

FECAL MICROBIOTA TRANSPLANT: OPENBIOME INFUSATE THERAPY GUIDELINE

I. PURPOSE

Fecal microbiota transplant (FMT) is the process of infusing donor stool directly into a recipient's gastrointestinal (GI) tract for the purpose of reconstituting normal microbial flora in diseased colons. The preponderance of evidence is for use with multiply relapsed pseudomembranous colitis and *Clostridium difficile* infection (CDI) that has failed standard antimicrobial therapy. Evidence exists for both duodenal (upper) and colonic (lower) routes of administration, however, pooled analysis of published literature estimates differing success rates (resolution of symptoms and lack of relapse) based on route, with an estimated 70-80% success rate for upper procedures and an estimated 85-95% success rate for lower procedures¹⁻⁶. Severe adverse events, including secondary infection by norovirus, gram-negative rod sepsis and development of later autoimmunity have been reported but at very low frequency (<1%), and there is a consensus that the procedure is safe^{7,8}. The most common adverse events reported have been constipation and irritable bowel syndrome symptoms (5-10%)^{7,8}. The Food and Drug Administration has stated in a guidance dated July 2013, that although it regards FMT as an investigational procedure, it will exercise enforcement discretion for IND requirements for the use of FMT to treat CDI not responding to standard therapies (Appendix A)⁹.

OpenBiome (Medford, MA) is a not-for-profit vendor that has partnered with over 200 hospitals to provide a frozen blended stool product from pre-screened standard donors, who are assessed as per protocol every 60 days (Appendices B-D)¹⁰. Donor screening is consistent with best practices literature and is consistent with prior practice at Stanford (Appendices B,C)^{10,11}. The OpenBiome product is a homogenized 250cc mixture of donor stool, glycerol and normal saline designed to be directly infused via either duodenum or colon after thawing. The published success rates using this product in multiply relapsed CDI via colonoscopy is 50/54 (92.5%)¹². Unrelated, standard donor stool is likely equivalent in efficacy to related donor stool¹⁷.

II. POLICY

A. Indications:

1. Confirmed CDI as defined by: diarrhea (≥ 3 loose or watery stools per day for at least 2 consecutive days) and a positive stool or rectal swab PCR for *C. difficile* toxin¹³.

AND

2. Using IDSA 2010 definitions of mild, moderate and severe CDI disease - meet ONE of the 3 criteria (A, B, or C) below^{11,13}:

- A. Recurrent or relapsing CDI as defined by either:
- a. At least 3 episodes of mild to moderate CDI and failure (recurrence or continued diarrhea meeting criteria (1) above) of a 6- to 8-week taper with vancomycin with or without an alternative antibiotic (eg. fidaxomicin, rifaximin, nitazoxanide).
 - b. At least 2 episodes of severe CDI resulting in hospitalization and associated with significant morbidity.
- B. Moderate/Severe CDI not responding (defined as continued diarrhea meeting criteria (1) above) to standard therapy (oral vancomycin or fidaxomicin, not metronidazole alone) for at least 14 days.
- C. Severe with clinical worsening on standard therapy (oral vancomycin +/- IV metronidazole or fidaxomicin) after 48 hours

B. Exclusion Criteria¹¹:

- Immunocompromise because of recent chemotherapy (within 6 weeks) or continued neutropenia), bone marrow or solid organ transplant.
- The presence of human immunodeficiency virus (HIV) infection with a CD4 count of less than 200.
- Use of immunosuppressive agents, such as high-dose corticosteroids (>20mg prednisone daily or equivalent), calcineurin inhibitors, mTOR inhibitors, or immunosuppressive biologic agents (e.g., anti-tumor necrosis factor, anti-integrin), .
- Pregnancy.
- Use of antibiotics other than for treatment of CDI at baseline.
- Admission to an intensive care unit with need for vasopressor medication
- Decompensated liver cirrhosis.
- Toxic megacolon or ileus present. (These exclusion criteria are particularly important, as consideration of fecal transplant should not delay life saving colectomy in surgical disease. Gut motility is likely necessary for treatment success with fecal transplantation).

C. Stanford CDI Treatment Guidelines:

Table 1. CDI Treatment Guidelines for SUH Indexed By Severity.

Clinical Severity/Stage	First Line Regimen	Alternative Therapy
Mild/Moderate	Metronidazole 500mg PO TIDx10-14d	Vancomycin 125 mg PO q6h x 10-14d.
Severe (WBC>15K, Cr >1.5x Baseline)	Vancomycin 125 mg PO q6h x 10-14d.	Fidaxomicin 200mg PO BIDx10d.
Severe Complicated (septic shock, ileus or toxic megacolon due to CDI)	SURGICAL AND INFECTIOUS DISEASES CONSULT Vancomycin 500mg PO q6h + Metronidazole IV 500mg TID. Consider PR Vancomycin 500mg in 100ml NS enema q6h	Replace Metronidazole IV with Tigecycline IV 50mg BID.
First Recurrence	Same as above based on severity	
Multiple Recurrence	For Severe Complicated – Treat as above until stable. For all others- if not previously used: Fidaxomicin 200mg PO BID x 10d	OR Vancomycin 125mg PO q6h for 14d followed by Rifaximin 400mg PO BID for 14d OR Vancomycin PO 125mg q6h x10d, then BID x7d, then qd x7d, then qod x21d OR Fecal Microbiota Transplant. Consult ID and GI

Based on 2010 Infectious Diseases Society of America (IDSA) and 2014 European Society of Clinical Microbiology and Infectious Diseases guidelines^{13,18}.

III. PROCEDURES

A. Consent:

Individual consent specific to FMT must be obtained and documented in the patient chart prior to any administration. Consent must conform to FDA specifications (Appendix A) and should include, at a minimum, a

statement that the use of FMT products to treat *C difficile* is investigational and a discussion of its potential risks⁹. Patients should also be informed that the infusion they are to receive is from an anonymous donor unknown to the physician via an outside vendor.

B. Infusion Procurement, Transport and Storage.

1. Procurement. Infusate will be procured and be on the SUH premises in advance of any procedure so that at least one stored 250cc aliquot is available for urgent use at any time, with the supply replenished after each use.

2. Transport, Cold Chain, Storage. Infusate is stored at -80 degrees C at the OpenBiome facility for no longer than 60 days and will be shipped on dry ice to the Stanford Health Care Endoscopy Unit for storage at -20 degrees C in biohazard labeled freezers. As per OpenBiome recommendations, Infusate will not be stored at -20 degrees C no longer than 6 months from processing as noted by dates stamped on the bottle^{5,10,14-16}. Product will be thawed and prepared as per manufacturer instructions prior to administration.

C. Infusion.

Due to superior efficacy, colonoscopy administration is recommended unless a specific contraindication exists (see appendix F if other modality necessary).

1. All patients^{1-6,11}:

a. Patients should be pretreated with anti-Clostridial antibiotic (oral vancomycin or fidaxomicin preferred) at treatment for at least 7 days (can be part of failing regimen that is indication for transplant). However, the course can be abbreviated to 48 hrs if CDI is severe and transplant is more urgent.

b. Antibiotics (including anti-CDI therapy) should be **stopped 48 hours prior** to the procedure if feasible to prevent residual killing effect after FMT administered, unless urgency or patient safety precludes this.

c. Patient will need to be NPO at least 6 hours prior to the procedure.

2. Via Colonoscopy^{3,5,11,14}

a. Patient should undergo preparatory bowel lavage with 4L polyethylene glycol (or equivalent) the night before.

b. Deliver at least 200 cc's of infusate via biopsy channel into

terminal ileum/cecum (as proximal as possible). If patient has pronounced diverticulosis, an additional 50 cc's can be reserved and dispensed directly onto areas with maximal diverticuli.

c. Can consider 2mg loperamide immediately prior to procedure to maximize transplant retention if mild/moderate disease. Loperamide contraindicated for severe CDI.

D. Post-procedure Monitoring³⁻⁵

Resolution of diarrhea symptoms is typically within 48-72 hours. Do not routinely recheck stool for *C. difficile*. Only reassess if patients have symptoms or recurrence of symptoms longer than 1 week after the procedure. Otherwise, no special post-procedural monitoring is necessary.

E. Adverse Advent and Efficacy Monitoring.

Due to the heterogenous nature of the OpenBiome product, close safety and efficacy monitoring is required and is the responsibility of the treating physician. Any adverse events with reasonable suspicion for being associated with FMT or failed procedures (as defined by failure to resolve symptoms within 1 week or relapsed disease within 1 year) should be reported to OpenBiome. This can be done via email to info@openbiome.org, with reporting paperwork found at www.openbiome.org.

IV. DOCUMENT INFORMATION

- A. Original Author/Date: Paul Ravi Waldron MD, MPH: 03/2015
- B. Gatekeeper: Division of Gastroenterology
- C. Distribution and Training Requirements: This procedure is kept in the Pharmacy Policy and Procedure Manual as well as in the Stanford Endoscopy Suite
- D. Review and Renewal Requirements: This document will be reviewed every three years. The Pharmaceutical and Therapeutics committee must approve any changes.
- E. Reviews/Revisions:
- F. Approvals:

V. REFERENCES

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Appendix A: July, 2013 FDA Guidance- Full Text:

“Guidance for Industry Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat Clostridium difficile Infection Not Responsive to Standard Therapies

This guidance represents the Food and Drug Administration’s (FDA’s) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

We, FDA, are informing members of the medical and scientific community, and other interested persons that we intend to exercise enforcement discretion regarding the investigational new drug (IND) requirements for the use of fecal microbiota for transplantation (FMT) to treat Clostridium difficile (C. difficile) infection not responding to standard therapies. FDA intends to exercise this discretion provided that the treating physician obtains adequate informed consent from the patient or his or her legally authorized representative for the use of FMT products. Informed consent should include, at a minimum, a statement that the use of FMT products to treat C. difficile is investigational and a discussion of its potential risks. FDA intends to exercise this discretion on an interim basis while the agency develops appropriate policies for the study and use of FMT products under IND. FDA’s guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA’s guidances means that something is suggested or recommended, but not required.

II. DISCUSSION

Fecal microbiota collected from healthy individuals are being investigated for use in the treatment of C. difficile infection. Published data suggest that the use of fecal microbiota to restore intestinal flora may be an effective therapy in the management of refractory C. difficile infection. However, the efficacy and safety profiles of this intervention have not yet been fully evaluated in controlled clinical trials.

Contains Nonbinding Recommendations. In the Federal Register of February 25, 2013 (78 FR 12763), FDA announced a public workshop, entitled “Fecal Microbiota for Transplantation.” The purpose of this workshop was to provide a forum for the exchange of information, knowledge, and experience among the medical and scientific community about the regulatory and scientific issues associated with FMT. The workshop to discuss the regulatory and scientific issues associated with FMT was held on May 2-3, 2013. FDA noted that use of FMT and clinical studies to

evaluate its safety and effectiveness are subject to regulation by FDA, and that the complex nature of FMT products presents specific scientific and regulatory challenges. During that workshop, and in subsequent communications, physicians and scientists expressed concern to FDA that FMT is not appropriate for study under the agency's IND regulations (21 CFR Part 312). Some health care providers stated that applying IND requirements will make FMT unavailable and suggested that an alternative regulatory approach is needed to ensure the widespread availability of FMT for individuals with C. difficile infection unresponsive to standard therapies. In the weeks since the workshop, FDA has received numerous inquiries about the application of the IND regulations to the administration of FMT products, and many expressed concern about the use of these products under IND. FDA acknowledges these concerns and intends to exercise enforcement discretion regarding the IND requirements for the use of FMT to treat C. difficile infection not responding to standard therapies. FDA intends to exercise this discretion provided that the treating physician obtains adequate informed consent from the patient or his or her legally authorized representative for the use of FMT products. Informed consent should include, at a minimum, a statement that the use of FMT products to treat C. difficile is investigational and a discussion of its potential risks. FDA intends to exercise this discretion while we further consider the matter. During this period of enforcement discretion, FDA will continue to work with any sponsors who wish to submit INDs for this use of FMT. This enforcement discretion policy does not extend to other uses of FMT. Data related to the use and study of FMT to treat diseases or conditions other than C. difficile infection are limited, and study of FMT for these other uses is not included in this enforcement policy.

*Appendix B: Comparison of Costs of Individual Donor Screens with OpenBiome Product
(Cost Data as of 3/7/15):*

Test	SUH List Cost	SUH Estimated Actual Cost	Individual Donor Assessed For (Y/N)?	Openbiome-Assessed for(Y/N)?
C Difficile Toxin B PCR	\$390.00	\$39.00	Y	Y
Routine Bacterial Culture for Enteric Pathogens	\$1,950.00	\$195.00	Y	Y
Fecal Giardia Antigen	\$103.00	\$10.30	Y	Y
Fecal Cryptosporidium antigen	\$103.00	\$10.30	Y	Y
Ova and parasites	\$200.00	\$20.00	Y	Y
Helicobacter Pylori Stool Ag	\$160.00	\$16.00	Y	Y
Norovirus PCR	Data not available	Data not available	Y	Y
Adenovirus Ag (40,41)	Data not available	Data not available	Y	Y
HIV, Type I and II	\$153.00	\$15.30	Y	Y
Hepatitis A IgM	\$125.00	\$12.50	Y	Y
Hepatitis B surface antigen	\$115.00	\$11.50	Y	Y
Hepatitis B core antibody (IgM)	\$131.00	\$13.10	Y	Y
Hepatitis C Ab	Data not available	Data not available	Y	Y
Syphilis EIA	Data not available	Data not available	Y	Y
Entamoeba Hystolytica Ab	Data not available	Data not available	Y	N
Strongyloides Ab	Data not available	Data not available	Y	N
VRE Screen	N/A	N/A	N	Y
Vibrio Culture	N/A	N/A	N	Y
AFB Stain for Cyclospora	N/A	N/A	N	Y
Liver Function Tests	N/A	N/A	N	Y

Complete Blood Count	N/A	N/A	N	Y
Totals	\$3,430.00<	\$343.00<		\$250.00

Appendix C: Openbiome Donor Screening Procedures

A. Clinical Assessment

Prior to enrollment, donors (age 16-50), receive informed consent with oversight from MIT's IRB and COUHES. Donors are interviewed by a healthcare professional to determine whether they meet the following exclusion criteria:

1. **Infectious risk factors:**
 - a. Known HIV, Hepatitis B or C infections or exposure within previous 12 months
 - b. High risk sexual behaviors
 - c. Use of illicit drugs
 - d. Tattoo or body piercing within previous 6 months
 - e. Incarceration or history of incarceration
 - f. Known current communicable disease
 - g. Other personal infectious disease risk factors including Creutzfeldt-Jakob disease (CJD)
 - h. Travel history to countries where risk of infectious diarrhea is elevated

2. **Potentially microbiome-mediated conditions:**
 - a. Gastrointestinal conditions (e.g., history of IBD, irritable bowel syndrome, chronic constipation, chronic diarrhea)
 - b. Atopic conditions (e.g., asthma, eczema, eosinophilic disorders of the gastrointestinal tract)
 - c. Autoimmune conditions
 - d. Chronic pain syndromes
 - e. Metabolic conditions including BMI
 - f. Neurological conditions
 - g. Psychiatric conditions
 - h. Cancer history
 - i. Surgeries / Other medical history
 - j. Current symptoms
 - k. Medications including antibiotics, antifungals, antivirals, and immunosuppressants
 - l. Diet
 - m. Family history (e.g., family history of IBD, colon cancer)

B. Laboratory Screening

Prospective donors that do not meet any of the exclusion criteria outlined above are then subjected to a battery of serological and stool-based assays to determine whether common infectious agents are present. All tests are outsourced to third-party Clinical Laboratory Improvement Amendments (CLIA) certified testing facilities. As a condition for participation in this program, donors are required to submit written authorization for the disclosure of the results of these tests to OpenBiome, in compliance with the Health Insurance Portability and Accountability Act (HIPAA). OpenBiome redacts all personal identifying information from each report and shares copies of raw diagnostic reports with its clinical partners. Documentation is provided for the battery of tests prior to enrollment of a donor and for tests performed at the end of the collection window. Positive results for any of the following assays are treated as exclusion criteria for all materials:

1. **Serologic testing:**
 - a. HIV antibody, type 1 and 2
 - b. Hepatitis A [IgM]
 - c. Hepatitis B panel [HBsAg, anti-HBc [IgG and IgM]]
 - d. Hepatitis C [HCV antibody]

 - e. Rapid plasma reagin test for *Treponema pallidum*
 - f. Liver function panel
 - g. Complete blood count
 - h. HTLV 1 and 2

2. **Stool testing:**
 - a. PCR assay for *Clostridium difficile* toxin B
 - b. Acid-fast stain for *Cyclospora*
 - c. Culture-based assays for common enteric pathogens (including *Salmonella*, *Shigella*, *Campylobacter*, enterohemorrhagic *E. coli* Shiga toxin)
 - d. Culture-based assay for *Vibrio*
 - e. *Giardia lamblia* fecal antigen
 - f. *Cryptosporidium* fecal antigen
 - g. Ova and parasites (including *Isospora*)
 - h. *Helicobacter pylori* fecal antigen
 - i. Real-time PCR assay for fecal Norovirus
 - j. Rotavirus and Adenovirus (Type 40/41) fecal antigen
 - k. Culture-based assay for fecal Vancomycin-resistant Enterococcus VRE

Appendix D: OpenBiome Donor Qualification and Infusion Processing

C. Continuous Requalification

Qualified Donors that meet the above criteria are enrolled to provide material for FMT. Donor material is collected for up to 60 days following the initial screening. During this collection window donors must not violate any of the risk factors identified in Part A above.

During a collection window, all material is quarantined until the donor has passed a second battery of serological and stool tests as described in Part B above. Material will be released for clinical use only after the donor has successfully completed both sets of assays (before and after the collection window). A seroconversion delay of 14 days is also factored in.

In the event that a donor is recruited to provide additional material beyond an initial 60 day collection window, additional testing is performed regularly at 60 day intervals. Repeat donors that have not been tested within 60 days will be treated as new donors subject to the same screenings described in Parts A and B above. This ensures that all donors (even long-term participants) are subject to regular health evaluation.

In the event that the donor experiences any abnormal symptoms of disease, including a change in bowel habit, donors are instructed to notify OpenBiome immediately. Donors discuss their symptoms with OpenBiome's Chief Medical Officer (CMO) and are directed to their primary care provider (PCP) if needed. If the clinician determines that the donor's symptoms would lead to stool that may impact the health of a recipient, the donor will be temporarily suspended from making further donations awaiting examination of the underlying symptoms by clinical assessment and/or any diagnostic tests. In the event that a diagnosis is confirmed that would impact the health of a recipient, the donor will be disenrolled at the discretion of the CMO and/or Safety Subcommittee of OpenBiome's Clinical Advisory Board (CAB). All material collected in the preceding collection window will be destroyed. In the event of transient or nonthreatening symptoms, donors will be re-enrolled when symptoms are resolved and at the discretion of the CMO and/or Safety Subcommittee of the CAB.

In addition to this qualitative exclusion by clinician discretion, OpenBiome also treats three or more loose stools passed in a 24-hour period (the medical definition of diarrhea) as absolute exclusion criteria, and material will not be collected for processing. All material collected from within 48 hours of two loose stools will be destroyed. All material collected from within 24 hours of a single loose stool will likewise be destroyed. Bowel movements associated with a period of constipation, specifically firm, hard pellets (Bristol Stool Form Scale Type 1) will not be collected for processing.

D. Production and Process Controls

1. The donor deposits stool in a commode, seals the lid, and places the collection container in one resealable LDPE plastic bag (Ri-Pac 2GN or similar) as secondary containment. Donors receive training to prevent contamination during collection.
2. The sealed sample collection container is transferred from the donor to a qualified technician to process the sample within one hour of passage.
3. The mass of the sample is measured, subtracting the tare weight of the collection container.
4. Samples are transferred to a UV-sterilized biosafety cabinet cleaned with a sporicidal agent dedicated for sample processing and not exposed to any other materials or processes in OpenBiome's facility.
5. Within the biosafety cabinet, the stool is transferred to a sterile filter bag. The filter bag fits around the collection commode entirely, so there is no risk of material escaping during this transfer process. All stool material will be added to the same side of the membrane in the filter bag.
6. An autoclaved or sterile filtered dilutant consisting of 12.5% glycerol and a normal saline buffer (0.90% w/v NaCl in water) is added to the filter bag.
7. The sample solution sealed inside the filter bag is then introduced to a homogenizer blender for 60 seconds to mix the materials.
8. Samples are then aliquoted into sterile bottles using sterile, disposable serological pipettes.
9. The bottles are then capped and frozen immediately at -80°C. Caps are sealed with tamper-evident, perforated PVC shrink bands to ensure samples have an additional level of containment and are not contaminated or tampered with during storage and distribution. Any samples not fully processed and frozen within 120 minutes of passage are destroyed.
10. Samples are delivered to clinicians on dry ice, in double-containment vessels, with temperature indicators to ensure that samples have not thawed during transportation.

Appendix F: Detailed instructions for alternate administration routes if colonoscopy contraindicated. NOTE: Will need expert consultation with experienced provider and to discuss with endoscopy unit in order to obtain approval prior to use.

1. Via Naso-duodenal tube

- a. Consider PPI for at least 2 doses prior to procedure, also consider peri-procedural anti-emetic to prevent vomiting of infusion unless specifically contraindicated.
- b. Place naso-duodenal tube either the night before or early morning of procedure, keeping in mind that it may take time to peristalsis past the pylorus. Confirm post-pyloric placement the morning prior to FMT with plain abdominal radiograph.
- c. Keep patient upright throughout procedure in case of vomiting. Gently stir/shake solution to homogenize. Fill a 60cc syringe with at least 50cc of solution, then infuse slowly over 2-3 minutes into ND tube. Repeat until solution is entirely used. Total time should be approximately 30 minutes. Leave ND tube in place for 30-60 minutes after infusion before withdrawing
- d. Would leave patients upright at least 45 degrees and monitor patients for at least 2-3 hours post procedure to ensure no complications and no vomiting of the infused material.

2. Via enteroscopy.

- a. Consider PPI for at least 2 doses prior to procedure, also consider peri-procedural anti-emetic to prevent vomiting of infusion unless specifically contraindicated.
- b. Keep patient at 45 degrees throughout procedure and after if possible to maximize anterograde flow of infusion and in case of vomiting. Advance endoscope as close to jejunum as anatomy permits. Fill a 60cc syringe with at least 50cc of solution, then infuse slowly over 2-3 minutes into access port. Repeat until solution is entirely used. Total time should be approximately 15-30 minutes. Expect some stool retrograde to pylorus, but should not be harmful.
- c. Would leave patients upright at least 45 degrees and monitor patients for at least 2-3 hours post procedure to ensure no complications and no vomiting of the infused material

3. Via enema. Need to arrange well in advance as additional infusate required.

a. Strongly consider 2mg loperamide immediately prior to procedure to maximize transplant retention if mild/moderate disease. Loperamide contraindicated for severe CDI.

b. Administer after first bowel movement of the day. Place 250cc of solution into large volume enema bag and administer enema. Encourage patient to hold infusate for as long as possible up to 6 hours (loperamide pretreatment as above may be helpful). If infusate not held at least 1 hour, would repeat procedure that day with another 250cc. Repeat on at least 2 successive days.