ORIGINAL RESEARCH

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Fecal Microbiota Transplantation Versus Vancomycin for Primary *Clostridioides difficile* Infection

A Randomized Controlled Trial

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Background: Fecal microbiota transplantation (FMT) is recommended for recurrent *Clostridioides difficile* infection (CDI), but its role in primary CDI is unclear.

Objective: To investigate the efficacy and safety of FMT in primary CDI.

Design: Randomized, open-label, noninferiority, multicenter trial. (ClinicalTrials.gov: NCT03796650)

Setting: Hospitals and primary care facilities in Norway.

Patients: Adults with CDI (*C difficile* toxin in stool and ≥3 loose stools daily) and no previous CDI within 365 days before enrollment.

Intervention: FMT without antibiotic pretreatment versus oral vancomycin, 125 mg 4 times daily for 10 days.

Measurements: The primary end point was clinical cure (firm stools or <3 bowel movements daily) at day 14 and no disease recurrence within 60 days with the assigned treatment alone.

Results: Of 104 randomly assigned patients, 100 received FMT or the first dose of vancomycin and were eligible for analysis. Clinical cure and no disease recurrence within 60 days without additional treatment was observed in 34 of 51 patients (66.7%) with FMT versus 30 of 49 (61.2%) with vancomycin (difference, 5.4 percentage points [95.2% CI, −13.5 to 24.4 percentage points]; *P* for noninferiority < 0.001, rejecting the hypothesis that response to FMT is 25 percentage points lower than response to vancomycin). Eleven patients in the FMT group and 4 in the vancomycin group had additional *C difficile* treatment. Clinical cure at day 14 and no recurrence with or without additional treatment was observed in 40 of 51 patients (78.4%) with FMT and 30 of 49 (61.2%) with vancomycin (difference, 17.2 percentage points [95.2% CI, −0.7 to 35.1 percentage points]). No significant differences in adverse events were observed between groups.

Limitations: Open-label design and reliance on clinical end points.

Conclusion: FMT may be considered as first-line therapy in primary CDI.

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Antibiotic-associated colitis due to *Clostridioides difficile* infection (CDI) is an important health problem worldwide (1, 2). Currently recommended therapy for primary infection is antibiotic treatment with vancomycin or fidaxomicin (3–5). Because 10% to 20% of patients experience 1 or more symptom recurrences after initial successful antibiotic therapy (3, 6), repeated and prolonged antibiotic regimens have often been necessary. Antibiotic therapy is expensive, causes considerable adverse effects and patient burden, and promotes antibiotic resistance, such as vancomycin-resistant Enterococcus (7). Reducing antibiotic use for any indication in general and for CDI specifically is desirable (8, 9).

In recent years, fecal microbiota transplantation (FMT) has markedly improved treatment for recurrent CDI (10, 11). FMT consists of direct instillation of fecal matter to the upper gastrointestinal tract (via capsules or duodenal infusion) or the lower gastrointestinal tract (via colonoscopy or enema), with the intention of restoring a normal functional colonic microenvironment. Currently, FMT is recommended for recurrent CDI. Because FMT addresses the cause of the infection, it may also be an effective alternative for patients with primary CDI; however, evidence is scarce (12–14).

We previously reported a proof-of-concept trial that indicated that FMT may be effective for primary

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CDI (12). A recent observational study supports these findings, but adequately powered randomized trials are not available (12–15). If FMT is noninferior to antibiotics in primary CDI, it would provide a valuable alternative to antibiotics for the large number of patients with primary CDI (16). In this article, we report the results of a phase 3 randomized trial of FMT versus vancomycin for patients with primary CDI.

METHODS

Trial Design and Oversight

We conducted an investigator-initiated, open-label, assessor-blinded, multicenter, noninferiority, phase 3 randomized clinical trial at 20 hospitals in Norway. The trial protocol is available at Annals.org. Eligible patients were identified by clinicians at the participating sites and general practitioners in the study areas.

Local study personnel approached each potentially eligible patient to provide information about the trial and assess eligibility. All participants provided written informed consent before randomization. The trial was approved by the Norwegian Medical Products Agency, the Regional Ethics Committee in South-East Norway, and the data protection officers at each participating hospital. The trial was registered at ClinicalTrials.gov (NCT03796650) and the European Union Drug Regulating Authorities Clinical Trials Database (2018-004580-31). The investigators vouch for the completeness and accuracy of the data and the fidelity of the trial to the protocol.

Eligibility Criteria

Patients were eligible if they were aged 18 years or older and had primary CDI, defined as diarrhea (≥3 loose stools per day), a positive stool test result for toxin-producing *C difficile* according to local procedures, and no diagnosis of CDI within 365 days before enrollment. We excluded patients with other stool pathogens known to cause diarrhea, ongoing antibiotic treatment for other infections that could not be stopped, inflammatory bowel disease, microscopic colitis, life expectancy of 3 months or less, serious immunodeficiency (defined as ongoing or recent chemotherapy and current or expected neutropenia with a neutrophil count $<0.500 \times 10^9$/L, or active severe immunocompromising disease), inability to comply with protocol requirements (for example, due to dementia), need for intensive care at enrollment, irritable bowel syndrome (diarrheal subtype), current or planned pregnancy or nursing, known or suspected toxic megacolon or ileus, total or subtotal colectomy, ileostomy or colostomy, more than 1 dose of *C difficile*–directed treatment (for example, 1 vancomycin capsule) administered, or contraindication for rectal catheter insertion or vancomycin.

Randomization and Trial Interventions

Patients were randomly assigned in a 1:1 ratio to either 1 FMT enema administered within 24 hours of randomization or standard-of-care treatment with 125 mg of oral vancomycin 4 times daily for 10 days. Both treatments were provided free of charge to all participants. The patient allocation sequence was computer-generated and was stratified by study site, with block sizes between 2 and 4 that were unknown to patients, site personnel, and investigators.

The FMT used in the trial was delivered by the Norwegian stool donor bank at the University Hospital of Northern Norway in Harstad, Norway (17). The bank has a quality assurance program with written procedures for rigorous donor and feces assessment in accordance with international recommendations (**Supplement Material 1**, available at Annals.org) to reduce risk for transmission of infectious pathogens and unknown disease-producing elements (18). FMT solutions consisted of 50 g of donor feces suspended in 120 mL of saline and 25 mL of glycerol and frozen at −80 °C. For use, they were thawed in water at 37 °C and diluted with 200 to 240 mL of saline (0.9% NaCl) in an enema bag.

Patients in the FMT group did not receive any antibiotic pretreatment. Before administration of FMT, patients were asked to empty their bladder and rectum, with no other preparation or sedation. The enema was administered to the rectum by trained health care personnel with the patient in a left lateral position. Immediately after administration, patients were asked to change position to distribute the FMT in the colon, as previously described (19).

Patients assigned to the vancomycin group received a 10-day course of 125-mg vancomycin capsules, as recommended in clinical guidelines (4, 20).

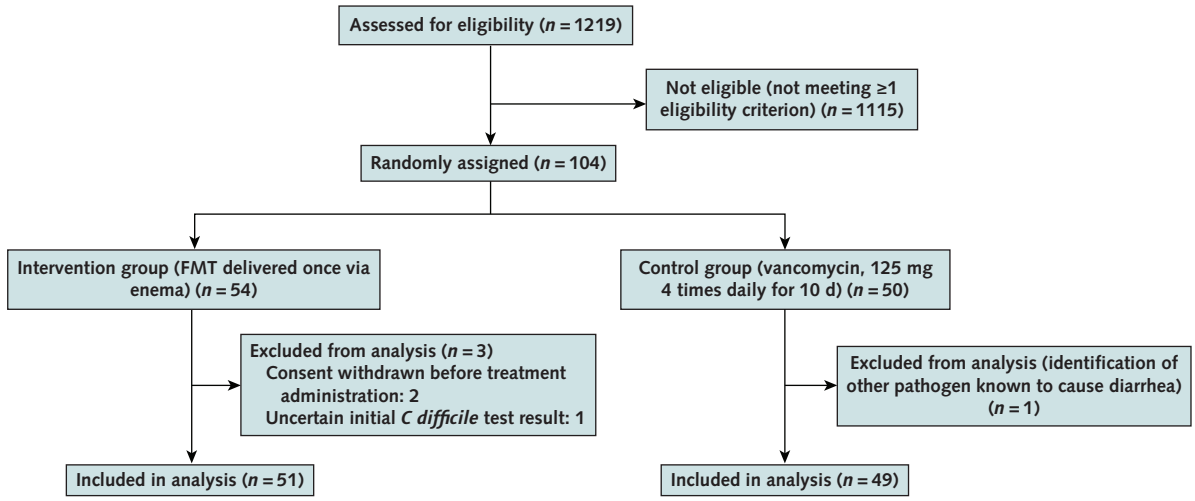
Patients in either treatment group who did not achieve clinical cure or had clinical deterioration before day 14 or recurrence of CDI were allowed additional treatment (metronidazole, vancomycin, fidaxomicin, or FMT) at the discretion of the treating physician.

Assessments and End Points

The primary end point was clinical cure at day 14 after the start of treatment with the assigned treatment alone and no recurrent CDI in the 60 days after the start of treatment. Clinical cure was defined as fewer than 3 stools per day or firm stools (Bristol Stool Chart type ≤4) for at least 48 hours at day 14. Key secondary end points were clinical cure at day 14 with or without additional treatment (metronidazole, vancomycin, fidaxomicin, or FMT) and no recurrent CDI within 60 days, and adverse events. In patients with clinical cure, recurrence was defined as all of the following: diarrhea for more than 48 hours during days 15 to 60 after onset of treatment, a positive stool test result for toxin-producing *C difficile*, and a clinical indication to start re-treatment as judged by the patient's physician.

We defined adverse events as any untoward medical occurrence, unintended disease or injury, or untoward

Figure 1. Study flow diagram.



C difficile = *Clostridioides difficile*; FMT = fecal microbiota transplantation.

clinical signs (including abnormal laboratory findings) after the start of treatment. Adverse events were classified as serious if they resulted in death or serious health deterioration, defined as a life-threatening illness or injury, permanent impairment of a body structure or body function, or requirement for a new or prolonged hospitalization. All adverse events and untoward medical occurrences were evaluated by assessors who were blinded to treatment allocation.

Data Collection and Management

Study data were registered in Viedoc clinical trial software and included patient characteristics (age, sex, antibiotic use before CDI, suspected source of CDI, and Charlson Comorbidity Index score [21]); study end points; additional treatment data; and patient-reported data from a diary of daily stool frequency and consistency, abdominal symptoms, and fever (yes or no) from day 1 through day 14 after the start of treatment. Patients assigned to the vancomycin group also recorded daily adherence to vancomycin. Blinded end point assessors called patients at day 60 (±5 days) to evaluate recurrence of CDI and adverse events during days 15 to 60.

Sample Size

Based on preliminary data, we expected that 65% of enrolled patients in both groups would achieve clinical cure at day 14 and no recurrence (5, 12, 14, 22, 23) (**Supplement Material 2**, available at Annals.org). With a 1-sided α level of 2.4% (equivalent to a 2-sided 95.2% CI), a noninferiority margin of 25 percentage points (absolute difference), power of 90%, and an expected 20% rate of loss to follow-up, we planned to include 188 patients in the trial (94 in each group). We prespecified a blinded interim analysis when 94 of the patients (50%) had reached the day 60 study end point, and unblinding and stopping of the trial was to be considered by the independent Data and Safety Monitoring Board (DSMB) if the noninferiority criterion for the primary end point was met with a *P* value of 0.005 or less. The O'Brien–Fleming method was applied for interim analyses (24, 25).

The absolute noninferiority margin of 25 percentage points was motivated by 3 advantages of FMT over first-line antibiotic therapy: 1) reduced use of antibiotics is a priority worldwide to reduce emerging antibiotic resistance; 2) FMT via enema is a minimally invasive, quick, one-off procedure compared with a 10-day antibiotic course; and 3) antibiotics such as vancomycin carry a risk for adverse effects and drug interactions. Even if FMT were to perform 25 percentage points worse (absolute difference) than vancomycin, 40% of patients with CDI would avoid long-lasting antibiotic treatment. Furthermore, patients who do not respond to FMT can receive rescue therapy with vancomycin. Due to the general advantages of FMT compared with antibiotics (vancomycin) and the ease of treating patients for whom FMT failed with antibiotics, a relatively wide margin of 25 percentage points makes sense from a clinical perspective. Our ethics committee (institutional review board in the United States) agreed with our reasoning and approved this margin.

Due to slow recruitment during the COVID-19 pandemic, the DSMB requested a blinded evaluation of the primary end point in August 2021, when 55 participants (29% of the planned sample size) had reached day 60. After reviewing the results, the DSMB requested that the prespecified interim analysis be postponed until 100 patients had reached day 60 (**Supplement Material 3**, available at Annals.org). This prespecified interim

analysis was conducted blinded in May 2024. After a review of the results, the DSMB requested unblinded data, and after reviewing the data, the DSMB recommended stopping the trial because the prespecified rule for confirming noninferiority for FMT compared with vancomycin was met and further enrollment and delay of publication of the results was deemed unethical.

Statistical Analysis

The main analyses were modified intention-to-treat analyses that included all randomly assigned patients who received the first assigned treatment dose (first vancomycin capsule or FMT enema). We also performed per protocol analyses that included all participants assigned to FMT who completed the treatment without a need for additional treatment, as well as patients who adhered to 75% or more of the assigned vancomycin capsules with no additional treatment.

We compared proportions of events in the 2 treatment groups with 95% CIs. Statistical tests for noninferiority (described earlier) were performed for primary and secondary efficacy end points, and tests for superiority (2-sided, $\alpha = 0.05$) were applied for safety outcomes. The last observations were carried forward for participants with missing data.

We performed prespecified subgroup analyses by patient sex, age, and Charlson Comorbidity Index score and sensitivity analyses with all missing data treated as failures and only patients with complete data included.

Role of the Funding Source

The study sponsors had no role in the study design; collection, analysis, or interpretation of the data; writing of the report; or the decision to submit the manuscript for publication.

RESULTS

From 1 June 2019 to 15 March 2024, we screened 1219 patients for eligibility (**Figure 1**; **Supplement Table 1**, available at Annals.org). One hundred four patients were eligible and were randomly assigned. Of these, 3 patients in the FMT group did not receive the assigned treatment and 1 patient assigned to vancomycin did not receive the first dose; these patients were excluded from the analyses. The trial was terminated on 2 July 2024 on a recommendation from the DSMB because the interim analysis criterion for noninferiority of the primary end point was met ($P = 0.001$ [**Supplement Material 3**]).

Baseline patient characteristics are presented in **Table 1**. Median patient age was similar between groups, and most patients had used antibiotics within the 3 months before enrollment.

Treatment Effects

The proportion of patients with clinical cure at day 14 with the assigned treatment alone was 70.6% (36 of 51) in the FMT group and 77.6% (38 of 49) in the vancomycin group (**Table 2**). Of these, 2 patients (5.6%) in the FMT group had disease recurrence compared with 8 (21.1%) in the vancomycin group between days 15 and 60. Thus, 34 of 51 patients assigned to FMT achieved the primary end point of clinical cure with the assigned treatment alone and no recurrence within 60 days (66.7% [95% CI, 52.1% to 79.2%]) versus 30 of 49 in the vancomycin group (61.2% [95% CI, 46.2% to 74.8%]) (**Figure 2** and **Table 2**), for a difference in treatment success of 5.4 percentage points (95.2% CI, −13.5 to 24.4 percentage points) and a *P* value less than 0.001 for noninferiority of FMT versus vancomycin.

Eleven patients in the FMT group and 4 in the vancomycin group received additional treatment, predominantly oral vancomycin (10 [91%] in the FMT group and 3 [75%] in the vancomycin group) (**Supplement Table 2**, available at Annals.org).

The proportion of patients who achieved the secondary end point of clinical cure at day 14 with or without additional treatment and no recurrent CDI before 60 days was 40 of 51 (78.4% [95% CI, 64.7% to 88.7%]) in the FMT group and 30 of 49 (61.2% [95%

Table 1. Patient Demographic and Clinical Characteristics at Baseline

Characteristic	FMT ($n = 51$)	Vancomycin ($n = 49$)
Median age (IQR), *y*	70 (51–79)	71 (58–77)
Female, *n (%)*	32 (62.8)	26 (53.1)
Source of infection, *n (%)*		
Community-acquired	36 (70.6)	27 (55.1)
Acquired in health care facility*	15 (29.4)	22 (44.9)
Antibiotic use in the previous 3 mo, *n (%)*	46 (90.2)	42 (85.7)
Proton-pump inhibitor use, *n (%)*	18 (35.3)	20 (40.8)
Charlson Comorbidity Index score, *n (%)*		
0–1	12 (23.5)	10 (20.4)
2–3	13 (25.5)	17 (34.7)
4–5	12 (23.5)	14 (28.6)
6–14	14 (27.5)	8 (16.3)
≥10 loose stools per day, *n (%)*	11 (21.6)	11 (22.5)
Median number of loose stools per day (IQR)	5 (3–8)	6 (4–9)
Blood samples		
Median C-reactive protein level (IQR), *mg/dL*	60 (12–106)	60 (35–115)
Leukocytosis (leukocyte count >15 × 10^9/L), *n (%)*	9 (17.7)	9 (18.4)
Renal failure (creatinine level >1.5 mg/dL), *n (%)*	10 (19.6)	12 (24.5)
Hypoalbuminemia (albumin <30 g/L), *n (%)*	12 (23.5)	13 (26.5)
Clinical examination findings, *n (%)*		
Abdominal tenderness	29 (56.9)	22 (44.9)
Fever (body temperature >38.5 °C)	1 (2.0)	0 (0)
Severe CDI†, *n (%)*	17 (33.3)	17 (34.7)

CDI = *Clostridioides difficile* infection; FMT = fecal microbiota transplantation.
* Hospital or nursing home.
† Defined as ≥1 of the following: leukocyte count >15 × 10^9/L, creatinine level >1.5 mg/dL, or fever (body temperature >38.5 °C).

Table 2. Treatment Effect of FMT Versus Vancomycin for Primary *Clostridioides difficile* Infection*

End Point	FMT ($n = 51$)		Vancomycin ($n = 49$)		Risk Difference (95.2% CI), *percentage points*	*P* Value for Noninferiority†
	Participants, *n (%)*	95% CI	Participants, *n (%)*	95% CI		
Primary end point	34 (66.7)	27 to 40	30 (61.2)	23 to 37	5.4 (−13.5 to 24.4)	<0.001
Clinical cure at day 14	36 (70.6)	–	38 (77.6)	–	–	–
Recurrence (days 15–60)‡	2 (5.6)	–	8 (21.1)	–	–	–
Secondary end point	40 (78.4)	33 to 45	30 (61.2)	23 to 37	17.2 (−0.7 to 35.1)	<0.001
Clinical cure at day 14	43 (84.3)	–	39 (79.6)	–	–	–
Recurrence (days 15–60)§	3 (7.0)	–	9 (23.1)	–	–	–

FMT = fecal microbiota transplantation.
* Eleven participants in the FMT group and 4 in the vancomycin group received additional treatment. The 95% CIs are not adjusted for early stopping of the trial and should not be used in place of hypothesis testing.
† The null hypothesis is rejected if the lower bound of the 95.2% CI is above −25 percentage points (delta).
‡ Among those with clinical cure without additional treatment.
§ Among those with clinical cure with or without additional treatment.

CI, 46.2% to 74.8%]) in the vancomycin group (Table 2). This equates to a difference in treatment success of 17.2 percentage points (95.2% CI, −0.7 to 35.1 percentage points) and a *P* value less than 0.001 for noninferiority of FMT versus vancomycin.

Subgroup analyses did not show significant differences in treatment effect by sex, age group, Charlson Comorbidity Index score, or CDI severity (Supplement Table 3, available at Annals.org).

Adverse Events

We observed no significant differences in the number of adverse events or serious adverse events between the treatment groups (Table 3; Supplement Tables 4 and 5, available at Annals.org). None of the reported adverse events were deemed to be related to the study treatment.

Seven patients (2 in the FMT group and 5 in the vancomycin group) died during the 60 days of follow-up. One death in each treatment group was due to recurrence of CDI. None of the deaths were deemed to be related to the study treatment.

Subgroup analyses showed no significant differences in the proportion of adverse events or severe adverse events by sex, age group, or Charlson Comorbidity Index score (Supplement Table 6, available at Annals.org).

Sensitivity Analyses

The proportions of missing data were similar between groups (Supplement Table 7, available at Annals.org). Sensitivity analyses of primary and secondary end points did not provide different results from the main analyses (Supplement Tables 8 and 9, available at Annals.org). Per protocol analyses of the primary and safety end points showed results similar to those of the main analyses (Supplement Tables 10 and 11, available at Annals.org).

DISCUSSION

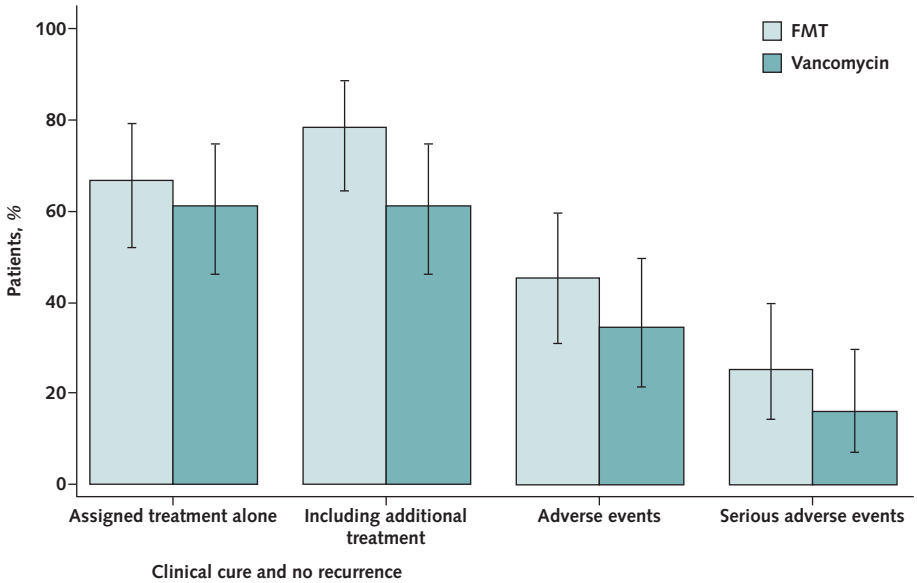
Our randomized trial shows that FMT is noninferior to standard-of-care vancomycin for patients with a first episode of CDI, with inferiority defined as a clinical cure rate with FMT that is more than 25 percentage points lower than with vancomycin. FMT even showed a 5.4% numerical superiority to vancomycin, which, although not statistically significant, indicates that FMT has the potential to change the current practice of antibiotic therapy and may establish FMT as a first-line treatment for primary CDI.

We used a noninferiority design for the trial because we believe it would be beneficial to administer FMT to patients with primary CDI and only treat with antibiotics those who are not cured with FMT or those who develop recurrence. If FMT is noninferior to standard-of-care vancomycin, it would significantly reduce antibiotic use, with a subsequent reduction in antimicrobial resistance. Our results indicate that it is reasonable to treat patients with primary CDI with FMT and provide antibiotics only to patients with ongoing symptoms or recurrence after FMT. Additional FMT doses may also be considered, as this has been shown to increase the treatment success rate in recurrent CDI (26).

Early stopping of randomized trials should be considered only if continuation would challenge ethical principles. We applied strict, prespecified stopping rules and blinded assessments of interim analyses by the independent DSMB as the basis for trial termination. The analysis after randomization of 104 patients established noninferiority of FMT compared with standard-of-care vancomycin. We therefore deemed it urgent to report our findings to the medical community and give all patients with primary CDI and their caregivers the chance to consider FMT.

Previous randomized trials of vancomycin in CDI have shown higher (5) or lower (27) rates of clinical

Figure 2. Proportion of patients with treatment effects and adverse events by treatment group.



The bars show the proportion of patients who achieved the primary and key secondary end points by treatment group. The error bars represent 95% CIs. Assigned treatment alone (primary end point): Clinical cure at day 14 and no disease recurrence with the assigned treatment alone. Including additional treatment (secondary end point): Clinical cure at day 14 and no recurrence with or without additional treatment. FMT = fecal microbiota transplantation.

cure without recurrence than the vancomycin group in our trial. It is reassuring that our cure and recurrence rates in the FMT group are similar to those in a recent observational study that used antibiotic pretreatment in most patients (15). In studies of FMT in recurrent CDI, the reported treatment success rate has been higher than (27) or similar to (28) our results. Higher success rates in recurrent infection may be due to a more select patient group. More than 40% of patients in our trial had a Charlson Comorbidity Index score of 4 or higher, indicating severe comorbidity (29), and one third of the included patients had severe CDI. However, by design, we did not include patients in need of intensive care treatment or with toxic megacolon due to severe CDI.

In contrast to previous trials, we administered FMT without antibiotic pretreatment (13, 14, 26). Our results show that such pretreatment may not be necessary to achieve clinical cure. Antibiotics (alone or in combination with FMT) involve important challenges, such as adverse effects and contraindications, allergic reactions, interactions with other drugs, costs, and the development of antibiotic-resistant bacteria.

FMT can be administered in oral capsules, via enemas, or through nasojejunal tubes or endoscopes (30–32). The optimal protocol and route of FMT instillation in recurrent CDI has not been established (28, 33). We used enema application, which is a simple bedside procedure that requires minimal training and equipment, little patient burden and time, and no sedation or premedication (22).

The main strengths of our trial are its randomized design and real-world clinical setting. A limitation is the reliance on clinical end points without stool tests for *C difficile* or FMT engraftment after treatment. Another limitation is the open-label design, which involves certain risks of bias. The unblinded investigators might have been inclined to manage signs of early treatment failure differently in the FMT and vancomycin groups. However, we believe that an inclination to start additional treatment would be stronger in patients who received FMT and thus would possibly result in an underestimation of its true effectiveness as first-line treatment for CDI. Also, we used vancomycin because it is the most used

Table 3. Adverse Events of FMT Versus Vancomycin for Primary *Clostridioides difficile* Infection*

Adverse Events	FMT ($n = 51$)		Vancomycin ($n = 49$)		Risk Ratio (95% CI)	Risk Difference (95% CI), *percentage points*
	Participants, *n (%)*	95% CI	Participants, *n (%)*	95% CI		
None	28 (54.9)	–	32 (65.3)	–	–	–
Any adverse event	23 (45.1)	16 to 30	17 (34.7)	11 to 24	1.30 (0.80 to 2.12)	10.4 (−8.7 to 29.5)
Any serious adverse event	13 (25.5)	7 to 20	8 (16.3)	4 to 15	1.56 (0.71 to 3.44)	9.2 (−6.7 to 25.0)

FMT = fecal microbiota transplantation.
* There was no statistically significant difference in the proportion of participants with adverse events.

antibiotic for the indication, but we did not compare FMT with fidaxomicin (3–5).

In conclusion, this randomized phase 3 trial indicates a potential role for FMT in primary CDI.

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