PERSPECTIVE

Treating *Clostridium difficile* Infection With Fecal Microbiota Transplantation

JOHAN S. BAKKEN,* THOMAS BORODY,‡ LAWRENCE J. BRANDT,§ JOEL V. BRILL,‖ DANIEL C. DEMARCO,¶ MARC ALARIC FRANZOS,# COLLEEN KELLY** ALEXANDER KHORUTS,‡‡ THOMAS LOUIE,§§ LAWRENCE P. MARTINELLI,‖‖ THOMAS A. MOORE,¶¶ GEORGE RUSSELL,## and CHRISTINA SURAWICZ,*** for the Fecal Microbiota Transplantation Workgroup

*St. Luke's Infectious Disease Associates, Duluth, Minnesota; ‡Centre for Digestive Diseases, Five Dock, New South Wales, Australia; §Division of Gastroenterology, Montefiore Medical Center/Albert Einstein College of Medicine, New York City, New York; ‖Predictive Health, LLC, Phoenix, Arizona; ¶Baylor University Medical Center, Dallas, Texas; #Marine Aircraft Group 24, Kaneohe Bay, Hawaii; **Women and Infant's Hospital, Providence, Rhode Island; ‡‡Department of Medicine and Center for Immunology, University of Minnesota, Minneapolis, Minnesota; §§University of Calgary, Alberta, Canada; ‖‖Consultants in Infectious Diseases, Lubbock, Texas; ¶¶Department of Infectious Diseases, Ochsner Health System, New Orleans, Louisiana; ##Massachusetts General Hospital for Children, Boston, Massachusetts; and ***Division of Gastroenterology, Department of Medicine, University of Washington School of Medicine, Seattle, Washington

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Clostridium difficile **infection is increasing in incidence, severity, and mortality. Treatment options are limited and appear to be losing efficacy. Recurrent disease is especially challenging; extended treatment with oral vancomycin is becoming increasingly common but is expensive. Fecal microbiota transplantation is safe, inexpensive, and effective; according to case and small series reports, about 90% of patients are cured. We discuss the rationale, methods, and use of fecal microbiota transplantation.**

Keywords: Clostridium difficile; Transplantation; Microbiota; Fecal Enema; Recurrent Infection; Diarrhea.

During the last 15 years, *Clostridium difficile* infection (CDI) has become epidemic and continues to gain momentum, with greater incidence, morbidity, and mortality than in past decades. In the United States, the National Hospital Discharge Survey revealed doubling of CDI diagnoses from 31/100,000 in 1996 to 61/100,000 in 2003.[1] This rise has been accompanied by increasing rates of colectomy and mortality during the same time period.[2] In 2010, the yearly incidence of CDI was estimated at 500,000, with mortality at 15,000–20,000,[3–5] and the cost of managing CDI was estimated to be at least $1 billion per year in the U.S. alone.[6] One major reason for this growing problem is the emergence of newer, more virulent, and more antibiotic-resistant strains including North American pulsed-field gel electrophoresis type 1, restriction endonuclease analysis group BI, and polymerase chain reaction (PCR) ribotype 027 (NAP1/BI/ 027) among others.[7,8] Although acquisition of CDI still occurs most commonly in health care facilities, it is increasingly recognized that CDI can also be acquired in the community by young, healthy individuals without prior exposure to antibiotics or hospitals. Furthermore, patients at greater risk are no longer just elderly people but also patients with inflammatory bowel disease, compromised immune systems, and peripartum women.[5,8]

As the *C difficile* epidemic continues to grow, the numbers of failed treatments and patients who experience relapses or recurrences also are increasing. Metronidazole and vancomycin are the first-line agents for *C difficile* treatment; however, recent data suggest that metronidazole is losing its efficacy, and expert opinion is shifting toward the use of vancomycin as first-line therapy.[9] Furthermore, the rates of recurrent and severe CDI continue to increase despite the efficacy of these agents. Recurrent CDI has been documented to occur in as many as 15%–30% of patients after an initial bout of CDI, and up to 65% of patients who experience 1 recurrence will have subsequent recurrences after antibiotic therapy is stopped.[10,11] Recurrent CDI can turn into a chronic, recalcitrant disease in which repeated bouts of infection can continue for years, leading to persistent use of antibiotics, repeated hospitalizations, and even death.

The basic pathophysiology of recurrent CDI is not completely understood. Antibiotics suppress and disrupt the distal bowel microbial communities that normally keep expansion of *C difficile* populations in check. Because *C difficile* spores are largely resistant to antibiotics, they can germinate back into vegetative forms after antibiotic treatment has been discontinued. If residual normal intestinal microbiota cannot restrain the infection, *C difficile* bacteria proliferate and once again produce toxins that cause destruction of colonic epithelial cells and return of inflammation with resultant disease symptoms. Although spores are thought to play a role in the pathophysiology of recurrent CDI, some patients might become reinfected

with different strains. In 1 series of patients with recurrent CDI, molecular analysis showed that 6 of 18 (33%) had a new strain.[12]

Different treatment options exist for recurrent CDI, most of which focus on further antibiotic management. Tapered and/or pulsed courses of vancomycin therapy are favored during a traditional 10-day to 14-day course of therapy. Patients from the placebo arm of 2 studies evaluating a probiotic adjunct to standard antibiotics for recurrent CDI were analyzed for recurrence rates. The overall recurrence rate was 44.8%. However, those who had a tapering course of vancomycin had a recurrence rate of 31%; those who received pulsed dosing of vancomycin had an even lower recurrence rate of 14%.[11] Although vancomycin regimens are widely used and effective in many patients, the use of antibiotics represents a double-edged sword by suppressing both the pathogen as well as the protective microbiota. Indeed, the repeated and chronic use of antibiotics to treat recurrent infection has an adverse effect on the intestinal flora. Vancomycin is a broad-spectrum antimicrobial agent with activity against almost all gram-positive aerobic and anaerobic organisms and thus might ultimately increase susceptibility to CDI by maintaining a persistently altered state of bowel flora.

Alternative antibiotics are being investigated, but their efficacy in patients with recurrent disease is unknown.[13] Fidaxomicin had a lower rate of recurrences compared with vancomycin in 2 studies, but its role in the therapy of recurrent CDI has not been established. *Clostridium difficile* toxin-binding resins are not curative and are best used as adjunctive agents to vancomycin.

The only currently available immunologic approach to treat CDI is administration of pooled intravenous immunoglobulin (IVIG). However, the role for this therapy in CDI remains unclear because the results of studies, all retrospective so far, have been equivocal at best.[14]

An alternative approach to treatment of recalcitrant CDI is to restore the damaged microbial intestinal communities. The efficacy of the probiotic *Saccharomyces boulardii* as an adjunct to antibiotics has been tested in 2 trials. Although it did not decrease recurrence rates in those with their first episode of CDI (19% compared with 24% with placebo), it did decrease the frequency of relapses in those with recurrent CDI (34.6% vs 64.7% with placebo).[10] However, a second trial showed *S boulardii* had efficacy only in the subset of patients who were given high-dose vancomycin (2 g/d) (16.7% compared with 50% with placebo). No significant benefit was seen in those given metronidazole or lower-dose vancomycin.[15] Although the probiotic *Lactobacillus* GG showed promise in case reports, recurrence rates were worse than placebo (37.5% vs 14.3% with placebo).[16] In a controlled, albeit underpowered, trial of *L plantarun* 299v as an adjunct to metronidazole in 11 patients with recurrent CDI, the probiotic arm had a lower recurrence rate (36%) compared with placebo (66%).[17] The data to date indicate that probiotics might have a role in treatment, but their efficacy is less than ideal.

In contrast, fecal transplantation, also known as fecal bacteriotherapy, is proving to be an effective alternative intervention. Case reports and small case series to date suggest that recurrent CDI can be cured with a single treatment. The material is readily available and very inexpensive. Because the exact agent or combination of agents that might affect the cure is unknown, the terms *fecal transplantation* and *fecal bacteriotherapy* will henceforth be replaced with the new term *fecal microbiota transplantation* (FMT). The rationale behind FMT is simple;

antibiotics and other factors disrupt the normal balance of colonic flora and reduce "colonization resistance," allowing pathogenic *C difficile* strains to grow, leading to the typical clinical presentations of diarrhea and pseudomembranous colitis; by reintroducing normal flora via donor feces, the imbalance can be corrected, the cycle can be interrupted, and normal bowel function can be reestablished.

The idea of FMT has parallels in the veterinary world, where the practice of transfaunation has been used for centuries to treat ruminants with severe ruminal acidosis and other gastrointestinal disorders and for the treatment of equine diarrhea.[18] In humans, the first use of FMT dates back at least to a 1958 case series of 4 patients with pseudomembranous enterocolitis.[19] Of note, 3 of 4 patients reported in the 1958 series were in a critical state when fecal enemas were administered, and in all patients, symptoms resolved within hours of FMT. The first documented case of confirmed CDI treated with FMT, a 65-year-old woman who had "prompt and complete normalization of bowel function, was reported in 1983 by Schwan et al.[20] At follow-up 9 months later, the patient remained asymptomatic. Up until 1989, retention enemas had been the most common technique for FMT. However, alternative methods subsequently included fecal infusion via duodenal tube in 1991, rectal tube in 1994, and colonoscopy in 1998. FMT for recurrent CDI has been reported to be successful whether given via colonoscopy,[21–23] nasogastric tube,[24,25] or enemas administered at home.[26] No clear superiority of one method over another has yet been demonstrated. However, of the approximately 200 cases reported, regardless of route, a mean success rate of 96% has been achieved.[27]

It is now well-appreciated that intestinal microbiota constitute a microbial organ that is integral to overall host physiology, including pivotal roles in metabolism and immune system function.[28] So far, recurrent CDI appears to represent the clearest known example of near-complete disruption of the intestinal microbiota resulting in gastrointestinal dysfunction. Until recently, the intestinal microbiota has been generally inaccessible to scientific study because most of its constituents could not be easily cultured in the laboratory. In part this is because individual microorganisms are highly specialized and exist in structured community networks that become disrupted in attempts at single cell cloning.

Chang et al[29] constructed 16S rRNA-encoding gene clone libraries from the fecal material of 4 patients with first-time CDI and 3 patients with recurrent CDI, performed phylogenetic analyses, and compared them with normal control samples. They found that the microbiomes of patients with an initial episode of CDI were largely intact at the phylum level, ie, the majority of sequences belonged to Bacteroidetes and Firmicutes, the 2 dominant bacterial phyla in the colon. However, major reduction and even disappearance of Bacteroidetes were noted in patients with recurrent CDI and were accompanied by markedly increased proportions in other phyla that normally are only minor constituents of fecal microbiota. Khoruts et al[30] compared the microbiota of a patient with recurrent CDI before and after FMT by using terminal-restriction fragment length polymorphism and 16S rRNA gene sequencing approaches. Before transplantation, the patient's microbiota were deficient in members of Bacteroidetes. Instead, they were composed of atypical bacterial populations such as *Veillonella, Clostridium, Lactobacillus, Streptococcus*, and unclassified bacteria similar to

Erysipelothrix. Two weeks after infusion of donor fecal suspension into the patient, the bacterial composition of her feces changed to closely resemble that of the donor, with dominance of Bacteroidaceae including *Bacteroides vulgatus*. Thirty-three days after the procedure, the patient's flora still was predominantly composed of multiple *Bacteroides* species, highlighting the durability of engrafted donor bacteria administered via FMT.

In summary, CDI exists today in epidemic proportions and continues to increase steadily along with rising rates of complications, including recurrent disease and death. Recurrent disease can become an especially difficult clinical challenge, particularly in older patients who need additional antibiotics for other indications, those with additional comorbidities, and patients presenting with severe disease. Although vancomycin is the only drug that is approved by the Food and Drug Administration (FDA) to treat CDI, it is clearly insufficient for many patients with recurrent disease. This predicament has forced a number of alternative therapies to be tried and to be developed. However, none has yet proved to be highly effective, safe, and inexpensive. In contrast, with a cumulative reported cure rate of >90%, negligible rate of significant adverse effects, and response of hours to days, FMT appears to fit these criteria. Furthermore, FMT is the only therapy that restores the phylogenetic richness of the recipient's intestinal microbiota without prolonging the perturbation of the normal microbiotic composition. Additional data are needed to assess the efficacy of FMT; however, because of the encouraging data to date and pending additional research data on the intestinal microbiome and metagenome, it appears to be an effective option for the treatment of refractory CDI. Therefore, we offer the following guidelines for its use.

I. Indications
Primary Indications

1. Recurrent or relapsing CDI.
   a. At least 3 episodes of mild to moderate CDI and failure of a 6- to 8-week taper with vancomycin with or without an alternative antibiotic (eg, rifaximin, nitazoxanide).
   b. At least 2 episodes of severe CDI resulting in hospitalization and associated with significant morbidity.

2. Moderate CDI not responding to standard therapy (vancomycin) for at least a week.

3. Severe (and perhaps even fulminant *C difficile* colitis) 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 to prevent further clinical deterioration.

II. Donor Selection
Choice of Donor

At this time, few or no data are available to suggest that any factors other than specific exclusion criteria based on medical history and laboratory testing would endorse a particular donor to be optimal. There might be certain advantages and disadvantages, however, which can be considered. Intimate contacts (eg, spouse, significant other) have the advantage of sharing infectious risk factors, which minimizes the risk of transmitting an infectious agent. Despite the possibility that an intimate contact might have a higher chance of being a *C difficile* carrier, limited experience has suggested that transplant of *C difficile*–containing stool from a carrier into a recipient with recurrent CDI does not necessarily adversely affect success of the procedure. Maternal-line first-degree relatives might have a theoretic advantage of sharing the greatest number of microbial species in their intestinal microbiota with the recipient. Therefore, it is conceivable that adaptive immune elements in the mucosal immune system (eg, antigen-specific antibody) might be more tolerant of microbiota derived from such donors. However, material from alternative donors has been equally effective in curing CDI. Similarly, it is possible to speculate that men might make preferred donors over women because women might harbor microbiota that are more apt to result in irritable bowel syndrome (IBS). Finally, there are certain advantages in using unrelated, healthy, but rigorously screened donors. Availability of this large donor source can facilitate execution of FMT. Furthermore, because intestinal microbiota have recently been theorized to be potentially involved in pathogenesis of a number of systemic diseases, healthy volunteer donor sources might have advantages, especially for young patients.

Donor Exclusion Criteria

Although the following represent absolute or relative contraindications to FMT, it is critically important to give primary consideration to the severity of the patient's illness. Mutual agreement to proceed with FMT between donor and recipient might trump the risk of transmitting an infectious disease if a risk-free alternative donor cannot be found in a timely fashion, or the condition of the potential recipient is so precarious that time is a critical factor in predicting mortality from CDI. At the same time, the physician performing FMT has to assume responsibility to independently evaluate the donor for potential risk and does not need to abide by recipient-donor agreement if the risk is believed to be unreasonably high. The primary purpose of questioning the donor is to ensure that the donor is in good health, the donation process is safe for the donor, and that any risk factors for diseases transmissible by stool can be identified. The donor interview is especially important to identify risks for diseases and conditions for which there are no laboratory tests, for which tests are not sensitive enough to detect infectious disease agents, and for which tests are unable to identify early-stage or window-period infections.

1. Absolute
   a. Risk of infectious agent. Consider using American Association of Blood Banks Donor History Questionnaire: http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/BloodDonorScreening/UCM213552.pdf
      - Known human immunodeficiency virus (HIV), hepatitis B or C infections
      - Known exposure to HIV or viral hepatitis (within the previous 12 months)
      - High-risk sexual behaviors (examples: sexual contact with anyone with HIV/acquired immune deficiency syndrome or hepatitis, men who have sex with men, sex for drugs or money)
      - Use of illicit drugs
      - Tattoo or body piercing within 6 months

- Incarceration or history of incarceration
- Known current communicable disease (eg, upper respiratory tract infection)
- Risk factors for variant Creutzfeldt–Jakob disease
- Travel (within the last 6 months) to areas of the world where diarrheal illnesses are endemic or risk of traveler's diarrhea is high

b. Gastrointestinal comorbidities.
- History of inflammatory bowel disease
- History of IBS, idiopathic chronic constipation, or chronic diarrhea
- History of gastrointestinal malignancy or known polyposis

c. Factors that can or do affect the composition of the intestinal microbiota.
- Antibiotics within the preceding 3 months
- Major immunosuppressive medications, eg, calcineurin inhibitors, exogenous glucocorticoids, biological agents, etc
- Systemic antineoplastic agents

d. Additional recipient-specific considerations.
- Recent ingestion of a potential allergen (eg, nuts) where recipient has a known allergy to this (these) agent(s).

2. Relative exclusion criteria that might be appropriate to consider.
a. History of major gastrointestinal surgery (eg, gastric bypass)
b. Metabolic syndrome
c. Systemic autoimmunity, eg, multiple sclerosis, connective tissue disease
d. Atopic diseases including asthma and eczema, eosinophilic disorders of the gastrointestinal tract
e. Chronic pain syndromes, eg, chronic fatigue syndrome, fibromyalgia

Donor Testing

Donor screening and testing for relevant communicable diseases should be performed. However, as before, it is critically important to give prime consideration to the patient's illness when weighing the delays inherent in waiting for the results of stool testing.

Consider using FDA guidelines for donors of human cells, tissues, and cellular and tissue-based products (HCT/Ps): http://www.fda.gov/BiologicsBloodVaccines/GuidanceCompliance RegulatoryInformation/Guidances/Tissue/ucm073964.htm.

The FDA recommends donor screening and testing for relevant communicable diseases for HCT/Ps. A communicable disease agent or disease is relevant if:

- it is one for which there might be a risk of transmission by stool either to the patient or to those people who might handle or otherwise come in contact with the stool; and

- it could be fatal or life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of body function or permanent damage to a body structure; and

Table 1. 2011 Clinical Diagnostic Laboratory Fee Schedule

HCPC	Modifier	National limit	Midpoint	Short description
86592		$6.01	$8.12	Syphilis test, nontreponemal, qualitative
86593		$6.19	$8.37	Syphilis test, nontreponemal, quantitative
86703		$19.30	$26.08	HIV-1/HIV-2 single assay
86703	QW	$19.30	$26.08	HIV-1/HIV-2 single assay
86704		$16.96	$22.92	Hepatitis B core antibody, total
86706		$15.12	$20.43	Hepatitis B surface antibody
86708		$17.43	$23.56	Hepatitis A antibody, total
86709		$15.84	$21.41	Hepatitis A antibody, IgM
86780		$18.63	$25.18	Treponema pallidum
86803		$20.08	$27.14	Hepatits C virus antibody
87045		$13.28	$17.94	Feces culture bacteria
87046		$13.28	$17.94	Stool culture bacteria each
87177		$12.52	$16.92	Ova and parasites smears
87207		$8.44	$11.40	Smear special stain
87209		$25.29	$34.18	Smear complex stain
87272		$16.88	$22.81	*Cryptosporidium* antigen IFA
87324		$16.88	$22.81	*Clostridium* antigen EIA
87328		$16.88	$22.81	*Cryptosporidium* antigen EIA
87329		$16.88	$22.81	*Giardia* antigen EIA
87338		$20.24	$20.24	*H pylori* stool antigen EIA
87340		$14.53	$19.64	Hepatitis B surface antigen EIA
87341		$14.53	$19.64	Hepatitis B surface antigen EIA
87493		$49.39	$66.74	*C difficile* amplified probe
87803		$16.88	$22.81	*Clostridium* toxin A with optic

HCPC, Healthcare Common Procedure Code.

- it is one for which appropriate screening measures have been developed and/or an appropriate screening test for donor specimens has been licensed, approved, or cleared for such use by FDA and is available.

The tests listed below, the respective Current Procedure Terminology codes, and fee schedules are listed in Table 1.

1. Stool testing
a. *C difficile* toxin B by PCR; if unavailable, then evaluation for toxins A and B by enzyme immunoassay (EIA)
b. Routine bacterial culture for enteric pathogens
c. Fecal *Giardia* antigen
d. Fecal *Cryptosporidium* antigen

    e. Acid-fast stain for *Cyclospora, Isospora,* and, if antigen testing unavailable, *Cryptosporidium*

    f. Ova and parasites

    g. *Helicobacter pylori* fecal antigen (for upper gastrointestinal [GI] routes of FMT administration)

2. Serologic testing (unless otherwise stated, all tests should be performed by using FDA-approved test methods):

    a. HIV, type 1 and 2

    b. Hepatitis A virus (HAV) immunoglobulin (Ig) M

    c. Hepatitis B surface antigen, hepatitis B core antibody (both IgG and IgM), and hepatitis B surface antibody

    d. Hepatitis C virus antibody

    e. Rapid plasma reagin and fluorescent treponemal antibody-absorbed

Confirmatory tests will be performed when a positive or reactive screening test result is received for such purposes as donor counseling or investigating discordant test results.

Serologic testing of the recipient for these agents is optional.

Donor Eligibility Determination and Testing When Stool Donors Are Sexually Intimate Partners of the Patient

There are situations in which determination of donor eligibility, donor screening and testing are not required (for example; reproductive cells or tissue donated by a sexually intimate partner of the recipient for reproductive use). Theoretically, sexually intimate contacts would have previously shared bodily fluids and exposure to relevant communicable diseases. Stool donation by an intimate partner for purposes of FMT should not significantly increase risk for the patient. In this circumstance, the physician performing FMT might consider an abbreviated version of the above testing. This could be very important in situations where FMT must be performed expeditiously (such as severe/fulminant *C difficile* infection) and there is insufficient time to await test results.

III. Recipient Exclusion Criteria

Many patients have significant comorbidities that should be considered before performing FMT; however, it is extremely rare for these to result in exclusion.

Considerations for Increased Risk of Adverse Events Should Be Given to:

1. Patients on major immunosuppressive agents including high-dose corticosteroids, calcineurin inhibitors, mammalian target of rapamycin (mTOR) inhibitors, lymphocyte-depleting biological agents, anti-tumor necrosis factor agents, and others; chemotherapeutic antineoplastic agents.

2. Patients with decompensated liver cirrhosis, advanced HIV/acquired immune deficiency syndrome, recent bone marrow transplant, or other cause of severe immunodeficiency.

IV. Protocol for Performing FMT

Donor Preparation

1. Consider the use of a gentle osmotic laxative the night before procedure.

2. Avoidance of any foods to which recipient might be allergic for 5 days before the procedure.

3. Instructions to notify the practitioner if any symptoms of infection (fevers, diarrhea, vomiting) occur between screening and time of donation.

Recipient Preparation

1. Large volume bowel prep regardless of route of FMT. The severity of the patient's illness might limit the ability to perform this step.

2. Loperamide (if giving FMT via enema or colonoscopy) is optional. Although described in some protocols to aid in the retention of transplanted material, others have performed FMT without it with similar rates of success.

3. If FMT is to be delivered by nasogastric tube, then a proton pump inhibitor should be given to the recipient the evening before and the morning of the procedure.

V. Preparation of Stool

Stool Handling/Storage

1. Use as soon as possible after passage, but certainly within 24 hours and preferably within 6 hours. Stool should be kept in an airtight container and might be chilled but should not be frozen.

2. Use of a hood if possible (stool is a level 2 biohazard).

3. Universal precautions. Those involved with mixing and/or handling the fecal transfusion material should wear a fluid-resistant gown, gloves, and mask with goggles or eye shield.

Fecal Microbiota Tranplantation Preparation

1. Although the choice of diluents might differ among practitioners, the use of either preservative-free normal saline for intravenous injection or 4% milk is preferred to dilute the stool sample.

2. For best results, a conventional household blender (dedicated to this purpose) should be used. The stool should be homogenized, adding more diluent as necessary, until it reaches a liquid slurry consistency.

3. The stool should be filtered to remove as much particulate matter as possible. This can be accomplished by using a number of methods (eg, gauze pads, urine stone strainers).

4. The finished stool slurry should be used immediately.

5. The ideal volume for instillation has not been established. However, smaller volumes (eg, 25–50 mL) should be used for delivery from above; larger volumes (eg, 250–500 mL) should be used for delivery from below.

VI. Means of Administering Stool

There are many unanswered questions regarding the best route of administering the FMT, and, indeed, the route might vary with the needs and status of the individual patient. Methods used to administer FMT have included fecal suspensions given via nasogastric and nasoduodenal tubes, through a colonoscope, or as a retention enema.[27]

VII. Evaluation of Success

Resolution of symptoms is the primary end point; absence of relapse within 8 weeks of FMT is the secondary end point.

Infectious Diseases Society of America/Society for Healthcare Epidemiology guidelines do not recommend *C difficile* testing in patients who do not have symptoms, because patients can be colonized with *C difficile* and not develop disease.[31]

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Reprint requests

Address requests for reprints to: Thomas A. Moore, MD, Department of Infectious Diseases, Ochsner Medical Center, 1514 Jefferson Highway, New Orleans, Louisiana 70121. e-mail: thmoore@ochsner.org; fax: (504) 842-5254.