Recurrent *Clostridium difficile* Colitis: Case Series Involving 18 Patients Treated with Donor Stool Administered via a Nasogastric Tube

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***Clostridium difficile*–associated diarrhea and colitis have emerged as major complications associated with use of systemic antimicrobials. In this study, the medical records for 18 subjects who received donor stool by nasogastric tube for recurrent *C. difficile* infection during a 9-year period at a single institution were retrospectively reviewed. During the period between the initial diagnosis of *C. difficile* colitis and the stool treatments, the 18 subjects received a total of 64 courses of antimicrobials (range, 2–7 courses; median, 3 courses). During the 90 days after receipt of treatment with stool, 2 patients died of unrelated illnesses. One of the 16 survivors experienced a single recurrence of *C. difficile* colitis during 90-day follow-up. No adverse effects associated with stool treatment were observed. Patients with recurrent *C. difficile* colitis may benefit from the introduction of stool from healthy donors via a nasogastric tube.**

Pseudomembranous colitis was first described in 1893 [1]. By the 1960s, most cases of pseudomembranous colitis were associated with previous use of antimicrobial agents. The role of *Clostridium difficile* as a cause of diarrhea was described in 1978 [2]. Today, *C. difficile* is a leading cause of antibiotic-associated diarrhea and pseudomembranous colitis [3–8]. The severity of *C. difficile* colitis ranges from mild cases, which require little more than the discontinuation of antimicrobials and supportive measures, to intractable diarrhea and severe, life-threatening illness. Mortality rates as high

has 24% have been reported in case series involving critically ill patients with *C. difficile* colitis [9, 10].

Recommended therapies for *C. difficile* colitis include oral administration of metronidazole or vancomycin. Antimicrobial intervention produces a clinical response in >90% of patients. Many patients experience no further symptoms after completion of therapy. However, asymptomatic carriage of *C. difficile* can be demonstrated in some patients [11].

The principal problem in cases of *C. difficile* colitis is symptomatic relapse after antimicrobial therapy has been completed. Previous experience in our institution indicates that most relapses occur within 7–10 days after completion of therapy, suggesting that relapse is due to recurrence rather than reinfection. The frequency of relapse has been reported to be 5%–50%, and the risk is most frequently estimated to be ∼20% [3–5, 12]. Once a patient has had a single relapse, the risk of subsequent relapses is significantly higher. As many as 26 relapses in a single patient have been reported [3].

Recurrent *C. difficile* colitis is generally treated with an additional course of metronidazole or vancomycin,

Table 1. Laboratory screening protocol for donor blood and stool samples obtained before stool transplantation.

Laboratory sample	Infectious agent	Laboratory test
Blood	HAV	HAV antibody (IgM and IgG)
	HBV	Antibody to hepatitis B surface antigen, antibody to hepatitis B core antigen
	HCV	HCV antibody (RIBA-II)
	HIV-1 and HIV-2	EIA
	Treponema pallidum	Rapid plasma reagin test
Stool	*Clostridium difficile*	Toxin A or toxin B (cytotoxin) detection
	Enteric bacterial pathogens	Selective stool culture
	Ova and parasites	Light microscopy

NOTE. HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; RIBA-II, recombinant immunoblot assay, second generation test.

and, for many patients, this therapy is successful. However, some patients develop a chronic, relapsing pattern of *C. difficile* colitis. Some regimens that have been tried in such patients include repeated and prolonged courses of orally administered metronidazole, vancomycin, combination metronidazole-vancomycin, combination rifampin-vancomycin [13], and treatment with cholestyramine after completion of a course of vancomycin therapy [3].

Limited experience in northern Europe and the United States with stool bacterial flora replacement has suggested that probiotic treatment regimens may resolve recurrent episodes of *C. difficile*–associated colitis [1, 14–20]. We report the results obtained in a study of patients with relapsing *C. difficile* infection treated with nasogastrically administered stool in a single institution during a 9-year period.

PATIENTS AND METHODS

Study approval. The methods used in this study were reviewed and approved by the Institutional Review Board at St. Mary's/Duluth Clinic Health System (SMDC; Duluth, MN).

Patients. This study was a retrospective review of the medical records of 19 consecutive patients referred to the principal investigator (J.A.) for nasogastric stool transplantation from June 1994 through August 2002. The inclusion criteria for the case series were (1) laboratory-confirmed diagnosis of *C. difficile* colitis (see Laboratory Documentation of *C. difficile* Infection), (2) ≥2 laboratory-confirmed relapses of *C. difficile* colitis after receipt of initial specific antimicrobial treatment, and (3) adequate clinical and laboratory documentation (by telephone or chart review) of the patient's posttransplantation course. One of the 19 patients who received the stool transplant was excluded from the case series because the patient's medical

record did not contain laboratory documentation of *C. difficile* infection. The remaining 18 patients are the subject of this report. The stool transplantation procedure is summarized in tables 1, 2, and 3.

Data collection. The medical records for the patients in this case series were examined for the following reasons: (1) to document the infectious process and identify the antimicrobial agent or agents that predisposed the patient to *C. difficile* enterocolitis, (2) to document the initial laboratory confirmation of *C. difficile* colitis, (3) to verify laboratory documentation of *C. difficile* colitis during the period before stool transplantation, (4) to document *C. difficile* treatment regimens administered before transplantation, (5) to verify laboratory documentation of *C. difficile* colitis during the 90 days after transplantation, (6) to document the clinical response to the stool transplantation, (7) to record any treatment for *C. difficile* colitis received during the 90-day posttransplantation period, and (8) to review any record of repeated hospitalization for diagnosis and treatment of diarrhea or any other acute infectious illness. The clinical course of patients after they underwent stool transplantation was documented by reviewing SMDC medical records or by obtaining records from the patients' institutions (referring hospitals or nursing homes).

Laboratory documentation of **C. difficile** *infection.* All submitted stool samples were examined at the Clinical Microbiology Laboratory at SMDC. From April 1994 through July 2001, Bartell's cytotoxin test kit (Bartell Laboratories) was used to test stool samples for presence of *C. difficile* cytotoxin (toxin B). Starting in August 2001, stool samples were tested for the presence of toxin A with use of the Triage Micro *C. difficile* assay (Biosite Diagnostics). Testing of stool samples was conducted in accordance with the directions provided by the manufacturer of each of the test kits. Culture for *C. difficile* was not performed with any of the stool samples.

Stool transplant donor screening. Individuals who had not received antimicrobial therapy for the past 6 months were considered to be suitable for potential stool donation. Preferred stool donors (in order of preference) were (1) individuals who had had intimate physical contact with the patients (spouse or significant partner), (2) family household members, or (3) any other healthy donors. During the 30 days before transplantation—usually the last 7 days—stool donors were screened for evidence of previous exposure to contagious infectious agents (table 1). Screening of blood included serologic testing for hepatitis A, B, and C viruses; HIV-1 and HIV-2; and syphilis. All donor stool samples were cultured for enteric bacterial pathogens, and each stool sample was screened by light microscopy for presence of ova and parasites in accordance with standard laboratory protocols for the Clinical Microbiology Laboratory at SMDC. Fifteen of the stool donors were members of the recipients' families; in the remaining 3 cases, family members

Table 2. Preparation of donor stool sample before stool transplantation.

Obtain stool sample ≤6 h before the transplantation procedure

Select a stool specimen (preferably a soft specimen) with a weight of ∼30 g or a volume of ∼2 cm³

Add 50–70 mL of sterile 0.9 N NaCl to the stool sample and homogenize with a household blender. Initially use the low setting until the sample breaks up; then, advance the speed gradually to the highest setting. Continue for 2–4 min until the sample is smooth.

Filter the suspension using a paper coffee filter. Allow adequate time for slow filtration to come to an end.

Refilter the suspension, again using a paper coffee filter. As before, allow adequate time for slow filtration.

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were not available as donors, and a healthy clinic staff volunteer was used as donor.

Stool transplantation protocol. Stool transplant specimens were prepared as outlined in table 2. Before the procedure, each stool transplant recipient was pretreated with a ≥4-day course of oral vancomycin (250 mg q8h) to reduce the *C. difficile* load (table 3). This treatment was discontinued on the evening before transplantation. Although this course of vancomycin reduced or eliminated diarrhea in most patients, the control of diarrhea per se was not the goal of the treatment. On the evening before the day of the stool transplantation and again on the morning of the transplantation, patients orally received 20 mg of omeprazole. On the morning of the procedure, a nasogastric tube was placed in the patient's stomach, and the tip placement position was confirmed by abdominal radiography. Twenty-five milliliters of the transplant stool suspension was drawn up in a syringe and instilled into the stomach via the nasogastric tube. The nasogastric tube was then flushed with 25 mL of sterile 0.9 N saline and removed. After the removal of the nasogastric tube, patients were allowed to resume a normal diet and physical activities immediately. After the transplantation, patients were monitored by telephone or clinic visit for any subsequent exacerbation or recurrence of diarrhea. During the weeks after the transplantation, stool specimens were examined for the presence of *C. difficile* toxin A in most patients (table 4).

RESULTS

Table 4 summarizes the demographic characteristics of and outcomes for the 18 subjects. The mean patient age (±SEM) was 73 ± 9 years (range, 51–88 years). Thirteen (72%) of the 18 patients were women. Five of the patients were hospitalized at the time of stool transplantation; the remaining 13 were treated in the outpatient gastroenterology clinic. Of those treated as outpatients, 3 were nursing home residents.

In all patients, the diagnosis of *C. difficile* colitis had been confirmed by ≥2 stool test results positive for *C. difficile* toxin. The mean period (±SEM) between diagnosis of *C. difficile* colitis and the stool transplantation was 102 ± 24 days (range, 25–497 days). During this period, the 18 patients had a combined total of 58 test results positive for *C. difficile* toxin (mean, 3.2 test results; range, 2–7 test results) and had received a combined total of 64 courses of antimicrobials (mean, 3.6 courses; range, 2–7 courses) (table 4). These treatments had been provided by the patients' referring physicians and included a variety of metronidazole and vancomycin regimens.

Two patients (patients 7 and 10) died shortly after undergoing stool transplantation and before additional stool samples could be obtained for *C. difficile* toxin analysis. Patient 7 was undergoing peritoneal dialysis for end-stage renal disease and was severely ill at the time of transplantation. Her condition remained unchanged immediately after the transplantation procedure. On the third day after the procedure, she developed peritonitis, and she died shortly thereafter. Patient 10 died as a result of pneumonia complicating chronic obstructive lung disease and atherosclerosis 14 days after the stool transplantation procedure.

After the stool transplantation, 14 of the 16 surviving patients submitted a total of 20 stool samples that were tested for *C. difficile* toxin. Patients 3 and 11 did not submit stool samples after undergoing stool transplantation. A telephone follow-up conversation with patient 3 and a review of the clinical record for patient 11 verified that neither patient had experienced a recurrence of diarrhea after the stool transplantation. Both patients remained free of diarrhea during the 90-day follow-up period.

Table 3. Preparation of stool transplant recipient and description of the transplantation procedure.

Treat the stool transplant recipient with vancomycin hydrochloride capsules (250 mg q8h) starting 4 days before the transplantation procedure. The last dose should be given on the evening before the transplantation.

Treat with omeprazole capsules (20 mg po) on the evening before and on the morning of the stool transplantation

Immediately before the stool transplantation, a nasogastric tube is placed. Radiography should be used to verify that the tube tip position is in the gastric antrum.

A total of 25 mL of the transplantation stool suspension is aspirated into a syringe and instilled into the recipient via the nasogastric tube

After the stool instillation, the nasogastric tube is flushed with 0.9 N NaCl. The nasogastric tube is then withdrawn.

The patient is permitted to resume a normal diet and all customary physical activities immediately after discharge from the gastroenterology clinic

The patient should be evaluated 14–28 days after transplantation with a routine outpatient interim history, physical examination, and stool examination for presence of *Clostridium difficile* toxin

Table 4. Demographic and clinical information for 18 patients treated for *Clostridium difficile* colitis with stool transplantation (ST).

Patient	Year	Age, years	Sex	Predisposing infection	Antimicrobial agents used before *C. difficile* infection	Antimicrobial courses before ST[a]	*C. difficile* test results before ST, negative/positive[b]	Days from diagnosis to ST	*C. difficile* test results after ST, negative/positive[c]	Outcome
1	1994	61	M	Pneumonia	Cpfx, Clm	3	1/2	73	4/0	Resolution
2	1994	76	F	SBO	Ctri	4	0/3	128	1/0	Resolution
3	1996	76	F	Postoperative wound infection	Amp, Gm	3	1/3	80	0/0[d]	Resolution
4	1996	72	F	Infected BKA	Clex, Cpfx	3	0/3	83	1/0	Resolution
5	1997	58	F	Postoperative wound infection	Cpfx	4	1/3	77	1/0	Resolution
6	1997	65	M	Septic bursitis	Cm, Pen	4	1/4	85	1/0	Resolution
7	1997	88	M	Pneumonia	Ctox	3	1/3	41	0/0[e]	Death
8	1998	79	M	SBO	Amox, Pip	2	0/2	87	0/1[f]	Treatment failure[f]
9	1998	82	F	Pneumonia	Ctri	5	0/5	126	1/0	Resolution
10	1999	83	F	Bronchitis	Clex	2	0/2	25	0/0[e]	Death
11	1999	71	F	Cellulitis	Cpfx, Cm, Pip, TMP-SMZ	3	0/3	57	0/0[d]	Resolution
12	1999	69	F	Chronic osteomyelitis	Ala	3	2/2	81	2/0	Resolution
13	2000	80	F	Urosepsis	Cpfx, Pip	4	0/3	87	1/0	Resolution
14	2000	77	F	Pneumonia	Cpfx	4	0/3	48	1/0	Resolution
15	2000	70	F	Pneumonia	Lev	2	0/2	76	2/0	Resolution
16	2001	71	F	*Helicobacter pylori* gastritis	Tet	7	0/7	497	2/0	Resolution
17	2002	77	M	Leukemia	Vm, Atm, Mtz	6	2/5	114	1/0	Resolution
18	2002	51	F	Crohn colitis	Clex, Pip, Taz	3	0/3	66	1/0	Resolution

NOTE. Ala, alatrofloxacin; Amox, amoxicillin; Amp, ampicillin; Atm, aztreonam; BKA, below knee amputation; Clex, cephalexin; Clm, clarithromycin; Cm, clindamycin; Cpfx, ciprofloxacin; Ctox, ceftizoxime; Ctri, ceftriaxone; Gm, gentamicin; Lev, levofloxacin; Mtz, metronidazole; Pen, penicillin VK; Pip, piperacillin; SBO, small bowel obstruction; TMP-SMZ, trimethoprim-sulfamethoxazole; Taz, tazobactam; Tet, tetracycline hydrochloride; Vm, vancomycin.

[a] No. of separate antibiotic treatment courses (metronidazole, vancomycin, or both) after diagnosis and before the ST.

[b] No. of negative/positive results of stool sample tests for the presence of *C. difficile* before the ST.

[c] No. of negative/positive results of stool sample tests for the presence of *C. difficile* in the 90 days after the ST.

[d] No posttreatment stool sample was obtained. Patients reported clinical resolution of diarrhea ≤1 week after the ST.

[e] Patient died before posttreatment stool sample for *C. difficile* toxin test could be obtained.

[f] Clinical relapse and positive stool test result after 17 days; no recurrence after single course of vancomycin.

Patient 8 developed diarrhea ∼17 days after undergoing stool transplantation, and the results of an additional *C. difficile* stool toxin test was positive. He was treated with a 10-day course of orally administered vancomycin, and the diarrhea resolved within 4 days. The patient did not experience any further episodes of diarrhea, and the stool *C. difficile* toxin test yielded a negative result 6 months later. There were no episodes of posttransplantation diarrhea among the remaining 15 patients who survived the 90-day follow-up period.

DISCUSSION

Stool flora is best understood as a complex, living, interdependent ecosystem. During periods of health, bacterial flora suppresses growth of *C. difficile* in the colon [21, 22]. Broad-spectrum antimicrobials have the potential to disrupt the balanced ecology of the stool flora, creating an opportunity for *C. difficile* overgrowth and attendant production of toxins, which are responsible for most of the clinical symptoms of *C. difficile* colitis. The fundamental problem in *C. difficile* colitis is not the presence of the pathogenic organism per se, but the absence of healthy flora to keep the growth of the pathogen suppressed [23–25]. Accordingly, one would anticipate that the restoration of bacterial homeostasis in the colon could resolve diarrhea states caused by uncontrolled growth of *C. difficile*.

In circumstances in which conventional therapies have failed, stool transplantation has several advantages over repeated treatment attempts with antimicrobial agents. Perhaps most importantly, transplantation breaks the cycle of antimicrobial use, which may perpetuate or renew the disruption of the intestinal flora. Moreover, stool transplantation reduces the risk of problems associated with antimicrobial use, such as the emergence

of antimicrobial-resistant enteric bacterial strains, allergic reactions, and cost.

The administration of a stool transplant via a nasogastric tube has been reported anecdotally in the medical literature [14, 15]. This route of administration requires less patient preparation, clinical time, patient inconvenience, and cost than administration of the transplant via a rectal tube or colonoscope.

In this series, patients were uniformly receptive to the prospect of stool transplantation. This is not surprising in light of the repeated antimicrobial treatment failures. None of the patients in this series raised objections to the proposed stool transplantation procedure on the basis that it "lacked aesthetic appeal" [26]. The beneficial effect of the stool transplantation was dramatic. In most instances, the patients felt much better within 12–24 h and reported marked resolution of symptoms. Only 1 of the patients experienced an additional episode of *C. difficile* colitis after undergoing stool transplantation. The cure rate for the 16 patients who survived was 94%; all surviving patients reported that bowel habits returned to the functional pattern that had preceded their first episode of *C. difficile* colitis.

Five patients in this series (patients 5, 10–12, and 14) were hospitalized and debilitated at the time of the transplantation. The other 13 patients were in relatively stable health at the time of the transplantation, and they listed relapsing *C. difficile* colitis as their principal health problem. The benefits of stool transplantation are perhaps best illustrated in this second group. These patients were experiencing both frustration and risk associated with chronic diarrhea, and most reported significant debility during the periods of exacerbated *C. difficile* colitis. Even the most robust of the patients in this series felt chronically ill, with periods of diarrhea, bloating, abdominal discomfort, weight loss, and malaise alternating with periods of relatively improved symptoms while receiving antimicrobial therapy.

No adverse effects associated with receipt of donor stool have previously been reported in the literature [1, 17–20]. The principal potential risk associated with stool transplantation is transmission of infectious agents contained in the donor stool [27, 28]. This risk may be minimized by obtaining stool from donors who have intimate physical contact with the recipient. Bjorneklett [23] points out that all mammals have a continuous need to replenish the intestinal tract with bacteria from the outside world to maintain an intact ecosystem. As such, the resident bowel flora is a product of our immediate environment. Thus, the risk of introducing new pathogens may be reduced by obtaining donor stool from an individual with whom the patient has had daily contact. The use of an nasogastric tube may also be associated with some risk. In our series, one patient who was extremely ill at the time of transplantation subsequently died of peritonitis, and the possibility that use of the nasogastric tube contributed to the peritonitis cannot be excluded.

There are some limitations to the conclusions that can be drawn from the results presented above. This study was a retrospective examination of an uncontrolled series of cases treated by a single clinician. The stool transplantation protocol used in this case series calls for a pretreatment course of vancomycin to reduce the infectious burden. It was not possible to differentiate between patients whose colitis resolved as a result of their pretransplantation course of vancomycin and those whose colitis improved as a result of the stool transplantation itself. However, each of the patients served as her or his own control, because multiple previous attempts at resolving the relapsing courses of diarrhea with oral antimicrobial therapy, including therapy with vancomycin, had failed.

Although the use of donor stool has yet to be subjected to a randomized, controlled trial, this therapy has the potential of providing patients and clinicians with an effective, low-risk, and inexpensive alternative to conventional antimicrobial treatment regimens. Additional studies will be needed before the results can be generalized for broader clinical use.

Acknowledgment

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