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Fecal Microbiota Transplant Protocol for *Clostridium Difficile* Infection

William M. Tauxe, MST¹, Tanvi Dhere, MD², Angela Ward, MSN, FNP², Lori D. Racsca, DO³, Jay B. Varkey, MD⁴, and Colleen S. Kraft, MD, MSc^{3,4}

¹Emory University School of Medicine, Emory University School of Medicine, Atlanta, Georgia

²Division of Digestive Diseases, Emory University School of Medicine, Atlanta, Georgia

³Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, Georgia

⁴Division of Infectious Diseases, Emory University School of Medicine, Atlanta, Georgia

Abstract

Fecal microbiota transplant has become more acceptable as a therapeutic for recurrent *Clostridium difficile* infection. The FDA has an enforcement discretion policy for practitioner's performing this therapy, which includes informed consent for this experimental treatment. This manuscript describes a typical procedure that can be followed that includes the important aspects of this preparation and treatment.

Keywords

FMT; fecal microbiota transplant; *Clostridium difficile*; CDI; stool

In a fecal microbiota transplant (FMT), donor stool is infused into a recipient's gastrointestinal tract.^{1,2} FMT, which is classified by the United States Food and Drug Administration (FDA) as an investigational new drug (IND), is currently under enforcement discretion by that organization to treat recurrent *Clostridium difficile* infection (CDI) not responsive to standard therapies.³ Thus, a formal IND application is currently advisable but not required before undertaking FMT as a treatment for CDI that has not improved after standard therapies.

The biologic plausibility that supports FMT is that normal nonpathogenic bacteria from donor stool specimens can repopulate the intestinal tract of the recipient and supplant an overgrowth of *C. difficile*.⁴ The FDA guidelines indicate that the FDA will exercise enforcement discretion regarding the new IND requirements for the use of fecal microbiota for transplantation to treat CDI not responsive to standard therapies. The enforcement policy dictates that the treating, licensed health care provider obtain adequate informed consent from the patient (or his or her legally authorized representative) for use of the FMT products. It is also required that the stool specimen is obtained from a donor known to the

*To whom correspondence should be addressed. colleen.kraft@emory.edu.

patient or known to the licensed health care provider treating the patient. In addition, the donor and stool must be qualified by screening and testing performed under the direction of the licensed health care provider for providing the FMT product that will be used to treat his or her patient.³

Our institution, Emory University, has performed more than 125 FMT procedures, with a greater than 90% success rate, as defined by cessation of diarrhea at 4 weeks after final treatment (which may include more than one FMT). All of our patients received 3 or more courses of anti-CDI antibiotics without resolution of CDI before they were referred for FMT. Herein, we summarize the laboratory tests and processes that our institution has developed to safely and efficiently perform FMT in a variety of clinical circumstances.

When patients with CDI arrive at the gastroenterology clinic for FMT, a physician or midlevel practitioner (nurse practitioner or physician's assistant) reviews their medical histories and explains the FMT process. Patients are asked about food and/or medication allergies; they are informed of the known and unknown risks of FMT. The practitioner warns patients that bloating, cramping, and/or constipation are commonly reported for a few days following the procedure. It is imperative that patients are told that there are rare reports of autoimmune diseases, such as rheumatoid arthritis and idiopathic thrombocytopenia, occurring after FMT. Also, they must be reminded of possible as-yet-unreported adverse effects from FMT due to its investigational status.

FMTs performed via colonoscopy carry the risks associated with colonoscopy, such as adverse sedative reaction and bowel perforation; other methods of FMT administration carry different risks. Appropriate documentation of informed consent should be entered into the patient's medical record, including mention of the investigational status of FMT and the known and unknown risks of the procedure.²

If the prospective recipient consents, the recipient is given the choice of using a donor stool specimen from a friend or family member. Alternatively, the recipient may use stool provided by standard donors known to the institution. Standard donors are selected for their health, availability for donation, and reliability. Donors should be confident in their ability to reliably produce a stool specimen on the morning of the procedure; having approved backup donors available may be a wise precaution.

All prospective donors are assigned an anonymous identification number before they fill out a modified donor questionnaire provided by the AABB (formerly known as the American Association of Blood Banks), (Figure 1); this form inquires about their health, diet, and potential risk factors for infectious diseases. Donors each void a stool specimen for analysis, and a phlebotomist performs a blood draw. Donors at our institution are tested for the following pathogens using the specified tests.⁵

Human immunodeficiency virus (HIV) types 1 and 2: antibody

Hepatitis A: immunoglobulin (Ig)M, IgG

Hepatitis B: hepatitis B surface antigen (HBsAg)

Hepatitis C: antibody

Salmonella, *Shigella*, and *Campylobacter*: routine bacterial stool culture

Treponema pallidum: rapid plasma reagin test (RPR; if results are positive, those findings are confirmed by antibody testing)

Ova and parasite: fecal screen

Carbapenem resistant *Enterobacteriaceae*: screening culture

Vancomycin resistant *Enterococcus*: screening culture

Helicobacter pylori: stool antigen

Clostridium difficile: polymerase chain reaction (PCR)

The questionnaire and test results from each prospective donor are reviewed to determine his or her suitability as a donor. Donors who test positive for the presence of potential pathogens are informed confidentially and referred for treatment, as appropriate. In such cases, alternative donors should be requested of or presented to the prospective FMT recipient. Donors who report significant exposure to 1 or more risk factors on their questionnaires are also deemed to be unsuitable donors. Standard donors must recomplete the questionnaire, and their blood and feces must be recollected for culturing and testing at least every 3 to 6 months to ensure that they remain suitable as candidates.

Once suitable donor(s) are identified, an appointment is made for colonoscopy. Although it is possible to perform FMT in the inpatient setting, we find it is most convenient when it is performed on an outpatient basis. We recommend that patients who are hospitalized with CDI have their diarrheal symptoms controlled using anti-CDI antibiotics and undergo FMT after they are discharged. FMT can have a role in the inpatient treatment of fulminant refractory CDI; however, we do not regularly practice FMT in this setting.

On the day of the FMT, donors collect and submit a stool specimen using a sterile collection kit provided in advance. They also submit a brief form (Figure 2) describing any recent changes to their health, diet, or bowel habits. Donors must attest that they have personally produced the stool specimen provided and report the time that they voided it. On receipt, donor stool is processed in a biosafety cabinet after donning appropriate personal protective equipment (gloves and fluid impervious gown). Using a sterile wooden blade and a plastic fecal concentrator kit (Fisher Scientific, Hanover Park, IL), approximately 50 grams of donor stool is emulsified in 250 mL of nonbuffered sterile saline. Particles should be eliminated or reduced to 1 to 2 mm in width to prevent clogging in the infusion tube during colonoscopy. The resulting solution is transported to the endoscopy suite in a sterile plastic flask (from which the saline was retrieved) with an airtight seal, within a sealed, opaque biohazard bag. The solution is stored at room temperature until the FMT is performed; the FMT infusion solution is infused within 6 hours of donor voiding. Donor specimens are discarded if they were voided more than 6 hours before FMT. Some institutions prefer to emulsify the donor stool specimen in the endoscopy suite using gauze as a filter.

Patients must meet clinical indications for colonoscopy before undergoing FMT delivered in this manner. Any suspicious lesions detected may be biopsied as usual. After appropriate anesthesia is administered, the colonoscope is advanced to the most proximal portion of the colon of the patient (typically, the cecum). This positioning ensures adequate distribution of the FMT solution throughout the colon. The donor stool solution is then instilled into the proximal colon.

Patients with CDI who are not suitable candidates for colonoscopy may receive FMT via an upper-gastrointestinal approach. We have performed FMT via sterile tubes advanced through the nares, mouth, or percutaneous endoscopic gastrostomy tube. Whatever means of access is used, the distal end of the infusion tube should preferably be advanced beyond the pyloric sphincter into the distal duodenum or jejunum. Postpyloric positioning should be confirmed via imaging before infusion of the stool solution.

Patients are instructed to stop taking any antibiotics or probiotics 24 to 48 hours before FMT. They are additionally advised not to restart taking those medications after the procedure and to try to avoid unnecessary antibiotic therapy in the future. Regardless of approach, all patients should undergo colonic purgation by ingesting polyethylene glycol the night before the procedure; a prescription is provided for this in advance.

If laboratory personnel are involved, they should document, via a transplantation preparation note in the medical records of the FMT recipient, their involvement in the process. The note should include the anonymous identification number of the fecal donor; the results and date of the most recent screening tests for the donor; and the times when the donor stool was voided, when it was delivered to the laboratory, when it was processed, and when it was delivered to the endoscopy suite (Figure 3).

Patients should be scheduled for clinical follow-up within 4 to 8 weeks after receiving FMT. If patients are feeling well, they often choose to skip the follow up appointment, but follow up is essential given the importance of making sure that there are no adverse events after this therapy. It is common for patients to experience some irregular bowel habits after FMT; these irregularities usually resolve within a few weeks. When present, constipation and diarrhea generally respond to over-the-counter medications. If continued symptoms of diarrhea persist 1 week after the procedure, patients should be tested for *C. difficile* via PCR; patients may be considered for repeat FMT if their results are positive.

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Abbreviations

FMT	fecal microbiota transplant
FDA	United States Food and Drug Administration
IND	investigational new drug
CDI	<i>Clostridium difficile</i> infection
HIV	human immunodeficiency virus
Ig	immunoglobulin
HBsAg	hepatitis B surface antigen
RPR	rapid plasma reagin
PCR	polymerase chain reaction
HIV	human immunodeficiency virus
<i>C. difficile</i>	<i>Clostridium difficile</i>
KPC, CRE	carbapenem resistant <i>Enterobacteriaceae</i>
VRE	vancomycin resistant enterococci

Fecal Transplant Donor History Questionnaire

Donor Name _____
Patient Name _____
Date _____

Please Circle Yes or No
*Answers will be kept strictly confidential, please answer honestly

Are you

- 1. Feeling healthy and well today? Yes No
2. Currently taking any medication for infection? Yes No

Have you

- 3. Taken any antibiotics within the past 3 months? Yes No
4. Had any fevers, vomiting, diarrhea or other symptoms infection within the past 4 weeks? Yes No

In the past 8 weeks have you

- 5. Had any vaccinations or other shots? Yes No
6. Had contact with someone who has had a recent smallpox vaccine? Yes No

In the past 12 months have you

- 7. Had a blood transfusion? Yes No
8. Had a transplant (organ, tissue, bone marrow)? Yes No
9. Had a skin or bone graft? Yes No
10. Come into contact with someone else's blood? Yes No
11. Had an accidental needle stick? Yes No
12. Had sexual contact with anyone who has HIV/AIDS? Yes No
13. Had sexual contact with a prostitute or anyone else who takes money or drugs as payment for sex? Yes No
14. Had sexual contact with anyone who has ever used needles to take drugs or steroids, or anything NOT prescribed by their doctor? Yes No
15. Had sexual contact with anyone who has hemophilia or has used clotting factor concentrates? Yes No
16. Female donors: Had sexual contact with a male who has ever had sexual contact with another male (male donors circle "I am male")? Yes No I am male
17. Had sexual contact with a person who has hepatitis? Yes No
18. Lived with a person who has hepatitis? Yes No
19. Had a tattoo? Yes No
20. Had an ear or body piercing? Yes No
21. Been treated for syphilis or gonorrhea? Yes No
22. Been in lockup, jail or prison for >72 hours? Yes No

In the past three years have you

- 23. Been outside the United States or Canada? Yes No
List location/time spent: _____

From 1980 through 1996

- 24. Did you spend time that adds up to three (3) months or more in the United Kingdom? Yes No
25. Were you a member of the U.S. military, a civilian military employee or a dependent member of the U.S. military? Yes No

From 1980 to the present, did you

- 26. Spend time that adds up to five (5) or more years in Europe? Yes No
27. Receive a blood transfusion in the United Kingdom or France? Yes No

From 1977 to the present, have you

- 28. Received money, drugs, or other payment for sex? Yes No
29. Male donors: had sexual contact with another male, even once (female donors circle "I am female")? Yes No I am female

Have you EVER

- 30. Tested positive for HIV/AIDS virus? Yes No
31. Used needles to take drugs or steroids or anything NOT prescribed by your doctor? Yes No
32. Used clotting factor concentrates? Yes No
33. Had viral hepatitis? Yes No
34. Had any type of cancer (including leukemia)? Yes No
35. Had sexual contact with anyone who was born or lived in Africa? Yes No
36. Been in Africa? Yes No
37. Had sex for drugs or money? Yes No
38. Had any of the following gastrointestinal diseases or other medical problems? Irritable bowel syndrome? Yes No
Crohn's disease? Yes No
Ulcerative Colitis? Yes No
Chronic diarrhea? Yes No
Gastrointestinal cancers? Yes No
Celiac disease? Yes No
Morbid obesity? Yes No
Metabolic syndrome? Yes No
Colon polyps? Yes No
Chronic fatigue? Yes No
Suppressed immune system? Yes No
Allergic disorder? Yes No
39. Received a dura mater (brain covering) graft? Yes No
40. Received growth hormone made from human pituitary glands? Yes No
41. Have any of your relatives had Creutzfeldt-Jakob disease? Yes No

General Medical History

- 42. Have you had any gastrointestinal surgery (for example: appendectomy, gallbladder surgery, gastric bypass) If yes, please list: _____ Yes No
43. Do you have any autoimmune diseases (for example: Rheumatoid arthritis, Multiple Sclerosis, Lupus) If yes, please list: _____ Yes No
44. Have you ever been treated for any cancer or malignancy? Yes No
45. What is your weight? _____ What is your height? _____

Figure 1. Donor questionnaire modified from the AABB questionnaire (formerly known as the American Association of Blood Banks).

Fecal Transplant Donor Submission Form

Today's Date: _____

I verify that this is my specimen. Signature: _____

Fecal Donor Identification Number: Fecal Donor _____

Questionnaire for Donor:

Time specimen collected _____

Are you feeling well today with no change in bowel habits? Yes No

Any unusual foods consumed in the past week (shellfish, etc)? Yes No

If Yes, please list: _____

Figure 2.
Fecal transplant donor submission form.

INTESTINAL MICROBIOTA TRANSPLANTATION NOTE

Donor testing and questionnaire was reviewed (Fecal Donor XXXX):

Hepatitis A: Negative.

Hepatitis B: Negative.

Hepatitis C: Negative.

HIV: Negative.

RPR: Negative.

C. difficile PCR: Negative.

Routine Stool culture: Negative.

Ova and Parasites: Negative.

Screen for CRE and VRE: Negative

H. pylori stool antigen: Negative

Stool was voided at XXXX, arrived in laboratory at XXXX, was processed at XXXX. XX grams of stool were emulsified in XXX ml of sterile saline, and was delivered to endoscopy suite.

Signed, XXXX

Figure 3.

Intestinal microbiota transplantation preparation procedure note. HIV indicates human immunodeficiency virus; RPR, rapid plasma reagin; *C. difficile*, *Clostridium difficile*; CRE, carbapenem resistant *Enterobacteriaceae*; VRE, vancomycin resistant enterococci; *H. pylori*, *Helicobacter pylori*.