Video Article

Fecal Microbiota Transplantation via Colonoscopy for Recurrent *C. difficile* Infection

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Abstract

Fecal Microbiota Transplantation (FMT) is a safe and highly effective treatment for recurrent and refractory *C. difficile* infection (CDI). Various methods of FMT administration have been reported in the literature including nasogastric tube, upper endoscopy, enema and colonoscopy. FMT *via* colonoscopy yields excellent cure rates and is also well tolerated. We have found that patients find this an acceptable and tolerable mode of delivery. At our Center, we have initiated a fecal transplant program for patients with recurrent or refractory CDI. We have developed a protocol using an iterative process of revision and have performed 24 fecal transplants on 22 patients with success rates comparable to the current published literature. A systematic approach to patient and donor screening, preparation of stool, and delivery of the stool maximizes therapeutic success. Here we detail each step of the FMT protocol that can be carried out at any endoscopy center with a high degree of safety and success.

Video Link

The video component of this article can be found at https://www.jove.com/video/52154/

Introduction

Fecal transplants for the treatment of pseumembranous colitis were first described in 1958[1]. However, reports of ingesting feces for the treatment of food poisoning and severe diarrhea date back as early as fourth century China[2]. Fecal microbiota transplantation (FMT) is also termed in the literature "fecal bacteriotherapy", "human probiotic infusion", "stool transplant", "intestinal microbiome restoration", and "fecal transfer". It involves collecting stool from a healthy, pre-screened donor and delivering a prepared slurry into the gastrointestinal tract of the recipient via nasogastric tube, esophagogastricduodenoscopy, colonoscopy, or enema[3]. Many case series have reported the efficacy of administration via NGT and enema, however more recent studies have shown that administration of donor stool *via* a colonoscopy is safe and highly effective[4]. While other methods such as nasogastric tube administration have been reported, delivery of donor stool via colonoscopy has less immediate side effects (*e.g.* abdominal bloating and nausea)[4] and we have found that patients are more accepting of the concept of FMT when it is performed by colonoscopy. One of the therapeutic advantages of FMT *via* colonoscopy is the reduction in colonic biomass due to the bowel lavage that is performed prior to the procedure[4].

Multiple studies have investigated the role of FMT for the treatment of colitis and diarrhea caused by the opportunistic pathogen *C. difficile* (CDI). The incidence of CDI continues to rise and is a major cause of morbidity and mortality with a large economic burden throughout the world. First line treatment for CDI consists of antibiotic therapy, however recurrence rates have been reported between 15-35%[5]. Several case series and reports have documented the safety and efficacy of FMT for CDI refractory to standard medical treatment with antibiotics[4,6-16]. A study looking at long term follow up of patients after FMT via colonoscopy for CDI reported a 91% primary cure rate in 77 patients[17].

At our Center (Brigham and Women's Hospital Division of Gastroenterology, Hepatology and Endoscopy), we initiated a fecal transplant program for patients with recurrent or refractory CDI. Appropriate candidates are defined as patients who have recurrent CDI (a history of 3 or more episodes, or 2 episodes that required hospitalization), or patients with refractory disease that is unresponsive to traditional antibiotics. We believe a systematic approach to all phases of this procedure maximizes efficacy. In this manuscript and accompanying video, we detail the protocol we have employed at our Center, which includes patient and donor screening, stool preparation, and the delivery of stool at the time of colonoscopy. This method has yielded positive results comparable to the published literature.

CASE PRESENTATION:

This patient represents a typical patient referred for fecal transplantation.

The patient is a 69 year-old woman with a history of chronic lymphocytic leukemia who had relapse of disease requiring further treatment with chemotherapy. She suffered from three episodes of CDI in the past year, and was therefore referred to our clinic for consideration of FMT prior to re-initiating chemotherapy. Her first episode of CDI occurred in October 2012. She had not had any preceding antibiotics. She was very ill in the ICU after presenting with septic shock and underwent diverting loop ileostomy with antegrade vancomycin enemas for a 6 week course in

combination with oral vancomycin given the severity of her illness. She did very well with resolution of her diarrhea and she was able to come off antibiotics. She developed a hernia around her stoma so it was reversed. Shortly after the ostomy reversal she again developed diarrhea and was found again to be *C. difficile* toxin positive. She completed another 6 week course of oral vancomycin and was able to taper off of it successfully. However several months later, she again developed diarrhea that was *C. difficile* toxin positive and was started on her third course of oral vancomycin. She was doing well on antibiotics when it was noted that her white count increased to >100 and she has found to have a recurrence of her CLL on bone marrow biopsy. Her oncologists were concerned about initiating chemotherapy without complete resolution of her CDI and so we were asked to perform FMT.

Protocol

NOTE: At the time of this manuscript publication an Investigational New Drug (IND) application is not required to perform an FMT for recurrent CDI in clinical practice. However, if FMTs are being performed as part of a study or for another indication, an IND or equivalent application may be required[18]. Regulatory agencies will likely continue to assess the safety and efficacy of FMT as applied to CDI and other medical conditions and so it is advised to check the regulatory requirements in your respective location prior to the initiation of an FMT program and every one to two months once actively performing FMT.

NOTE Candidates must be willing to consent to the fecal transplant as well as the colonoscopy.

1. Identification of Appropriate Candidates for FMT

1. Patients who have relapsing CDI or patients with refractory disease that is unresponsive to traditional antibiotics are appropriate candidates for FMT.
   NOTE: relapsing CDI is defined as a history of three or more episodes of CDI confirmed by toxin testing or PCR, or two episodes that required hospitalization.
2. Ensure the patient is able to undergo a colonoscopy safely. This is at the discretion of the endoscopist.

2. Stool Donor Selection

NOTE: Stool Donor selection applies to the treatment of CDI and may not be applicable to the treatment of other disorders.

1. Ensure the patient identifies a donor. Potential donors should be present with the recipient at the time of the initial gastroenterology clinic visit. Donors may be spouses, family members, or friends. Donors may live in the same residence as the recipient as long as other criteria are met.

3. Donor Eligibility

1. Inclusion Criteria: Ensure that the donor is a healthy adult (≥18 years old) and has a daily formed bowel movement.
2. Exclusion Criteria:
   1. Ensure that the donor is not taking antibiotics or has not taken antibiotics in the prior three months or any medication for an infection.
   2. Ensure that the donor does not have a history of constipation or use laxatives chronically. Additionally, ensure the donor does not have a history of Inflammatory Bowel Disease, chronic diarrhea, microscopic colitis, a personal history of intestinal/colonic malignancy, or a history of gastric bypass/other weight loss surgery.
   3. Ensure the donor has not recently traveled (within the last three months) to an area where infectious diarrhea is a concern. If they have traveled and experienced diarrhea they should be exluded.
   4. Ensure that the donor is not taking any immunosuppressive agents and is not on systemic chemotherapy.
   5. Ensure that the donor does not have metabolic syndrome, autoimmune conditions or atopic diseases.
3. Obtain written consent from the donor and recipient prior to screening given the sensitive nature of the screening tests. Reassure both parties that test results will not be shared with the other party.

4. Screening

NOTE: This screening protocol was adapted for the patients at Brigham and Women's Hospital in Massachusetts, U.S.A. Consider consulting the infectious disease department and hospital infection control prior to initiating the FMT protocol to make sure all appropriate screening tests have been considered.

1. Recipient:
   1. At the time of the initial clinic visit, send the following laboratory tests for recipient screening (to establish baseline testing for these infectious diseases and to ensure there is no question of transmission in the future).
   2. Perform Hepatitis A (IgG and IgM), Hepatitis B (HbsAg/Ab and HbcAb), Hepatitis C Ab, HIV-1/2 (Ab and viral load) and Syphilis (TP-IgG) laboratory blood tests.
   3. Obtain a thorough history of food allergies at this initial assessment.
2. Donor:
   1. Coordinate with the microbiology laboratory before screening to ensure formed stool is not discarded.
   2. Order the below laboratory tests for donor screening if the donor meets eligibility criteria as per **section 3**.
   3. Perform Hepatitis A (IgG and IgM), Hepatitis B (HBsAg/Ab and HBcAb), Hepatitis C Ab, HIV-1/2 (Ab and viral load) and Syphilis (TP-IgG) laboratory blood tests.

4. Perform *C. difficile* (by culture), routine stool culture, Giardia antigen, Cryptosporidium antigen and ova and parasites laboratory stool tests.
5. Screen the donor no more than 30 days but preferably 1 - 2 weeks prior to the scheduled procedure.
   NOTE: If the donor develops diarrhea or liquid stool they are not longer eligible for donation.

3. Counsel the donor on foods to avoid based on the recipient's food allergies. The donor should not ingest foods to which the recipient is allergic for the 5 days before the donation.

5. Pre-procedure Preparation

1. Recipient:
   1. At the initial clinic visit, if the recipient is not already on oral vancomycin, start vancomycin 125 mg every 6 hr for at least seven to ten days prior to the procedure.
   2. Provide the recipient with the endoscopy center's instructions for pre-colonoscopy bowel preparation to be done the day before the scheduled procedure. Recipients should also follow the endoscopy center's standard dietary instructions for the week prior to the procedure.
   3. Instruct the recipient to take their last dose of vancomycin the night before the procedure.

2. Donor:
   1. Provide the donor with several stool collection cups. Label toilet inserts (hats) and cups with the recipient's label as well as 3 empty specimen containers. Ask the donor to begin stool collection no more than 6 hr prior to processing (time of procedure).
      NOTE: If the donor provides multiple stool samples, they should be labeled with dates and times. Use the freshest sample (one filled specimen cup will suffice).
   2. Ensure that the recipient to brings the donor's stool sample with them to the procedure.
   3. Store the stool samples at room temperature. Exclude any unformed stool. Discard any unused stool in a sanitary sewer system (unless saving for research purposes).

6. Stool Preparation

NOTE: Ensure this procedure is discussed and approved by the hospital's infection control department.

1. Wear personal protective equipment when preparing the stool.
2. Prepare stool in the endoscopy room in a designated work area in which there is an eighteen inch splash zone that prevents contamination of other materials.
3. Prior to stool preparation, clean the designated area with hospital-approved disinfectant.
4. Cover the area with a disposable pad to avoid contamination.
5. Transfer the formed stool into a fourteen ounce single speed blender and add 500 cc of normal saline.
6. Blend the contents for at least one minute or until it reaches a liquid slurry consistency. Be careful to avoid spillage when removing the lid of the blender.
7. Pour the solution through the strainer into a plastic eight quart basin to eliminate any solid waste. Discard the strainer.
8. Draw up the strained solution into 60 cc luer lock syringes (approximately eight to nine for a standard FMT by colonoscopy). Draw up an extra 60 cc of normal saline for flushes.

7. Fecal Transplant via Colonoscopy

1. Wear personal protective equipment in accordance with the endoscopy unit policies while performing or assisting with the infusion.
2. Consider light sedation, if possible, so that the patient may be able to cooperate with retaining the stool after the procedure.
3. Perform a colonoscopy to the terminal ileum (or as far as technically feasible). On insertion of the colonscope, lavage and suction any residual liquid stool.
4. Inspect the mucosal walls for evidence of inflammation but mucosal biopsies are not routinely performed during the FMT procedure.
   NOTE: Determine whether or not a full colonoscopy is safe due to the degree of inflammation. If not,consider a more limited flexible sigmoidoscopy with infusion (use half of the stool slurry).
5. Infuse 60 cc (one syringe) once in the terminal ileum via the biopsy channel of the colonoscope using the biopsy channel cap with extension tubing.
6. Between applications of stool syringes, flush the channel with normal saline to avoid clogging.
7. Infuse another 60 cc of stool into the cecum and then repeat in the right colon.
8. Continue infusing 30 cc every five to ten cm while evenly distributing the slurry on all four colon wall quadrants until the mid-transverse colon is reached. Remember to flush with saline in between stool syringes.
   NOTE: If the slurry is very viscous it may be necessary to push with considerable force on the syringe. Be careful that the biopsy channel cap does not separate from the colonoscope and cause spillage of stool contents. Frequent flushing will allow for easier passage of the slurry. If there is continued difficulty in pushing the slurry, consider re-straining the remaining donor stool for a second time or diluting further with normal saline.
9. Aspirate excess air upon withdrawal when changing syringe barrels while being careful not to suction any liquid stool.
   NOTE: If the patient has known fecal incontinence, the last syringe should be infused no lower than the hepatic flexure to avoid leakage during and post procedure.
10. Once the colonoscopy with FMT is complete, advise the patient to retain the stool as long as they can. They may resume their regular diet and medications two hours after the colonoscopy is complete.

8. Colonoscopy with FMT Clean Up

1. Perform post procedure equipment reprocessing, environment cleaning/disinfection and waste disposal as per hospital protocol.
2. Dispose of all fecal material in the appropriate biohazard container.
3. Bring the colonoscope to the decontamination area for routine processing per standard protocol.
4. Dispose of the blender and strainer with any other soiled waste.
   NOTE: If single use blenders and strainers are not feasible at an individual institution alternate mixing methods can be considered. One example: passing the stool through a stainless steel potato ricer that can be cleaned in an autoclave. We recommend discussing any potential methods with your facility's infection control department.
5. Decontaminate all surfaces that were used for the procedure using the facility-approved products.

9. Follow Up

1. Arrange a follow up appointment in gastroenterology clinic for the patient approximately 30 days after the FMT.
2. Counsel the patient about the risk of *C. difficile* recurrence with future courses of antibiotics.

10. Reporting of Adverse Events

1. Although FMT is considered to be a safe procedure, it is strongly advised to keep track of all adverse events felt to be associated with the procedure and to report them to the appropriate regulatory boards.
2. In order to document the long-term safety of FMT, keep a reliable database that can be periodically queried.

Representative Results

We have performed 24 FMTs on 22 patients at our Center (**Table 1**) using the above protocol. Nine patients had concurrent IBD (six with Crohn's disease and three with ulcerative colitis). All nine had resolution of CDI. One of the patients with Crohn's disease was status post a total colectomy for Crohn's colitis. He initially underwent FMT via colonoscopy however after experiencing a recurrence two weeks post FMT he underwent a second FMT via upper endoscopy which resulted in CDI resolution. Eleven out of thirteen of the non-IBD patients had complete resolution of symptoms related to *C. difficile* after one FMT with an average length of follow up of 3 months [2 weeks - 17 months]. One patient underwent a second FMT, which resulted in resolution of CDI. The second patient who relapsed after FMT opted to not have a second transplant. There were no complications related to the procedure or the FMT (*i.e.* infections, flare of IBD, nausea, vomiting, abdominal pain, or GI bleeding) during the limited to date follow up. One patient with IBD did experience self limited abdominal pain one day post-FMT.

Table 1: Characteristics of Patients who Underwent Fecal Microbiota Transplantation at our Center.

Age	Sex	No. of Positive C.diff tests prior to FMT	Recurrent or Refractory CDI	Donor Relation	Concurrent IBD: yes or no	Recurrence post FMT	Complications Related to FMT
85	F	4	Recurrent	Daughter	No	No	None
57	F	3	Recurrent	Friend	No	No	None
60	F	3	Recurrent	Friend	No	No	None
74	F	3	Recurrent	Son	No	No	None
78	M	2	Recurrent	Son	No	Yes	None
64	F	3	Recurrent	Son-in-Law	No	No	None
59	F	4	Recurrent	Boyfriend	No	No	None
69	F	3	Recurrent	Husband	No	No	None
61	F	5	Recurrent	Husband	No	No	None
82	F	3	Refractory	Daughter	No	No	None
43	F	5	Recurrent	Daughter	No	No	None
*89	F	4	Refractory	Granddaughter	No	Yes***	None
				Daughter	No	No	None
43	F	5	Refractory	Husband	No	No	None
22	M	5	Refractory	Mother	Yes	No	None
23	F	3	Recurrent	Mother	Yes	No	None
22	F	3	Recurrent	Mother	Yes	No	None
32	M	3	Recurrent	Brother-in Law	Yes	No	Pain x 1 day
56	F	3	Recurrent	Sister	Yes	No	None
42*	M	>5	Recurrent	Brother	Yes	Yes	None
				Friend	Yes	No	None
31	F	3	Recurrent	Friend	Yes	No	None
39	F	3	Refractory	Brother	Yes	No	None
83	F	3	Recurrent	Husband	Yes	No	None

*Second FMT was performed on the same patient described for procedure 12. This was done via upper endoscopy and with a different donor given his complicated anatomy.

*** Recurred one week post FMT so second FMT was performed

Please click here to view a larger version of this table.

Discussion

Fecal transplants have been shown to be an effective and safe treatment for recurrent CDI. We have outlined a standard protocol for FMT *via* colonoscopy and included our results for 22 patients who underwent the procedure for recurrent CDI. Our results thus far are comparable to published data for recurrent disease with only one patient recurring one month post FMT. A critical step of the procedure is the prescreening visit to ensure that the donor is suitable and that the patient has no contraindications to undergoing a colonoscopy. Screening generally takes three to four days to complete and the procedure can be scheduled shortly thereafter.

Slight modifications may have to be made depending on the patient. The patient that required two FMTs also had Crohn's disease and was status post total colectomy with ileo-anal anastomosis. His first transplant was *via* a colonoscope in which we instilled stool at 90 cm from the anus into his small intestine. When his *C. difficile* recurred, we proceeded with a second FMT via small bowel enteroscopy resulting in resolution. As mentioned in the protocol, a more limited flexible sigmoidoscopy can be performed if there is evidence of significant inflammation or the patient cannot tolerate a full colonoscopy.

A limitation of FMT may be insurance coverage. In the United States, not all commercial insurance companies cover this procedure. Therefore, it is important to check with the patient's insurance carrier prior to FMT and a medical necessity letter is often needed.

In conclusion, FMT is an effective therapy for recurrent CDI and holds promise for the treatment of other disease processes, such as autoimmune diseases and inflammatory bowel disease. In the near future, advances such as the creation of "stool banks" may obviate the need for stool donors and streamline the pre-procedure stool screening process. Although the safety profile of colonoscopy with FMT appears to be excellent, the long-term consequences are not yet known.

In regards to the 69 year-old woman in the case presentation, she underwent a successful FMT and had normalization of her bowel movements within 2 days of the procedure. She underwent further treatment of her CLL with chemotherapy and has remained *C. difficile* free for more then six months.

Disclosures

The authors have nothing to disclose relevant to the material presented in this manuscript.

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