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CLINICAL AT

Fecal Microbiota Transplantation Is Superior to Fidaxomicin for Treatment of Recurrent *Clostridium difficile* Infection

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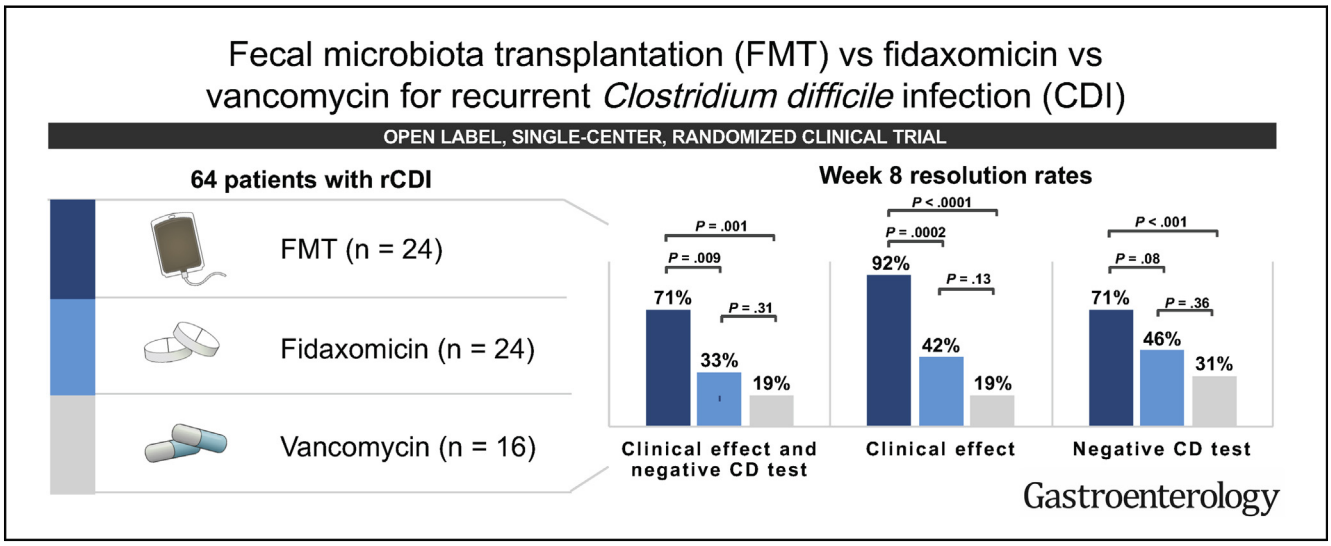

See Covering the Cover synopsis on page 1225.

BACKGROUND & AIMS: Fecal microbiota transplantation (FMT) is recommended for treatment of recurrent *Clostridium difficile* infection (rCDI). We performed a single-center randomized trial to compare the effects of FMT with those of fidaxomicin and vancomycin. **METHODS:** We studied consecutive adults with rCDI seen at a gastroenterology clinic in Denmark from April 5, 2016 through June 10, 2018. Patients were randomly assigned to a group that received FMT, applied by colonoscopy or nasojejunal tube, after 4–10 days of vancomycin (125 mg 4 times daily; FMTv; n = 24), 10 days of fidaxomicin (200 mg twice daily; n = 24), or 10 days of vancomycin (125 mg 4 times daily; n = 16). Patients who had rCDI after this course of treatment and patients who could not be randomly assigned to groups were offered rescue FMTv. The primary outcome was combined clinical resolution and a negative result from a polymerase chain reaction test for *Clostridium difficile* (CD) toxin 8 weeks after the allocated treatment. Secondary end points included clinical resolution at week 8. **RESULTS:** All 64 patients received their assigned treatment. The combination of clinical resolution and negative results from the test for CD were observed in 17 patients given FMTv (71%), 8 patients given fidaxomicin (33%), and 3 patients given vancomycin (19%; $P = .009$ for FMTv vs fidaxomicin; $P = .001$ for FMTv vs vancomycin; $P = .31$ for fidaxomicin vs vancomycin). Clinical resolution was observed in 22 patients given FMTv (92%), 10 patients given fidaxomicin (42%), and 3 patients given vancomycin (19%; $P = .0002$; $P < .0001$; $P = .13$). Results did not differ significantly between patients who received FMTv as their initial therapy and patients who received rescue FMTv. There was 1 serious adverse event that might have been related to FMTv. **CONCLUSIONS:** In a randomized trial of patients with rCDI, we found the FMTv combination superior to fidaxomicin or vancomycin based on end points of clinical and microbiological resolution or clinical resolution alone. ClinicalTrials.gov, number NCT02743234; EudraCT, j.no 2015-003004-24.

Keywords: Microbiome; Bacteria; Comparison; Antibiotic.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Clostridium difficile infection (CDI) is a major cause of nosocomial diarrhea and occurrence is increasing both in hospital settings and in the community, posing a serious public health challenge.

NEW FINDINGS

The combination of vancomycin and fecal microbiota transplantation (FMT) was superior to fidaxomicin or vancomycin in patients with recurrent *Clostridium difficile* infection (rCDI), based on endpoints of clinical and microbiological resolution or clinical resolution alone.

LIMITATIONS

The study included very few patients infected with *Clostridium difficile* ribotype 027.

IMPACT

Patients with rCDI should be treated with the combination of vancomycin and FMT. Adverse events should be monitored closely.

Clostridium difficile (CD) infection (CDI) is a major cause of nosocomial diarrhea and constitutes 20%–30% of antibiotic-associated diarrhea.[1] The occurrence of CDI is increasing in hospital settings and in the community, and the disease poses a serious public health challenge.[2–5] Risk factors for developing CDI include advanced age, comorbidity, and recent antibiotic use.[6] Ninety-day mortality is up to 22%, and CDI is a contributing factor in up to 40% of these deaths.[6–8] The recurrence risk is 20% and increases with age older than 65 years, severe underlying disease, and use of antibiotics or proton pump inhibitors.[9–11] Patients who have 1 recurrent CDI (rCDI) have a 45% risk of further recurrence.[12] In patients with multiple recurrences, the risk of further recurrence approaches 75%.[13,14]

Fecal microbiota transplantation (FMT) is an emerging therapeutic option for patients with rCDI.[15–17] Resolution rates of 70%–90% after FMT for rCDI have been consistently reported in observational studies[18–22] and randomized clinical trials.[13,14,23–25] FMT could induce sustained symptom resolution and general well-being[26] and could be effective in complicated or severe CDI.[27,28] In the initial clinical trials, it was superior to high-dose[14] and tapered[13] vancomycin and placebo.[23] Its role in a generic treatment algorithm remains to be determined,[29,30] and its effect has not been compared with recently developed, orally ingested, nonabsorbable antibiotics such as fidaxomicin.[31] Although fidaxomycin and vancomycin are equal as initial therapies for CDI, the recurrence rate is lower with fidaxomicin than with vancomycin.[32–35] Its effects in rCDI have been described in observational studies[36,37] and in subgroups in clinical trials.[38]

In this study, we compared the effects of FMT, fidaxomicin, and standard-dose vancomycin for rCDI.

Methods

Study Design

This was a randomized, active-comparator, open-label clinical trial that was carried out in a public referral gastroenterology center in Denmark. All patients who were referred for rCDI from April 5, 2016 to June 10, 2018 were consecutively screened for project participation.

Study Participants and Inclusion Criteria

Of 120 consecutive patients referred during the study period, we randomized 64 adult patients with rCDI and documented recurrence within 8 weeks after stopping anti-CDI treatment. Inclusion criteria were age at least 18 years, at least 3 more liquid stools (Bristol 6–7) per day, a positive polymerase chain reaction test result for CD toxin A, toxin B, or binary toxin, and at least 1 prior treatment course with vancomycin or fidaxomicin for CDI. The exclusion criteria were pregnancy or breastfeeding, inability to speak or understand the Danish language, any ongoing antibiotic treatment, use of drugs with a known interaction with vancomycin or fidaxomicin, allergy to either study drug, fulminant colitis that contraindicated medical treatment, or the treating physician's evaluation that the patient could not tolerate project inclusion (Supplementary Figure 1). All patients had fecal tests performed for *Salmonella*, *Campylobacter*, *Yersinia*, and *Shigella* species. Active inflammatory bowel disease was treated concomitantly. Because randomization was performed before initiating treatment and one of the treatment arms included standard vancomycin, project participation implied a risk of up to 2 further recurrences. In frail or septic patients, this was considered unethical, and these patients were not randomized.

Study Interventions

Patients were randomized to FMT preceded by 4–10 days of vancomycin 125 mg 4 times daily (FMTv; n = 24), 10 days of fidaxomicin (Dificlir, Astellas Pharma, Leiden, Holland) 200 mg 2 times daily (n = 24), or 10 days of standard treatment of vancomycin (Vancocin, Strides Arcolab, Watford, UK) 125 mg 4 times daily (n = 16). All treatments were provided to the patients free of charge. All patients were included by a study investigator.

Patients who had rCDI after the primary allocated treatment were offered rescue FMTv (Supplementary Figure 1).

Patients who could not be randomized because they fulfilled at least 1 exclusion criterion (Supplementary Figure 1) were offered FMTv off protocol. Clinical characteristics and FMT outcome data for these patients were evaluated as an observational follow-up study.

Abbreviations used in this paper: **AE, adverse event; CD, *Clostridium difficile*; CDI, *Clostridium difficile* infection; CI, confidence interval; FMT, fecal microbiota transplantation; FMTv, fecal microbiota transplantation preceded by vancomycin; rCDI, recurrent *Clostridium difficile* infection; SAE, serious adverse event.**

Most current article

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FMT was carried out using a frozen–thawed single-donor solution of donor feces 50 g that was applied using colonoscopy or a nasojejunal tube as previously described[17] and as outlined in the Supplementary Appendix. Healthy feces donors were recruited and screened at the public blood center at Aarhus University Hospital (Aarhus, Denmark).[39] All donations were voluntary, and donation and handling were carried out according to the National Danish Tissue Act. Colonoscopically delivered donor feces was applied to the patient after standard lavage and with one third delivered into the terminal ileum, one third in the cecum, and one third anally to the hepatic flexure. Nasojejunal delivered feces was applied for 10 minutes with the patient sitting and after an overnight fast. Delivery mode was decided after a dialogue with the patient. As a first choice, we advocated for colonoscopy because this is associated with the highest rate of success and allowed for differential diagnostics in patients who had not had a previous colonoscopy. In frail patients who could not tolerate bowel lavage or in patients whose previous colonoscopy had been technically difficult because of adhesions, we advocated for nasojejunal tube delivery.

Outcome Measures

The primary end point was combined clinical resolution and a negative CD test result without the need for rescue FMTv or colectomy 8 weeks after the initial treatment. Secondary end points included clinical resolution at week 8, a negative CD test result at week 8, combined clinical resolution and negative CD test result at week 1, clinical resolution at week 1, and a negative CD test result at week 1. Patients who had clinical recurrence and had a positive CD test result before or at week 8 were offered rescue FMTv with similar follow-up. Patients who could not be randomized were offered FMTv off protocol with similar follow-up at 1 and 8 weeks.

For comparison with other previously published clinical trials, a post hoc outcome measure was defined: resolution of CD-associated diarrhea (ie, clinical resolution or persistent diarrhea with a negative CD test result).

The CD test was performed as an in-house or, for urgent diagnosis, as a GeneXpert (Xpert C. difficile BT, Cepheid, Sweden) polymerase chain reaction targeting genes for toxin A (in house only), toxin B, and binary toxin, and the deletion in position 117 in the *tcd*C gene (*tcd*C-Δ-117) to detect CD ribotype 027. Any combination of toxins was considered a positive test result. For a positive test result for binary toxin or *tcd*C-Δ-117, a specimen was referred to the Danish reference laboratory at the Statens Serum Institut (Copenhagen, Denmark).

Adverse Events

Adverse events (AEs) and serious AEs (SAEs) might be underreported in FMT studies.[40–42] We prospectively documented AEs and SAEs, as defined by published guidelines,[43–45] in all randomized patients. Immediate complications to FMT (ie, those that occurred within 24 hours) were documented separately.

Statistical Analyses

A sample size calculation was performed before initiating the trial.[46] To detect a minimal clinically relevant difference of 40% between FMTv and fidaxomicin in the primary outcome, and estimating that FMTv would achieve 80% power and fidaxomicin would achieve 40% power and using a type I error of 0.05 and a type II error of 0.20 (80% power), we calculated that 22 patients were needed in each treatment group. After allowing for a dropout rate of 10%, we included 24 patients for fidaxomicin and 24 patients for FMTv.

All data were entered prospectively in standardized case report forms using Research Data Capture (REDCap) software (www.redcap.au.dk). After validation by the Good Clinical Practice Unit as described below and double entry of key variables, data were exported unedited for statistical analyses. Predefined syntax commands developed in SPSS 20 for Windows (IBM Corp, Armonk, NY) were used for all analyses. Continuous variables are reported as medians (ranges). Outcome frequencies are reported as percentages with 95% confidence intervals (CIs).[47,48] Bivariate comparisons were carried out using the χ^2 test and Kruskal-Wallis analysis of variance. A statistical significance level of .05 was applied.

To identify patient risk factors for failure after FMT, we conducted a forward stepwise logistic regression analysis with set probabilities for entry (.05) and removal (.10) in the model that included a constant. Only covariates that were statistically significantly associated with failure with a significance level of .01 to adjust for multiple comparisons were included in the regression analysis.

Ethical Considerations

All patients provided written informed consent before inclusion. The study protocol was approved by the Central Denmark Region Ethics Committee (j.no. 1-10-72-2577-15) and by the Danish Medicines Agency (j.no. 2015092214). Data storage was approved by the Danish Data Protection Agency (j.no. 1-16-02-15-16). The study was conducted according to the principles for Good Clinical Practice and was monitored by the Good Clinical Practice Unit at the Aarhus and Aalborg University Hospitals (j. no. 2015/589). Before initiation, the trial protocol was registered in publicly accessible databases (ClinicalTrials.gov, identifier NCT02743234, www.clinicaltrials.gov; EudraCT, j. no. 2015-003004-24, www.clinicaltrialsregister.eu). All authors had access to the study data and reviewed and approved the final report.

Results

Study Participants and Primary Treatment

From April 5, 2016 to June 10, 2018, 120 consecutively referred patients were screened for participation (Supplementary Figure 1). We randomized 64 adult patients with documented rCDI. Randomized patients had a median age of 68 years, low comorbidity with a median Charlson comorbidity score of 1, and a median of 4 previous CDI episodes (Table 1). Fifteen (23%) had inflammatory bowel disease. No randomized patients had CD ribotype 027.

All 64 randomized patients received the allocated treatment. In patients randomized to FMTv (n = 24), 19 (79%) received the fecal transplant through colonoscopy and 5 (21%) received the transplant through a nasojejunal tube in accord with doctor–patient agreement. Six different healthy donors delivered feces for the study. The study was terminated after inclusion of all patients and according to the protocol.

Of the 120 patients screened for inclusion, 56 could not be randomized (Supplementary Figure 1). The most

Table 1. Characteristics of Patients (n = 64) Randomized to FMTv, Fidaxomicin, or Vancomycin

Parameter	FMTv (n = 24)	Fidaxomicin monotherapy (n = 24)	Vancomycin monotherapy (n = 16)	*P* value[a]
Age (*y*), median (range)	68 (22–90)	64 (24–87)	72 (21–92)	.78
Body mass index (kg/m^2), median (range)	23.1 (16.3–47.4)	23.7 (14.1–36.3)	22.0 (15.2–34.7)	.73
Women, n (%)	20 (83)	13 (54)	11 (69)	.09
Charlson comorbidity index score, median (range)	1 (0–5)	1 (0–3)	2 (0–7)	.35
WHO performance score, median (range)	1 (0–3)	1 (0–3)	1 (0–4)	.99
General well-being (score[b]), median (range)	60 (4–90)	50 (20–90)	50 (0–80)	.50
Hospital admission at inclusion, n (%)	2 (8)	2 (8)	2 (13)	.90
Intensive care admission <1 mo before inclusion, n (%)	0 (0)	0 (0)	0 (0)	N/A
Feeding tube in situ, n (%)	2 (8)	2 (8)	1 (6)	.37
Previous CDIs (*n*), median (range)	4 (2–7)	4 (2–10)	3 (2–9)	.28
Previous CDI treatments, n (%)				
Metronidazole	19 (79)	16 (67)	13 (81)	.49
Vancomycin	24 (100)	24 (100)	16 (100)	.73
Fidaxomicin	1 (4)	2 (8)	0 (0)	.47
Ribotype 027, n (%)	0 (0)	0 (0)	0 (0)	N/A
Liquid stools per 24 h (*n*), median (range)	7 (3–31)	6 (3–12)	8 (4–20)	.69
Duration of symptoms of current CDI (*d*), median (range)	9 (4–112)	14 (1–152)	12 (2–36)	.51
Duration since onset of first CDI (*d*), median (range)	141 (30–963)	147 (35–883)	88 (25–663)	.19
PPI use, n (%)	9 (38)	11 (46)	6 (38)	.81
IBD, n (%)				.99
No	19 (79)	18 (75)	12 (75)	
Yes, remission	4 (17)	5 (21)	3 (19)	
Yes, active	1 (4)	1 (4)	1 (6)	
Immunosuppressant therapy, n (%)	4 (17)	4 (17)	2 (13)	.92
Hemoglobin (*mmol/L*), mean (95% CI)				
Women (reference range 7.0–8.6 mmol/L)	7.7 (7.2–8.2)	8.1 (7.5–8.7)	7.6 (7.0–8.2)	.31
Men (reference range 8.3–10.5 mmol/L)	9.4 (7.7–11.0)	8.6 (7.6–9.5)	8.3 (7.1–9.6)	.41
Plasma albumin (*g/L*), mean (95% CI) [reference range 36–45 g/L]	35 (33–37)	36 (33–38)	35 (32–38)	.81
C-reactive protein (*mmol/L*), mean (95% CI) [reference range <4.0 mmol/L]	28 (12–45)	10 (4–15)	27 (7–47)	.12
Leukocyte count ($\times 10^9$/L), mean (95% CI) [reference range 3–10 $\times 10^9$/L]	9.7 (8.1–11.3)	9.1 (7.2–10.9)	11.4 (4.3–18.5)	.64

IBD, inflammatory bowel disease; N/A, Not applicable; PPI, proton pump inhibitor; WHO, World Health Organization.
[a]By Kruskal-Wallis 1-way analysis of variance for alphanumeric variables and χ^2 test for categorical data.
[b]Score of overall well-being ranged from 0 to 100, with 0 as the worst possible and 100 as the best possible.

common reason for exclusion from the trial was the physician's evaluation that the patients could not tolerate inclusion (n = 19). Most of these patients had sepsis, fulminant colitis, or general deterioration. Patients who could not consent to participation (n = 12) had progressive dementia or somnolence. Patients who could not be randomized had a statistically significantly higher comorbidity score, poorer performance, lower plasma albumin and hemoglobin levels, and higher C-reactive protein level than randomized patients (Table 2). Although 6 (11%, 95% CI 4–22) of the 64 randomized patients were hospitalized at inclusion, 31 (55%, 95% CI 41–69) of the 56 patients with failed screening were hospitalized ($P < .0001$).

Primary Outcome

Combined clinical resolution and negative CD test result were achieved in 17 (71%, 95% CI 49–87) of 24 patients with FMTv, 8 (33%, 95% CI 16–55) of 24 patients with fidaxomicin, and 3 (19%, 95% CI 5–46) of 16 patients with vancomycin ($P = .009$ for FMTv vs fidaxomicin; $P = .001$ for FMTv vs vancomycin; $P = .31$ for fidaxomicin vs vancomycin; Figure 1).

Secondary Outcomes

Clinical resolution was obtained in 22 (92%, 95% CI 73–99) of 24 patients treated with FMTv, 10 (42%, 95% CI 22–63) of 24 treated with fidaxomicin, and 3 (19%, 95% CI 4–46) of 16 treated with vancomycin (Figure 1). All outcome data are presented in Table 3.

Although 7 patients who were randomized to FMTv did not attain the combined primary outcome, 5 (71%, 95% CI 29–96) of these had clinical resolution and did not require or request rescue FMT. The corresponding figures in patients randomized to fidaxomicin and vancomycin monotherapies were 2 of 16 (13%, 95% CI 4–36) and 0 of 13 (0%, 95% CI 0–23), respectively ($P < .001$). We observed no differences in effect relative to method (colonoscopy vs nasojejunal tube) or donor (data not shown).

Table 2. Characteristics of Patients Who Were Randomized or Failed Screening and Were Offered FMTv Off Protocol

Parameter	Randomized (n = 64)	Screen failure (n = 56)	*P* value[a]
Age (*y*), median (range)	68 (21–92)	71 (19–94)	.30
Body mass index (kg/m^2), median (range)	23.5 (14.1–47.1)	24.0 (13.8–36.5)	.80
Women, n (%)	44 (69)	26 (46)	.01
Charlson comorbidity index score, median (range)	1 (0–7)	3 (0–7)	<.0001
WHO performance score, median (range)	1 (0–4)	3 (0–4)	<.0001
Hospital admission at inclusion, n (%)	6 (10)	31 (55)	<.0001
Intensive care admission <1 mo before inclusion, n (%)	0 (0)	2 (4)	.13
Feeding tube in situ, n (%)	3 (5)	3 (5)	.87
Previous CDIs (*n*), median (range)	4 (2–10)	4 (2–10)	.57
Previous CDI treatments, n (%)			
Metronidazole	48 (75)	44 (79)	.64
Vancomycin	64 (100)	56 (100)	.81
Fidaxomicin	3 (5)	2 (4)	.76
Ribotype 027, n (%)	0 (0)	3 (5)	.08
Duration of symptoms of current CDI (*d*), median (range)	13 (1–152)	7 (1–362)	.05
Duration since onset of first CDI (*d*), median (range)	136 (25–963)	118 (35–4885)	.81
PPI use, n (%)	26 (41)	30 (54)	.16
IBD, n (%)			.80
No	49 (77)	45 (80)	
Yes, remission	12 (19)	8 (14)	
Yes, active	3 (5)	3 (5)	
Immunosuppressant therapy, n (%)	10 (16)	16 (29)	.09
Hemoglobin (*mmol/L*), mean (95% CI)			
Women (reference range 7.0–8.6 mmol/L)	8.1 (7.5–8.7)	7.6 (7.0–8.2)	.003
Men (reference range 8.3–10.5 mmol/L)	8.6 (7.6–9.5)	8.3 (7.1–9.6)	<.001
Plasma albumin (*g/L*), mean (95% CI) [reference range 36–45 g/L]	36 (19–44)	31 (14–44)	.002
C-reactive protein (*mmol/L*), mean (95% CI) [reference range <4.0 mmol/L]	9.2 (0.0–147.2)	29.1 (1.0–165.6)	.003
Leukocyte count ($\times 10^9$/L), mean (95% CI) [reference range 3–10 $\times 10^9$/L]	8.5 (1.2–60.0)	9.2 (2.2–21.7)	.97

IBD, inflammatory bowel disease; PPI, proton pump inhibitor; WHO, World Health Organization.
[a]By Kruskal-Wallis 1-way analysis of variance for alphanumeric variables and χ^2 test for categorical data.

Rescue FMT for Patients With Recurrence After Allocated Treatment

Of the 64 randomized patients, 24 had clinical relapse and a positive CD test result before or at 8 weeks after the allocated treatment. All these patients had rescue FMTv performed, delivered by colonoscopy (n = 18) or nasojejunal tube (n = 6). Overall, 20 (83%, 95% CI 63–95) of the 24 patients who received rescue FMTv had clinical resolution and a negative CD test result at 8 weeks after rescue FMTv: 1 of 2 patients (50%, 95% CI 1–99) initially allocated to FMTv, 9 of 11 patients (82%, 95% CI 48–97) initially allocated to fidaxomicin, and 10 of 11 patients (91%, 95% CI 59–100) initially allocated to vancomycin. The treatment responses were similar across primary treatment arms (P = .36) and similar to the effects in patients initially randomized to FMTv (P = .20).

FMT Performed in Patients Who Could Not Be Randomized

Of the 56 patients with failed screening, off-protocol FMTv was performed in 49 (88%) and consisted of 1–3 FMT treatments preceded by vancomycin. At week 8 after FMTv, 39 (80%, 95% CI 66–90) had clinical resolution and a negative CD test result, which was similar to the rates in the patients who were randomized to primary FMTv and the patients who received rescue FMTv after failure of the primary allocated antibiotic treatment in the randomized trial (P = .43).

Risk Factors for FMT Failure

Of 95 patients who had FMT as primary or rescue treatment or after screen failure, 11 (12%) had rCDI at or before week 8. In a logistic regression analysis, we analyzed risk factors for failure (Supplementary Table 1). In bivariate analyses, only the Charlson comorbidity index score and baseline hemoglobin level were statistically significantly associated with FMT failure (odds ratios 1.5 [95% CI 1.1–1.9] and 0.5 [95% CI 1.1–3.8], respectively). In the final regression model, hemoglobin was the strongest and only statistically significant covariate associated with failure of FMT, with an odds ratio of 0.5 (95% CI 0.3–0.99) per point increase in hemoglobin. Mean hemoglobin in patients with FMT failure was 6.7 mmol/L (95% CI 5.7–7.7) in women and 6.0 mmol/L (95% CI 4.8–7.2) in men compared with 7.3 mmol/L (95% CI 7.0–7.7) in women and 7.9 mmol/L (95% CI 7.4–8.4) in men who had resolution (P = .003). The presence of anemia (ie, hemoglobin level below the sex-specific reference interval) was associated with a 6.3 times increased risk of failure of (95% CI 1.3–30.9).

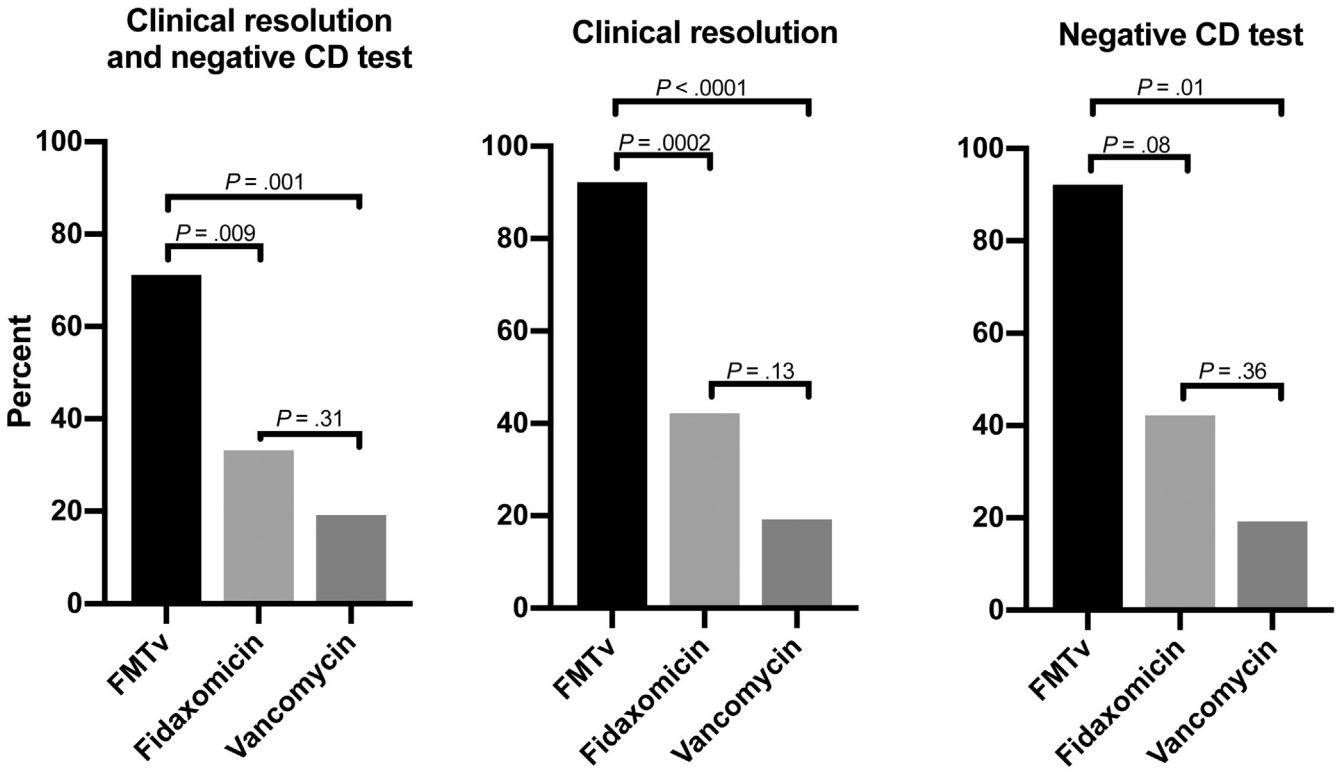

Figure 1. Clinical and microbiological resolution of CDI after 1 of the following treatments: FMTv (n = 24), fidaxomicin (n = 24), or standard treatment with vancomycin (n = 16).

Adverse Events

Immediate complications of FMTv included any AE that occurred up to 24 hours after the procedure. Of the 24 patients allocated to FMTv, 14 (58%, 95% CI 37–78) had no side effects. Ten patients (42%, 95% CI 22–63%) experienced transient abdominal pain (n = 1), bloating (n = 5), constipation (n = 1), or diarrhea (n = 3). One SAE could be related to FMTv: a 50-year-old woman developed a sepsis-like clinical picture with pyrexia, convulsions, vomiting, and diarrhea in her private home for 3 hours the evening after an uncomplicated FMT delivered by colonoscopy. Although perceived life-threatening, the patient was not admitted to the hospital and had complete recovery within 24 hours without further treatment. Of 22 patients with rescue FMT, AEs were observed in 4: headache and dizziness (n = 1), bloating (n = 1), pain and vomiting (n = 1), and pain and nausea (n = 1). Three of these patients had FMT performed by colonoscopy and 1 by nasojejunal tube.

During 8-week follow-up, 29 (45%) of all patients experienced a total of 48 AEs, not including rCDI (Supplementary Table 2). We observed no differences among the 3 treatment groups for the frequency of AEs or SAEs as a whole or when sub-grouped into gastrointestinal-related symptoms, non-gastrointestinal infections, or other AEs, with the important exception of CDI recurrence. One patient had small bowel bacterial overgrowth after primary FMTv. The FMTv had been delivered colonoscopically, and the condition resolved after 6 days of treatment with rifaximin 400 mg twice daily.

No deaths occurred. No AEs could be related specifically to a specific antibiotic treatment. We observed no statistically significant changes in body weight, plasma albumin, or hemoglobin in the randomized patients during the 8-week follow-up (data not shown).

Discussion

This is the first clinical trial to compare the effects of FMT for rCDI with those of fidaxomicin. We found that FMT delivered by colonoscopy or nasojejunal tube after a short course of vancomycin was superior to fidaxomicin and standard-dose vancomycin monotherapies. Rescue FMT delivered to patients with recurrence after their primary allocated treatment and FMT delivered to patients who could not be randomized yielded similar clinical results.

An overall clinical effect of FMTv of 92% is in accordance with findings in previous clinical trials.[14,49] Most previous studies defined resolution as clinical resolution or absence of CD-associated diarrhea. The use of either definition did not change our outcome rates or relative differences between treatments.

The finding that fidaxomicin was inferior to FMTv for rCDI is of clinical importance. Fidaxomycin and vancomycin are equivalent for the initial therapy of CDI, but the recurrence rate is lower with fidaxomicin than with vancomycin.[32–35] In the present study, the resolution rates for fidaxomicin and vancomycin were not statistically significantly different, but this study was not powered to

Table 3. Primary and Secondary Outcomes in a Clinical Trial With FMTv vs Fidaxomicin Monotherapy vs Vancomycin Monotherapy

Parameter	FMTv (n = 24)	Fidaxomicin monotherapy (n = 24)	Vancomycin monotherapy (n = 16)	*P* values		
				FMTv vs fidaxomicin	FMTv vs vancomycin	Fidaxomicin vs vancomycin
Clinical resolution and negative CD test at week 8, n (%) [% range]	17 (71) [49–87[a]]	8 (33) [16–55]	3 (19) [7–43]	.009	.001	.31
Clinical resolution at week 8, n (%) [% range]	22 (92) [73–99]	10 (42) [22–63]	3 (19) [4–46]	.0002	<.0001	.13
Negative CD test at week 8, n (%)[% range]	17 (71) [49–87]	11 (46) [26–67]	5 (31) [11–59]	.08	.01	.36
Resolution of diarrhea or diarrhea with negative CD test at week 8, n (%) [% range]	22 (92) [73–99]	13 (54) [33–74]	5 (31) [11–59]	.003	<.0001	.15
Clinical resolution and negative CD test at week 1, n (%) [% range]	13 (54) [33–74]	9 (38) [19–59]	2 (13) [2–38]	.25	.01	.10
Clinical resolution at week 1, n (%) [% range]	21 (88) [68–97]	14 (58) [37–78]	6 (38) [15–65]	.02	.002	.27
Negative CD test at week 1, n (%) [% range]	16 (67) [45–84]	14 (58) [37–78]	7 (44) [20–70]	.55	.21	.48
Resolution of diarrhea or diarrhea with negative CD test at week 1, n (%) [% range]	24 (100) [86–100]	19 (79) [58–93]	11 (69) [41–89]	.02	.003	.46

NOTE. The primary end point was combined clinical resolution and negative CD toxin polymerase chain reaction test result at 8 weeks. Secondary end points included clinical resolution at week 8, negative CD test result at week 8, combined clinical resolution and negative CD test result at week 1, clinical resolution at week 1, and negative CD test result at week 1. A post hoc secondary outcome, resolution of CD-associated diarrhea, was defined to allow comparison with previously published clinical trials. All measures are provided as percentages with 95% CIs. *P* values were obtained using χ^2 test in bivariate comparisons.

demonstrate a difference between the 2 antibiotics, and no inference in this regard should be made from the present study. The choice of treatment should be balanced according to risks and benefits.

Because antibiotic treatment at time of assessment was an exclusion criterion, patients who were considered too frail or for other reasons unable to wait to start treatment were not randomized in the present study. Patients whose screening failed had higher comorbidity and hospitalization rates than patients who were randomized. The finding of comparable resolution rates in randomized patients who were randomized to primary FMTv, patients who had rescue FMTv after failure of the primary antibiotics treatment, and patients who received FMTv after screen failure gives the present study high generalizability.

A low baseline hemoglobin level was a strong predictor of failure of FMTv in the present study. This new finding could prove clinically relevant and could be useful for a priori identification of patients who would benefit from multiple FMT procedures.[50] The presence of anemia could reflect the overall burden of disease and longstanding inflammation and better reflect frailty than variables such as patient age and comorbidity.[51] This finding needs to be validated in other patient cohorts.

It might be clinically important that 5 of 7 patients who had positive CD test results at 8 weeks after primary FMTv experienced clinical resolution and did not require rescue FMT. Other studies have reported only the results of CD toxin tests in patients with persistent diarrhea, and this practice is in accordance with recent guidelines.[52] The impact of a positive CD test result despite clinical resolution is unclear. Our use of a toxin test instead of fecal cultures might have overestimated the occurrence of clinically relevant carrier status. Future studies should examine whether toxin carrier status is a risk factor for future CDI recurrence or for dissemination of CD spores causing nosocomial infections.

Important limitations include the absence of patients infected with CD ribotype 027. Therefore, our results might not be generalizable to patients with a high frequency of ribotype 027. Study interventions were unblinded, and observer bias might have affected reporting. To obtain an objective outcome measure, we applied the CD toxin test to all patients at all time points.

In conclusion, FMTv was superior to fidaxomicin and vancomycin monotherapies for rCDI for combined clinical and microbiological resolution and clinical resolution alone. Resolution rates similar to those in patients randomized to FMT were found in patients who had been randomized to antibiotic treatment and were offered rescue FMT after CDI recurrence and in patients who could not be randomized and were offered FMT off protocol.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2018.12.019.

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Author contributions: Christian Lodberg Hvas, Simon Mark Dahl Jørgensen, and Jens Frederik Dahlerup had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All data from randomized patients were reviewed and validated by the Good Clinical Practice Unit at Aarhus and Aalborg University Hospitals, Denmark. Christian Lodberg Hvas and Jens Frederik Dahlerup conceived and designed the study. Christian Lodberg Hvas, Simon Mark Dahl Jørgensen, Søren Peter Jørgensen, Merete Storgaard, Lars Lemming, Mette Mejlby Hansen, Christian Erikstrup, and Jens Frederik Dahlerup acquired, analyzed, or interpreted the data. Christian Lodberg Hvas, Simon Mark Dahl Jørgensen, and Jens Frederik Dahlerup drafted the manuscript. Christian Lodberg Hvas, Simon Mark Dahl Jørgensen, Søren Peter Jørgensen, Merete Storgaard, Lars Lemming, Mette Mejlby Hansen, Christian Erikstrup, and Jens Frederik Dahlerup critically reviewed the manuscript for important intellectual content.

Conflicts of interest
All authors disclose no conflicts of interest.

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Supplementary Appendix: Clinical Framework for the Delivery of FMT in Compliance With the National Danish Tissue Act

Regulatory Framework

The study was conducted in an established clinical FMT service established in a public university hospital and compliant with the Danish Tissue Act. The National Tissue Act is derived from the European Tissue and Cell Directive. Currently in Denmark, no public authorities regulate institutions that perform FMT, although the National Board of Health strongly recommends that FMT institutions follow the handling, safety, and documentation principles that are provisioned in the Danish Tissue Act.

The established FMT service is separated into 3 main activities: (1) donor selection and screening, (2) laboratory processing, and (3) clinical application.

Donor Selection and Screening

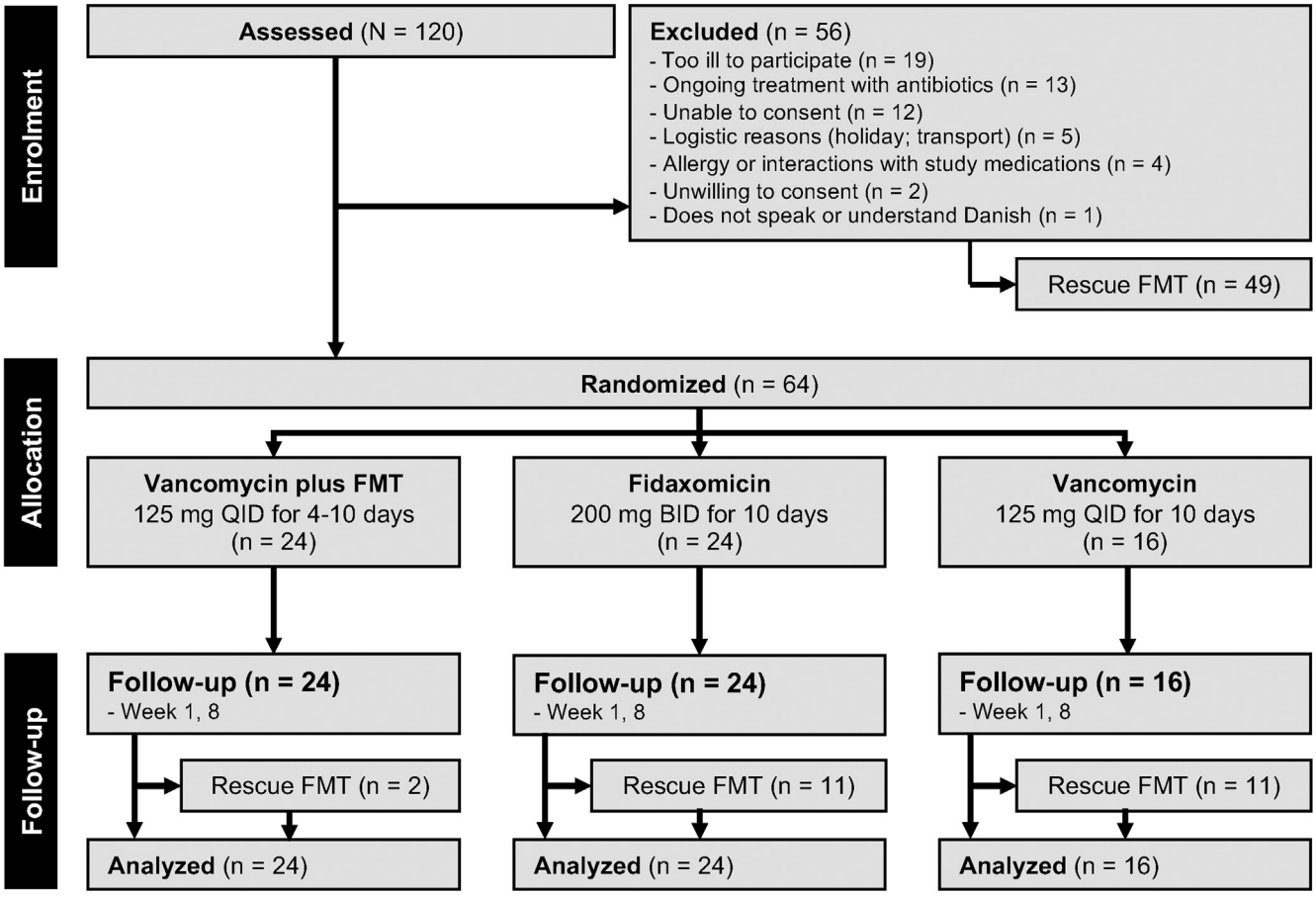
Voluntary feces donors were identified and recruited at the public blood center. The donors were approached in person during the time of donating blood or plasma. Subsequently, all donors fulfilled all criteria to donate blood. Feces donors were recruited consecutively. Donors who consented were enrolled in a stepwise screening program. The content of the screening program was adopted according to previously published protocols and consensus reports. Donors completed an electronic questionnaire that addressed gastrointestinal complaints, risk behavior, and diet and ruled out risk factors. Donors who were found eligible progressed to screening of blood and feces. Blood samples were obtained on site, and the donor received a fecal collection kit to collect a fecal sample from the next defecation at home. The fecal samples were received and tested at the department of clinical microbiology. When all screening results were present, the donors were contacted by phone, and eligible donors were booked for a consultation with a gastroenterologist to formally become active feces donors. All active feces donors donated in rounds of 5 donations within a 2-month period. At the beginning and ending of each round, the donors were retested on all screening parameters for release of the donor material. At each donation, the donor declared in writing to be in good health, that no health changes had occurred, and that the donor had delivered the donor feces.

Laboratory Processing

Donations were delivered from the feces donors' home and brought to the laboratory within 2 hours. The donation was collected in a food-approved plastic bag and placed in an airtight container. The container was placed in a cooler bag, validated for transportation of biological substances. At the FMT laboratory, the feces donation was processed to produce and preserve consistent fecal suspensions applicable for clinical application. The processing procedures were performed in a sterilized fume cupboard to avoid contamination. The feces donation was diluted with normal 0.9% NaCl and blended using a donor-dedicated household blender. Then, the suspension was passed through a filter to remove debris. A 10% glycerol titer was added to improve bacterial viability when aliquoted into CryoBags and stored at -80°C. Each CryoBag contained a minimum of 50 g of donor feces. All CryoBags were kept in quarantine until the donor had completed an entire donation round and all screening results were present and approved. When requested, released CryoBags were thawed for 45 minutes before administration. The fecal suspension had to be administered within 4 hours. We kept 2 safety samples from each CryoBag that could be tested in case of SAEs related to FMT.

Clinical Application

The clinical application procedures are described in detail in the main text.



Supplementary Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram. BID, twice daily; QID, 4 times daily.

Supplementary Table 1. Risk Estimates for FMT Failure by Logistic Regression

Parameter	Variable name	OR (95% CI)	*P* value	Comment
Age (*y*)	Alder_aar	1.02 (0.98–1.06)	.30	
Age >65 y	Alder_2kat	3.54 (0.72–17.40)	.12	
Body mass index (kg/m^2)	B1_bmi	0.99 (0.86–1.13)	.42	
Female sex	B1_gender	1.67 (0.48–5.94)	.42	
Charlson comorbidity index score	B1_charlson	1.46 (1.12–1.91)	.006	In model
≥2 vs 0–1	Charlson_2kat2	4.50 (0.92–22.08)	.06	
≥3 vs 0–2	Charlson_2kat3	4.56 (1.13–18.47)	.03	
WHO performance score	B1_who	1.76 (1.05–2.93)	.03	
Hospital admission at inclusion	Hospital	2.28 (0.64–8.10)	.20	
Intensive care admission	Intensiv	N/A	1.00	
Feeding tube in situ	tube	2.00 (0.20–19.71)	.55	
Previous CDIs (*n*)	B1_cdicount	0.92 (0.64–1.34)	.68	
Previous CDI treatments				
Metronidazole	Tidlab_1	0.48 (0.13–1.81)	.28	
Vancomycin	Tidlab_2	N/A	1.00	
Fidaxomicin	Tidlab_3	N/A	1.00	
Ribotype 027	Cd027	N/A	1.00	
Liquid stools per 24 h (*n*)	B1_stoolcount	1.10 (0.93–1.29)	.29	
Duration of symptoms of current CDI	Duration_present	1.00 (0.93–1.29)	.75	
Duration since onset of first CDI	Duration_total	1.00 (1.00–1.00)	.15	
PPI use	B1_ppi	1.26 (0.36–4.44)	.72	
IBD	B1_ibd	0.43 (0.07–2.76)	.38	
Immunosuppressant therapy	B1_immunosuppressant	2.01 (0.55–7.96)	.28	
Hemoglobin	B1_hgb	0.43 (0.24–0.79)	.006	In model
Anemia yes vs no	B1_hgb2kat	6.27 (1.27–30.94)	.03	
Plasma albumin	B1_albumin	1.05 (0.97–1.15)	.21	
C-reactive protein	B1_crp	1.00 (0.98–1.01)	.72	
Leukocyte count	B1_leukocyt	1.10 (0.91–1.32)	.34	

IBD, inflammatory bowel disease; N/A, Not applicable; OR, odds ratio; PPI, proton pump inhibitor; WHO, World Health Organization.

Supplementary Table 2. AEs and SAEs (n = 48) in 29 Patients More Than 2 Days and up to 8 Weeks After FMTv, Fidaxomicin Monotherapy, or Vancomycin Monotherapy, Excluding rCDI

Category	Event	Causality	FMTv (n = 24)	Fidaxomicin (n = 24)	Vancomycin (n = 16)	*P* value
All AEs	All events mentioned below	N/A	12 (50)	9 (38)	8 (50)	.62
SAEs	Hospitalization	Unrelated	5 (21)	6 (25)	4 (25)	.93
GI symptoms without treatment	Nausea, vomiting, bloating, flatulence, diarrhea, slimy stools, constipation	Probably	4 (17)	3 (13)	2 (13)	.89
GI symptoms with treatment	Reflux, small bowel bacterial overgrowth, active inflammatory bowel disease	Probably	2 (8)	3 (13)	0 (0)	.35
Non-GI infections	Pneumonia, urinary tract infection, sepsis, erysipelas, coxitis, otitis, influenza	Unrelated	4 (17)	2 (8)	2 (13)	.68
Other AEs	Headache, dizziness, shivering, blurred vision, weight loss, weight gain	Possibly	3 (13)	2 (8)	1 (6)	.78
Other AEs	Alcohol intoxication, hoarseness, cerebral commotion, adrenal gland adenoma, confusion, erythema, encephalopathy, cholecystectomy, fracture, edema, renal insufficiency	Unrelated	4 (17)	3 (13)	3 (19)	.85

NOTE. Causality to the allocated treatment was evaluated according to published guidelines.[53] Data are presented as number (percentage) of patients with at least 1 event.
GI, gastrointestinal; N/A, Not applicable.