clostridium difficile*
*Clostridioides difficile*
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RESUMEN

*Introducción:* El trasplante de microbiota fecal (TMF) es un tratamiento avalado por evidencia científica amplia y muy efectivo en el manejo de la infección por *Clostridioides difficile* (CD). El objetivo de este estudio es analizar su efectividad y seguridad en un ámbito de práctica clínica real.
*Métodos:* Estudio observacional retrospectivo, unicéntrico y descriptivo en el que se recogieron todos los TMF realizados entre mayo de 2016 y diciembre de 2020. Se definió como éxito técnico la administración exitosa del preparado fecal en el tracto gastrointestinal del receptor y éxito clínico la desaparición de la diarrea en las primeras 72 horas tras el procedimiento y ausencia de recurrencia a las 8 semanas.

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*Resultados:* Se realizaron 15 TMF a 13 pacientes. La mediana de edad fue de 79 años (rango: 40 a 98 años); siendo el 60% mujeres y el 33,3% dependientes. La indicación del TMF fue la recurrencia de la infección por CD en el 84.6%. Todos los TMF se realizaron por colonoscopia y de donantes emparentados. Con un primer procedimiento, el TMF fue efectivo en 11 de 13 pacientes (84.61 %; IC 95%; 54.55–98.07). El tiempo hasta la resolución de los síntomas fue menos de 48 horas en todos los casos. El seguimiento postrasplante fue de 25.66 ± 17.5 meses. No se registraron complicaciones precoces ni tardías significativas en el seguimiento.
*Conclusión:* El TMF es un procedimiento sencillo, eficaz y seguro en la infección por CD incluso en pacientes de edad muy avanzada o con grandes comorbilidades.
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## Introduction

The gut microbiota is composed of an enormous variety of microorganisms such as bacteria, archaea and yeasts and plays a key role in the homeostasis of the human body, intervening in functions such as immune response, inflammatory processes, energy metabolism and the proper functioning of the nervous system[1,2]. It is currently considered a ñew organ, with an estimated weight of around one kilogram in an average adult and with a gene content 150 times greater than that of the human genome[3].

In recent years the said microbiome has been identified as a modifiable therapeutic target for the treatment of a wide variety of pathologies which could be related to dysregulated microbiota profiles (dysbiosis). There has therefore been a renewed and increasing interest in faecal microbiota transplantation (FMT), a practice with several centuries of history.

The current main indication for FMT is Clostridioides difficile (CD) infection[4,5]. CD frequently colonises the gastrointestinal tract (GIT) as a consequence of intestinal dysbiosis caused by antibiotics, and can cause anything from mild diarrhoea to severe cases of pseudomembranous colitis or toxic megacolon. Its incidence is increasing and it is the leading cause of hospital-acquired diarrhoea in developed countries[6].

The response rate to conventional antibiotic treatment is around 90%[7], with a recurrence rate of 20%–25%[8] and increasing considerably after a first recurrence, reaching rates of 40% and up to 45%–65% in the case of two or more recurrences[9].

In this context, FMT is of particular interest. Its use in recurrent disease has shown cure rates of 85%–94%[10–12]. Its clinical success is based on its ability to restore the composition and diversity of the intestinal bacterial community, with reductions in proteobacteria and verrucomicrobia phyla associated with increases in bacteroidetes and firmicutes[3].

Although its efficacy has been demonstrated in several studies[10–13], it is possible that the different effectiveness rates achieved in these studies have to do with issues that are still under study, such as the route of administration, the amount of faeces to be administered, the selection of the donor, the number of procedures or the use of fresh vs. frozen faeces.

The aim of this study was to evaluate the efficacy and safety of FMT in a routine clinical practice setting, presenting the clinical experience accumulated in our centre over the last five years on this promising therapeutic alternative.

## Methods

### *Study criteria, design and data collection*

Observational, retrospective and descriptive study that collects the experience of all FMT performed at the Hospital Universitario Puerta de Hierro Majadahonda between May 2016 and December 2020.

All patients undergoing FMT according to standard clinical practice were included and the data for the study were collected from the electronic medical record. No exclusion criteria were defined beyond the criteria of the patients' treating clinicians when offering or not offering FMT as a therapeutic alternative in CD disease.

Patients' CD disease was managed according to the recommendations contained in commonly used clinical practice guidelines such as the Infectious Diseases Society of America (IDSA) 2018[14]. Grading the severity of CD infection also followed the criteria in the guidelines: mild infection is defined as <15,000 leukocytes/mm3 and creatinine <1.5 mg/dL; moderate if >15,000 leukocytes/mm3 or creatinine >1.5 mg/dL; and severe in patients with arterial hypotension, shock, ileus or megacolon.

The indication for FMT was based on the clinical judgement of the patients' treating physicians for one of three reasons: recurrent CD infection, refractoriness to first-line antibiotic treatment or severe/fulminating CD colitis.

Technical success of FMT was defined as the successful administration of the donor faecal preparation into the recipient's GIT. Clinical success of FMT was defined as the disappearance of diarrhoea within 72 h after FMT, together with the absence of recurrence of symptomatology within the first eight weeks.

### *Description of the FMT protocol in our centre*

The FMT protocol at our centre follows the principles set out in the current European consensus guidelines[4]. The multidisciplinary team is made up of the Digestive System, Internal Medicine-Infectious Diseases and Microbiology departments. The Digestive and Infectious Diseases services are responsible for the clinical follow-up of patients throughout their CD disease process. Once the indication for FMT has been established, the stool donor is selected and screened, which is performed on an outpatient basis. CD disease is managed according to standard clinical practice while the donor selection and validation/screening process is carried out, which usually takes no more than a week from the time the patient is considered for FMT. The protocol accepted in the European clinical practice guidelines is followed, according to which the donor (normally related to the patient, to speed up the process of obtaining the donor and proposing the preliminary study) is subjected to exhaustive screening to ensure suitability and safety of the procedure by means of a complete anamnesis, physical examination and analysis of possible pathogens in both blood and stool samples. During the entire process, the patient is treated with antibiotics until just before the colonoscopy for the FMT. Antibiotic treatment, in case of recurrent disease, is not used with curative intent and is left only as a maintenance treatment until the FMT can be performed, after which time no further antibiotics are administered. In the event that the patient remains asymptomatic with the antibiotics received previously and until the FMT, FMT would not be performed.

The Microbiology Service is responsible for handling and analysing samples from both potential donors and the recipient patient. On the day of the procedure, the selected donor must provide a fresh stool sample to the microbiology laboratory for processing. Donor selection and validation is carried out in the same

episode in which the donor is given the FMT (from the third episode onwards), so donors are not screened for possible future needs. The administration of the donor faecal preparation is done in less than 6 h after processing. If there is a surplus of processed faecal preparation from the donor, it can be stored at -80 °C and can be used in the future in another patient or in the same patient.

For the FMT procedure by colonoscopy, the patient must be prepared with an oral evacuating solution of polyethylene glycol. Once sedation has been administered, the endoscope is inserted into the caecum, using low $CO_2$ insufflation. During insertion, cleaning and aspiration of all detected liquid faecal debris is carried out and an evaluation of the colonic mucosa is performed until the caecum is reached. When the tube is withdrawn from the caecum, the donor preparation is instilled through the working channel of the endoscope, using half in the caecum and right colon, a quarter in the transverse colon and the remaining quarter in the left colon.

After the procedure, the patient remains under observation in the Endoscopy Unit for at least half an hour and according to the protocol, 4 mg of oral loperamide should be administered if there is no contraindication. Antibiotics against CD are maintained until the patient starts colonoscopy preparation; no antibiotics should be administered after FMT.

### *Ethical aspects*

The protocol of the present study adheres to the principles of the Declaration of Helsinki (World Medical Assembly of June 1964) and was approved by the Medical Research Ethics Committee of the sponsoring centre.

### *Statistical analysis*

Continuous variables are shown as mean and standard deviation (SD) or as median and interquartile range (IQR), depending on whether or not normality can be assumed (which was assessed using the Saphiro-Wilk test). Qualitative variables are presented as absolute and relative frequencies. All statistical analyses were performed with Stata V 13.0 (Statacorp, Texas, United States of America).

## Results

### *Baseline characteristics of the study population*

Between May 2016 and December 2020, 15 FMTs were performed on 13 patients. One procedure was excluded from the final analysis as it had more than 5% of missing variables. The median age of patients at the time of the procedure was 79 years (range: 40–98 years); 60% were female. Among the main comorbidities, 33.3% were dependent patients. The most common medications were: immunosuppressants in 13.3%, PPIs in 80% and antiplatelet or anticoagulants in 46.6%. Table 1 summarises the baseline characteristics of the patients under study, as well as the first FMT performed.

**Table 1**
Comorbidities of the study population and characteristics of the first faecal microbiota transplant.

| Age | Sex | Comorbidities | Previous episodes s | Indication | Days of antibiotic treatment until FMT | Clinical success | Time until symptom resolution (hours) |
|---|---|---|---|---|---|---|---|
| 72 | M | COPD pulmonary adenocarcinoma | 1 | Severe colitis | 4 | Yes | 24 |
| 81 | W | CKD, monorenal, COPD, heart disease | 5 | Recurrence | 7 | Yes | 24 |
| 98 | W | Myasthenia gravis | 5 | Recurrence | 6 | Yes | 24 |
| 47 | W | Diffuse axonal injury with post-traumatic dementia due to traffic accident. Totally dependent | 8 | Recurrence | 10 | No | |
| 87 | W | Heart disease | 4 | Recurrence | 5 | Yes | 24 |
| 40 | M | PTE with pulmonary infarcts | 3 | Recurrence | 4 | Yes | 24 |
| 69 | W | Ulcerative colitis on treatment with vedolizumab | 2 | Recurrence | 7 | Yes | 24 |
| 90 | W | Chronic lymphatic leukaemia | 4 | Recurrence | 6 | Yes | 24 |
| 43 | M | Tetraplegia as a sequel of meningoencephalitis, dependant | 3 | Recurrence | 3 | Yes | 24 |
| 92 | M | COPD, Parkinson's disease, dependent | 3 | Recurrence | 9 | Yes | 48 |
| 79 | M | Heart disease, COPD, dependentd | 1 | Lack of primary efficacy | 21 | No | |
| 88 | W | Child-A cirrhosis, heart disease, Parkinson's disease, dependent | 4 | Recurrence | 6 | Yes | 24 |
| 83 | W | ileocolonic and perianal Crohn's disease treated with ustekinumabohn | 3 | Recurrence | 9 | Yes | 24 |

COPD: Chronic Obstructive Pulmonary Disease; FMT: Faecal Microbiota Transplantation; KD: Chronic Kidney Disease; PTE: Pulmonary Thromboembolism.

**Table 2**
Technical aspects of colonoscopy.

| | |
|---|---|
| Overall cleansing | Good (7–8–9):60%<br>Normal (5–6): 13%<br>Poor (<6): 27% |
| Up to caecum | 87% |
| Tolerance | Good: 87%<br>Normal: 13% |
| Endoscopic findings | No alterations: 66%<br>Mild colitis: 13%<br>Polyps: 20%<br>Diverticulosis: 20%<br>Pseudomembranous colitis: 8%<br>Ulcerative pancolitis with moderate activity: 8%;<br>Moderate Crohn's disease |
| Volume infused | 450 ± 50 mL |
| Technical success | 100% |
| Procedural complications | None |
| Loperamide | 4 mg at 47% administered following colonoscopy |

Colonic cleansing was assessed according to the Boston scale.

*Indication for FMT. Previous CD disease in treated patients*

The indication for FMT was severe or fulminant colitis in one patient, lack of primary response to antibiotics in another patient and recurrence of CD infection in the remaining 11 (84.6%). The median number of previous CD episodes was 3 [IQR: 2–4] with a range of one to eight episodes. Eighty per cent had received antibiotics prior to the first episode of CD, with penicillins and cephalosporins (73.3%) and quinolones (33%) being the most commonly used. Forty per cent received more than one antibiotic as a trigger for the first episode of CD. Acquisition of CD infection was community-acquired in eleven patients (73.3%), and associated with socio-health care in four (26.7%).

*FMT procedures and technical aspects of it*

Prior to FMT, 87% of patients were positive for toxin and CD PCR in faeces. Regarding pre-transplant laboratory variables, leukocytes were 11.71 ± 7.5/mm$^3$ and creatinine was 0.6 ± 0.31 mg/dL. All FMTs were performed by colonoscopy and from related donors (children or grandchildren of the patients). From the donor screening performed, two donors from different patients were discarded (in one case because they were on antibiotic treatment and in another case because the sample did not meet microbiological quality standards). In 13 (86.7%) cases fresh faeces were used and in two (13.3%) frozen faeces (in both cases where clinical success was not achieved with the first procedure). Antibiotic treatment was discontinued once colonoscopy preparation was started and no antibiotics were administered after FMT. No patient improved with antibiotic treatment prior to FMT. Technical aspects of FMT can be found in Table 2.

*Effectiveness*

FMT was effective in 11 of 13 patients (84.61%; 95% CI 54.55–98.07). Two patients had recurrence of symptoms after the first FMT, so they underwent FMT again after one month in both cases, with subsequent resolution of symptoms and no recurrence in the first eight weeks, so the efficacy with two FMT procedures was 100%. The time to resolution of symptoms was less than 48 h in all patients.

*Follow-up and safety*

Post-transplant follow-up up to the time of writing this manuscript is 25.66 ± 17.5 months. Only one patient died three months after FMT due to an episode of congestive heart failure in the context of a new episode of CD colitis. After clinical success was achieved at eight weeks and with the exception of this patient, no new episodes of recurrent CD infection were observed during the entire follow-up period. There were no immediate or mid- to long-term complications related to the FMT procedure.

## Discussion

FMT is a therapeutic practice that has been increasingly used in recent years, and is indicated in cases of two or more episodes of CD, episodes refractory to antibiotic treatment or fulminant episodes after 48 h of antibiotic treatment[4,5]. However, although it is a technique endorsed by the main scientific societies, it is currently not widely used in Spain and other European countries[15].

The median age of our patients was 79 years (range: 40–98 years), which is higher than that described in most published studies, as reflected in the most recent meta-analyses (mean age 65.8 years)[16]. The oldest patient in our series was 98 years old when the procedure was performed, making her one of the oldest patients in whom FMT has been performed, as reported in the literature.

The most frequent indication for faecal microbiota transplantation was recurrent infection, in 11 patients (84.6%). This is currently the most studied and widespread indication for FMT[8]; it is estimated that more than 70% of patients with a first recurrence will have multiple recurrences[17]. From the second episode onwards, faecal microbiota transplantation could be considered[4,5].

Among the associated risk factors, 80% had been treated with antibiotics. Antibiotics are the main risk factor for CD disease, as they promote dysbiosis[17,18]. Although CD is described as an eminently nosocomial pathogen, it is estimated that community-acquired cases are on the rise, accounting for up to 30% of the total[19]. In our study, this was the most frequent mode of acquisition (73.3%), as most of the patients had multiple recurrences and were at home.

Clinical success was achieved with one FMT in 11 of 13 patients (84.61%; 95% CI 54.55–98.07), with a total of two patients presenting recurrence within the first eight weeks. After a further FMT their condition was successfully resolved. Therefore, a 100% success rate can be considered with two procedures. These findings are in line with the literature, which puts the efficacy with one procedure at around 84%, and 92% with two[16,19,20]. Particularly striking is the increase in efficacy following repeat FMT[21]. This underlines the importance of remembering that some patients may require more than one FMT. To date, it has not been clearly established what is the ideal number of infusions or in which subgroup of patients more than one initial FMT would be indicated. Risk factors for treatment failure include severe or pseudomembranous cases, hospitalisation, inflammatory bowel disease, immunosuppression and poor colonoscopy preparation[22–24].

The most recent meta-analyses indicate that colonoscopy is superior in overall efficacy to other forms of administration, such as upper endoscopy, enemas or oral capsules[16,19,20,25]. The amount of faeces to be infused could also be a factor to be taken into account, as amounts of less than 50 g have shown lower efficacy[20,26].

Regarding the use of fresh or frozen faeces, no differences have been seen in cure rates[16,19–21,27]. In our case, fresh faeces were used in the majority of cases (86.7%). However, in two cases (13.3%)

frozen faeces were used. The use of frozen stool has the advantage of being able to store already processed samples, which can be readily available in case of clinical need[28].

While the efficacy of FMT has been evaluated in multiple studies, information regarding its long-term safety is more limited, as many of the observed studies include a follow-up time of less than one month. In our study the follow-up time was $25.66 \pm 17.5$ months and no adverse effects related to FMT were observed in the short or long term. The main adverse effects reported in the literature include gastrointestinal adverse effects in up to 19% of cases, being more frequent in upper gastrointestinal infusions. alta[29] Serious adverse effects are less than 2% and the most reported cases are bronchoaspiration in upper gastrointestinal infusions[19,29,30].

The main limitations of the present study are the small sample size and the retrospective nature of the study. In addition, the patients received antibiotic treatment until FMT was performed, so even if they did not improve prior to FMT, it is not possible to rule out with complete certainty that the antibiotic treatment administered prior to FMT contributed to the clinical success of FMT.

In short, FMT is shown to be an effective, safe and simple procedure, which will probably allow its use to become widespread and available in a large number of centres at a low cost.

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## Conflict of interests

The authors have no conflict of interests to declare.

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