Duodenal Infusion of Donor Feces for Recurrent Clostridium difficile

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ABSTRACT

BACKGROUND
Recurrent Clostridium difficile infection is difficult to treat, and failure rates for antibiotic therapy are high. We studied the effect of duodenal infusion of donor feces in patients with recurrent C. difficile infection.

METHODS
We randomly assigned patients to receive one of three therapies: an initial vancomycin regimen (500 mg orally four times per day for 4 days), followed by bowel lavage and subsequent infusion of a solution of donor feces through a nasoduodenal tube; a standard vancomycin regimen (500 mg orally four times per day for 14 days); or a standard vancomycin regimen with bowel lavage. The primary end point was the resolution of diarrhea associated with C. difficile infection without relapse after 10 weeks.

RESULTS
The study was stopped after an interim analysis. Of 16 patients in the infusion group, 13 (81%) had resolution of C. difficile–associated diarrhea after the first infusion. The 3 remaining patients received a second infusion with feces from a different donor, with resolution in 2 patients. Resolution of C. difficile infection occurred in 4 of 13 patients (31%) receiving vancomycin alone and in 3 of 13 patients (23%) receiving vancomycin with bowel lavage (P<0.001 for both comparisons with the infusion group). No significant differences in adverse events among the three study groups were observed except for mild diarrhea and abdominal cramping in the infusion group on the infusion day. After donor-feces infusion, patients showed increased fecal bacterial diversity, similar to that in healthy donors, with an increase in Bacteroidetes species and clostridium clusters IV and XIVa and a decrease in Proteobacteria species.

CONCLUSIONS
The infusion of donor feces was significantly more effective for the treatment of recurrent C. difficile infection than the use of vancomycin. (Funded by the Netherlands Organization for Health Research and Development and the Netherlands Organization for Scientific Research; Netherlands Trial Register number, NTR1177.)
**STUDY DESIGN**

The complete methods are included in the Supplementary Appendix, which along with the research protocol is available with the full text of this article at NEJM.org.

In this open-label, randomized, controlled trial, we compared three treatment regimens: the infusion of donor feces preceded by an abbreviated regimen of vancomycin and bowel lavage, a standard vancomycin regimen, and a standard vancomycin regimen with bowel lavage.

The study was conducted at the Academic Medical Center in Amsterdam. Patients who had been admitted to referring hospitals were visited by the study physicians, who performed the randomization. All participants provided written informed consent. A data and safety monitoring board monitored the trial on an ongoing basis. The research protocol was approved by the ethics committee at the Academic Medical Center. The first and last two authors vouch for the accuracy and completeness of the reported data and for the fidelity of the report to the study protocol.

**METHODS**

**STUDY POPULATION**

Included in the study were patients who were at least 18 years of age and who had a life expectancy of at least 3 months and a relapse of *C. difficile* infection after at least one course of adequate antibiotic therapy (≥10 days of vancomycin at a dose of ≥125 mg four times per day or ≥10 days of metronidazole at a dose of 500 mg three times per day). *C. difficile* infection was defined as diarrhea (≥3 loose or watery stools per day for at least 2 consecutive days or ≥8 loose stools in 48 hours) and a positive stool test for *C. difficile* toxin. Available isolates were characterized by polymerase-chain-reaction (PCR) ribotyping.16

Exclusion criteria were prolonged compromised immunity because of recent chemotherapy, the presence of human immunodeficiency virus (HIV) infection with a CD4 count of less than 240, or prolonged use of prednisolone at a dose of at least 60 mg per day; pregnancy; use of antibiotics other than for treatment of *C. difficile* infection at baseline; admission to an intensive care unit; or need for vasopressor medication.

**TREATMENTS**

Patients received an abbreviated regimen of vancomycin (500 mg orally four times per day for 4 or 5 days), followed by bowel lavage with 4 liters of macrogol solution (Klean-Prep) on the last day of antibiotic treatment and the infusion of a suspension of donor feces through a nasoduodenal tube the next day; a standard vancomycin regimen (500 mg orally four times per day for 14 days); or a standard vancomycin regimen with bowel lavage on day 4 or 5. Patients in whom recurrent *C. difficile* infection developed after the first donor-feces infusion were given a second infusion with feces from a different donor. Patients in whom antibiotic therapy failed were offered treatment with donor feces off protocol.

**INFUSION OF DONOR FECES**

Donors (<60 years of age) were volunteers who were initially screened using a questionnaire addressing risk factors for potentially transmissible diseases. Donor feces were screened for parasites (including *Blastocystis hominis* and *Dientamoeba fragilis*), *C. difficile*, and enteropathogenic bacteria. Blood was screened for antibodies to HIV; human T-cell lymphotropic virus types 1 and 2; hepatitis A, B, and C; cytomegalovirus; Epstein-Barr virus; *Treponema pallidum*; *Strongyloides stercoralis*; and Ent-
amoeba histolytica. A donor pool was created, and screening was repeated every 4 months. Before donation, another questionnaire was used to screen for recent illnesses.

Feces were collected by the donor on the day of infusion and immediately transported to the hospital. Feces were diluted with 500 ml of sterile saline (0.9%). This solution was stirred, and the supernatant strained and poured in a sterile bottle. Within 6 hours after collection of feces by the donor, the solution was infused through a nasoduodenal tube (2 to 3 minutes per 50 ml). The tube was removed 30 minutes after the infusion, and patients were monitored for 2 hours. For patients who had been admitted at referring hospitals, the donor-feces solution was produced at the study center and immediately transported and infused by a study physician.

OUTCOMES
The primary end point was cure without relapse within 10 weeks after the initiation of therapy. For patients in the infusion group who required a second infusion of donor feces, follow-up was extended to 10 weeks after the second infusion. The secondary end point was cure without relapse after 5 weeks. Cure was defined as an absence of diarrhea or persistent diarrhea that could be explained by other causes with three consecutive negative stool tests for C. difficile toxin. Relapse was defined as diarrhea with a positive stool test for C. difficile toxin. An adjudication committee whose members were unaware of study-group assignments decided which patients were cured.

Patients kept a stool diary and were questioned about stool frequency and consistency, medication use, and adverse effects on days 7, 14, 21, 35, and 70 after the initiation of vancomycin. Stool tests for C. difficile toxin were performed in a central laboratory (Premier Toxins A&B, Meridian Bioscience) on days 14, 21, 35, and 70 and whenever diarrhea occurred.

ANALYSIS OF FECAL MICROBIOTA
We analyzed the fecal microbiota for bacterial diversity by extracting DNA from samples from patients before and after donor-feces infusion and from the respective donor samples.20 We then characterized 16S ribosomal RNA gene amplicons using the Human Intestinal Tract Chip (HITChip), a phylogenetic microarray, as described previously.21 We estimated the diversity of the bacterial communities before and after donor-feces infusion using Simpson’s Reciprocal Index of diversity,22 on a scale ranging from 1 to 250, with higher values indicating greater diversity.

STATISTICAL ANALYSIS
The objective was to determine the superiority of donor-feces infusion, as compared with vancomycin, both without and with bowel lavage. A cure rate of 90% for donor-feces infusion13,14 and of 60% for antibiotic therapy2,6 was assumed. Per group, 38 patients were needed to achieve a power of 80% to detect a difference between groups with a one-sided level of significance of 0.025. To account for dropouts, we planned to enroll 40 patients per group. All analyses were performed on a modified intention-to-treat basis with the exclusion of one patient who required high-dose prednisolone treatment after randomization but before the study treatment was initiated. Differences in cure rates were assessed with Fisher’s exact probability test. Since the trial was terminated early according to the Haybittle–Peto rule (i.e., P<0.001 for the primary end point), rate ratios for the primary end point (overall cure) were calculated with their exact 99.9% confidence interval.

On the basis of Simpson’s Reciprocal Index of diversity,22 the statistical significance of a change in microbiota diversity was assessed with the use of a paired-samples Student t-test. A principal component analysis was performed on profiles derived from the HITChip phylogenetic microarray.21 Wilcoxon signed-rank tests were performed with the application of the Benjamini–Hochberg approach to determine microbial groups that were significantly different in matched pairs of fecal samples obtained from patients before and after infusion.23

RESULTS

PATIENTS AND TERMINATION OF THE TRIAL
From January 2008 through April 2010, a total of 43 patients were randomly assigned to receive donor-feces infusion (17 patients), vancomycin (13), or vancomycin and bowel lavage (13). Initially, the inclusion of 40 patients per study group was planned. Because most patients in both control groups had a relapse, the data and safety monitoring board performed the interim efficacy analysis and advised termination of the trial, as
described in the Supplementary Appendix. At that time, 43 patients were included, with one of them subsequently excluded from further analysis (Table 1 and Fig. 1). In 39 patients, a positive toxin test before inclusion was confirmed by a positive \textit{C. difficile} culture. PCR ribotyping was performed on strains obtained from 34 patients (see the Supplementary Appendix).

Forty-one patients completed the study protocol. One patient in the vancomycin-only group was discharged home from the hospital after the initiation of vancomycin. At home, the patient decided to discontinue all medication because of severe heart failure and chronic obstructive pulmonary disease and died 13 days after randomization, without providing data on response. In the intention-to-treat analysis, vancomycin therapy was considered to have failed in this patient. Another patient in the infusion group required high-dose prednisolone because of a rapid decrease in renal-graft function. The patient had received a renal transplant from an unrelated donor 11 months before study enrollment, and graft dysfunction was noted immediately after randomization but before the study treatment was initiated. At that time, the nephrologist objected.

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Donor-Feces Infusion (N = 16)</th>
<th>Vancomycin Only (N = 13)</th>
<th>Vancomycin and Bowel Lavage (N = 13)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>73±13</td>
<td>66±14</td>
<td>69±16</td>
<td>0.39</td>
</tr>
<tr>
<td>Body-mass index‡</td>
<td>22±3</td>
<td>22±4</td>
<td>24±4</td>
<td>0.41</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>8 (50)</td>
<td>7 (54)</td>
<td>3 (23)</td>
<td>0.22</td>
</tr>
<tr>
<td>Karnofsky performance status§</td>
<td>50±18</td>
<td>50±17</td>
<td>56±21</td>
<td>0.62</td>
</tr>
<tr>
<td>Median Charlson comorbidity index (range) — score¶</td>
<td>3 (0–4)</td>
<td>1 (0–8)</td>
<td>1 (0–6)</td>
<td>0.53</td>
</tr>
<tr>
<td>Median recurrences of CDI (range) — no.</td>
<td>3 (1–5)</td>
<td>3 (1–4)</td>
<td>2 (1–9)</td>
<td>0.69</td>
</tr>
<tr>
<td>Previous failure of tapered vancomycin therapy — no. (%)</td>
<td>10 (62)</td>
<td>8 (62)</td>
<td>6 (46)</td>
<td>0.63</td>
</tr>
<tr>
<td>Reported antibiotic use before CDI — no. (%)</td>
<td>16 (100)</td>
<td>12 (92)</td>
<td>13 (100)</td>
<td>0.62</td>
</tr>
<tr>
<td>Hospital-acquired CDI infection — no. (%)</td>
<td>10 (62)</td>
<td>6 (46)</td>
<td>10 (77)</td>
<td>0.27</td>
</tr>
<tr>
<td>Admitted to a hospital at study inclusion — no. (%)</td>
<td>5 (31)</td>
<td>4 (31)</td>
<td>4 (31)</td>
<td>1.00</td>
</tr>
<tr>
<td>Days of antibiotic use for CDI since first diagnosis — no.</td>
<td>63±41</td>
<td>51±27</td>
<td>49±38</td>
<td>0.56</td>
</tr>
<tr>
<td>Use of proton-pump inhibitor — no. (%)</td>
<td>13 (81)</td>
<td>10 (77)</td>
<td>11 (85)</td>
<td>0.88</td>
</tr>
<tr>
<td>ICU admission in preceding month — no. (%)</td>
<td>1 (6)</td>
<td>0</td>
<td>1 (8)</td>
<td>1.00</td>
</tr>
<tr>
<td>Feeding tube present — no. (%)</td>
<td>3 (19)</td>
<td>2 (15)</td>
<td>2 (15)</td>
<td>0.96</td>
</tr>
<tr>
<td>Median stool frequency per 24 hr (range) — no.</td>
<td>5 (3–20)</td>
<td>5 (3–12)</td>
<td>5 (3–10)</td>
<td>0.72</td>
</tr>
<tr>
<td>Leukocyte count — per \text{mm}³**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>8000</td>
<td>8100</td>
<td>6500</td>
<td>0.39</td>
</tr>
<tr>
<td>Range</td>
<td>4000–15,000</td>
<td>4000–23,000</td>
<td>3000–14,000</td>
<td></td>
</tr>
<tr>
<td>Albumin — g/dl**</td>
<td>3.7±0.7</td>
<td>3.8±0.7</td>
<td>3.9±0.8</td>
<td>0.66</td>
</tr>
<tr>
<td>Median creatinine (range) — mg/dl**</td>
<td>1.3 (0.6–10.3)</td>
<td>1.0 (0.5–1.8)</td>
<td>0.9 (0.6–5.2)</td>
<td>0.26</td>
</tr>
<tr>
<td>Ribotype 027 in first sample — no. (%) ††</td>
<td>3 (23)</td>
<td>1 (11)</td>
<td>0</td>
<td>0.28</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. To convert the values for creatinine to micromoles per liter, multiply by 88.4. CDI denotes \textit{Clostridium difficile} infection, and ICU intensive care unit.
† P values are for the overall comparison among the three groups.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The Karnofsky performance status ranges from 0 to 100, with higher scores indicating improved functional status.
¶ Scores on the Charlson comorbidity index range from 0 to 6 for each of 17 indicators, with higher scores indicating greater severity of illness.
| Data were missing for one patient in the infusion group and one in the vancomycin-only group.
** Data were missing for one patient in the vancomycin-only group.
†† Data for ribotype 027 (a more virulent strain of \textit{C. difficile}) were missing for three patients in the infusion group, four in the vancomycin-only group, and two in the group receiving vancomycin with bowel lavage.
to treatment with donor feces. The patient was treated with vancomycin for 45 days, had a recurrence 41 days after cessation of vancomycin, and was subsequently cured by donor-feces infusion. This patient was excluded from the analysis because of a clinically driven protocol deviation, which meant that the patient's response to treatment could not be evaluated.

**DONORS**

Of 77 candidates, 25 donors were approved (see the Supplementary Appendix for results of donor screening). Feces from 15 donors were used for 43 infusions in the infusion group and for patients who had a relapse after vancomycin treatment. A mean (±SD) of 141±71 g of feces was infused. The mean time from defecation to infusion was 3.1±1.9 hours.

**STUDY OUTCOMES**

Of 16 patients in the infusion group, 13 (81%) were cured after the first infusion of donor feces. The 3 remaining patients received a second infusion with feces from a different donor at 14, 50, and 53 days after randomization; of these patients, 2 were subsequently cured. Overall, donor feces cured 15 of 16 patients (94%). Resolution of infection occurred in 4 of 13 patients (31%) in the vancomycin-alone group and in 3 of 13 patients (23%) in the group receiving vancomycin with bowel lavage. Donor-feces infusion was statistically superior to both vancomycin regimens (P<0.01 for both comparisons after the first infusion and P<0.001 for overall cure rates) (Fig. 2). The overall cure rate ratio of donor-feces infusion was 3.05 as compared with vancomycin alone (99.9% confidence interval [CI], 1.08 to 290.05).
and 4.05 as compared with vancomycin with bowel lavage (99.9% CI, 1.21 to 290.12).

The median time to recurrence was 23 days (range, 13 to 43) after the initiation of vancomycin alone and 25 days (range, 18 to 70) after the initiation of vancomycin with bowel lavage. Five weeks after the initiation of therapy, there was a recurrence of infection in 1 of 16 patients (6%) in the infusion group, 8 of 13 (62%) in the vancomycin-alone group, and 7 of 13 (54%) in the group receiving vancomycin with bowel lavage.

Fourteen patients who were cured reported having diarrhea during follow-up; these episodes were short and self-limited in 10 patients. Three patients had a preexistent defecation frequency of at least three stools per day, a frequency that was markedly increased during episodes with C. difficile infection and returned to normal after donor-feces infusion. In these patients, toxin tests were repeatedly negative, and there was no clinical suspicion of recurrence. One patient in the vancomycin-only group had persistent diarrhea, with repeatedly negative toxin tests; this patient was considered to have had a response, although there was clinical suspicion of recurrence.

Eighteen patients who had a relapse after initial antibiotic treatment received off-protocol donor-feces infusions; of these patients, 15 (83%) were cured. Eleven patients were cured after one donor-feces infusion, and 4 patients were cured after a second infusion.

**ADVERSE EVENTS**

A complete description of adverse events is included in the Supplementary Appendix. Immediately after donor-feces infusion, most patients (94%) had diarrhea. In addition, cramping (31%) and belching (19%) were reported (Table 2). In all patients, these symptoms resolved within 3 hours. During follow-up, three patients who were treated with donor feces (19%) had constipation. No other adverse events related to study treatment were reported. The death of one patient from severe heart failure and chronic obstructive pulmonary disease in the vancomycin-only group was considered to be unrelated to the study drug.

Table 2. Adverse Events in 16 Patients in the Infusion Group.*

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>On Day of Infusion of Donor Feces</th>
<th>During Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of events</td>
<td></td>
</tr>
<tr>
<td>Belching</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal cramps</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2 (associated with cramping)</td>
<td>0</td>
</tr>
<tr>
<td>Infection</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hospital admission</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other adverse event</td>
<td>1§</td>
<td>1‡</td>
</tr>
</tbody>
</table>

* Adverse events that were reported on the day of donor-feces infusion and those that were reported during follow-up are listed separately. NA denotes not applicable.
† During follow-up, one patient with recurrent urinary tract infections had a urinary tract infection for which antibiotics were prescribed. Another patient had fever during hemodialysis for which antibiotics were prescribed; cultures remained negative.
‡ On day 56, one patient was hospitalized for symptomatic choledocholithiasis, for which endoscopic retrograde cholangiopancreatography and stone extraction were performed.
§ One patient with autonomic dysfunction had dizziness combined with diarrhea after donor-feces infusion.
Fecal Microbiota

The Simpson’s Reciprocal Index of diversity of fecal microbiota obtained from nine patients who were evaluated before the donor-feces infusion was consistently low (mean, 57±26) and increased within 2 weeks after infusion to 179±42 (P<0.001), becoming undistinguishable from the fecal microbiota diversity level of the donors (mean, 172±54) (Fig. 3). In eight patients for whom samples were available, the diversity of fecal microbiota remained undistinguishable from that of the donor during follow-up.

In addition, a principal component analysis was performed on the phylogenetic microarray profiles of each sample. This unsupervised analysis showed that nearly 50% of the variation in the data was explained by the first two principal components, indicating a major shift in the patients’ microbiota after donor-feces infusion toward that of the donors (Fig. S2 in the Supplementary Appendix).

After donor-feces infusion, we observed quantitative changes in relevant groups of intestinal bacteria (P<0.05) (Table S2 in the Supplementary Appendix). These changes included increased numbers of Bacteroidetes species and of clostridium clusters IV and XIVa (by a factor of 2 to 4 for both groups) and decreased numbers of Proteobacteria (by a factor of up to 100).

Discussion

In this small, open-label, randomized, controlled trial, we found that the infusion of donor feces is a potential therapeutic strategy against recurrent C. difficile infection. Our study population of mainly elderly patients reflects the population in whom C. difficile infection develops in daily practice. However, we excluded three groups of patients at risk for recurrent C. difficile infection. Patients with prolonged immunodeficiency were excluded to prevent the potential translocation of infused intestinal bacteria. Infectious complications were not observed after donor infusion in our study and have not been reported in the literature.15 Also, critically ill patients who were admitted to an intensive care unit (ICU) were excluded. However, C. difficile infection in the ICU is associated with high death rates,24 and anecdotal reports have shown promising results of donor-feces infusion in critically ill patients.25,26 The third excluded group comprised patients requiring additional antibiotics to treat infections other than C. difficile because it seems reasonable to postpone donor-feces infusion until antibiotics can be stopped, enabling colonization of the bowel with healthy donor feces.

Although our study was designed for patients with any recurrence of C. difficile infection, only 8 of 43 patients were included after a first relapse, reflecting the reluctance of patients and physicians to choose donor-feces infusion at an early stage. The efficacy of antibiotic therapy decreases with subsequent recurrences, and it seems reasonable to initiate treatment with donor-feces infusion after the second or third relapse. It has yet to be established whether other promising treatment strategies, such as fidaxomycin or infusion of antibodies against clostridium toxins,3,27 are effective against recurrent C. difficile infection.

The power calculation of our study was based on the efficacy of vancomycin for a first recurrence of C. difficile infection. Because most patients had several relapses before inclusion in the study (typically, after a failure of vancomycin therapy), the efficacy of vancomycin in our study was considerably lower than expected, which prob-
ably contributed to the findings of a difference between study groups. At study termination, 16 patients had been treated with donor-feces infusion. The success rate of donor-feces infusion was extended off protocol in another 18 patients who had initially been assigned to receive antibiotic therapy. A prolonged tapering schedule of vancomycin may be prescribed for recurrent C. difficile infection and was not incorporated into the trial for practical reasons. This may be a limitation of our study, although 56% of the patients were unsuccessfully treated with prolonged and tapering vancomycin schedules before inclusion.

Several questions remain unanswered. The optimal protocol for donor-feces infusion is unknown. We pretreated patients with vancomycin and bowel lavage, following a protocol that was effective in previously published case series. Bowel lavage was incorporated to reduce the pathogenic bowel content, facilitating colonization of healthy donor microbiota. Whether bowel lavage indeed contributes to the efficacy of donor-feces infusion is not known. However, the possibility that bowel lavage itself cures C. difficile is unlikely, since no benefit was seen in the second control group, in whom vancomycin was combined with bowel lavage. Furthermore, the amount of feces required and the importance of varying potential routes of infusion (nasoduodenal tube, enema, or colonoscopy) are unknown since the literature reports many different treatment protocols. In our study, infusion of a relatively large amount of feces through a nasoduodenal tube had an acceptable adverse-event profile and was logistically manageable.

The mechanism underlying the efficacy of donor-feces infusion is probably the reestablishment of the normal microbiota as a host defense against C. difficile. Changes in the gut bacterial phyla Firmicutes and Bacteroidetes were associated with C. difficile infection. We found that the fecal microbiota in patients with C. difficile infection had a reduced bacterial diversity, as compared with healthy persons, extending previous observations. Infusion of donor feces resulted in improvement in the microbial diversity, which persisted over time. Also, there was an increase in Bacteroidetes species and clostridium clusters IV and XIVA (Firmicutes), whereas Proteobacteria species decreased.

In conclusion, in patients with recurrent C. difficile infection, the infusion of donor feces, as compared with vancomycin therapy, resulted in better treatment outcomes. In particular, patients with multiple relapses of C. difficile infection benefited from this unconventional approach.

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References

10. Idem. Asymptomatic carriage of Clostridium difficile and serum levels of IgG.

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