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Alimentary Tract

Clinical effectiveness of bidirectional fecal microbiota transfer in the treatment of recurrent *Clostridioides difficile* infections

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ABSTRACT

Background: Fecal microbiota transfer (FMT) has become a standard of care in the prevention of multiple recurrent *Clostridioides difficile* (rCDI) infection.
Aim: While primary cure rates range from 70–80% following a single treatment using monodirectional approaches, cure rates of combination treatment remain largely unknown.
Methods: In a retrospective case-control study, outcomes following simultaneous bidirectional FMT (bFMT) with combined endoscopic application into the upper and lower gastrointestinal tract, compared to standard routes of application (endoscopy via upper or lower gastrointestinal tract and oral capsules; abbreviated UGIT, LGIT and CAP) on day 30 and 90 after FMT were assessed. Statistical matching partners were identified using number of recurrences (<3; ≥3), age and gender.
Results: Primary cure rates at D30 and D90 for bFMT were 100% (p=.001). The matched control groups showed cure rates of 81.3% for LGIT (p=.010), 62.5% for UGIT (p=.000) and 78.1% for CAP (p=.005) on D30 and 81.3% for LGIT (p=.010), 59.4% for UGIT (p=.000) and 71.9% for CAP (p=.001) on D90.
Conclusion: In our analysis, bFMT on the same day significantly increased primary cure rate at D30 and D90. These data require prospective confirmation but suggest that route of application may play a significant role in optimizing patient outcomes. ClinicalTrials.gov no: NCT02681068

1. Introduction

Clostridioides difficile is the most frequent cause of infectious nosocomial and antibiotic-associated diarrhea worldwide. *Clostridioides difficile* colonizes approximately 4–15% of the world population and up to 3–21% of hospitalized patients [1]. Progress from

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colonization to *Clostridioides difficile* infection (CDI) is usually triggered by exposure to antibiotics, resulting in an alteration of the physiological intestinal microbiota. These alterations result in activation of *C. difficile* toxin production with subsequent watery diarrhea, pseudomembranous colitis and other CDI associated complications [2].

Besides association with antibiotic exposure, another typical clinical feature of CDI is its recurrent pattern (rCDI). rCDI may occur spontaneously after successful treatment of an initial episode of CDI, but is often triggered by repeated antibiotic or immunosuppressive exposure [3]. Fecal microbiota transfer (FMT) can help prevent recurrent infection with *C. difficile* and has become a recognized treatment option in case of lack of sustained response to antibiotic treatment of CDI [4].

Data from FMT treatments in Germany is captured in the MicroTrans Registry and previous assessments of the data have revealed significant heterogeneity in the applied treatment methods, including the applied routes of application. The different approaches included use of enemas, endoscopy via lower gastrointestinal tract (LGIT), via upper gastrointestinal tract (UGIT) and per oral capsules (CAP) [5]. Besides these monodirectional FMT approaches, the MicroTrans Registry also holds data from patients treated with simultaneous bidirectional FMT (bFMT), in which endoscopic application via UGIT and LGIT is performed on the same day. Outcome data on combination FMT and this approach in particular are scarce [6].

To further evaluate this approach we performed a retrospective case-control study assessing the clinical effectiveness of bidirectional fecal microbiota transfer in the treatment of recurrent *Clostridioides difficile* infections.

2. Material and methods

2.1. MicroTrans registry

The data analyzed was taken from the German MicroTrans Registry, a retrospective observational multicenter study that collects data from patients who received FMT for rCDI. Currently data are collected at 35 sites using an online electronic case report form (eCRF) at ClinicalSurveys.net. The eCRF includes variables such as age, gender, pre-existing diseases, Eastern Cooperative Oncology Group (ECOG) status, FMT indication, number of FMTs, previous antibiotic treatment, other medication, bowel lavage, route of FMT, AEs (adverse events), short term cure (D30) and long term cure (D90).

2.2. Definitions

Primary cure was defined as documented absence of rCDI after a single FMT treatment on day 30 and 90 (D30 and D90). rCDI was defined based on the ESCMID (European Society of Clinical Microbiology and Infectious Diseases) criteria [4]. Treatment failure was defined as occurrence of another episode of CDI within D30 or D90.

2.3. Fecal microbiota transfer

Fecal microbiota transfer (FMT) describes a procedure in which processed feces donor material, often from anonymous donors selected by the corresponding clinic, is administered into the patient's intestine. The aim here is to rebuild a possibly damaged microbiota, in order to prevent and treat the pathogenic colonization of the *Clostridioides difficile* bacterium in the intestinal microbiota. In this retrospective case control study, a total of 4 groups are controlled among each other. Bidirectional fecal microbiota transfer (bFMT) was defined as an endoscopic FMT application into the upper and lower GI tract, as opposed to standard routes of application (endoscopy via upper or lower gastrointestinal tract and oral capsules; UGIT, LGIT, CAP). As there is no standardized procedure for the application method in Germany and furthermore it is still part of the research, the application method is determined by the individual centers themselves. The FMT characteristics such as type of material, grams of donor material, donor selection as well as antibiotic pre-treatment are compared in Table 1.

Table 1
FMT characteristics at first microbiota transfer for case and control groups.

	bFMT	UGIT	LGIT	CAP
FMT material (no.)				
fresh	31	24	19	0
frozen	1	1	3	32
unknown	0	7	10	0
Grams of donor material				
mean (g)	no data*	117.4	200.6	147.5
median (g)	no data*	77.5	140	140
unknown (no.)	no data*	20	15	2
Milliliters of suspension material				
mean (ml)	385	203.8	303.2	142.8
median (ml)	350	195	250	200
unknown (no.)	0	8	1	17
Cryoconservation of FMT material				
mean (days)	n/a	n/a	51.5	45.7
median (days)	n/a	n/a	51.5	32
unknown (no.)	1	1	1	1
Antibiotic pre-treatment (no.)				
vancomycin	23	23	21	14
fidaxomicin	4	0	3	10
metronidazole	1	1	0	0
rifaximin	0	0	1	0
fidaxomicin + vancomycin	0	0	0	2
metronidazole + vancomycin	1	3	1	0
rifaximin + vancomycin	0	0	1	0
no antibiotic pre-treatment	2	4	4	5
unknown	1	1	1	1
Donor selection (no.)				
anonymous	31	9	16	30
related	1	11	8	1
life partner	0	5	3	1
friends	0	0	1	0
unknown	0	7	4	0
	$n=32$	$n=32$	$n=32$	$n=32$

* The FMT products of the bFMT were always manufactured on the basis of the entire fecal donation of the donor, therefore there is no information about the weight. FMT, fecal microbiota transfer. bFMT, bidirectional fecal microbiota transfer. LGIT, lower gastrointestinal tract. UGIT, upper gastrointestinal tract. CAP, Capsule.

2.4. Case selection and statistical analysis

For identification of valid cases, the MicroTrans Registry was searched for patients receiving an FMT as secondary prophylaxis for rCDI and for whom follow-up data until D90 was available (s. Fig. 1). For a route of application to be established as a separate category, >5 cases needed to be documented in the database. This excludes application into the stomach ($n=5$) and another bidirectional application method, i.e. lower gastrointestinal tract and capsules ($n=1$), from the analysis. In a next step, bFMT cases were identified within the eligible patient group and matched 1:1 to a control from the UGIT, LGIT and CAP group, each. The matching process was based on the number of recurrences, which was binary coded for this study (<3; ≥3). The variables age and gender were also included in the matching process. If age and gender matching was not possible following the given criteria, the closest possible matching partner with respect to age was selected. Patient characteristics are given in Table 2. The respective significances were calculated with Pearson's Chi-square test using SPSS Statistics Ver. 26.

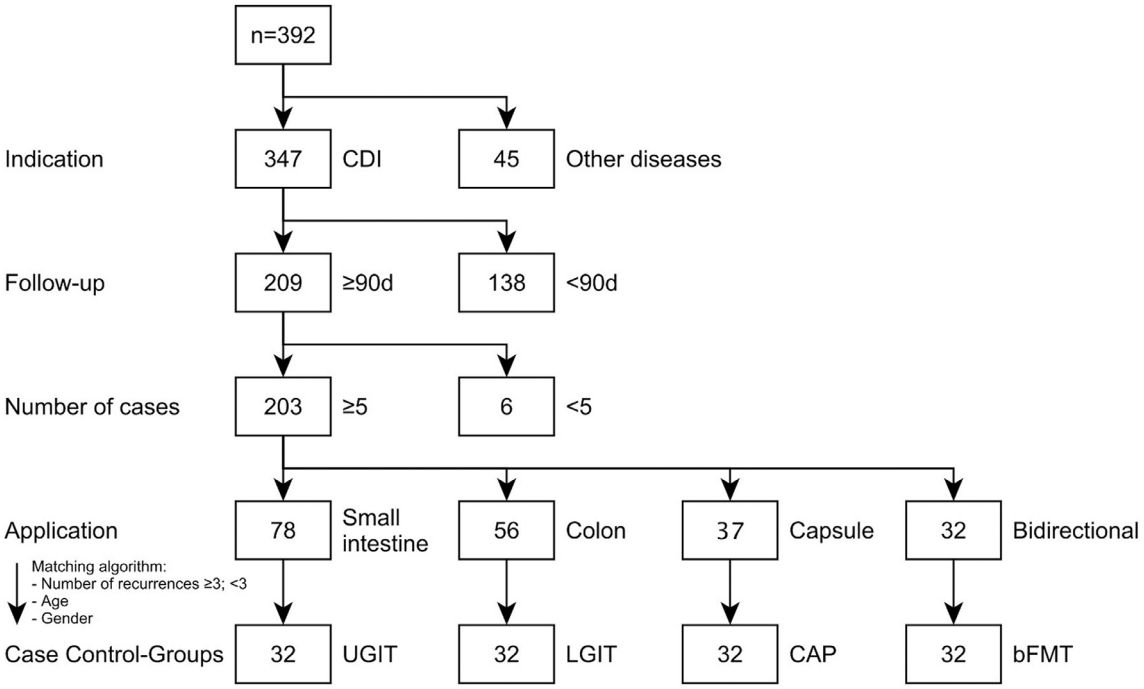

Fig. 1. Consort diagram indicating case numbers identified when employing inclusion & exclusion criteria.
There is no bFMT case which has been observed for less than 90 days and for an indication other than the rCDI. >5 cases per application are needed to be recognized as application method in this study. bFMT, bidirectional fecal microbiota transplantation. LGIT, lower gastrointestinal tract. UGIT, upper gastrointestinal tract. CAP, Capsule. rCDI, recurrent *Clostridioides difficile* infection.

In addition, an overall significance was calculated from all control groups and also from all other cases in the MicroTrans database that had a follow-up time of at least 90 days (s. Table 3).

2.5. Ethical compliance

This study protocol complies with the ethical requirements of the Declaration of Helsinki of 1975 as reflected in a priori approval by the institution's human research committee. The MicroTrans Registry was first approved by the Ethics Committee of the University Hospital Cologne, Germany (ID: 14–295, 29.12.2014) and is registered at ClinicalTrials.gov (no: NCT02681068). Since this is a retrospective registry collecting an anonymized dataset, applicable German law does not require informed consent. All authors had access to the study data and reviewed and approved the final manuscript.

3. Results

At the time of data retrieval (April 24, 2020), 392 FMT records from the MicroTrans Registry were accessible of which 347 (88.5%) had been performed to treat rCDI. 203 (58.5%) of these were evaluable for D90 analysis with more than 5 cases per application route (s. Fig. 1).

Overall, 32 patients had received a simultaneous bFMT at the Endoscopy Center in Starnberg, Germany. Each control group (UGIT, LGIT, CAP) comprised 32 patients. 8 centers contributed data to LGIT, 7 centers to UGIT and 2 centers to CAP. The median age in the bFMT group was 78.0 years with a mean of 73.3 years (IQR: 68.8–85). In the matched control groups, median age was 74 years with a mean of 70.9 years (IQR: 63–82.5). The majority of patients in the case (25/32; 78.1%) and control groups (71/96; 74.0%) were female. The number of recurrences had a median of 3 (IQR: 2–4) in the bFMT group, 3 (IQR: 3–4) in the UGIT group, 3 (IQR: 3–4) in the LGIT group and 3 (IQR: 3–4) in the CAP group. No patient with less than the 2nd recurrence received FMT treatment. Further patient characteristics are listed in Table 2.

In the bFMT group, there was no case of recurrence at D30 and D90. In the matched LGIT group 6/32 patients experienced a recurrence until D30 and D90 (18.8%; p=.010; relative risk (RR) 0.813; CI: 0.688–0.960). In the UGIT group, 12/32 (37.5%) patients experienced a recurrence until D30 ($p\leq$.000; RR 0.625; CI: 0.478–0.817) and 13/32 (40.6%) until D90 ($p\leq$.000; RR 0.594; CI: 0.446–0.791). In the CAP group, 7/32 (21.9%) experienced a recurrence until D30 (p=.005; RR 0.781; CI: 0.650–0.938) and 9/32 (28.1%) until D90 (p=.001; RR 0.719; CI: 0.579–0.893).

If all control groups are pooled, 25/96 (26.0%) patients showed a recurrence until D30 (p=.001; RR 0.740; CI: 0.657–0.833) and 28/96 (29.1%) until D90 (p=.001; RR 0.708; CI: 0.623–0.805).

In all 171 evaluated non-bFMT cases, 39/171 (22.8%) patients experienced a recurrence until D30 (p=.004; RR 0.784; CI: 0.724–0.848) and 41/171 (24.0%) until D90 (p=.002; RR 0.760; CI: 0.699–0.827). An outcome comparison for all evaluable FMT cases in the MicroTrans Registry is given in Table 3. This calculates to a NNT (number needed to treat) for bFMT of 4.6 for D30 and 4.2 for D90 (s. Table 4).

Of all patients comprised in the case control groups, one patient with bFMT showed nausea and constipation (1/32; 3.1%) as a treatment related side effect. There were no adverse reactions reported by patients with side effects in the LGIT group (0/32), 4/32 (12.5%) in the UGIT group and 2/32 (6.3%) in the CAP group. In total, 2 patients had severe side effects (aspiration and bleeding of small intestine), both in UGIT group. An outcome comparison for all application routes is given in Fig. 2.

4. Discussion

The general dominance of FMT over antibiotic therapy with vancomycin or fidaxomicin alone is well established. A single-

Table 2
Patient characteristics at first microbiota transfer for case and control group.

	Case (bFMT)	Control (UGIT + LGIT + CAP)
Number of cases	32	96
Age		
Median (IQR)	78 (68.5–85)	74 (63–82.5)
Gender		
Female - no. (%)	25 (78.1)	71 (74.0)
ECOG		
Median (IQR)	2 (1–3)	1 (0.5–3)
Comorbidities - no. (%)		
Cardiovascular	23 (71.8)	53 (55.2)
Endocrinological	11 (34.4)	31 (32.3)
Gastrointestinal (except CDI)	4 (12.5)	29 (30.2)
Nephrological	9 (28.1)	29 (30.2)
Hematological/oncological	4 (12.5)	19 (20.7)
Pulmonary	10 (31.3)	25 (26.0)
Neurological	2 (6.3)	13 (13.5)
Psychiatric	1 (3.1)	18 (18.8)
Orthopedic	1 (3.1)	11 (11.5)
Rheumatological	0 (0.0)	8 (8.3)
Urological	2 (6.3)	3 (3.1)
Other	4 (12.5)	13 (13.5)
Immunosuppression - no. (%)	2 (6.3)	20 (20.8)
CDI recurrences		
Median (IQR)	3 (2–4)	3 (1–4)
≥3 - no. (%)	29 (90.6)	85 (88.5)
Antibiotic pre-treatment - no. (%)	29 (90.6)	80 (83.3)
Bowel lavage - no. (%)	32 (100.0)	58 (60.4)
Adverse events - no. (%)	1 (3.1)	6 (6.3)
Outcome - no. (%)		
D30	32 (100.0)	71 (74.0)
D90	32 (100.0)	68 (73.9)

bFMT, bidirectional fecal microbiota transfer. LGIT, lower gastrointestinal tract. UGIT, upper gastrointestinal tract. CAP, Capsule. IQR, interquartile range. ECOG, Eastern Cooperative Oncology Group. CDI, *Clostridioides difficile* infection.

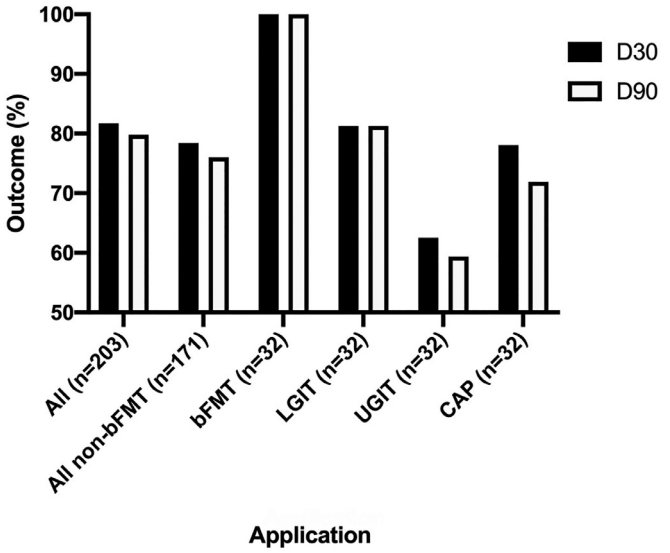

Fig. 2. Outcome comparisation for all applications of the MicroTrans Registry. bFMT, bidirectional fecal microbiota transfer. LGIT, lower gastrointestinal tract. UGIT, upper gastrointestinal tract. CAP, Capsule.

center, randomized trial by Hvas et al. with 64 patients showed superiority of FMT over drug treatment [7]. These findings are supported by a recent meta-analysis which identified six randomized controlled trials and seven uncontrolled trials, comprising 610 patients of which 439 experienced clinical cure (weighted pool rate (WPR) 76.1%; 95% confidence interval (CI), 66.4%–85.7%). Cure rates were lower for patients treated in controlled (139/216 patients; WPR, 67.7%; 95% CI, 54.2%–81.3%) as opposed to uncontrolled trials (300/394 patients; WPR, 82.7%; 71.1%–94.3%; $P < .001$) and for patients treated with an enema as opposed to colonoscopic delivery (WPR, 66.3% vs 87.4%; $P < .001$) [8]. The results of our case control study suggest that response to FMT may be further improved by use of bFMT.

In addition, previous data suggest that adverse drug reactions attributed to conventional FMT are rare, if donor screening and FMT application are carried out correctly. Reported rates of minor and usually transient reactions are below 10% and usually affect the gastrointestinal tract [9–12]. Serious adverse drug reactions have mostly been observed as a consequence of incomplete donor screening [13] or as a complication related to the endoscopy procedure and not to FMT material. Side effects concern endoscopic application via the UGIT in particular. In a previous MicroTrans analysis comprising 256 patients, we documented cases of aspiration pneumonia ($n = 2$), hemorrhage ($n = 1$) and loss of a tooth ($n = 1$) occurring during UGIT endoscopy [5]. Similar cases have been identified by other authors [14]. Even though these events are rare, they could have been avoided by the use of another application strategy, e.g. endoscopy via the LGIT or use of oral capsules. Particular the lower application route does not involve any endoscopy-related risk or inconvenience for the patients, and most capsule based approaches do not even require a bowel lavage prior to treatment.

While capsule FMT may be considered the safest procedure, our analysis shows a substantially higher primary response to bFMT when compared to treatment with oral capsules [15]. In clinical practice, local availability of these approaches and patient preference will be crucial determinants in the choice of route of application. Physicians should offer a transparent and balanced discussion to their patients, in order to explain these differences in the risk-benefit ratio of different FMT approaches.

The primary cure rate of 100% associated with bFMT at D30 and D90 is substantiated by observations of another group. Dutta et al. reported a comparable sustained response rate of 100% in 32 patients with a follow-up of 9.7–34 months (mean: 20.6 months). The reasons for bFMT being associated with such a significant increase in the response rate remains unexplored. Dutta et al. discuss prolonged bacterial contact time of FMT material with the gut mucosa following dual administration and subsequent improved bacterial engraftment, as well as the delivery of a large volume of FMT product without rapid colonic expulsion as potential mechanisms [6].

Table 3
Short and long term response on D30 and D90 for all and for individual FMT methods/modes of application.

Application	D30	D90
All FMT methods	166/203 (81.7%)	162/203 (79.8%)
All non-bFMT methods	134/171 (78.4%)	130/171 (76.0%)
Bidirectional FMT	32/32 (100%)	32/32 (100%)
Colonic FMT	47/56 (83.9%)	47/56 (83.9%)
Small Intestinal FMT	59/78 (75.6%)	57/78 (73.1%)
Capsule FMT	28/37 (75.7%)	26/37 (70.3%)

FMT, fecal microbiota transfer. bFMT, bidirectional fecal microbiota transfer.

Table 4
Statistical significance of all evaluated groups compared to bFMT.

Case	Control	n	Chi-square ($\chi 2$)	p-value	RR	NNT
bFMT $n=32$	MicroTrans Total D30	203	8.467	0.004	0.784 (CI: 0.724–0.848)	4.6
bFMT $n=32$	MicroTrans Total D90	203	9.614	0.002	0.760 (CI: 0.699–0.827)	4.2
bFMT $n=32$	Case-Control Total D30	128	10.356	0.001	0.740 (CI: 0.657–0.833)	3.8
bFMT $n=32$	Case-Control Total D90	128	11.947	0.001	0.708 (CI: 0.623–0.805)	3.4
bFMT $n=32$	LGIT D30	64	6.621	0.010	0.813 (CI: 0.688–0.960)	5.3
bFMT $n=32$	LGIT D90	64	6.621	0.010	0.813 (CI: 0.688–0.960)	5.3
bFMT $n=32$	UGIT D30	64	14.769	0.000	0.625 (CI: 0.478–0.817)	2.7
bFMT $n=32$	UGIT D90	64	16.314	0.000	0.594 (CI: 0.446–0.791)	2.5
bFMT $n=32$	CAP D30	64	7.860	0.005	0.781 (CI: 0.650–0.938)	4.6
bFMT $n=32$	CAP D90	64	10.473	0.001	0.719 (CI: 0.579–0.893)	3.6

bFMT, bidirectional fecal microbiota transfer. LGIT, lower gastrointestinal tract. UGIT, upper gastrointestinal tract. CAP, Capsule.

In addition to improved retention of large volumes we suggest that increased dosage may play a role in facilitating sustained response. At the site performing the bFMT, the FMT products were always manufactured on the basis of the entire fecal donation of the donor and were administered on the same day. On average, a single fecal donation surpasses 50 g (personal knowledge, unpublished). This may be compared to all CAP FMT products were the capsules were produced on the basis of exactly 50 g feces. Therefore, patients receiving bFMT were on average exposed to a higher dosage than those receiving CAP FMT. For treatments performed in the UGIT and LGIT groups, exact information on individual applied volumes is not available. As outlined in Table 1, the amount of suspension applied was highest in the bFMT group (mean 385 ml; median 350 ml), but still less than when adding the amounts applied in the LGIT and UGIT groups. Whether the therapeutic effect of an increased suspension volume used during monodirectional application would achieve similar effects to bFMT remains unknown. It is also possible that coverage of the entire relevant treatment region by the simultaneous bidirectional application increases the probability of a positive outcome. Dose dependency of response to FMT has recently become an issue of intense discussion in the FMT community. While a meta-analysis supports the use of fecal dosages of at least 50 g [16], an interventional trial found no difference in response between patients receiving FMT products based on 22.5 g vs. 45 g of stool. Patient numbers in this study were, however, very limited, therefore a FMT-dose cut-off evaluation does not seem reasonable at this point [17].

The overall lack of larger randomized trials and/or dose finding studies in the field of FMT may be identified as a limitation to the present expansion of clinical knowledge. Like our registry, most available data is retrospective and often lacks the level of resolution that is necessary to resolve issues of statistical confounding. For this reason, we were only able to use relatively simple parameters such as number of recurrences, age and gender for matching. As it is not yet known whether the treatment-specific variables such as ribotype 027, pre-existing conditions, donor selection, pre-treatment or pre-medication influence outcome, they were not considered in the matching process. It is important to mention that all patients in the CAP group received frozen preparations and experienced more frequent use of fidaxomicin compared to the other groups. Likewise, the choice of donor, as shown in Table 1, almost all patients in the bFMT (31/32) and CAP groups (30/32) received the fecal donation from anonymously selected donors, compared to the LGIT and UGIT groups, where patients often received donor material from relatives or life partners. Whether these differences have an impact on the individual outcome of the patient remains unknown.

Since all bFMT cases were performed at one center, a possible bias cannot be ruled out. No other bFMT cases are reported in Germany so far. Our favourable outcome for bFMT is additionally limited by the overall small sample size in the bFMT group ($n=32$) and the retrospective nature of the reported case-control study. Future prospective investigations with randomized, multicentric design are needed to generate more robust data.

In conclusion, the exact mechanisms of action of bFMT still needs to be determined and the substantially higher cure rates require confirmation in a prospective, multicentric setting and larger treatment groups. Nevertheless, the identification of high sustained response rates in combination with an acceptable safety profile in two large case series suggests that bFMT may have the potential to become a superior choice in the treatment of rCDI.

Declaration of Competing Interest

Maria J.G.T. Vehreschild has served at the speakers bureau of Akademie für Infektionsmedizin, Ärztekammer Nordrhein, Astellas Pharma, Basilea, Gilead Sciences, Merck/MSD, Organobalance, and Pfizer, received research funding from 3 M, Evonik, Glycom, Astellas Pharma, DaVolterra, Gilead Sciences, MaaT Pharma, Merck/MSD, Morphochem, Organobalance, and Seres Therapeutics and is a consultant to Alb-Fils Kliniken GmbH, Arderypharm, Astellas Pharma, Ferring, DaVolterra, MaaT Pharma, and Merck/MSD.

Andreas Stallmach served as a speaker, a consultant and/or an advisory board member for Astellas Pharma, Ferring Arzneimittel GmbH, Institute AllergoSan, MSD and Summit Therapeutics.

Martin Storr served as a speaker, a consultant and/or an advisory board member for Astellas Pharma and MSD.

The remaining authors declare no conflict of interest.

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