CLINICAL AT

Fecal Transplantation, Through Colonoscopy, Is Effective Therapy for Recurrent *Clostridium difficile* Infection

EERO MATTILA,[*] RAIJA UUSITALO–SEPPÄLÄ,[‡] MAARIT WUORELA,[§] LAURA LEHTOLA,[‖] HEIMO NURMI,[¶] MATTI RISTIKANKARE,[#] VEIKKO MOILANEN,[**] KIMMO SALMINEN,[§,¶] MAARIA SEPPÄLÄ,[§] PETRI S. MATTILA,[‡‡] VELI–JUKKA ANTTILA,[*] and PERTTU ARKKILA[§§]

*[*]Department of Infectious Diseases, [‡‡]Department of Otorhinolaryngology, and [§§]Department of Gastroenterology, Helsinki University Central Hospital, Helsinki; [‡]Department of Infectious Diseases and **Department of Gastroenterology, Satakunta Central Hospital, Pori; [§]Turku City Hospital, Turku; [‖]Maria Hospital, Helsinki City Hospital, Helsinki; [¶]Department of Medicine, Turku University Central Hospital, Turku; [#]Laakso Hospital, Helsinki City Hospital, Helsinki, Finland*

BACKGROUND & AIMS: Treatment of recurrent *Clostridium difficile* infection (CDI) with antibiotics leads to recurrences in up to 50% of patients. We investigated the efficacy of fecal transplantation in treatment of recurrent CDI. **METHODS:** We reviewed records from 70 patients with recurrent CDI who had undergone fecal transplantation. Fecal transplantation was performed at colonoscopy by infusing fresh donor feces into cecum. Before transplantation, the patients had whole-bowel lavage with polyethylene glycol solution. Clinical failure was defined as persistent or recurrent symptoms and signs, and a need for new therapy. **RESULTS:** During the first 12 weeks after fecal transplantation, symptoms resolved in all patients who did not have strain 027 *C difficile* infections. Of 36 patients with 027 *C difficile* infection, 32 (89%) had a favorable response; all 4 nonresponders had a pre-existing serious condition, caused by a long-lasting diarrheal disease or comorbidity and subsequently died of colitis. During the first year after transplantation, 4 patients with an initial favorable response had a relapse after receiving antibiotics for unrelated causes; 2 were treated successfully with another fecal transplantation and 2 with antibiotics for CDI. Ten patients died of unrelated illnesses within 1 year after transplantation. No immediate complications of fecal transplantation were observed. **CONCLUSIONS: Fecal transplantation through colonoscopy seems to be an effective treatment for recurrent CDI and also for recurrent CDI caused by the virulent *C difficile* 027 strain.**

Keywords: Bacteriotherapy; Gut Microbiota; Refractory *C difficile*.

Clostridium difficile infection (CDI) is a common cause of both community- and hospital-acquired diarrhea, usually occurring after exposure to antibiotics. During the past few years, *C difficile* infection has become more frequent, more severe, more refractory to standard treatment, and more likely to relapse.[1–4] Current treatment with metronidazole or vancomycin against CDI is suboptimal, especially in terms of high recurrence rates. Both of these antibiotics alter the normal gut flora that provides colonization resistance against *C difficile*.[5]

After successful initial therapy, up to 35% of patients experience a symptomatic recurrence after discontinuation of antibiotics for CDI.[6] A subset of patients will have multiple recurrences, and subsequent relapses occur in up to 50%–65% of patients.[7] Relapse is seen more frequently in individuals older than age 65 and requiring prolonged hospital stays. Also, recurrent CDI is associated with severe complications of megacolon, perforation, shock, or death.[8] A number of new approaches have been used to treat multiple CDI recurrences. New drugs have been introduced including rifaximin,[9] nitazoxanide,[10] and fidaxomicin.[11] Immune therapy has been used such as intravenous immunoglobulin,[12] intravenous *C difficile* toxin–specific monoclonal antibodies,[13] and oral bovine antibody–enriched whey,[14,15] as well as active vaccination.[16] Also, probiotic regimens with *Saccharomyces boulardii*[17] and *Lactobacillus*,[18] and infection with a nontoxigenic *C difficile* strain,[19] have been used. However, all currently available treatment modalities have limited efficacy. Sometimes multiple relapses are extremely difficult to prevent without continuous vancomycin therapy. At present, there are few attractive choices or strategies for the treatment of a relapsing disease.[20]

The re-establishment of the normal composition of the intestinal flora by fecal transplantation was first described in 1958.[21] Despite this, there are still only a few published reports[22–26] on fecal bacteriotherapy (fecal transplantation) in the treatment of recurrent CDI. In previous reports, various different transplantation methods have been used including stool infusion to the duodenum through a nasogastric tube or fecal enemas.

Fecal transplantation in refractory cases of CDI have been used only occasionally in Finland since the 1990s.[27] *C difficile* ribotype 027 was detected for the first time in Finland in 2007.[28] After the appearance of ribotype 027, there were more patients with relapses of *C difficile* infection and the relapses also were more difficult to treat with conventional antibiotic therapy for CDI. This encouraged the use of fecal transplantation for CDI, and it became a treatment option for selected patients.

Abbreviation used in this paper: CDI, *Clostridium difficile* infection.

0016-5085/$36.00
doi:10.1053/j.gastro.2011.11.037

We previously presented an abstract of the preliminary results of 37 patients from our series.[29] Here, we report the comprehensive results of our retrospective study of 70 patients with recurrent CDI treated with colonoscopy-administered stool in 5 different centers. The stool transplantations were performed using a standard method in all centers.

Patients and Methods

Patients

This study was a retrospective review of all patients treated by fecal transplantation through colonoscopy in 5 hospitals: Helsinki University Central Hospital, Turku University Central Hospital, Satakunta Central Hospital, Turku Municipal Hospital, and Helsinki Municipal Hospital, from November 2007 though February 2010. The criterion for fecal transplantation in these hospitals was laboratory-confirmed recurrent CDI (positive culture and toxin) despite antimicrobial treatment for CDI. All patients were refractive to standard therapy, and fecal transplantation was used as a salvage therapy after attempts of conventional therapy had failed. Only patients who had received fecal transplantation through colonoscopy according to the predetermined protocol using colonoscopy were included in the study.

Patient records were evaluated retrospectively. All the participating centers had electronic patient records including patient history, laboratory findings, and official information on the survival of the patient, which facilitated a reliable review of the information gathered in the study.

Strain typing of isolated *C difficile* colonies was performed using the DiversiLab system (bioMérieux, Marcy l'Etoile, France). This method is based on polymerase chain reaction amplification of repetitive extragenic palindromic sequences and it reliably can distinguish *C difficile* ribotype 027 strain from other strains.[30]

Stool Transplant Donor Screening

Individuals who had not received antimicrobial therapy for the past 6 months and who did not have any intestinal symptoms were considered to be suitable for stool donation. Preferred stool donors were as follows: (1) relatives, (2) individuals who had intimate physical contact with the patients (spouse or significant partner), or (3) any other healthy donors. Our protocol for donor screening is summarized in Table 1. Blood samples of the donors included total blood count, C-reactive protein, creatinine, and liver enzyme levels. All stools were freshly passed. Sixty-one of the stool donors were close relatives or other household members. In the remaining 9 cases, family members were not eligible or available as donors, and a healthy volunteer donated the stool. There were no food restrictions or recommendations for donors.

Table 1. Screening of Donors

Sample	Infectious agents to be tested	Laboratory tests
Stool	*C difficile*	Culture and toxin A/B test
	Enteric bacterial pathogens	Selective media culture
	Ova and parasites	Light microscopy
Serum	HBV	HBV surface antigen
	HCV	Anti-HCV antibodies by EIA
	HIV 1 and HIV 2	Anti-HIV antibodies by EIA
	Treponema pallidum	Plasma reagin test

EIA, enzyme immunoassay; HIV, human immunodeficiency virus.

Table 2. Fecal Transplant Procedure

Pretreatment for 4 or more days with vancomycin or metronidazole; discontinued 36 hours or more before transplant
Donor stool obtained within 6 hours of transplant (20–30 mL)
Donor stool manually homogenized in 100–200 mL of water
100-mL suspension is infused into the cecum through the biopsy channel

Fecal Transplantation

Preparation of donor stool and the patient for the procedure is presented in Table 2. The patients were pretreated with vancomycin or metronidazole until a reduction of symptoms occurred. This treatment was discontinued an average of 36 hours before the transplantation. Colonic lavage was performed by oral ingestion of 4 L of a polyethylene glycol solution (Colonsteril; Orion Oyj, Espoo, Finland) that contained 25 mmol/L NaCl, 40 mmol/L Na_2SO_4, 10 mmol/L KCl, 20 mmol/L $NaHCO_3$, and 60 mg/mL polyethylene glycol. Ileocolonoscopy was performed by an experienced endoscopist. During endoscopy no evident contraindications for fecal transplantation could be observed in any of the patients prepared for the transplantation. Biopsy specimens were taken when considered appropriate by the endoscopist. The patients were given instructions for home cleaning and disinfection to reduce the possibility of *C difficile* re-infection at home. The patients were advised to contact the hospital if they had any exacerbations of the symptoms or recurrence of diarrhea after transplantation. Most of the patients had a scheduled visit to the clinic or were contacted by telephone 12 weeks after the transplantation. Treatment failure was defined as persisting diarrhea with a positive *C difficile* toxin stool test.

Study Approval

Fecal transplantations and the retrospective review of the patient records were approved by the institutional review boards of all the participating centers. All the patients were informed about the experimental nature of this treatment procedure and about the available results in other previously published reports and possible risks of the procedure. All of the patients provided informed consent.

Results

Patient Characteristics

The mean age of the 70 patients was 73 years (range, 22–90 y). Forty-two (60%) of the 70 patients were women. Sixty (86%) of the patients were outpatients. All the patients were positive for *C difficile* stool cultures and had a positive *C difficile* toxin test. The 027 ribotype strain was found in 36 (51%) patients.

The mean time between the diagnosis of CDI and the initial stool transplantation was 133 days (range, 46–360 days). There were a mean of 3.5 (range, 1–12) laboratory-proven previous episodes of CDI before transplantation (Table 3). The patients had an average of 4.5 courses of