Fecal Microbiota Transplantation: A Practical Update for the Infectious Disease Specialist

Thomas Moore,1 Andres Rodriguez,2 and Johan S. Bakken3

1Infectious Disease Consultants (IDC) of Kansas, Wichita; 2Infectious Disease Society of America, Arlington, Virginia; and 3Section of Infectious Diseases, St. Luke’s Hospital, Duluth, Minnesota

Fecal microbiota transplantation (FMT) has been shown to be a superior therapeutic modality for the treatment of recurrent Clostridium difficile infection (RCDI). Recently the US Food and Drug Administration (FDA) determined that human stool should be classified as a biological agent and its use should be regulated to ensure patient safety. Consequently, the FDA determined that prescribers of FMT must possess an approved investigational new drug (IND) permit to administer FMT for the purpose of conducting research or treating any gastrointestinal condition other than RCDI. Although an IND is not required for use of FMT to treat RCDI, an IND is strongly encouraged and may ultimately be required. This article provides step-by-step guidance to infectious disease specialists on how to navigate the regulatory requirements and successfully obtain an IND before they can begin to use FMT as part of their clinical practice.

Keywords. Clostridium difficile; diarrhea; recurrent; fecal microbiota transplantation.

The incidence, morbidity, mortality, and costs of Clostridium difficile infection (CDI) have been steadily increasing over the last decade, and CDI is now the leading nosocomial infection in the United States [1]. In 2010, the incidence of CDI in the United States was estimated at 500,000 cases per year, with 15,000–20,000 associated deaths [2, 3] and annual costs exceeding $1 billion [4]. As the rates of all CDIs have increased, so has the rate of difficult-to-treat cases, including severe and recurrent CDI (RCDI).

The colon microbiota is a complex, interdependent ecosystem that performs many tasks. A particularly important task is the defense against invasion by exogenous bacterial species (often called “colonization resistance”) [5]. Homeostasis of the indigenous gut flora is easily disrupted by antibiotic administration, which disrupts and reduces the bacterial diversity, a condition known as dysbiosis. If the patient is exposed to C. difficile during a period of dysbiosis, colonization resistance may not be robust enough to prevent C. difficile overgrowth [6].

RCDI

RCDI is defined as an episode of C. difficile that occurs 8 weeks or less after the onset of an initial episode of CDI that resolved with or without therapy [5]. During periods of intestinal dysbiosis, C. difficile spores that persist from the initial infection may germinate into vegetative forms after antibiotic treatment has been discontinued. Conventional treatment with metronidazole or vancomycin has the unintended side effect of further altering the colonic microbiota, thus possibly increasing susceptibility to recurrence or reinfection. RCDI can turn into a chronic, recalcitrant disease with repeated bouts of infection that continue for months or years, leading to persistent use of antibiotics, colectomy, repeated hospitalizations, and even death.

Fecal Microbiota Transplantation

Conventional treatment choices for RCDI have previously been limited to metronidazole and vancomycin. Attempts to restore the indigenous flora and resolve
colonic dysbiosis have taken the form of probiotics, prebiotics, and fecal microbiota therapy (FMT), in which a healthy ecosystem is transplanted directly into the colon [6]. While these processes have not been directly compared in clinical trials, recent data support the use of FMT as the fastest method for effectively treating individuals with RCDI and restoring the colonic microbiome [7].

The first use of FMT in humans dates back to a 1958 case series of 4 patients with pseudomembranous enterocolitis [8]. Until 1989, retention enemas had been the most common technique for FMT. However, alternative methods subsequently have included fecal infusion via nasoduodenal tube in 1991, rectal tube in 1994, and colonoscopy in 1998 [9]. At this time, a variety of methods for FMT delivery are being used throughout the world. No method has yet been demonstrated to be clearly superior over another. Of the more than 700 cases reported to date, FMT has demonstrated rapid response and a cure rate in excess of 90%, with a negligible significant adverse event rate, regardless of route [10].

**INDICATIONS**

In 2010, a multispecialty workgroup [9] defined the primary indications for FMT to include the following:

- Recurrent or relapsing CDI:
  - Three or more episodes of mild to moderate CDI and failure of a 6- to 8-week taper with vancomycin with or without alternative antibiotic agents.
  - At least 2 episodes of CDI that result in hospitalization and are associated with significant morbidity.
- Moderate CDI not responding to standard therapy (vancomycin or fidaxomicin) for at least 1 week.
- Severe (and perhaps even fulminant CDI) with no response to standard therapy after 48 hours.

In all cases, primary consideration must be given to the severity and pace of the patient’s CDI when deciding whether early use of FMT is appropriate for the prevention of further clinical deterioration. Details regarding donor selection, screening, sample preparation, and administration details have been published previously and are not reviewed here [9, 11].

**FEDERAL REGULATIONS**

The US Food and Drug Administration (FDA) has the legal imperative to oversee the use of any substance intended to prevent, treat, or cure any disease or condition. With reports of increasing use of FMT for RCDI, the Center for Biologics Evaluation and Research of the FDA ruled in autumn 2012 that human feces constitutes a drug, as defined in section 351 (i) of the Public Health Service Act [42 U.S.C. 262(i)] and section 201(g) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 321(g)]. This had the unintended consequence of putting fecal material for use in FMT under the jurisdiction of hospital pharmacies, requiring storage of the fecal product in the pharmacy itself. Understandably, hospital pharmacists nearly universally viewed this as an unwelcome development.

In February 2013, the FDA announced that because FMT had not yet been approved by the agency for any specific clinical indication, it constituted an investigational agent that required providers to hold an investigational new drug (IND) permit. The FDA and National Institutes of Health subsequently convened a public workshop in May in order to address scientific and regulatory issues surrounding the use of FMT, and the decision was upheld. Shortly thereafter, the Infectious Diseases Society of America (IDSA) created another collaborative FMT workgroup that consisted of interested parties within the IDSA, Centers for Disease Control and Prevention, American Gastroenterological Association, and American College of Gastroenterology. Under the aegis of the IDSA, this workgroup petitioned the FDA to relax its enforcement, given the complexity of IND applications and its burden on physicians treating acutely ill patients. As a result of these efforts, in June the FDA announced its intention to exercise enforcement discretion regarding the required IND applications for use of FMT to treat individual cases of RCDI. In these cases, an IND is encouraged but not required. Pending further action by the agency, this decision eliminated the need for an IND to treat single cases of RCDI, providing that all recipients of FMT sign an informed consent form that clearly states that the procedure is investigational and outlines all potential risks. However, an IND for use of FMT is still required for treating conditions other than *C. difficile* infection and for the purpose of conducting research. In the future, IDSA member support will become available at www.idsociety.org. The website will contain online links to FDA forms 1571, 1572, and 3674; FMT protocol; and informed consent templates as well as a geographical map of FMT provider sites with contact information throughout the United States and Canada.

**IND PROCESS**

**Which IND Should Be Filed and by Whom?**

In the United States an IND application should be filed whenever clinical studies are planned for a new drug/biologic (FMT) in humans. A clinician/investigator can file 1 of the following 3 types of IND for use of FMT:

- An emergency IND can be submitted if the clinical situation does not allow time for an IND submission, for individual patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist. This is an
attractive option for physicians who care for acutely ill patients or who plan on performing FMT very infrequently. Guidance from the FDA on this form of IND can be found at: http://www.fda.gov/regulatoryinformation/guidances/ucm126491.htm.

- An expanded access (treatment) IND can be submitted for experimental therapies that show promise in clinical testing for serious or immediately life-threatening conditions. This option should be used by clinicians/investigators who anticipate treating more than a few patients with RCDI. It should be noted, however, that this IND is not yet allowed for individuals aged <18 years due to the lack of available data to support its use.

- An investigator (research) IND is submitted by an investigator (with or without subinvestigators) who both initiates and conducts the investigation and under whose immediate direction FMT is administered or dispensed. This option should be used if data gathered on patients enrolled in the protocol are to be used later for research. This IND should also be filed if FMT is intended to be used for a condition other than RCDI.

**How to Apply for an IND**

All successful IND applications require the following elements: a sponsor, a treatment protocol that includes a detailed informed consent form, local institutional review board (IRB) approval, and completed FDA forms 1571, 1572, and 3574. Once completed, all of the required documents for an initial IND submission should be mailed to the following address: Food and Drug Administration, Center for Drug Evaluation and Research, Therapeutic Biological Products Document Room, 5901-B Ammendale Road, Beltsville, MD 20705–1266. Further details on the submission process can be found at: http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/ucm071098.htm.

**Sponsor**

All IND applications require a sponsor and, in the case of FMT, would consist of the individual filing the application. There can only be 1 sponsor for an IND, and the sponsor has specific responsibilities that are outlined in subpart D of 21CFR 312.50–312.70 and are summarized below. Further details can be found at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312&showFR=1&subpartNode=21:5.0.1.1.3.4.

Sponsors are responsible for selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring that the trial is properly monitored, ensuring that the investigation is conducted in accordance with the plan and protocols contained in the IND, and ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks associated with the drug. The sponsor is required to monitor the progress of all investigations being conducted under the IND, including review and evaluation of the evidence relating to the safety and effectiveness of the drug and important discussions with the IRB, which should be promptly communicated with the FDA.

The 3 forms described here are required when an IND application is submitted. Each form must be submitted in triplicate (an original and 2 photocopies are acceptable). In the following, we provide suggested language for completion of each form.

**Form 1571: Describes the Title and the Aim of the FMT Research Project**

The initial IND submission and each subsequent submission to the IND must be accompanied by FDA form 1571. The FDA will assign an IND number once the application has undergone a preliminary review, but study enrollment should not be initiated until 30 days after the FDA receives the IND unless the FDA provides earlier notification that studies may begin (eg, for emergency INDs). Revised applications require tracking of changes and must have unique numbers. Form 1571 can be obtained at: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083533.pdf.

Section 5, Name of Drug: Fecal microbiota transplantation (FMT)—biologically active human fecal material

Section 7, Proposed Indication for Use: C. difficile infection (CDI)— recurrent, severe, and/or complicated. CDI is not considered to be a rare infection, thus, FMT does not qualify for an orphan drug designation.

Section 13, Contents of Application: Parts 2–4 can be addressed in the form of a cover letter; however, the sponsor is expected to provide some background information about FMT. It does not need to be an exhaustive literature review but should provide the FDA with a rationale behind the proposed treatment, with citations of relevant literature supporting its use. For example: “The concept of FMT is to restore the fecal microbiologic diversity of a patient with CDI by directly instilling fecal material collected from a healthy donor. This has been proven effective in numerous case reports and retrospective case series [9, 12] in patients with recurrent CDI resulting in superior cure rates compared to previously reported cure rates with standard therapy. Most recently, an open-label, randomized, controlled trial directly comparing FMT with two different antibiotic regimens clearly demonstrated the superiority of FMT in patients with recurrent CDI” [7]. Part 5 (Investigator’s Brochure): Creation of a brochure will be necessary if the applicant plans to conduct the study at multiple sites, and a copy will need to be submitted with the IND to the FDA. A brochure is not required for emergency INDs. The purpose of the brochure is to provide coinvestigators involved in the trial with the information necessary to participate and should include—in lieu of the treatment protocol, if desired—a brief summary, introductory statement, background of the disease, summary of...
known safety and efficacy data, description of the product, proposed indications, dosing form/regimen, route of planned administration, description of the instillation technique, and other information about the clinical trial (ie, data to be gathered, time points, endpoints, and similar information). The brochure should be reviewed annually and revised when necessary to include any new relevant information.

Part 6 (Protocols). Section a, Study Protocol: This section will require the submission of the study protocol itself. The protocol must provide detailed information about patient (recipient) and donor evaluation and testing procedures. Guidance has been published previously [11] and can be used as a template. The protocol should include detailed information regarding the collection and handling of fecal material, methods of preparation of the fecal sample as well as the dose, route, and duration of administration. Details regarding endpoints (eg, resolution of diarrhea, conversion to negative C. difficile testing by toxin assay and/or polymerase chain reaction) and long-term follow-up of treated patients must also be included. If the sponsor has created a case report form to collect data, the form should be included with the IND application.

The protocol must include a description of risks associated with FMT, including those not yet reported (eg, intestinal perforation, sepsis, transmission of an infectious agent from the donor stool [13]). If the protocol will include endoscopy, the risks associated with these procedures should be discussed separately. An informed consent form that includes specific language explaining that FMT is an investigational procedure that may be associated with potential defined risks should also be included with the IND application. The protocol must have a section detailing the potential adverse events (AEs) the clinician/investigator plans to capture. Most protocols should outline specific AEs at baseline and solicit potential AEs at follow-up visits; however, unsolicited AEs (symptoms that patients volunteer) may need to be recorded as well. All documented AEs should be reported to the FDA in a timely fashion—within 7 calendar days for serious AEs (eg, death, illness requiring hospitalization). Detailed guidance for safety reporting requirement can be found at: http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/UCM333226.pdf.

The sponsor must monitor all enrolled patients for AEs, maintain records documenting AEs, and periodically (at least annually) review and analyze the data for evidence of trends. An IND safety report should be submitted to the FDA when there is a serious and unexpected adverse reaction, an increased occurrence of serious suspected adverse reactions over that listed in the protocol, or when other studies suggest a significant risk to humans treated with FMT. Serious AEs should be reported promptly to the local IRB. Additionally, annual safety reports need to be submitted to the local IRB, and the report should include a description and frequency of observed AEs, number/percentage of patients who experienced a relapse during the first 12 weeks post-FMT, and number/percentage of patients who required additional courses of FMT. The sponsor will need to report how the data will be monitored for AEs (eg, Data Safety and Monitoring Board, frequency of data review).

The clinician will need to submit the protocol for review by the IRB. Certification of local IRB approval of the treatment protocol must accompany the IND application.

Sections b–d may be completed by filling out form 1572, which is addressed in the next section. However, it may be advisable to submit both the local IRB certification as well as a completed form 1572 (see below).

Part 7 (Chemistry, Manufacturing, and Control Data): This requires a brief description of donor material. An example of appropriate language would include statements about the heterogeneity of human stool from person to person; however, human stool consists mostly of bacteria and water.

Part 8 (Pharmacology and Toxicology Data): This section should include a statement of the potential risks associated with FMT. However, it should be emphasized that the overall risk is low and there have been no significant reported complications to date.

Form 1572: Description of the Investigators and the Sponsoring Treatment Facility

This form should include detailed information about the principal investigator and any subinvestigators as well as the sponsoring facility (hospital, clinic, physician’s office) where the investigation will be taking place. The name and address of the local IRB that has approved the FMT treatment protocol should be included under part 5. Form 1572 is available at: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf.

Form 3674: Clinical Trials Certification of Compliance

Title VIII requires that an IND application be accompanied by a certification that all applicable requirements of the Public Health Service Act (42 USC § 282(j)) have been met. This requirement can be met by completing and submitting FDA form 3674 with FDA forms 1571 and 1572. For individuals submitting an IND application for local use of FMT, box A, part 9 should be checked. However, as results of clinical trials of FMT are published, this may change. Future FMT issues that currently are being researched in the medical community and/or being discussed by the FMT workgroup established by the FDA include the following:

- Establishment of national or regional “stool banks”—repositories of stool, including frozen stool aliquots, collected from well-defined and screened donors. The most suitable location for a repository stool bank and how such a program should be financed is currently unknown.
- Establishment of a national FMT registry; however, no firm decisions have yet been made regarding the location, funding, or maintenance of such a registry.
• Commercialization of stool products. Several private biological research companies are currently engaged in phase 1 and 2 clinical trials comparing human stool collected from well-defined and screened donors to standard antibiotic therapy. It will likely take several years before an “off-the-shelf” product will become available.

• Development of reconstituted human fecal flora. Preliminary results from current research hold promise that patients suffering from RCDI may one day be treated with a “cocktail” of crucial members of the microbiota [12].

CONCLUSIONS

FMT has been shown to be a superior therapeutic modality for the treatment of RCDI. Despite the significant lack of knowledge about the fecal microbiota and the consequences of its alteration, studies have shown that FMT is highly successful at correcting the intestinal dysbiosis seen in patients with RCDI. FMT has been recommended as therapy for mild to moderate RCDI, and patients with severe CDI with or without toxic megacolon have also responded favorably to this treatment modality. The FDA has mandated that any provider who prescribes FMT must possess an approved IND to administer FMT for the purpose of conducting research or for treating any gastrointestinal condition other than RCDI. The FDA is currently working to draft specific guidelines to guide physicians on the use of FMT. Until such guidelines are released, the FDA will exercise enforcement discretion regarding IND applications for the use of FMT to treat individual cases of RCDI, provided that the patient has signed an informed consent form that outlines the potential risks and clearly states that FMT is an investigational procedure. In these cases, an IND is encouraged but not required. As of this writing, the FDA is still seeking comments on this issue, and it is unclear whether the IND exception will be sustained. Clinicians wishing to ensure access to FMT for their patients in the future are advised to file an IND. The use of an IND will also allow collection of more data on the efficacy and safety of FMT and likely further support its use.

Note

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References