Open Forum Infectious Diseases
CORRESPONDENCE

Fecal Microbiota Transplantation by Freeze-Dried Oral Capsules for Recurrent *Clostridium difficile* Infection

To the Editor—Fecal microbiota transplantation (FMT) is a highly effective therapy for recurrent *Clostridium difficile* infection (CDI) [1]. However, the methods of administration used most frequently—colonoscopy, nasoduodenal infusion, and enema—are inconvenient for patients and healthcare facilities. Thus, recent demonstrations that FMT can be administered via oral capsules and as a frozen preparation have been important advances [2–5]. Louie et al [4] formulated fresh stool suspensions from related donors into oral capsules and Youngster et al [5] capsulized frozen suspensions from unrelated donors, both with success rates of 90% or higher with 1 or 2 treatments. We postulated that freeze-dried fecal material delivered via oral capsules would provide similar efficacy while providing greater stability and palatability. Beginning in February 2015, we incorporated this method of preparation into the FMT programs at MetroHealth Medical Center and the Cleveland Veterans Affairs Medical Center. Subsequently, another center has reported successful treatment of 1 patient by FMT with freeze-dried capsules [6]. Here, we report our experience testing viability of freeze-dried fecal material and treating 20 patients with recurrent CDI by FMT via freeze-dried oral capsules. The Institutional Review Boards of the Cleveland VA Medical Center and MetroHealth Medical Center deemed the study to be exempt from review because it was a case series describing routine patient management.

We compared viable bacterial counts from resuspended freeze-dried versus nonfreeze-dried frozen FMT material. Fresh stool from a healthy donor was simultaneously processed by 2 methods: (1) mixing 1:4 weight/volume in sterile phosphate-buffered saline (PBS) containing 10% sucrose as a lyoprotectant and sieving as described by Hamilton et al [2] followed by freezing at −80°C; (2) preparing as in no. 1 but with the fresh suspension immediately transferred to a freeze-drying device (Thermo Fisher Scientific, Waltham, MA) and dried for 24 hours under vacuum at −20°C. Prior to culture, freeze-dried powder was resuspended in prereduced PBS and frozen material was thawed. To quantify bacterial populations, dilutions of the suspensions were cultured under anaerobic and aerobic conditions on selective and nonselective media. Colonies with unique morphology were subjected to identification and susceptibility testing in accordance with Clinical Laboratories Standards Institute guidelines.

For FMT procedures, a single donor, known to the provider administering the capsules, was used. The donor, who was <60 years of age with no significant medical problems, completed a screening questionnaire adapted from Bakken et al [7] and screening laboratory tests including antibodies to hepatitis A, B, and C, human immunodeficiency virus, and *Treponema pallidum*. Donor feces were screened for enteric pathogens, *C difficile*, and ova and parasites. We administered 20 to 40 capsules (size 0 capsules containing approximately 60 mg of freeze-dried stool enclosed in size 00 capsules) prepared from approximately 40 grams of stool, with the entire dose taken in the outpatient clinic or with a portion taken home for later consumption. Although the number of capsules varied, the initial stool weight was consistently approximately 40 grams. *Clostridium difficile* infection therapy was discontinued 2 days before the FMT procedure. The initial 8 patients received a preprocedure magnesium citrate laxative, but subsequent patients did not because there was evidence that FMT via oral capsules can be successful without preprocedure laxatives [7].

The concentration of total anaerobes per milliliter for freeze-dried versus thawed frozen preparations was 8.5 ± 0.5 and 9.1 ± 0.2 $\log_{10}$ colony-forming units (CFU), respectively ($P = .15$). For each preparation, the predominant anaerobes were *Clostridium* spp, including *Clostridium butyricum*, *Clostridium sporogenes*, *Clostridium ramosum*, and *Clostridium paraputrificum*, and *Bacteroides* spp with bifidobacteria being present at 2–3 log lower concentrations. For both preparations, the counts of aerobic and facultative organisms, including enterococci and *Escherichia coli*, ranged from 4.3 to 5.0 $\log_{10}$ CFU/mL. Similar bacterial concentrations were obtained from freeze-dried FMT material maintained at room temperature for 72 hours and from 5 additional freeze-dried preparations.

Of 20 recurrent CDI patients treated, 17 (85%) had resolution of diarrhea without recurrence of CDI after 1 FMT procedure. Of the 3 patients who failed the first FMT procedure, 1 resolved after a second FMT, 1 resolved after a course of fidaxomicin, and 1 failed a second FMT and was maintained on chronic suppressive vancomycin therapy. The characteristics of the patients are shown in Table 1. The average length of follow up was 204 days (range, 31–408). No adverse effects were reported.

In summary, freeze-dried stool preparations provided high concentrations of viable bacteria with a predominance of anaerobes. The freeze-drying procedure is easy to perform and may offer greater palatability and flexibility in delivery of FMT to patients. Our initial clinical experience suggests that oral administration of FMT using freeze-dried preparations is promising and worthy of further study.

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Table 1. Baseline Characteristics and Outcomes of the 20 Patients With Recurrent *Clostridium difficile* Infection (CDI) Treated by Fecal Microbiota Transplantation (FMT) Using Oral Freeze-Dried Capsules[a]

Characteristic	Value
Age [year, mean (range)]	68 (36–89)
Male sex	8 (40)
No. of prior CDI episodes, median (range)	4 (3–6)
Clinical conditions	
Diabetes mellitus	7 (35)
Chronic pulmonary disease	3 (15)
End-stage renal disease	5 (25)
Cancer	3 (15)
Heart disease	5 (25)
Ulcerative colitis[b]	1 (5)
Long-term care facility residence	3 (15)
Failed prior vancomycin taper	15 (75)
Failed prior fidaxomicin therapy	5 (25)
Failed prior FMT via colonoscopy	3 (15)
Outcome	
Resolution of CDI with 1 FMT via freeze-dried capsules	17 (85)
Resolution of CDI with 2 FMT via freeze-dried capsules	1 (5)
Failure to resolve CDI with 1 FMT via freeze-dried capsules with subsequent resolution with a course of fidaxomicin	1 (5)
Failure to resolve CDI with 2 FMT via freeze-dried capsules[c]	1 (5)
Death due to any cause within 8 wk after FMT[d]	0 (0)

[a] Data are no. (%) of patients, unless otherwise specified.

[b] The patient with ulcerative colitis had chronic active ulcerative colitis. His CDI episodes were associated with an increase in frequency and decrease in consistency of stools that responded to CDI therapy.

[c] The patient who failed 2 FMT procedures was a 73-year-old woman with diabetes and chronic kidney disease stage 3 who has subsequently been managed with chronic oral vancomycin suppressive therapy.

[d] One patient had only 31 days of follow up post-FMT.

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