ORIGINAL PAPERS

Fecal microbiota transplantation in the intestinal decolonization of carbapenamase-producing *enterobacteriaceae*

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ABSTRACT

Background and aims: fecal microbiota transplantation (FMT) is effective for recurrent *Clostridium difficile infection* (CDI). Intestinal decolonization of carbapenamase-producing *enterobacteriaceae* (CPE) can prevent transmission and infection by these agents. The aim of this study was to assess CPE decolonization after FMT.

Methods: this was a case-series study that consecutively included all CPE-carriers that underwent FMT between 2014 and 2019. The indications included refractory/recurrent CDI and CPE-decolonization.

Results: out of 21 CPE-carriers, eight were excluded due to incomplete post-FMT testing. CPE decolonization was confirmed in 76.9 % (n = 10). The median decolonization time was 16-weeks (IQR-23) and ranged from two to 53 weeks.

Conclusion: FMT may be used in the clinical practice for CPE-decolonization as an alternative to combined antibiotic regimens.

Keywords: Fecal microbiota transplantation. Carbapenamase-producing *enterobacteriaceae.* Multidrug-resistant infections. Decolonization. Intestinal carriage.

Author´s contributions: Silva JC performed the research, analyzed the data and wrote the paper. Ponte A designed the study. Silva JC, Ponte A, Rolando P, Gomes AC and Afecto E performed the procedures. Mota M established the protocol and performed the donor evaluation and screening as well as fecal microbiota sample processing. Vieira N and Oliveira R assisted protocol establishment. Mota-Carvalho N assisted donor evaluation and screening. Ponte A, Mota M, Pinho R and Carvalho J critically revised the paper for important intellectual content.

Ethical statement: All patients or their legal substitutes gave written informed consent for the procedure. The study protocol was approved in January-2016 by the ethical review board of Centro Hospitalar Vila Nova de Gaia e Espinho for the following indications: refractory CDI, recurrent CDI and CPE decolonization.

INTRODUCTION

Fecal microbiota transplantation (FMT) has been shown to be more effective and durable than standard treatment protocols for recurrent *Clostridium difficile* infection (CDI), reaching a success rate of up to 95 % (1-3). Furthermore, several other areas of potential interest for application have been highlighted, namely inflammatory bowel disease, irritable bowel syndrome, hepatic encephalopathy and eradication of multidrug-resistant (MDR) microorganisms (1). Intestinal colonization by carbapenamase-producing *enterobacteriaceae* (CPE) has been increasingly reported (4-7). It is estimated that 10 % of patients will develop CPE infections, which are often associated with treatment failure and mortality rates higher than 50 % (8,9). CPE decolonization can prevent transmission and infection by these agents. Thus, FMT may be a potential alternative to currently used combined antibiotic regimens (10).

The aim of this study was to assess the CPE carrier status after-FMT in a population of patients colonized by CPE undergoing FMT.

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METHODS

Patient selection and data collection

A retrospective analysis was performed in a cohort of patients who underwent FMT between June, 2014 and October, 2019 in our department. The study protocol was approved for the following indications: refractory CDI, recurrent CDI and CPE decolonization. Patients older than 18 years with positive CPE screening prior to FMT and no immunosuppressive conditions were included. Patients without screening for CPE intestinal colonization after FMT or without follow-up were excluded. CPE colonization was considered as the presence of ≥ 1 positive test for CPE through molecular biology or culture techniques.

FMT protocol

The institutional protocol for FMT used was developed to standardize the criteria of recipients, donors and the procedure itself (3). Donors were unrelated volunteers selected and screened based on medical history and laboratory testing, as detailed in our unit protocol (3). All patients underwent bowel preparation (4l-polyethyleneglycol) the night before the procedure. Proton-pump inhibitors were given to the recipient the evening before and the morning of the procedure.

All CDI patients maintained the antibiotic prescription until the day before the FMT. The initial CDI episode treatment included vancomycin, fidaxomicin or metronidazole. For recurrent CDI, a pulsed/tapered vancomycin regimen, a ten-day course of fidaxomicin or a standard course of vancomycin (if metronidazole was used for the primary episode) were used (2). No patients underwent combined antibiotic therapy for CDI nor CPE decolonization.

FMT procedures were performed by esophagogastroduodenoscopy (EGD) with progression to the distal duodenum, where 50 cc of a processed suspension of fresh stool from an unrelated donor collected between 4-24 hours before the procedure was delivered. Patients were followed-up in order to monitor FMT-related adverse events. No antibiotic treatment was administered after FMT.

CPE colonization testing and post-FMT follow-up

Testing for CPE colonization was performed by two methodologies according to our institution protocol. On hospital admission, patients at risk of MDR infections were screened for CPE colonization via molecular biology techniques in a rectal swab. Screening was performed by culture of a rectal swab sample in the outpatient setting as well as in hospitalized patients.

After FMT, patients were contacted by the Infection Control Group for ambulatory CPE testing. Recruitment and testing intervals were conditioned by local resources and the patient's functional condition. The authors further recruited patients who were lost to follow-up for CPE testing. Decolonization was assumed when three consecutive negative screening tests were obtained with at least a one-week interval between them. CPE eradication was not considered in patients with < 3 or nonconsecutive negative screenings after FMT.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) program version 26 was used. Categorical variables are summarized as frequencies and percentages. The Chi-squared test or Fisher's exact test was used to compare categorical variables. Continuous variables were expressed as the mean (μ) and standard deviation (SD) or median and interquartile range (IQR).

RESULTS

Figure 1 summarizes patient selection and clinical outcomes according to FMT indication. Forty-nine procedures were performed in our unit between June, 2015 and June, 2019. Out of 21 CPE-carriers that underwent FMT, eight were excluded due to loss of follow-up after FMT. Subsequently, 13 patients were included, 61.5 % were female (n = 8), with a mean age of 61.8 ± 21.0 years. In all cases, FMT was performed by EGD. No procedure-related complications were reported. Refractory/recurrent CDI was the indication in 61.5 % (n = 8). FMT lead to CDI cure defined as the resolution of diarrhea within two months after the procedure in all cases. CPE decolonization was the indication for FMT in the remaining 38.5 % (n = 5).

CPE decolonization was confirmed in 76.9 % (n = 10) (Table 1). Globally, the decolonization rate in our cohort of 21 CPE-carriers was 47.6 % (n = 10). The median decolonization time was 16-weeks (IQR 23) and ranged from two to 53 weeks. Regarding indication, decolonization occurred in 75.0 % (n = 6) when FMT was performed due to refractory/recurrent CDI and in 80.0 % (n = 4) when primary CPE decolonization motivated the procedure (p = 0.685). No patient developed CPE infections.

DISCUSSION

In this case series, CPE decolonization after FMT reached a success rate of 76.9 %. Thus, FMT may be used in the clinical practice for MDR decontamination and as a public health intervention to minimize cases of severe and refractory infections caused by those agents. The literature on FMT for CPE decolonization is scarce and mostly limited to case reports and small-uncontrolled studies (11). Saha S et al. performed a systematic review that mostly included case-reports and uncontrolled studies and reported an MDR eradication rate from 37.5 % to 87.5 %. Nonetheless, this review included different patient populations, MDR agents, microbiological techniques and definitions of decolonization. Thus, the evidence was also of low quality (12). Similarly, Tavoukjian V et al. performed a systematic review and meta-analysis reporting decolonization rates up to 67.0 %. Nevertheless, patients with CDI were excluded and the definition of decolonization varied significantly (13).

Huttner et al. conducted a multicenter randomized controlled trial (RCT) to assess a combined strategy of oral antibiotics followed by frozen FMT for CPE and/or extended

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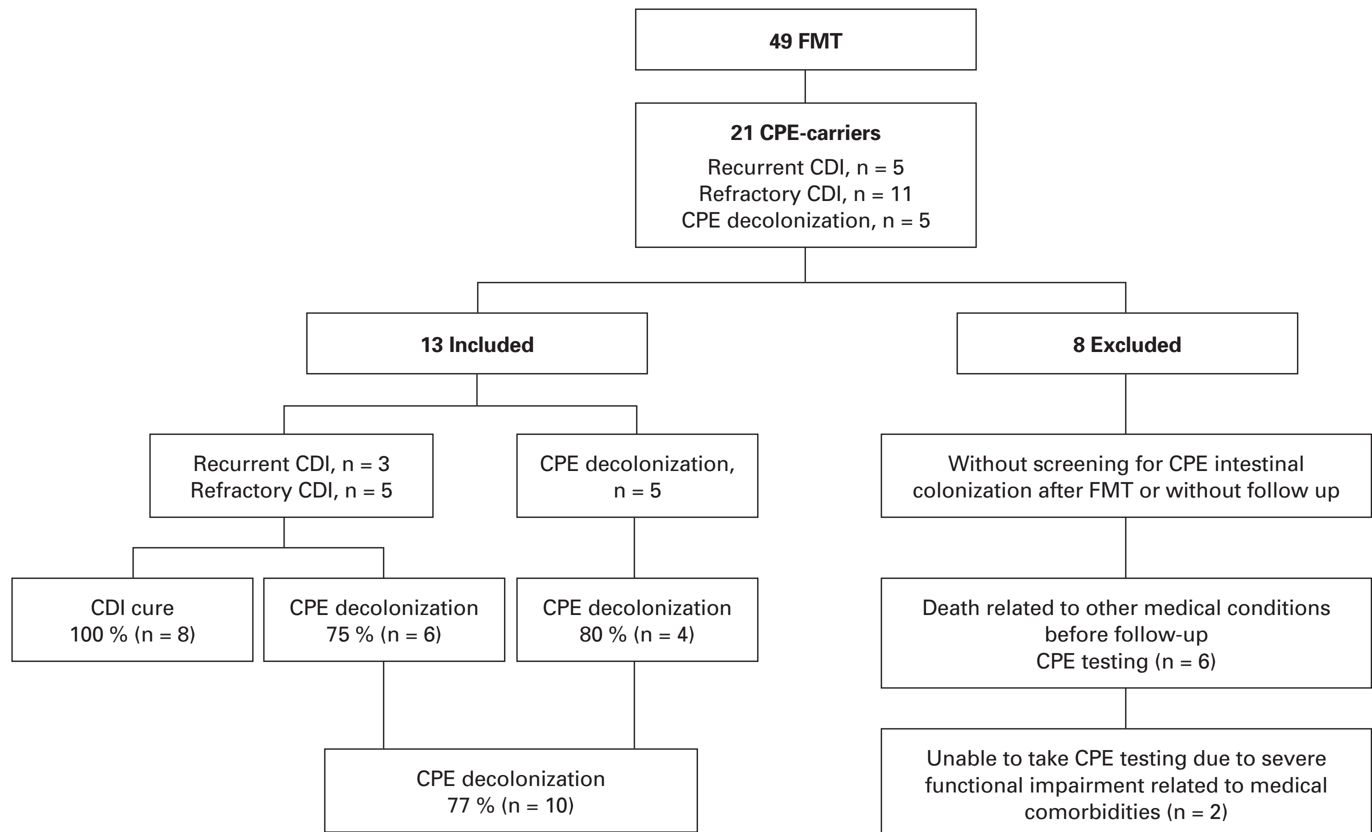

Fig. 1. *Patient selection and clinical outcomes according to FMT indication (CPE: carbapenamase-producing* enterobacteriaceae; *FMT: fecal microbiota transplantation; CDI:* Clostridium difficile *infection).*

Table 1. *Characterization of patients with decolonization of CPE after FMT*

No. of patients (n = 11)	Age (yr)	Gender	FMT indication	TMF route	3 negative screening tests after FMT	Time to 3rd negative screening (weeks)
Patient 1	66	Female	Recurrent CDI	EGD	Yes	17
Patient 2	87	Male	Refractory CDI	EGD	No	
Patient 3	71	Female	Refractory CDI	EGD	Yes	14
Patient 4	70	Female	Recurrent CDI	EGD	Yes	4
Patient 5	64	Male	Recurrent CDI	EGD	Yes	18
Patient 6	79	Female	Refractory CDI	EGD	No	
Patient 7	21	Female	CPE decolonization	EGD	Yes	2
Patient 8	27	Female	CPE decolonization	EGD	Yes	53
Patient 9	55	Male	CPE decolonization	EGD	Yes	28
Patient 10	46	Female	CPE decolonization	EGD	Yes	12
Patient 11	51	Male	CPE decolonization	EGD	No	
Patient 12	80	Male	Refractory CDI	EGD	Yes	6
Patient 13	86	Female	Refractory CDI	EGD	Yes	31

CPE: carbapenamase-producing *enterobacteriaceae*; FMT: fecal microbiota transplantation; CDI: *Clostridium difficile* infection; EGD: esophagogastroduodenoscopy; yr: years.

spectrum b-lactamases *enterobacteriaceae* (ESBL-E) decolonization. Non-absorbable antibiotics followed by FMT slightly decreased ESBL/CPE carriage (41 %) compared to controls (29 %). However, this difference was not statistically significant, potentially due to early trial-termination and a failure to achieve the planned sample size (14).

Our study has several limitations. Due to high morbimortality secondary to medical comorbidities, 38 % of CPE carriers were not submitted to screening after FMT. Moreover, recruitment and testing intervals after FMT were conditioned by the patient's characteristics and local resources. Time to decolonization varied widely due to follow-up protocol heterogeneity. Prompt and systematic testing after FMT according to a rigorous predefined protocol might mitigate the number of lost patients in further studies. Furthermore, spontaneous decolonization was not evaluated, even though the evidence suggests that it occurs later and less often (13).

Although this and other case studies do not constitute sufficient evidence to recommend the routine use of FMT in patients colonized by MDR agents, it reinforces the concept of post-FMT CPE decolonization. Currently, there are several clinical trials underway due to the urgent need for high-quality prospective data and a consensus definition for decolonization.

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