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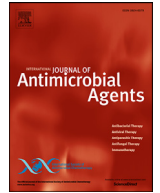
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Faecal microbiota transplantation shortens the colonisation period and allows re-entry of patients carrying carbapenemase-producing bacteria into medical care facilities

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ABSTRACT

Background: Colonisation with carbapenemase-producing Enterobacteriaceae or Acinetobacter (CPE/A) is associated with complex medical care requiring implementation of specific isolation policies and limitation of patient discharge to other medical facilities. Faecal microbiota transplantation (FMT) has been proposed in order to reduce the duration of gut colonisation.

Objectives: This study investigated whether a dedicated protocol of FMT could reduce the negatation time of CPE/A intestinal carriage in patients whose medical care has been delayed due to such colonisation.

Method: A matched case-control retrospective study between patients who received FMT treatment and those who did not among CPE/A-colonised patients addressed for initial clustering at the current institute. The study adjusted two controls per case based on sex, age, bacterial species, and carbapenemase type. The primary outcome was delay in negatation of rectal-swab cultures.

Results: At day 14 post FMT, 8/10 (80%) treated patients were cleared for intestinal CPE/A carriage. In the control group, 2/20 (10%) had spontaneous clearance at day 14 after CPE/A diagnosis. Faecal microbiota transplantation led patients to reduce the delay in decolonisation (median 3 days post FMT for treated patients vs. 50.5 days after the first documentation of digestive carriage for control patients) and discharge from hospital (median 19.5 days post FMT for treated patients vs. 41 for control patients).

Conclusion: Faecal microbiota transplantation is a safe and time-saving procedure to discharge CPE/A-colonised patients from the hospital. A standardised protocol, including 5 days of antibiotic treatment, bowel cleansing and systematic indwelling devices removal, should improve protocol effectiveness.

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1. Introduction

Since the first description of a plasmidic Enterobacteriaceae carbapenemase, *Klebsiella pneumoniae* (*K. pneumoniae*) carbapenemase (KPC) in the USA [1], a wide variety of plasmid-borne resistance mechanisms have been described, mainly through metalloenzymes such as New Delhi Metallo-beta-lactamase (NDM) or oxacillinases type OXA-48-like carbapenemases. Current epidemiology of carbapenemase-producing Enterobacteriaceae (CPE)

shows a global dissemination with endemic distributions and outbreaks, leading to public health concerns [2,3]. Spread occurs by transmission from one patient to another, and super-spreaders are likely to carry a higher bacterial charge to colonisation sites such as the rectum [4].

The average time for spontaneous colonisation of the CPE after hospital discharge has been estimated at 387 days [5]. Carbapenemase-producing Enterobacteriaceae colonisation would expose a patient to a controversial increased risk of developing infections, which occurs in 16.5% of CPE-colonised patients (with variations ranging from 0–89%, depending on the study), associated with overall mortality ranging 30–75% among infected and 10% among colonised patients [6]. Such infections represent a major therapeutic challenge, given the limited treatment

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options available [7]. Economic burdens of CPE/A outbreaks are cost-consuming and time-consuming, requiring the implementation of patient isolation, cohorting policies, and screening of contact patients [8]. The estimated cost of a CPE outbreak has been evaluated at \$474 474 according to Gagnaire et al. [9] (2-months outbreak in Saint-Etienne, France) and €100 000 per month according to Semin-Pelletier et al. (2-months outbreak in Nantes, France) [10]. Such colonisation has also resulted in a significant increase (almost double) in the length of hospital stays [11,12], delay in optimal medical care, and loss of medical opportunities [13].

The high efficacy of faecal microbiota transplantation (FMT) performed after a short course of vancomycin (81%) in patients with a relapsing *Clostridium difficile* infection (CDI) [14] led to its addition to the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for relapsing CDI management [15], and early use has been shown to significantly reduce mortality of severe CDI (17% mortality rate in the FMT group vs. 69% in the non-FMT group) [16]. The adverse effects of FMT are low and consist mainly of functional intestinal disorders, with few life-threatening adverse events (0.34% Gram-negative bacteraemia, 0.25% deaths, and 0.25% perforations in 1190 CDI FMT-treated cases in a systematic literature review) [17].

Faecal microbiota transplantation has been suggested for treating diseases other than CDI, including eradication of pathogenic and multi-resistant enteric microorganisms [18]. In 2016, a review of successful multidrug-resistant (MDR) bacteria decolonisation described FMT procedures for many purposes, including decolonisation of three CPE carrier patients [19]. A first procedure of FMT in an 82-year-old female with persistent asymptomatic stool carriage of an OXA-48 carbapenemase-producing *K. pneumoniae* was conducted at the current institute and resulted in intestinal decolonisation, allowing her to benefit from a rehabilitation centre and then be transferred to a long-term care facility [20]. Faecal microbiota transplantation was reported to be efficient in CPE and vancomycin-resistant Enterococcus (VRE)-colonised patients [21]. Moreover, a prospective study in blood-disorder-harboring patients demonstrated the efficacy of FMT in restoring microbiota diversity and decolonising antibiotic-resistant bacteria, including CPE [22]. It is believed that 24 cases of FMT have been recorded to date for this indication [19–22].

The current study aimed to evaluate the impact of FMT on the delay of digestive decolonisation in long-term CPE/A-colonised patients, for whom transfer to a specialised medical care unit was compromised.

2. Methods

2.1. Study design

A single-centre study with retrospective matched case-control analysis to evaluate the effects of FMT on the clearance of CPE/A digestive carriage. The study reviewed medical records and laboratory data on FMTs performed between January 14, 2015 and October 20, 2017 in patients whose digestive tracts were colonised by CPE/A, and who were admitted to the institution for initial clustering and decolonisation purpose (cases). Data were also collected from CPE/A-colonised patients who were hospitalised at the University Teaching Hospital between November 1, 2014 and October 27, 2017, but did not receive FMT (controls) and compared the delay in clearance of CPE/A digestive carriage in both populations.

2.2. Inclusion criteria

Inclusion criteria were: age \geq 18 years, CPE/A colonisation confirmed by at least one positive out of three consecutive rectal swabs at daily intervals, agreement with procedure for FMT-treated

patient, and long-lasting colonisation as an obstacle to consecutive medical care in a specialised centre such as a rehabilitation centre.

2.3. Exclusion criteria

Exclusion criteria were: declined consent, pregnancy or breast-feeding, immunosuppression (HIV with CD4 $<$ 200/mm³, immunosuppressive therapy, neutropenia $<$ 0.5 G/L), patients for whom CPE/A colonisation was associated with acute CPE/A infection requiring antibiotic therapy at the time of FMT, occlusive syndrome or ileus, digestive perforation, and no need for decolonisation (patients returning home or whose colonisation was not an obstacle for further medical care).

2.4. Matching controls

Two CPE/A-colonised control patients per case were matched based on sex, age, bacterial species and carbapenemase type. The diagnosing clearance threshold differs for the two groups. The FMT-treated patients were hospitalised in the Infectious Diseases Department, where a protocol is currently available in both terms of treatment and follow-up of CPE/A colonisation. The control patients were hospitalised throughout the University Teaching Hospital and were identified through a database recording the positively tested patients for rectal CPE/A microbiologic identification.

2.5. Mapping of colonised sites

Patients who underwent FMT were previously sampled for various colonisation sites (urine, pharynx, nasopharynx, and rectum) and additional potential sites (gastrostomy, skin, wound, etc) to assess mapping of the CPE/A-colonised sites. Mapping was established on three consecutive days prior to FMT protocol.

2.6. Microbiological identification

Rectal swab confirmed CPE/A digestive colonisation. Each swab was plated onto chromID CARBA SMART selective media (Biomérieux, Marcy l'Etoile, France). Suspect colonies were subjected to MALDI-TOF MS analysis as previously described [23]. In case of identification of Enterobacteriaceae members, antibiotic susceptibility was performed according to EUCAST recommendations using the disk-diffusion method. MICs were determined using the Etest method (Biomérieux) for colistin, imipenem, ertapenem, tigecycline, minocycline, and fosfomicin. Carbapenemase-producing isolates were confirmed using β CARBATM test (Bio-Rad, Marnes-la-Coquette, France). Positive or uninterpretable results were confirmed by real-time PCR targeting OXA-48, NDM-1 and KPC genes [24] using CFX96 Real-Time PCR Detection System (Biorad).

2.7. Faecal microbiota transplantation preparation and controls

Donors were recruited according to the French authorities' recommendations [25].

2.8. Treatment protocol

Eight days before FMT, a 3-day nasopharyngeal decolonisation (in case of nasopharyngeal carriage) was performed using chlorhexidine gluconate 0.12% as a local gargling treatment of the mouth and swab application in nasal cavities. Five days prior to FMT, the patients received their first bowel wash (until stools became watery and clear). An oral non-absorbable bi-antibiotic pre-treatment was then administered. The first-choice regimen consisted of 5 days of colistin 6 MUI every 6 h and aminoglycoside

(either gentamicin or amikacin) 200 mg every 6 h in CPE/A sensitive, replaced by other antibiotics such as sulfadiazine (1 g three times a day) or fusidic acid (500 mg six times a day) in case of resistance, according to isolated CPE/A antibiotic susceptibility.

One day prior to FMT, the patient received a second bowel wash and was given a proton-pump inhibitor (pantoprazole 40 mg twice a day), which was carried out for 48 h.

2.9. Faecal microbiota transplantation

On the day of FMT, all present indwelling catheters (urinary, gastrostomy, etc) were replaced and the patient was moved to a new bedroom in order to limit the possibility of recolonisation through environmental pathogens. A nasogastric tube (after X-ray check of the tube position) or gastrostomy tube (if patient was equipped) was used to instill 300–400 mL of an aseptically-prepared mixture of 50 g of stool diluted in 0.9% NaCl into an empty stomach, after oral administration of antiemetic treatment (metoclopramide 10 mg) and instillation of a solution of 150 mL sodium bicarbonate 1.4%.

2.10. Follow-up

Rectal swabs were performed at days 3, 7, 14 and 21 to assess FMT success. Long-term follow-up (up to 6 months) was proposed for FMT-treated patients. Clearance was considered if rectal decolonisation occurred, confirmed on three successive negative rectal swabs within 2 weeks following FMT, whereas spontaneous decolonisation was considered achieved after a first negative rectal swab for control patients. Primary outcome (decolonisation period) was CPE/A clearance delay from the FMT for FMT-treated patients and from first documented digestive CPE/A colonisation for control patients.

2.11. Ethics

All FMTs were conducted after obtaining written informed consent (signed either by patients or their family, according to their medical condition), as required by the French legislation. Faecal microbiota transplantation was only considered for CPE/A-colonised patients for whom rehabilitation, surgery or chemotherapies were indicated and were likely to be delayed, based on the argument that CPE/A carriage would lead to a consecutive loss of chances. The study was approved by the Institutional Review Board Ethics Committee under number 2017-009.

2.12. Statistical analysis

Statistical analysis was performed using spreadsheet software Calc version 5.1.6.2 (Libreoffice). Student's *t*-test or χ^2 test, if appropriate, were used to compare the quantitative variables of the two groups (FMT-treated and control). Fisher's exact test was used to compare clearance rates in FMT-treated group and control group at day 14 post-FMT (treated) and day 14 post-documentation (control). Student's *t*-test was used to compare mean delays in discharge from the hospital between FMT-treated and control patients. Univariate Kaplan-Meier curve with Log rank analysis was performed using GraphPad Prism Version 4.03 for Windows (GraphPad software Inc., La Jolla California, USA). As for the Kaplan-Meier analysis, day 0 of comparison was considered to be FMT for patients who received FMT (second FMT for patients who received two FMTs) and first CPE/A documentation for control patients.

3. Results

3.1. Population characteristics

Thirty (10 cases, 20 controls) patients were included in the study, for whom the main characteristics are summarised in Supplementary Tables A and B. Associated CPE/A infections were documented in four cases and 12 controls. The CPE/A directed antibiotic therapies were administered to the FMT-treated patients: three (Patients 2, 3, 9) with CPE/A infections were cured but still colonised before administration of the FMT; one (Patient 4) was still under antibiotic treatment for a chronic osteoarticular infection at the time of FMT (performed after 3 of 12 weeks of antibiotic therapy) that was continued after FMT to complete 3 months of therapy; one (Patient 2) was treated for a urinary infection that occurred after receiving FMT in the context of persistent urinary carriage; and two received CPE/A directed antibiotic therapy for urinary decolonisation purposes without evidence of urinary infection. Additional CPE/A carriage concerned: nasopharynx or pharynx (five of eight) and urine (6 of 12). No significant differences in the main characteristics were found between cases and control patients, except that fewer FMT-treated patients had been hospitalised in rehabilitation facilities in the previous 6 months (Table 1).

3.2. Faecal microbiota transplantation characteristics

Fifteen FMTs were performed for 10 patients (five patients received two FMTs) (Fig. 1). Mean delay for diagnosis of intestinal carriage before FMT was 72.3 days (SD 36.4). Faecal microbiota transplantation was preceded by a chlorhexidine nasopharyngeal lavage for all nasopharyngeal CPE/A carriers except two (first FMT of Patient 2 and first FMT of Patient 3). All but two FMTs ($n=13$) were performed after 5 days of antibiotic treatment. The two first FMTs (Patient 1 and Patient 2) were performed after a 1-day antibiotic course. Antimicrobial agents used for decontamination were fosfomycin ($n=1$) and colistin ($n=12$) alone ($n=1$) or in association ($n=11$) with another antibiotic. Associated antibiotics were fusidic acid ($n=3$), amikacin ($n=2$), gentamicin ($n=2$), doxycycline ($n=1$), sulfadiazine ($n=2$), fosfomycin and gentamicin ($n=1$).

3.3. Faecal microbiota transplantation results

At day 14 post FMT, 8/10 treated patients (80%) fulfilled CPE/A clearance criteria. In the control group, 2/20 (10%) were negative for detection of digestive CPE/A at day 14 post documentation. One-tailed *P*-value highlighted a significant difference ($P < 0.001$) in the clearance rate between both groups. Overall FMT success rate reached 53.8% (8 of 15). Success rate after a first FMT was 40% (4 of 10). Five of the six unsuccessfully treated patients underwent a second FMT, after which the success rate per patient reached 80% ($n=8$). Three months after FMT, two patients (Patients 3 and 7) still tested positive for CPE digestive carriage. Patient 7 died 3.5 months after FMT, after several months of refusing therapeutic options against pulmonary adenocarcinoma (he was still considered a CPE carrier on the date of death). Six months after FMT, 9/10 treated patients (90%) were negative for digestive CPE/A (including a spontaneous decolonisation).

The median decolonisation period was 3 days post FMT for treated patients (mean 28.8 days, SD 54.2) vs. 50.5 days post documentation for control patients (mean 104.4 days, SD 130.7). The median delay of discharge from the hospital was 19.5 days post FMT for treated patients (mean 26.6 days, SD 23.3) vs. 41 days post documentation for control patients (mean 49.5 days, SD 40.1). No

Table 1
Comparison of the main characteristics of faecal microbiota transplantation-treated patients and control patients.

Patients characteristics	Total (n = 30)	FMT (n = 10)	Control (n = 20)	P-value
Age [§] (range)	59.9 (21–88)	59.2 (22–88)	60.3 (21–86)	0.20*
Age [§] > 60 years	16	6	10	0.60**
Male gender [§] (%)	24 (80)	8 (80)	16 (80)	1.00**
Hospitalisation				
< 6 months				
ICU	21	5	16	0.09**
Surgery	17	8	9	0.07**
Medicine	14	6	8	0.30**
Rehabilitation	10	6	4	0.03**
Comorbidities				
Renal failure	10	3	7	0.78**
Haemodialysis	2	1	1	0.60**
Cirrhosis	1	0	1	0.47**
Charlson Index	4.9	5.3	4.8	0.76*
Associated infection	16	4	12	0.30**
Colonisation sites				
Nasal/pharynx	13	5	8	0.60**
Urines	18	6	12	1.00**
Stool	30	10	20	1.00**

[§] matched factors.

* two-tailed *P*-value calculated by paired Student *t*-test.

** *P*-value calculated by χ^2 test.

significant difference in the mean delay of discharge could be observed (*P* 0.059). Discharge sites were either a rehabilitation centre (*n* = 6), home (*n* = 3) or hospital (*n* = 1) for FMT-treated patients.

The hospital stay, from the pre-FMT intervention (i.e. nasopharyngeal chlorhexidine decontamination and oral antibiotic treatment) to the discharge, for patients who underwent a successful FMT ranged from 10 (Patient 8, who returned home) to 77 days (Patient 4, whose discharge from a re-education centre was delayed by initial lack of rights to social security and development of a catheter-associated infection) (Fig. 1).

3.4. Kaplan-Meier compared analysis of faecal microbiota transplantation-treated and untreated colonised patients

Comparative Kaplan-Meier analysis of FMT-treated and untreated colonised patients is presented in Fig. 2. Log Rank tests using χ^2 revealed a significant difference in decolonisation rate at 1, 3 and 6 months, with a respective *P*-values of < 0.001, 0.013 and 0.0066 (median decolonisation of 4.5 days for FMT-treated patients, median decolonisation of 50.5 days for control patients).

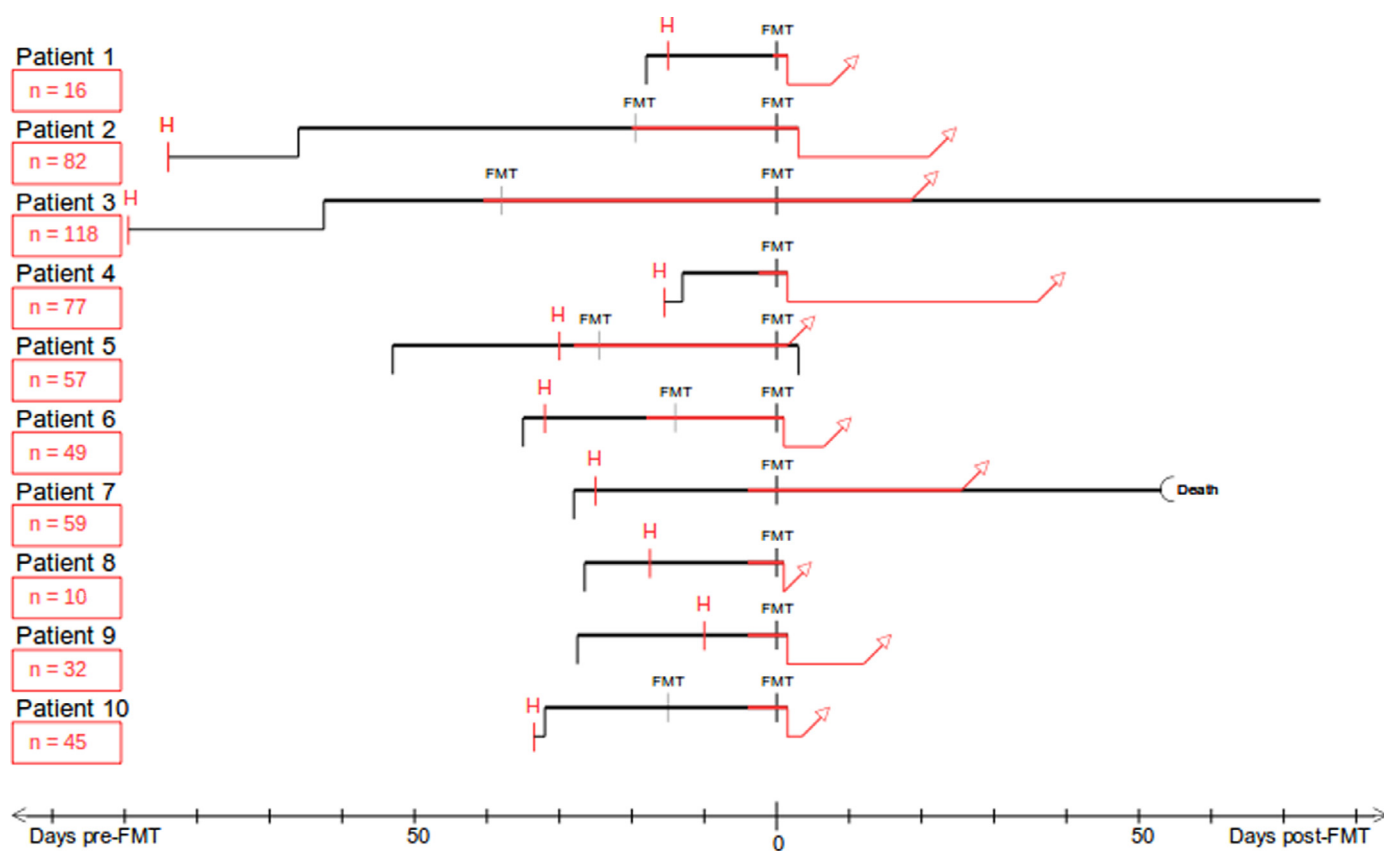
4. Discussion

Spontaneous decolonisation of intestinal carriage in CPE-colonised patients is a common event; however, natural clearance of the bacteria is slow. Zimmermann et al. reported a mean length of 387 days (95% CI 312–463), and 78% of their patients still had positive cultures at the third month of follow-up [5]. While colonisation with CPE leads to conflicting data on mortality, indirect mortality and morbidity are questionable. In their study on the loss of chance, Matt et al. reported that 75% of their patients had difficulties accessing care, especially surgery (66% of patients) [13]. Of 12 patients, seven (58%) returned home, two were transferred to a rehabilitation centre, one was still treated in their unit, one returned to the street, and one died; this highlighted the problematic outcome of these patients [13]. From experience, some of these patients indirectly die, as they are denied access to care because of isolation procedures (unpublished). Consequently, following experience using FMT towards this goal [20], the main objective is to shorten the clearance of CPE/A. The current study reported that FMT, according to protocol, is able to significantly reduce decolonisation time.

Studies on FMTs performed with the aim of CPE decolonisation are limited by their small sample sizes, which is due to the small amount of treated patients (*n* = 6 in Davido et al. [21] and *n* = 20 in Bilinski et al. [22]), and linked to ethical restrictions in proposing an invasive (use of nasogastric tube) and time-consuming procedure with comprehensible psychological reservations. To date, these studies have not had control populations to compare their results. The current study retrospectively chose control patients among identified CPE/A carriers from the whole of the University Teaching Hospital according to matching criteria. A substantial amount of them (9 of 20) who were not hospitalised in the Infectious Diseases department returned home and were not submitted to the procedure consisting of clinical and microbiological follow-up. Due to the lack of information, it was decided to define the threshold at one negative swab for control patients vs. three successive negative swabs for treated patients, with an assumed risk of underestimation of CPE/A time of clearance in favour of the control group compared to the treated group.

The average duration of colonisation was difficult to objectively compare in the current study, since some of the control patients are still colonised to date. Higher cure rates were observed than those observed in previous studies (Table 2) [21,22]. Davido et al. showed FMT to be effective for highly resistant enteric bacteria (CPE and VRE) in three of eight patients at 1 month and 3 months (including two of six CPE carriers, 33.3%). In a population including patients with blood disorders, Bilinski et al. were able to demonstrate a benefit of FMT, with efficacy on CPE carriage at 1 week for 12 of 20 patients (60%) and at 1 month for 12 of 16 patients (75%). Significant differences compared to the former FMT protocols [21,22] were the use of 3-day chlorhexidine nasopharyngeal decontamination for nasopharyngeal CPE/A carriers, repeat bowel lavages (two bowel lavages: one on the day before the onset of antibiotic pre-treatment, a second one the day before FMT itself), and a 5-day antimicrobial treatment prior to FMT. The current study observed that supplementary sites, other than urinary and digestive tracts, were often colonised (such as pharynx, skin, medical indwelling devices), which is consistent with previous observations [26], and suggested risks of contiguity recolonisation from untreated sites that can be avoided by local decolonisation procedures [27].

The human gut contains up to 3.8×10^{13} bacteria [28] that represent $54.7 \pm 1.7\%$ of stool weight [29]. Consequently, it is



Legend :

- H** | Date of hospitalization
- FMT** | Date of FMT
- FMT** | Date of former FMT
- ↗** Discharge from hospital
- Death** Death

n = Hospital stay from (first) pre-FMT intervention to discharge (figured as red line)

— Documented colonization (bold)
— Documented uncolonized time (unbold)

Fig. 1. Chronogram of the 10 faecal microbiota transplantation-treated patients. Highlighted segments represent the period of carriage (from documentation to the first negative sample for the faecal microbiota transplantation-treated patients fulfilling clearance criteria). Abbreviations: FMT, faecal microbiota transplantation

Table 2

Comparison of the characteristics of faecal microbiota transplantation in the different cohort studies reported to date.

	CPE cohort (n)	Bacteria	FMT route administration	Antibiotic pre-treatment	Bowel lavage	Iterative FMT	Success rate (% patients)	Crude success rate at 1 month (% FMT)
Davido et al.	8	VRE, CPE	Nasoduodenal tube	N	Y	N	37.5	25
Bilinski et al.	20	VRE, CPE, ESBL	Nasoduodenal tube	N	Y	Y	75	60
Current study	10	CPE, CPA	Nasogastric tube	Y	Y	Y (5)	80	53.8

Abbreviations: FMT, faecal microbiota transplantation; VRE, vancomycin-resistant enterococcus; CPE, carbapenemase-producing Enterobacteriaceae; CPE/A, carbapenemase-producing Enterobacteriaceae/Acinetobacter (CPE/A); ESBL, extended spectrum β -Lactamase

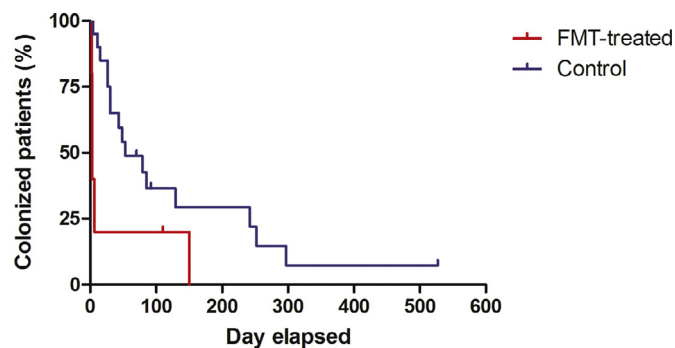


Fig. 2. Effect of faecal microbiota transplantation on carbapenemase-producing Enterobacteriaceae/Acinetobacter carriage.

Kaplan-Meier colonisation persistence compared analysis between CPE colonised control patients (blue) and long term CPE/A colonised patients treated with faecal microbiota transplantation (FMT) (red). Log rank test at 1 month (< 0.001), 3 months (0.013) and 6 months (0.0066) shows a significant difference in duration of CPE colonisation.

CPE/A, carbapenemase-producing Enterobacteriaceae/Acinetobacter

considered that the success rate of FMT might correlate with bowel preparation and that transplantation may have better chances of success if transplanted on empty and antibiotic pre-treated intestines. Based on those considerations, and supplemented by current experience, it is considered that an optimised FMT protocol should include: (1) chlorhexidine decontamination of nasopharyngeal colonised sites; (2) drastic reduction of intestinal content by two successive efficient bowel washes (one before antibiotic treatment, one before FMT); (3) 5-day prolonged treatment with high doses of antibiotics; (4) post-FMT environmental decontamination to limit recolonisation from environmental bacteria or colonised medical material, with room transfer and removal of medical tubes and catheters. For instance, Patient 2 underwent two FMTs. Following the first FMT, recolonisation was documented on stools, urine and gastrostomy button, requiring removal of all possible medical materials on the next performed FMT, after which no recolonisation could be documented. Unusual antibiotic pre-treatment was conducted for patients whose documented colonising CPE developed (Patient 5) or initially hosted (Patient 6) resistances to both gentamicin and amikacin. Both received the addition of colistin and fusidic acid, which were previously tested in synergic tests and showed in vitro efficacy. Such combinations, supported by recent studies on extensively-resistant *Acinetobacter baumannii*-infected mice, improve the efficacy of colistin by the addition of fusidic acid [30].

In conclusion, an optimised FMT protocol in CPE/A-colonised patients lead to a substantial reduction in decolonisation time, and significant difference in the carriage issue, allowing better access to care within a reasonable time. As in previous studies, this study was limited by the restricted size of the treated ($n = 10$) and control ($n = 20$) populations. Easier access to frozen/dried capsula should facilitate the FMT procedure, make it available for routine use, and help to overcome patients' reservations, leading to more frequent use of FMT for CPE/A decolonisation. This study should therefore be confirmed by a larger, more direct, ideally prospective case-control study.

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Declarations

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Competing Interests

None.

Ethical Approval

Approved by the Institutional Review Board Ethics Committee under number 2017-009.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2018.11.014.

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