ORIGINAL ARTICLE

Fecal Microbiota Transplant in Patients With Recurrent *Clostridium Difficile* Infection

A Retrospective Multicenter Observational Study From the MicroTrans Registry

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SUMMARY

Background: The clinical effectiveness of fecal microbiota transplant (FMT) for the treatment of recurrent *Clostridium difficile* infections (rCDI) has been demonstrated in randomized controlled trials. To assess the current status of FMT in Germany with respect to active centers, local standards, clinical effectiveness and safety, the MicroTrans Registry (NCT02681068) was established.

Methods: In a long-term retrospective multicenter observational study by the German Clinical Microbiome Study Group (GCMSG), primary and secondary cure on day 30 and 90, as well as occurrence of treatment-related adverse events were assessed. In addition to patient demographic data, we provide an overview of the FMT procedures and techniques used at different centers.

Results: Overall, 133 eligible patients from 33 centers were included, of which 64.7% were female (n = 86). The mean age was 75 years (interquartile range: 59.5–81.5). Administration via the duodenal route (n = 59; 44.4%) was the most frequently applied option, followed by colonic (n = 55; 41.1%), capsule (n = 13; 9.8%), and gastric administration (n = 4; 3.0%). Primary cure on day 30 and 90 was achieved in 84.2% (n = 101/120) and 78.3% (n = 72/92) of patients, respectively. Including re-treatment, secondary response was achieved in 87.5% (d 30; n = 105/120) and 85.9% (d 90; n = 79/92), respectively. Treatment-related adverse events were documented in 16 patients (12.0%).

Conclusion: FMT is a safe and effective treatment option for rCDI. However, FMT is currently available only in few centers in Germany, and treatment options vary from one center to another.

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Clostridium difficile infection (CDI) is the leading cause of health-care related diarrhea worldwide (1, 2). Conservative treatment of CDI currently relies on the antibiotics metronidazole, vancomycin and fidaxomicin (3). Following treatment with these antibiotics, 9.0–26.9% of patients develop recurrent CDI (rCDI) (4).

Fecal microbiota transplant (FMT) has been recognized as a feasible and effective procedure decades ago, however, the first randomized trial assessing the clinical efficacy of FMT by duodenal infusions, achieving sustained clinical cure in over 90% of patients with rCDI was not published until 2013 (5). The success of this previously unpopular approach fueled various research efforts. In this context, other routes of application, i.e.

- gastric,
- colonic,
- rectal,
- or per capsule,

as well as improvement of FMT product storage using cryopreservation were assessed with favorable results (6–8). While most of these studies were observational, limited to one interventional treatment arm or to a small number of patients, a milestone randomized double-blind trial assessing the clinical efficacy of frozen as opposed to fresh FMT enemas in 232 adults was recently published and confirmed non-inferiority of frozen preparations (9). Inspired by the clinical impact of FMT and its rapid technical improvement, the interest of physicians in integrating FMT into their clinical armamentarium against rCDI is growing (10, 11). In this setting, physicians are likely to encounter difficulties when searching for reliable standards with respect to donor screening, microbiota preparation, and route of administration. At the same time, colleagues considering referral of patients for FMT have difficulties identifying qualified centers.

To assess the current status of FMT in Germany with respect to active centers, local standard procedures, as well as clinical effectiveness and safety, we have created the MicroTrans Registry and herewith present results of its first dataset.

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BOX

The captured patient-level data included:

- Age
- Sex
- Height
- Weight
- Comorbidities
- ECOG status (Eastern Cooperative Oncology Group)
- Indication for fecal microbiota transplant (FMT)
- Antibiotic therapy and chemotherapy in the pre-transplant period
- Immunosuppression
- Bowel-movement pre/post-transplant
- Fresh or frozen FMT preparation
- Co-medication with FMT
- Duration of storage
- Route of administration
- Response to treatment
- Primary and secondary cure on day 30 and 90
- Follow-up
- Adverse events
- Attributable mortality
- Overall mortality

Patients and methods

This is a long-term, retrospective, multicenter, observational study by the German Clinical Microbiome Study Group (GCMSG), registered at ClinicalTrials.gov under registration no. NCT02681068. A survey requesting information on the status of implementation of FMT was sent out to all member departments of the German Society of Digestive and Metabolic Diseases (DGVS), as well as to all medical centers that had already published reports or press releases of FMT performed at their institution. All centers that responded to this initial survey were contacted for detailed data from individual patients. Centers with no human resources for documentation were provided with a documentation assistant from the GCMSG.

Only patients undergoing FMT for recurrent or refractory CDI could be documented in an online eCRF (electronic case report form) from ClinicalSurveys.Net (12). CDI was defined as per the recent ESCMID (European Society for Clinical Microbiology and Infectious Diseases) guidelines (3). The standards used for conduct of FMT at the participating centers were at the discretion of the attending physician. Details on the captured patient-level data are shown in the *Box*.

Adverse events (AE) were documented only if considered at least potentially related to FMT. Data was entered into the database based on a review of the patient charts. Anonymized data from all participating centers were exported, tabulated, and analyzed centrally.

Response to FMT treatment was defined as absence of diarrhea after FMT for at least 48 hours. Primary cure at day 30 and day 90 was defined as resolution of CDI after FMT until the respective time point. Secondary cure criteria were fulfilled, if one or more further FMTs were necessary to achieve a sustained day 30 or day 90 response. Recurrence was defined as the occurrence of CDI after an initial response to treatment.

Statistical analyses were carried out using IBM SPSS Statistics software. Analysis of frequencies was performed in a descriptive fashion.

The study protocol was approved by the local ethics committees of each participating center.

Results

Overall, 720 German medical centers were contacted, of which 366 responded. Among them, we identified 39 medical centers performing FMT. Out of these, 33 centers documented 147 patients between January 2014 and February 2016. 133 of these met our inclusion criteria, while 14 documented patients had received an FMT for an indication other than rCDI. The median number of patients documented per site was 2 (range: 1–24). Patients were treated between November 2011 and July 2015.

The patient characteristics are shown in *Table 1*. Most patients receiving FMT were females (n=86; 64.7%) of advanced age (median: 75 years; interquartile

range [IQR]: 59.5–81.5). The median ECOG score was 2 (IQR: 1–3). The most frequently documented comorbidities consisted of the following types of condition:

- Cardiovascular (n = 79; 59.4%)
- Gastrointestinal (n = 43; 32.3%)
- Endocrinological (n = 40; 30.1%)
- Nephrological (n = 34; 25.6%).

A total of 3 patients (2.3%) had received chemotherapy within the last three months prior to FMT or were immunosuppressed for other reasons (n = 19; 14.3%). The median number of episodes before undergoing FMT was three (IQR: 1–4). The mean time to FMT after first diagnosis of CDI was 120 days (IQR: 60–210). Sixteen patients (12.0%) received FMT due to lack of response to all standard treatments. For treatment of previous episodes, most patients received sequential metronidazole and vancomycin (n = 61; 45.9%) or metronidazole, vancomycin and fidaxomicin (n = 34; 25.6%).

The characteristics of all first FMT procedures are shown in Table 2. Antibiotic induction treatment immediately preceding the FMT procedure was administered in 99 cases (74.4%), with oral vancomycin being by far the most frequently chosen option (n = 71; 53.4%). A bowel lavage prior to the FMT procedure was performed in 117 cases (88.0%). Frozen preparations were used in 20 cases (15.0%). Administration via the duodenal route (n = 59; 44.4%) was the most frequently applied option, followed by colonic (n = 55; 41.1%), capsule (n = 13; 9.8%) and gastric administration (n = 4; 3.0%).

A total of 16 patients (12.0%) experienced an AE. The following types of AE were classified as certainly or probably related: nausea, fever, abdominal pain, belching, emesis, throat/retrosternal discomfort, aspiration pneumonia (acquired during endoscopy), loss of a tooth (during endoscopy), irritable bowel syndrome, and hemorrhage (during endoscopy). A possible relationship was considered for food intolerance, weight gain, and polyneuropathy. None of these patients died within the following 30 days of the documented AE.

Information on response to treatment was available in 132 cases (99.2%). Of these, 124 (93.2%) experienced a favourable response to treatment within a median of 1 day (IQR: 0–3). Median follow-up was 141 days (IQR: 50–353). Maximum follow-up was 1825 days. Primary cure on day 30 was achieved in 101 of 120 patients (84.2%) and on day 90 in 72 out of 92 patients (78.3%). Duration of follow-up did not reach 30 and 90 days in 12 (9.1%) and 40 (30.3%) patients, respectively.

A second FMT was administered to 18 patients (13.5%), and one patient (0.8%) received four FMT procedures. Seven of the associated recurrences were possibly triggered by antibiotic treatment. Including re-treatment, secondary response on day 30 and 90 was achieved in 87.5% (n = 105/120) and 85.9% (n = 79/92).

TABLE 1

Patient characteristics at 1st FMT

Number of patients, n	133
Age (years)	
Median	75.0
IQR	59.5–81.5
Female, n (%)	86 (64.7)
Body mass index	
Median	22.6
Range	19.8–25.1
ECOG performance score, value	
Median	2
IQR	1–3
Comorbidities, n (%)	
Cardiovascular	79 (59.4)
Gastrointestinal (except CDI)	43 (32.3)
Endocrinological	40 (30.1)
Nephrological	34 (25.6)
Pulmonary	26 (19.5)
Psychiatric	20 (15.0)
Neurological	11 (8.4)
Urological	4 (3.0)
Rheumatological	4 (3.0)
Other*	8 (6.0)
None	10 (13.3)
Transplantation, n (%)	
Solid organ	5 (3.8)
Allogeneic stem cell	1 (0.8)
Immunosuppression, n (%)	
Chemotherapy	3 (2.3)
Other immunosuppressive medication	19 (14.3)
CDI recurrences before FMT, n	
Median	3
IQR	1–4
Type of sequential pre-treatment, n (%)	
Metronidazole only	4 (3.0)
Vancomycin only	13 (9.8)
Fidaxomicin only	2 (1.5)
Metronidazole + vancomycin	61 (45.9)
Vancomycin + fidaxomicin	8 (6.0)
Metronidazole + vancomycin + fidaxomicin	34 (25.6)
Unknown	11 (8.3)

FMT, fecal microbiota transplant; IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group (ECOG score range: 0–5); CDI, *Clostridium difficile* infection.

*Other: oncological 3 (2.3%), orthopedic 3 (2.3%), dermatological 1 (0.8%), ophthalmological 1 (0.8%)

TABLE 2

Procedure characteristics of 1st FMT

Number of patients, n	133
Antibiotic induction therapy, n (%)	
Metronidazole only	1 (0.8)
Vancomycin only	71 (53.4)
Fidaxomicin only	7 (5.3)
Rifaximin only	6 (4.5)
Combination	14 (10.5)
None	28 (21.1)
Unknown	6 (4.5)
Antimotility agent, n (%)	31 (24.8)
Proton pump inhibitor, n (%)	31 (24.8)
Frozen preparations, n (%)	20 (15.0)
Bowel lavage, n (%)	117 (88.0)
Type of application, n (%)	
Gastric	4 (3.0)
– Direct endoscopic	4 (3.0)
– Tube	0
Duodenal/jejunal	59 (44.4)
– Direct endoscopic	40 (30.1)
– Tube	19 (14.3)
Rectum/colon/terminal ileum	55 (41.4)
– Direct endoscopic	55 (41.4)
– Tube	0
Combination* ¹	2 (1.5)
Capsule	13 (9.8)
Patients with adverse event, n (%)	16 (12.0)
Type of adverse event, n (%)	
Nausea	5 (3.8)
Fever	3 (2.3)
Abdominal pain	3 (2.3)
Belching	2 (1.5)
Emesis	2 (1.5)
Food intolerance* ²	2 (1.5)
Throat/retrosternal discomfort	2 (1.5)
Aspiration pneumonia	1 (0.8)
Hemorrhage	1 (0.8)
Irritable bowel syndrome	1 (0.8)
Loss of a tooth	1 (0.8)
Polyneuropathy	1 (0.8)
Weight gain* ³	1 (0.8)

FMT, fecal microbiota transplant

*¹ direct endoscopic jejunal + direct endoscopic colon

*² 1 x spinach and salad, 1 x not further specified

*³ 10 kg over 12 months after FMT

Response by route of administration, antibiotic induction therapy, and performance of a preparatory bowel lavage is given in *Table 3*. Patients receiving FMT by application into the rectum/colon/terminal ileum experienced a primary response on day 30 and 90 in 89.6% (n = 43/48) and 83.3% (n = 25/30). For patients receiving FMT by application into the duodenum/jejunum, the respective results were 78.9% (n = 45/57) and 74.0% (n = 37/50). Patients taking capsules were cured in 84.6% (n = 11/13) and 83.3% (n = 10/12) of cases. Response rates were similar in patients with and without antibiotic induction therapy and with and without a preparatory bowel lavage, respectively.

During the observational period, seven patients (5.3%) died, two of them within 90 days of FMT. In six cases, the cause of death was not related to rCDI (solid tumor, hematological malignancy, urinary tract infection, pulmonary embolism, pneumonia (n = 2). In one patient, recurrence of CDI 7 days after FMT contributed to her death. A cerebrovascular accident was, however, provided as the primary cause of death.

Discussion

The MicroTrans Registry is the first structured documentation of procedures, clinical effectiveness, and safety of FMT in Germany. We documented a primary and secondary cure rate at day 90 of 84.2% and 85.9%, respectively. In the two largest US American observational studies, one in elderly patients and one in immunocompromised patients treated for rCDI, comparable 90 day primary and secondary cure rates of 78.0–82.5% and 89.0–95.9%, respectively, were observed (7, 13). An overview of outcomes available from the literature is shown in *Table 4*.

We recognized a trend towards improved response associated with application via the lower gastrointestinal route, followed by encapsulated frozen oral preparations. Furthermore, response rates were similar in patients with and without antibiotic induction therapy and with and without preparatory bowel lavage, respectively (*Table 3*). However, these findings do not allow any conclusions on the impact of these measures on clinical effectiveness of FMT, since there are a number of limitations to our retrospective data collection, e.g. centers using the duodenal route as their standard may also be following different pre-FMT procedures that may impact treatment success. At this point, our data do not yet allow logistic regression analysis addressing all relevant confounders. However, we have identified this point as one key question that merits further attention from our study group.

The scope and severity of AE in our study and previous observational studies are difficult to compare, since standards for adverse event reporting differed between studies. However, if only events potentially related to FMT are considered and compared, self-limiting gastrointestinal events in direct temporary association with the FMT dominate the AE spectrum. In major interventional and non-interventional studies

as well as our own observation, aspiration during endoscopy was the most consistently, yet unfrequently reported serious adverse event (5, 7, 9, 13).

eTable 2 gives an overview of all adverse events documented in published randomized trials with a suspected relation to FMT.

Limitations

Our study was limited by the inherent problems of observational studies. Follow-up differed widely, most likely due to the majority of patients being admitted specifically for their FMT procedure and being discharged shortly after the intervention. In the absence of a further rCDI or other medical problems, patients may be less likely to re-contact the performing institutions. This presumably indicates that our primary and secondary cure rates reflect clinical sustainability, since patients not returning are more likely to have experienced cure.

Conclusion

Concerning methodological aspects, we were able to show that FMT has already been implemented in a considerable number of German medical centers. However, treatment approaches differ considerably. To improve reproducibility of results and assure patient safety, harmonization of protocols for selection of eligible patients, donor screening, processing of stool samples, and administration of FMT products is urgently needed.

Only four centers documented more than 10 patients. Since documentation is not mandatory, it is possible that the participating centers documented fewer patients than actually treated. Irrespectively of this possible documentation bias, it may be assumed that some centers will emerge as top performers with respect to patient numbers, especially when considering the high costs, human resources, and time-consuming processes required to implement and maintain FMT as a readily available treatment option. This is especially relevant to physicians practicing within the German health care system, which currently does not provide reimbursement of the costs of FMT to the performing institution. Reimbursement and further regulation of FMT seems imperative, to ensure quality and safety of this very effective procedure. The favorable results from clinical trials should expedite implementation of reimbursement; however, the financial and regulatory status of FMT remains a matter of controversy in many countries, resulting in divergent decisions by the relevant authorities. The US Food and Drug Administration has set up a comparatively simple process to register an FMT in a clinical setting as well as to file an investigational new drug application as a basis for conducting a clinical trial. Presently, FMT is classified by German authorities as a medical drug regulated by the German Medicines Act (personal communication). Therefore, physicians in Germany may only perform FMT as a so-called *individuelle Heilversuch* (treatment of last resort). The conduct

TABLE 3

Primary response on day 30 and 90 by route of application, antibiotic induction therapy, and performance of bowel lavage

Type	D30	D90
Primary response/ total evaluable (%)	101/120 (84.2)	72/92 (78.3)
Route of application (%)		
Gastric	4/4 (100.0)	2/2 (100.0)
Duodenal/jejunal	45/57 (78.9)	37/50 (74.0)
Rectum/colon/ terminal ileum	43/48 (89.6)	25/30 (83.3)
Capsule	11/13 (84.6)	10/12 (83.3)
Combination* ¹	2/2 (100.0)	2/2 (100.0)
Antibiotic induction therapy (%) ^{*2}		
Yes	80/95 (84.2)	59/75 (78.7)
No	21/25 (84.0)	13/17 (76.5)
Bowel lavage (%)		
Yes	88/105 (83.8)	64/82 (78.0)
No	13/15 (86.7)	8/10 (80.0)

*¹ direct endoscopic jejunal + direct endoscopic colonic

*² information on this variable not available for 6 patients

of randomized controlled trials in Germany remains challenging, due to the high requirements set by the Medicines Act.

The data presented here represent a starting point for the continuous documentation of FMT in Germany. In our future analyses, we will focus in more detail on long-term safety aspects, and on the importance of supportive measures such as bowel lavage, route of administration, antibiotic induction therapy, proton pump inhibitor administration etc., for achieving a favorable treatment outcome. Additional centers, not only in Germany, but also on an international level, are invited to participate in this ongoing study.

Conflict of interest statement

Anne Fischer has received authors honoraria from CMEExtra.

Professor Storr has received consultancy fees and honoraria for speaking at scientific meetings from Astellas.

Dr. Lübbert has received consultancy fees from MSD as well as reimbursement of conference fees, travel and accommodation costs, and honoraria for preparing scientific meetings from Astellas and MSD. He received funds paid into a third-party account from Astellas.

Dr. Tacke has received reimbursement of travel costs and conference fees from Pfizer and speaker fees from Merck and Astellas.

Professor Cornely has received consultancy fees from Amplyx, Anacor, Astellas, Basilea, Cidara, Da Volterra, Daiichi Sankyo, F2G, Genentech/Roche, Gilead, Matinas, MedPace, Merck/MSD, Merck Serono, Paratek Pharmaceuticals, Pfizer, Sanofi Pasteur, Scynexis, Seres Therapeutics, Summit, Vical, and Vifor. He received honoraria for speaking at scientific meetings from Astellas, Basilea, Gilead, Merck/MSD, and Pfizer. He received funds for research projects that he initiated from 3M, Actelion, Astellas, AstraZeneca, Basilea, Bayer, Celgene, Cubist/Optimer, Genzyme, Gilead, GSK, Merck/MSD, Miltenyi, NanoMR, Pfizer, Quintiles, Scynexis, The Medicine Company, and Viropharma.

Professor Stallmach has received consultancy fees from Astellas, MSD, and Summit.

KEY MESSAGES

- This research is the first attempt to establish structured documentation of procedures, clinical effectiveness, and safety of fecal microbiota transplant (FMT) in Germany.
- In Germany, FMT has been implemented in clinical practice, but standards differ substantially between centers.
- Primary cure on day 30 and 90 was achieved in 84.2% (n = 101/120) and 78.3% (n = 72/92) of patients, respectively. Including re-treatment, secondary response was achieved in 87.5% (day 30; n = 105/120) and 85.9% (day 90; n = 79/92), respectively.
- While most patients received treatment through the upper intestine, there was a trend towards higher response rates associated with treatment through the lower intestine.
- There were no severe drug-related adverse events causing death within 30 days of their occurrence.

Dr. Vehreschild has received consultancy fees from Berlin Chemie, MSD/Merck, and Astellas. She received honoraria for preparing scientific meetings from Pfizer, MSD/Merck, Gilead, Organobalance, and Astellas. She received funds for a research project that she initiated from 3M, Astellas, Da Volterra, and Gilead.

Professor Lerch has received consultancy and reviewer fees and received funds for a research project that he initiated from Astellas and Norgine.

Dr. Hagel, Dr. Ehlermann, Dr. Frank, Dr. Tüffers, Professor Sturm, Dr. Link, Dr. Siebenhaar, Professor Glück, Erhard Siegel, Dr. Goeser, Professor Kölb, Professor Lohse, Dr. Maier, Dr. Schürle, Dr. Kandzi, Dr. Demir, and Dr. Solbach declare no conflicts of interest.

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REFERENCES

1. Lessa FC, Winston LG, McDonald LC, Emerging Infections Program CdST: Burden of Clostridium difficile infection in the United States. *N Engl J Med* 2015; 372: 2369–70.
2. Leffler DA, Lamont JT: Clostridium difficile Infection. *N Engl J Med* 2015; 373: 287–8.
3. Debast SB, Bauer MP, Kuijper EJ: European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for Clostridium difficile infection. *Clin Microbiol Infect* 2014; 20 (Suppl 2): 1–26.
4. Cornely OA, Nathwani D, Ivanescu C, Odufowora-Sita O, Retsa P, Odeyemi IA: Clinical efficacy of fidaxomicin compared with vancomycin and metronidazole in Clostridium difficile infections: a meta-analysis and indirect treatment comparison. *J Antimicrob Chemother* 2014; 69: 2892–900.
5. van Nood E, Vrieze A, Nieuwdorp M, et al.: Duodenal infusion of donor feces for recurrent Clostridium difficile. *N Engl J Med* 2013; 368: 407–15.
6. Youngster I, Russell GH, Pindar C, Ziv-Baran T, Sauk J, Hohmann EL: Oral, capsulized, frozen fecal microbiota transplantation for relapsing Clostridium difficile infection. *JAMA* 2014; 312: 1772–8.
7. Agrawal M, Aroniadis OC, Brandt LJ, et al.: The long-term efficacy and safety of fecal microbiota transplant for recurrent, severe, and complicated clostridium difficile infection in 146 elderly individuals. *J Clin Gastroenterol* 2016; 50: 403–7.
8. Cammarota G, Masucci L, Ianiro G, et al.: Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent Clostridium difficile infection. *Aliment Pharmacol Ther* 2015; 41: 835–43.
9. Lee CH, Steiner T, Petrof EO, et al.: Frozen vs fresh fecal microbiota transplantation and clinical resolution of diarrhea in patients with recurrent clostridium difficile Infection: A randomized clinical trial. *JAMA* 2016; 315: 142–9.
10. Kleger A, Schnell J, Essig A, et al.: Fecal transplant in refractory Clostridium difficile colitis. *Dtsch Arztebl Int* 2013; 110: 108–15.
11. Lubbert C, John E, von Muller L: Clostridium difficile infection: guideline-based diagnosis and treatment. *Dtsch Arztebl Int* 2014; 111: 723–31.
12. Vehreschild JJ, Rüping MJ, Farowski F, Cornely OA: ClinicalSurveys.net—a web-based research portal for rare infectious diseases. *Mycoses* 2009; 52: 391.
13. Kelly CR, Ihunnah C, Fischer M, et al.: Fecal microbiota transplant for treatment of Clostridium difficile infection in immunocompromised patients. *Am J Gastroenterol* 2014; 109: 1065–71.

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Supplementary material to:

Fecal Microbiota Transplant in Patients With Recurrent Clostridium Difficile Infection

A Retrospective Multicenter Observational Study From the MicroTrans Registry

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eTABLE 1

Overview of studies assessing clinical response to fecal microbiota transplant (FMT) (studies including at least 10 patients)

Application	Year	Author	Journal	Design	N	Cumulative response
Colonoscopy(17), gastroscopy (1)	1998	Lund-Tonnesen	Tidsskr Nor Laegeforen	Case series	18	83%
Gastric tube	2003	Aas	CID	Case series	18	83%
Colonoscopy + enema	2007	Wettstein	Congress abstract	Case series	18	83%
Enema	2008	Louie	Congress abstract	Case series	45	95%
Gastric tube	2009	MacConnachie	Q J Med	Case series	15	86%
Colonoscopy	2010	Arkkila	Congress abstract	Case series	37	92%
Colonoscopy	2010	Rohlke	J Clin Gastroenterol	Case series	19	100%
Colonoscopy	2010	Yoon	J Clin Gastroenterol	Case series	12	100%
Duodenoscopy (38), colonoscopy (2)	2010	Garborg	Scand J Infect Dis	Case series	40	83%
Colonoscopy	2011	Mattila	Gastroenterology	Case series	70	94%
Colonoscopy	2011	Mellows	J Okla State Med Assoc	Case series	13	92%
Jejun tube	2011	Polak	Klin Mikrobiol Infekc Lek	Case series	15	78%
Colonoscopy	2012	Brandt	Am J Gastroenterol	Case series	77	91%
Enema	2012	Kassam	Arch Intern Med	Case series	27	93%
Colonoscopy	2012	Hamilton	Am J Gastroenterol	Case series	43	95%
Colonoscopy	2012	Kelly	J Clin Gastroenterol	Case series	26	92%
Gastric tube	2013	Rubin	Anaerobe	Case series	75	79%
Duodenal tube	2013	Van Nood	NEJM	Randomized, phase III	16	94%
Colonoscopy (11), duodenal tube (1)	2013	Pathak	Clin Exp Gastroenterol	Case series	12	100%
Enema	2014	Emanuelsson	Scand J Infect Dis	Case series	23	70%
Enema	2014	Lee	Eur J Clin Microbiol Infect Dis	Case series	94	86%
Colonoscopy	2014	Allegretti	J Vis Exp.	Case series	22	100%
Capsules	2014	Youngster	JAMA	Phase II	20	90%
Colonoscopy	2014	Kelly	Am J Gastroenterol	Case series	80	89%
Colonoscopy	2014	Ray	Ochsner J	Case series	20	100%
Colonoscopy	2014	Khan	Can J Gastroenterol Hepatol	Case series	20	100%
Colonoscopy	2015	Cammarota	Aliment Pharmacol Ther	Randomized, phase III	20	90%
Colonoscopy	2015	Satokari	Aliment Pharmacol Ther	Case series	49	88%
Gastric tube (13), colonoscopy (1)	2015	Zainah	Dig Dis Sci	Case series	14	79%
Capsules	2015	Hirsch	BMC Infect Dis	Case series	19	89%
Gastric tube	2015	Kronman	J Pediatr Gastroenterol Nutr.	Case series	10	90%
Colonoscopy, gastroscopy (no information on distribution)	2015	Mandalia	Int J Colorectal Dis	Case series	95	98%

Colonoscopy	2016	Khoruts	Clin Gastroenterol Hepatol	Case series	229	92%
Enema	2016	Lee	JAMA	Randomized, phase III	219	73%
Colonoscopy (118), gastric tube (16), sigmoidoscopy (9), enema (3)	2016	Agrawal	J Clin Gastroenterol	Case series	146	96%
Colonoscopy (16), gastroscopy (1)	2016	Aroniadis	J Clin Gastroenterol	Case series	17	94%
Overall	1998– 2016	n.a.	n.a.	34 studies: 32 x case series 1 x phase II 3 x phase III	957	89%

eTABLE 2

Overview of adverse events and serious adverse events identified in randomized controlled trials with a suspected relation to fecal microbiota transplant (FMT)*

Adverse events considered related to FMT:	
During/immediatly after FMT	
Diarrhoea	n = 187 (73.3%)
Abdominal pain	n = 39 (15.3%)
Nausea	n = 10 (3.9%)
Belching	n = 3 (1.2%)
Follow-up	
Constipation	n = 47 (18.4%)
Bloating	n = 55 (21.7%)
Serious adverse events considered related to FMT	
During/immediatly after FMT	none
Follow up	none

* van Nood 2013, Cammarota 2015, Lee 2016, n = 255 (information in Lee 2016 was provided in % only. Therefore, absolute numbers were derived from these percentages and may differ slightly from the original numbers)