HHS Public Access

Author manuscript

*Am J Gastroenterol*. Author manuscript; available in PMC 2017 August 01.

Published in final edited form as:

*Am J Gastroenterol*. 2014 July ; 109(7): 1065–1071. doi:10.1038/ajg.2014.133.

# Fecal Microbiota Transplant for Treatment of *Clostridium difficile* Infection in Immunocompromised Patients

**Colleen R. Kelly, MD, FACG**[1], **Chioma Ihunnah, MD, MPH**[1], **Monika Fischer, MD, MSCR**[2], **Alexander Khoruts, MD**[3], **Christina Surawicz, MD, MACG**[4], **Anita Afzali, MD, MPH**[4], **Olga Aroniadis, MD**[5], **Amy Barto, MD**[6], **Thomas Borody, MD, PhD, FACG**[7], **Andrea Giovanelli, BS**[8], **Shelley Gordon, MD, PhD**[9], **Michael Gluck, MD**[10], **Elizabeth L. Hohmann, MD**[11], **Dina Kao, MD**[12], **John Y. Kao, MD**[13], **Daniel P. McQuillen, MD**[6], **Mark Mellow, MD, FACG**[14], **Kevin M. Rank, MD**[3], **Krishna Rao, MD**[13], **Arnab Ray, MD**[15], **Margot A. Schwartz, MD, MPH**[10], **Namita Singh, MD**[16], **Neil Stollman, MD, FACG**[8], **David L. Suskind, MD**[16], **Stephen M. Vindigni, MD, MPH**[4], **Ilan Youngster, MD**[11], and **Lawrence Brandt, MD, MACG**[5]

[1]Division of Gastroenterology, Brown Alpert Medical School, Women's Medicine Collaborative, Alpert Medical School of Brown University, Providence, Rhode Island, USA

[2]Indiana University School of Medicine, Indianapolis, Indiana, USA

[3]University of Minnesota Medical School, Minneapolis, Minnesota, USA

[4]University of Washington School of Medicine, Seattle, Washington, USA

[5]Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York, USA

[6]Lahey Clinic Hospital and Medical Center, Tufts University School of Medicine, Burlington, Massachusetts, USA

[7]Centre for Digestive Diseases, Five Dock, Sydney, New South Wales, Australia

[8]Northern California Gastroenterology Consultants, Inc., Oakland, California, USA

[9]California Pacific Medical Center, San Francisco, California, USA

**Correspondence:** Colleen R. Kelly, MD, FACG, Division of Gastroenterology, Brown Alpert Medical School, Women's Medicine Collaborative, 146 West River Street, Providence, Rhode Island 02904, USA. colleen_r_kelly@brown.edu.

Colleen R. Kelly affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

**Guarantor of the article:** Colleen R. Kelly, MD, FACG.

**Specific author of contributions:** Colleen R. Kelly—involved in the study design, as well as in the planning, conducting, and collection and interpretation of data for this study and in drafting/editing the manuscript. Chioma Ihunnah—involved in the planning, collection and interpretation of data for this study, and in drafting the manuscript. Monika Fischer and Alexander Khoruts—involved in data collection and drafting/editing of the manuscript. Christina Surawicz—involved in data collection and editing of the manuscript. Anita Afzali, Olga Aroniadis, Amy Barto, Thomas Borody, Andrea Giovanell, Shelley Gordon, Michael Gluck, Elizabeth L. Hohmann, Daniel P. McQuillen, Mark Mellow, Dina Kao, John Y. Kao, Kevin M. Rank, Krishna Rao, Arnab Ray, Margot A. Schwartz, Namita Singh, Neil Stollman, David L. Suskind, Stephen M. Vindigni, and Ilan Youngster—involved in data collection. Lawrence J. Brandt—involved in data collection and editing the manuscript. All the above-mentioned authors have approved the final draft submitted.

**Potential competing interests:** Kelly C.R.: US endoscopy, Inc., Consultant; Seres health, Site PI for clinical trial. Khoruts A.: CIPAC, Ltd, Research Support. Brandt L.: Optimer Pharmaceuticals, Inc, Speaker's Bureau and Research support. Borody, T.: has patents filed in the field of FMT. Stollman N.: Speaker's Bureaus: Optimer Pharmaceuticals, Inc.; Aptalis Pharma; and Otsuka America, Inc; on the advisory board for Doximity; and on the American College of Gastroenterology board of governors. Gordon S.: Cubist, Pharmaceuticals, Inc., Speaker's Bureau. Mellow M.: Optimer Pharmaceuticals, Inc., Speaker's Bureau.

[10]Virginia Mason Medical Center, Seattle, Washington, USA

[11]Massachusetts General Hospital and Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, USA

[12]University of Alberta, Edmonton, Alberta, Canada

[13]University of Michigan, Ann Arbor, Michigan, USA

[14]Integris Baptist Medical Center, Oklahoma, Oklahoma, USA

[15]Ochsner Clinic Foundation, New Orleans, Louisiana, USA

[16]Seattle Children's Hospital, Seattle, Washington, USA

## Abstract

**OBJECTIVES—**Patients who are immunocompromised (IC) are at increased risk of *Clostridium difficile* infection (CDI), which has increased to epidemic proportions over the past decade. Fecal microbiota transplantation (FMT) appears effective for the treatment of CDI, although there is concern that IC patients may be at increased risk of having adverse events (AEs) related to FMT. This study describes the multicenter experience of FMT in IC patients.

**METHODS—**A multicenter retrospective series was performed on the use of FMT in IC patients with CDI that was recurrent, refractory, or severe. We aimed to describe rates of CDI cure after FMT as well as AEs experienced by IC patients after FMT. A 32-item questionnaire soliciting demographic and pre- and post-FMT data was completed for 99 patients at 16 centers, of whom 80 were eligible for inclusion. Outcomes included (i) rates of CDI cure after FMT, (ii) serious adverse events (SAEs) such as death or hospitalization within 12 weeks of FMT, (iii) infection within 12 weeks of FMT, and (iv) AEs (related and unrelated) to FMT.

**RESULTS—**Cases included adult (75) and pediatric (5) patients treated with FMT for recurrent (55%), refractory (11%), and severe and/or overlap of recurrent/refractory and severe CDI (34%). In all, 79% were outpatients at the time of FMT. The mean follow-up period between FMT and data collection was 11 months (range 3–46 months). Reasons for IC included: HIV/AIDS (3), solid organ transplant (19), oncologic condition (7), immunosuppressive therapy for inflammatory bowel disease (IBD; 36), and other medical conditions/medications (15). The CDI cure rate after a single FMT was 78%, with 62 patients suffering no recurrence at least 12 weeks post FMT. Twelve patients underwent repeat FMT, of whom eight had no further CDI. Thus, the overall cure rate was 89%. Twelve (15%) had any SAE within 12 weeks post FMT, of which 10 were hospitalizations. Two deaths occurred within 12 weeks of FMT, one of which was the result of aspiration during sedation for FMT administered via colonoscopy; the other was unrelated to FMT. None suffered infections definitely related to FMT, but two patients developed unrelated infections and five had self-limited diarrheal illness in which no causal organism was identified. One patient had a superficial mucosal tear caused by the colonoscopy performed for the FMT, and three patients reported mild, self-limited abdominal discomfort post FMT. Five (14% of IBD patients) experienced disease flare post FMT. Three ulcerative colitis (UC) patients underwent colectomy related to course of UC > 100 days after FMT.

**CONCLUSIONS—**This series demonstrates the effective use of FMT for CDI in IC patients with few SAEs or related AEs. Importantly, there were no related infectious complications in these high-risk patients.

## INTRODUCTION

*Clostridium difficile* infection (CDI) is responsible for 15–25% of nosocomial antibiotic-associated diarrhea (1) and has increased rapidly in the past decade (2) to an incidence of 10.4 cases per 1,000 patient admissions (3). Recurrence is a common management problem and occurs in up to 20% of patients after initial CDI treatment (4). Current guidelines recommend a tapering course of vancomycin after a second recurrence; however, up to 60% of patients do not respond to this treatment strategy or develop further recurrence after the vancomycin is stopped (5).

Initially described for treatment of pseudomembranous enterocolitis in 1958 (6), fecal microbiota transplant (FMT) has proven to be efficacious and safe in numerous case series (7) and a recently published clinical trial (8). The use of FMT among immunocompromised (IC) patients with CDI has been limited due to concerns about its safety in this population. Published guidelines recommend avoidance of fecal transplant in solid organ transplant (SOT) recipients because of the theoretic potential for infection (9) and caution even against the use of probiotics in IC hosts because of the rare complication of superinfection (including bloodstream infections), which has been reported from these “nonpathogenic” organisms (10,11). A recent guidance issued by the FMT working group specified that considerations for increased risk of adverse events (AEs) should be given to patients on major immunosuppressive agents and patients with decompensated liver cirrhosis, advanced HIV/AIDS, recent bone marrow transplant, or other causes of severe immunodeficiency (12). Furthermore, the Food and Drug Administration/Center for Biologics Evaluation and Research recommended that patients who were IC for any reason be excluded from the first randomized trial of FMT in this country (13). Successful treatment of CDI in two SOT recipients was recently described (14); however, to date, no study has systematically investigated the safety and efficacy of FMT in a larger cohort of IC patients. We and colleagues at other medical centers offering FMT have treated a number of IC patients with FMT. By this collective experience we aim to describe rates of CDI cure in this population as well as AEs experienced by IC patients after FMT.

## METHODS

We performed a retrospective study of IC patients with CDI who underwent FMT at 16 medical centers nationally and internationally. The study was approved by the Lifespan Institutional Review Board and the protocol was then made available to any center participating in the study for institution-specific Institutional Review Board approval. The methods used to administer FMT differed among sites, although most (12 of 16) exclusively used an endo scopic lower gastrointestinal route of administration. Informed consent had been obtained from all patients before FMT. A 32-item data collection form was developed, which elicited demographic data, CDI characteristics, and pre- and post-FMT data for each patient. Patients were included if they were IC and had undergone FMT to treat recurrent,

refractory, severe, or complicated CDI unresponsive to standard therapy. Definitions used to classify recurrent, severe, and complicated CDI for this study were based on the recently published American College of Gastroenterology (11) and working group (12) guidelines.

1. Recurrent or relapsing CDI: At least three episodes of mild-to-moderate CDI and failure of a 6- to 8-week taper with vancomycin with or without an alternative antibiotic (e.g., fidaxomicin, rifaximin) or at least two episodes of severe CDI resulting in hospitalization and associated with significant morbidity.
2. Refractory CDI: Moderate CDI not responding to standard therapy (vancomycin) for at least a week.
3. Severe CDI: white blood cells ≥15,000 cells/$mm^3$, albumin < 3g/dl, and abdominal tenderness.
4. Complicated CDI is defined by at least one of the following: Admission to the intensive care unit, hypotension with or without the use of vasopressors, fever ≥38.5 °C, ileus or significant abdominal distention, mental status changes, white blood cells ≥35,000 cells/$mm^3$, or < 2 cells/$mm^3$, serum lactate > 2.2 mmol/l, or any evidence of end-organ failure.

At least 12 weeks of post-FMT follow-up data were required for the patient's data to be included in the analysis. We assumed that all recurrences (15) and most short-term complications of FMT (such as infection) would have occurred within this time period. We included patients who were IC at the time of FMT as a result of one or more of the following: HIV infection (any CD4 count), AIDS-defining diagnosis or CD4 < 200/$mm^3$, inherited or primary immune disorders, and immunodeficient or immunosuppressed from a medical condition/medication including current or recent (< 3 mos) treatment with anti-neoplastic agent or immunosuppressant medications (including but not limited to monoclonal antibodies to B and T cells, anti-tumor necrosis factor agents, glucocorticoids, antimetabolites (azathioprine, 6-mercaptopurine, methotrexate), calcineurin inhibitors (tacrolimus, cyclosporine), and mycophenolate mofetil).

Data collected included demographic information, reason for IC status, treatment with immunosuppressant medication, other significant medical conditions, CDI treatments before and peri-FMT, indication for FMT (recurrent, refractory, or severe/complicated CDI), post-FMT mortality and hospitalizations, post-FMT AEs and serious adverse events (SAEs), and outcomes (CDI recurrence post FMT, need for colectomy, and response to second FMT if required). Sixteen centers submitted data collection forms for 99 patients. Patients were excluded from analysis if FMT was conducted for reasons other than CDI, if they did not meet the criteria for IC or if they did not have a minimum of 12 weeks post-FMT follow-up.

The primary outcomes were CDI cure and any SAEs or AEs within 12 weeks post FMT. Cure was defined as absence of diarrhea, or marked reduction in stool frequency without the need for further anti-CDI therapy. This definition of cure was used in recent CDI clinical trials (16) and, consistent with published practice guidelines (1,11), stool was not routinely tested for *C. difficile* toxin to confirm cure at most centers. AEs were defined as any untoward medical occurrence in a patient to whom FMT was administered. The AE did not

necessarily need to have a causal relationship with the treatment and thus we included unfavorable signs or symptoms or disease temporally associated with the use of FMT, whether or not related to the FMT. AEs could be clinically significant changes from baseline physical exam, laboratory tests, or other diagnostic investigations, complications related to the procedure used to administer FMT, or new events or pre-existing conditions that became aggravated or worsened in severity or frequency within 12 weeks post FMT. SAEs were defined as any death, life-threatening experience, unplanned hospitalization, or important medical event within 12 weeks after FMT. AEs and SAEs were determined to be related, probably or possibly, or unrelated to FMT. Secondary outcomes were CDI recurrence, need for colectomy, and response to repeat FMT. Cure rates and percentages were calculated after one FMT and more than one FMT for the population. Rates and percentages were also calculated for SAEs, AEs, and inflammatory bowel disease (IBD) flares.

## RESULTS

### Study patient characteristics

Data collection forms were completed for 99 patients who had received FMT at one of the study centers. Of these, 19 were excluded from analysis because they had undergone FMT for treatment of IBD alone (15 patients), did not meet criteria for IC (2 patients), or were lost to follow-up before having their 12-week post-FMT follow-up (2 patients). Eighty patients were included in the final analysis (Table 1a). The study population included similar numbers of men (42, 52%) and women (38, 48%). The majority of these patients were adults (75 of 80, 94%) and the mean age of the adults treated was 53 years (range: 20–88 years). Reasons for IC included IBD patients treated with immunosuppressive agents (36, 45%), SOT recipients (19, 24%), and patients IC because of severe or end-stage chronic medical conditions (15, 19%). In addition, there were seven (9%) patients with cancer who were receiving antineoplastic agents concurrently or in the 3 months before FMT, and three (3%) patients had HIV/AIDs. Specific immunosuppressant agents used, indications, and numbers of patients exposed are listed in Table 1b. Recurrent CDI was the most common indication for FMT (44 of 80, 55%). Nine (11%) patients received FMT for refractory CDI and 27 (34%) met criteria for severe or complicated CDI. However, most of these “severe” patients had been treated with a course of anti-CDI therapy and were no longer acutely ill at the time of FMT, which was performed to prevent further recurrence. FMT was conducted as a hospital inpatient in 17 (21.2%) patients and 63 (78.8%) received FMT as outpatients, suggesting that the majority of these patients were clinically stable at the time of FMT. All but one patient had been treated with vancomycin before FMT and 67 (84%) had received multiple, prolonged, or tapering courses of vancomycin. Other therapies used unsuccessfully before FMT included metronidazole (55 patients; 69%), fidaxomicin (23; 29%), rifaximin (13; 16%), and probiotics (30; 38%).

### Outcomes

**Efficacy—**Resolution of CDI occurred in 62 (78%) patients after a single FMT. Twelve patients who either had recurrence or did not respond after one FMT underwent repeat FMT, of whom eight were cured. Thus, *overall cure* (defined as resolution of CDI after one or more FMTs) within a minimum of 12 weeks was observed in 70 (89%) patients. In the

subset of patients with IBD, resolution of CDI occurred in 31 patients (86%) after a single FMT, with an overall cure in 34 (94%).

**Safety—**SAEs were observed in 12 (15%) patients within 12 weeks post FMT (Table 2). Two deaths occurred. One patient, whose diarrhea ceased after FMT, died 13 days post-FMT secondary to progressive pneumonia, for which she was treated with antibiotics before and after FMT. The other, a SOT recipient with advanced esophageal cancer, cachexia, and ongoing diarrhea from CDI unresponsive to vancomycin and metronidazole, died of respiratory failure 1 day post FMT as a result of a witnessed aspiration at the time of sedation for the colonoscopy used to administer the FMT. There were 10 hospitalizations within 12 weeks of FMT. One patient was hospitalized with self-limited abdominal pain, which occurred after the colonoscopy used to administer FMT and was thus related to FMT. Three hospitalizations were unrelated to FMT and one case of influenza was probably unrelated as the donor did not develop influenza within the follow-up period. Four patients were hospitalized with flares of IBD possibly related to FMT. One catheter line infection requiring hospitalization occurred and was probably unrelated to FMT. There were no infectious complications directly attributable to FMT. Three deaths were reported outside of the 12-week post-FMT period and were not considered as SAEs. All occurred more than 6 months after FMT and were related to chronic progressive illnesses unrelated to CDI.

We observed 12 (15%) patients with AEs (Table 2). Of these, four were related, five were possibly related, and three were unrelated to FMT. Three patients underwent colectomy, although none were for CDI. One patient with ulcerative colitis (UC) had a colectomy less than 1 month post FMT for progressively worsening UC, which had not improved after treatment of CDI. Another patient with UC underwent colectomy 105 days post FMT for indeterminate colitis and a third UC patient underwent colectomy 293 days post FMT for worsening UC. Patients with IBD did not experience a higher incidence of SAEs (11%) or AEs (14%) compared with patients IC because of other conditions (18% SAEs; 16% AEs) $P \leq 0.3224$.

## DISCUSSION

IC patients are particularly at risk of CDI. *C. difficile* is the most common cause of bacterial diarrhea in persons with HIV infection and has its highest incidence in those with advanced HIV disease/AIDS (17). Organ transplant recipients are also observed to suffer higher frequency of CDI. Retrospective case series of patients after SOT report an overall CDI incidence of 3.5–16% in kidney transplant recipients and is as high as 31% in lung transplant recipients (9). Furthermore, 20% of SOT patients who acquired CDI did not have any recent antibiotic exposure, which suggests that IC status may be an independent risk factor for CDI (18). Increased length of stay in hospitals and extended-care facilities in addition to multiple exposures to broad-spectrum antibiotics increases the risk of CDI in this population of patients (19,20). However, disruptions of both the innate and adaptive immune responses are additional factors, as the signaling pathways involved in the recruitment of neutrophils mitigate inflammation in acute infection (21) and patients with increased anti-toxin A and B IgG antibodies may be at decreased risk of suffering recurrences of CDI compared with those who have reduced levels of the antibody (22,23).

CDI presents an especially difficult challenge in patients with underlying IBD, which is associated with a disrupted mucosal barrier in the gut, altered mucosal immunity, and systemic immunosuppression with medications. IBD patients develop CDI at a threefold higher rate compared with the general population and have an estimated 10% life time chance to contract *C. difficile* (24,25). Increases in hospitalizations, mortality, and colectomy rates over the past decade in CDI-IBD patients are well demonstrated (26–29). Up to 19% of the patients with an IBD flare test positive for *C. difficile* (30). Immunosuppressive medications commonly used in this patient population multiply the risk of CDI; above all, corticosteroids confer a threefold increase in CDI and twofold increase in mortality (31,32).

In this multicenter series, 89% of IC patients achieved symptom resolution after FMT for *C. difficile* infection and most CDI resolved after a single FMT. Rates of cure were similar to those observed in previous studies (7,8). This study is the first to systematically report safety outcomes in FMT and the first to address the question of efficacy and safety of FMT for CDI in IC patients. IC patients have previously been excluded from controlled FMT studies (8,13) because of concern about bacterial translocation and infection. In these 80 patients who underwent FMT at 16 centers, there were no deaths or documented infections that occurred after FMT as a result of the transplanted microbiota itself. One death occurred as a result of the procedure used to re-administer a second FMT in a severely ill patient.

It is noteworthy that 14% of the patients with IBD experienced complications post FMT in the form of a disease exacerbation; three of whom were treated with steroids and one patient required a colectomy within 1 month of FMT. Colonic disease activity in these patients at the time of FMT ranged from mild to severe. However, all are known to have had severe (and oft en refractory) disease leading up to FMT and, despite short-term complications, three benefited from FMT in terms of their CDI and the course of their IBD. It is not possible to determine whether these flares were attributable to FMT, CDI, or progression of the underlying disease. However, IBD flare after FMT to treat CDI in a patient with previously quiescent UC has been reported (33) and fevers along with temporary elevations of C-reactive protein levels have been described in small series of UC patients treated with FMT for IBD (34,35). Certainly, prospective studies regarding safety and efficacy of FMT in this population are warranted.

Physicians may be reluctant to prescribe FMT in IC patients presuming they are “high risk,” although there has not previously been evidence either for or against this belief in this population. In fact, patients with recurrent CDI have been shown to have a marked expansion of members of the *Enterobacteriaceae* family of Proteobacteria in their gut microbiota (36–38), which are frequently relatively invasive pathobionts that may be responsible for other infectious complications in these patients (39). In contrast, FMT leads to restoration of dominance of Bacteroidetes and Firmicutes in the distal gut microbiota. It is reasonable to expect that normalized gut microbial ecology should improve colonization resistance to potential pathogens in IC patients.

This study has several weaknesses. Because of the retrospective design, data collection may be incomplete. Moreover, patients were not solicited for AEs, which may be underestimated.

Detailed clinical information regarding disease history, extent, and severity, including endoscopic and histologic findings before and after FMT, for IBD patients was not collected. Diarrheal symptoms are a common symptom in IBD and the high prevalence of IBD could have distorted the efficacy rate in this population, given the symptom-based criteria we used to define cure. Nevertheless, rates of cure after FMT were high in this subset of patients. Other potential confounding factors such as the discontinuation of chemotherapy or treatment changes in IBD patients could also have had an impact on diarrheal symptoms. The population treated is very heterogenous. Collecting more data on the course of immunocompromising illnesses in each of these patients would have been helpful in identifying potential confounders and stratifying patients as sickest to healthiest among this IC group. The multicenter design made standardization of data points challenging, yet the FMT-performing clinicians followed each patient closely, and all centers provided sufficient details to answer the 32-item survey tool required to analyze the primary outcomes. There is no consensus guideline for the administration of FMT in terms of the donor screening, amount of stool infused, route of administration, or follow-up evaluations. However, this study, performed at multiple sites, each with its own FMT protocol, supports an overall curative effect seen among IC patients despite practice variation. Classification of CDI was based on specific clinical criteria, although the data collection survey did not distinguish between severe and complicated CDI or allow submitting centers to specify which criteria for severe or complicated disease were fulfilled. Patients may have been classified as severe on the basis of leukocytosis or low albumin (not necessarily sepsis or organ failure). Furthermore, it is unknown at what time point FMT was performed in some of these severe patients, although most of the centers in this study perform FMT after a course of vancomycin when patients have improved clinically but are at risk for further recurrence. The fact that the majority of these FMTs were performed as outpatient procedures supports that most patients in this series were not acutely ill at the time of FMT. Ultimately, a prospective cohort study of patients with complex CDI or a matched case–control series would be reasonable to further investigate the use of FMT for CDI in IC patients, while minimizing some of these biases.

FMT is not without risk, which may be greater in acutely ill patients. In the experience of several of the coauthors, there is limited efficacy to a single FMT performed at the time of acute CDI, and delaying FMT or performing a second FMT after the patient has finished a course of anti-CDI therapy may be the best course (40). We believe it is prudent to consider less invasive means of administering FMT (such as enema or unsedated sigmoidoscopy) in patients with severe or complicated CDI or significant comorbidities. Withholding FMT and/or administering vancomycin indefinitely to prevent further CDI recurrence is another option when treating patients with a limited life expectancy in whom the risk of FMT may outweigh benefits. In conclusion, this study showed that FMT appears to be a safe and effective treatment for recurrent, refractory, or severe CDI in this high-risk population of IC patients.’

## Acknowledgments

**Financial Support:** NIH 1R21DK093839-01A1; NIH R21 AI091907.

## References


1. Cohen SH, Gerding DN, Johnson S, et al. Clinical Practice Guidelines for Clostridium difficile Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Infect Control Hosp Epidemiol. 2010; 31:431–55. [PubMed: 20307191]
2. McDonald LC, Owings M, Jernigan DB. *Clostridium difficile* infection in patients discharged from US short stay hospitals, 1996–2003. Emerg Infect Dis. 2006; 12:409–15. [PubMed: 16704777]
3. King RN, Lager SL. Incidence of *Clostridium difficile* infections in patients receiving antimicrobial and acid-suppression therapy. Pharmacotherapy. 2011; 31:642–8. [PubMed: 21923450]
4. McFarland LV, Surawicz CM, Rubin M, et al. Recurrent *Clostridium difficile* disease: epidemiology and clinical characteristics. Infect Control Hosp Epidemiol. 1999; 20:43–50. [PubMed: 9927265]
5. McFarland LV. Alternative treatments for *Clostridium difficile* disease: what really works? J Med Microbiol. 2005; 54:101–11. [PubMed: 15673502]
6. Eiseman B, Silen W, Bascom GS, et al. Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis. Surgery. 1958; 44:854. [PubMed: 13592638]
7. Kassam Z, Lee CH, Yuan Y, et al. Fecal microbiota transplantation for *Clostridium difficile* infection: systematic review and meta-analysis. Am J Gastroenterol. 2013; 108:500–8. [PubMed: 23511459]
8. Van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*. N Engl J Med. 2013; 368:407–15. [PubMed: 23323867]
9. Dubberke ER, Burdette SE, et al. *Clostridium difficile* infections in solid organ transplantation. Am J Transplant. 2013; 13:42–9. [PubMed: 23464997]
10. Munoz P, Bouza E, Cuenca-Estrella M, et al. *Saccharomyces cerevisiae* fungemia: an emerging infectious disease. Clin Infect Dis. 2005; 40:1625–34. [PubMed: 15889360]
11. Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections. Am J Gastroenterol. 2013; 108:478–98. [PubMed: 23439232]
12. Bakken JS, Borody T, Brandt LJ, et al. Treating *Clostridium difficile* infection with fecal microbiota transplantation. Clin Gastroenterol Hepatol. 2011; 9:1044–9. [PubMed: 21871249]
13. Kelly, C., Brandt, L. Fecal Transplant for Relapsing *C difficile* infection. Trial in progress. Accessed December 27, 2013 at: http://clinicaltrials.gov/ct2/show/NCT01703494?term=FMT+providence&rank=1
14. Friedman-Moraco RJ, Mehta AK, Lyon GM, et al. Fecal microbiota transplantation for refractory *Clostridium difficile* colitis in solid organ transplant recipients. Am J Transplant. 2014; 14:477–80. [PubMed: 24433460]
15. Figueroa I, Johnson S, Sambol SP, et al. Relapse versus reinfection: recurrent *Clostridium difficile* infection following fidaxomicin or vancomycin. Clin Infect Dis. 2012; 55(Suppl 2):S104–9. [PubMed: 22752857]
16. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomycin versus vancomycin for *Clostridium difficile* infection. N Engl J Med. 2011; 364:422–31. [PubMed: 21288078]
17. Sanchez TH, Brooks JT, Sullivan PS, et al. Bacterial diarrhea in persons with HIV infection, United States, 1992–2002. Clin Infect Dis. 2005; 41:1621–7. [PubMed: 16267735]
18. West M, Pirenne J, Chavers B, et al. *Clostridium difficile* colitis after kidney and kidney pancreas transplantation. Clin Transplant. 1999; 13:318–23. [PubMed: 10485373]
19. Gorschluter M, Glasmacher A, Hahn C, et al. *Clostridium difficile* infection in patients with neutropenia. Clin Infect Dis. 2001; 33:786–91. [PubMed: 11512083]
20. Anand A, Glatt AE. *Clostridium difficile* infection associated with antineoplastic chemotherapy: a review. Clin Infect Dis. 1993; 17:109–13. [PubMed: 8353229]
21. Buffie CG, Pamer EG. Microbiota-mediated colonization resistance against intestinal pathogens. Nat Rev Immunol. 2013; 13:790–801. [PubMed: 24096337]
22. Kyne L, Warny M, Qamar A, et al. Association between antibody response to toxin A and protection against recurrent *Clostridium difficile* diarrhea. Lancet. 2001; 357:189–93. [PubMed: 11213096]

23. Leav BA, Blair B, Leney M, et al. Serum anti-toxin B antibody correlates with protection from recurrent *Clostridium difficile* infection (CDI). Vaccine. 2010; 28:965–9. [PubMed: 19941990]
24. Rodemann JF, Dubberke ER, Reske KA, et al. Incidence of *Clostridium difficile* infection in inflammatory bowel disease. Clin Gastroenterol Hepatol. 2007; 5:339–44. [PubMed: 17368233]
25. Binion DG. *Clostridium difficile* infection in patients with inflammatory bowel disease. Gastroenterol Hepatol (NY). 2012; 8:615–7.
26. Ananthakrishnan AN, McGinley EL, Binion DG, et al. A nationwide analysis of changes in severity and outcomes of inflammatory bowel disease hospitalizations. J Gastrointest Surg. 2011; 15:267–76. [PubMed: 21108015]
27. Ananthakrishnan AN, McGinley EL, Saeian K, et al. Temporal trends in disease outcomes related to *Clostridium difficile* infection in patients with inflammatory bowel disease. Inflamm Bowel Dis. 2011; 17:976–83. [PubMed: 20824818]
28. Nguyen GC, Kaplan CG, Harris ML, et al. A national survey of the prevalence and impact of *Clostridium difficile* infection among hospitalized inflammatory bowel disease patients. Am J Gastroenterol. 2008; 103:1443–50. [PubMed: 18513271]
29. Jen MH, Saxena S, Bottle A, et al. Increased health burden associated with *Clostridium difficile* diarrhoea in patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2011; 33:1322–31. [PubMed: 21517920]
30. Meyer AM, Ramzan NN, Loftus EV Jr, et al. The diagnostic yield of stool pathogen studies during relapses of inflammatory bowel disease. J Clin Gastroenterol. 2004; 38:772–5. [PubMed: 15365403]
31. Schneeweiss S, Korzenik J, Solomon DH, et al. Infliximab and other immunomodulating drugs in patients with inflammatory bowel disease and the risk of serious bacterial infections. Aliment Pharmacol Ther. 2009; 30:253–64. [PubMed: 19438424]
32. Das R, Feuerstadt P, Brandt LJ. Glucocorticoids are associated with increased risk of short-term mortality in hospitalized patients with clostridium difficile-associated disease. Am J Gastroenterol. 2010; 105:2040–9. [PubMed: 20389295]
33. De Leon L, Watson J, Kelly C. transient flare of ulcerative colitis after fecal microbiota transplantation for recurrent *Clostridium difficile* infection. Clin Gastroenterol Hepatol. 2013; 11:1036–8. [PubMed: 23669309]
34. Angelberger S, Reinisch W, Makristathis A, et al. Temporal bacterial community dynamics vary among ulcerative colitis patients after fecal micro-biota transplantation. Am J Gastroenterol. 2013; 108:1620–30. [PubMed: 24060759]
35. Kump PK, Grochenig HP, Lackner S, et al. Alteration of intestinal dysbiosis by fecal microbiota transplantation does not induce remission in patients with chronic active ulcerative colitis. Inflamm Bowel Dis. 2013; 19:2155–65. [PubMed: 23899544]
36. Chang JY, Antonopoulos DA, Kalra A, et al. Decreased diversity of the fecal microbiome in recurrent *Clostridium difficile* associated diarrhea. J Infect Dis. 2008; 197:435–6. [PubMed: 18199029]
37. Hamilton MJ, Weingarden AR, et al. High-thoughput DNA sequence analysis reveals stable engraft ment of gut microbiota following transplantation of previously frozen fecal bacteria. Gut Microbes. 2013; 4:125–35. [PubMed: 23333862]
38. Weingarden AR, Chen C, Bobr A, et al. Microbiota transplantation restores normal fecal bile acid composition in recurrent clostridium difficile infection. Am J Physiol Gastrointest Liver Physiol. 2014; 306:G310–9. [PubMed: 24284963]
39. Chow J, Tang H, Mazmanian SK. Pathobionts of the gastrointestinal micro-biota and inflammatory disease. Curr Opin Immunol. 2011; 23:473–80. [PubMed: 21856139]
40. Weingarden A, Hamilton M, Sadowsky M, et al. Resolution of severe *Clostridium difficile* infection following sequential fecal microbiota transplantation. J Clin Gastroenterol. 2013; 47:735–7. [PubMed: 23632358]

## Study Highlights

**WHAT IS CURRENT KNOWLEDGE**

- ✓ *C. difficile* infection (CDI) is common in immunocompromised patients.
- ✓ Fecal microbiota transplantation (FMT) appears effective and is indicated for the treatment of CDI not responding to standard therapies.

**WHAT IS NEW HERE**

- ✓ FMT appears to be effective and safe in immunocompromised patients.
- ✓ Immunocompromised patients do not appear to be at high risk of infection transmitted by FMT.
- ✓ Patients with IBD may experience disease flare following FMT, although whether this is precipitated by the CDI, FMT itself, or progression of the underlying disease state is not known.

**Table 1a**

Study patient demographics and pre-FMT data

| **Total number of study patients** | **80** |
|---|---|
| Adults | 75 (94%) |
| Women | 38 (48%) |
| Men | 42 (52%) |
| Mean adult age (years) | 53 (range 20–88) |
| Mean pediatric age (years) | 10.9 (range 6.5–16) |
| Mean follow-up (months) | 11 (range 3–46) |
| *CDI Classification before FMT* | |
| Recurrent | 44 (55%) |
| Refractory | 9 (11%) |
| Severe/complicated | 1 (1%) |
| Overlap (severe/complicated and recurrent or refractory) | 26 (33%) |
| *Reason for immunocompromise* | |
| Immunosuppressive agents for IBD | 36 |
| Solid organ transplant recipients | 19 |
| HIV/AIDS | 3 |
| Cancer and treatment with antineoplastic agents | 7 |
| Other chronic medical conditions[a] | 15 |

CDI, *Clostridium difficile* infection; FMT, fecal microbiota transplantation; IBD, inflammatory bowel disease.

[a]Conditions included: rheumatoid arthritis (4), adrenal insufficiency, cirrhosis/end-stage liver disease (6), end-stage renal disease (ESRD) on hemodialysis (HD) and panhypopituitarism, end-stage chronic obstructive pulmonary disease on chronic steroids, ESRD on HD and allograft failure, Sjogren's disease.

## Table 1b

Immunosuppressant agents used concurrently or within 3 months of FMT, indication, and number of patients exposed

| Agent | Indication(s) | Number of patients exposed |
|---|---|---|
| Tumor necrosis factor-alpha inhibitors[a] | IBD | 16 |
| Alpha-4 integrin inhibitor | IBD | 2 |
| Steroids | SOT, COPD, IBD, RA, adrenal insufficiency | 30 |
| Antimetabolites[b] | IBD, RA, SOT | 19 |
| Calcineurin inhibitors[c] | SOT | 18 |
| Other anti-rejection agents[d] | SOT | 7 |
| Antineoplastic agents[e] | Cancer | 8 |
| Other immunomodulary agents[f] | RA, Sjogren's | 3 |

COPD, chronic obstructive pulmonary disease; FMT, fecal microbiota transplantation; IBD, inflammatory bowel disease; RA, rheumatoid arthritis; SOT, solid organ transplant.

[a] Infliximab, adalimumab, certolizumab.

[b] Methotrexate, azathioprine, 6-mercaptopurine.

[c] Tacrolimus, cyclosporine.

[d] Sirolimus, mycophenolate mofetil.

[e] Bevacizumab, adriamycin, fludarabine, 5-FU, cisplatin, bleomycin, dasatanib, lenalidomide.

[f] Leflunomide, plaquenil, rituximab.

## Table 2

Adverse events

| Adverse event | Number of patients sustaining this AE | Reason for Immunocompromise | Day post-FMT event occurred |
|---|---|---|---|
| *Deaths*[a] | | | |
| Pneumonia | 1 | SOT | 13 |
| Aspiration | 1 | SOT and esophageal cancer | 1 |
| *Hospitalizations*[a] | | | |
| Fever, diarrhea, encephalopathy and pancytopenia | 1 | Cirrhosis and non-Hodgkin's lymphoma | 4 |
| Abdominal pain post FMT colonoscopy | 1 | SOT | 0 |
| IBD flare: Crohn's (2), UC (1) | 3 | IBD | < 84 |
| Cerebrovascular accident; nausea and vomiting | 1 | ESRD and panhypopituitarism | 21 |
| Colectomy | 1 | IBD | < 28 |
| Fall and sustained hip fracture | 1 | End-stage COPD | 84 |
| Influenza B and diarrhea (non-CDI) | 1 | SOT | 3 |
| Catheter infection | 1 | Cancer | 14 |
| *Other adverse events* | | | |
| Self-limited diarrheal illness | 3 | ESRD; Sjogren's; SOT | ≤84 |
| Fever | 1 | SOT | 1 |
| Bloating and abdominal discomfort immediately post FMT | 3 | HIV; ESRD; IBD | 1–2 |
| Hip pain | 1 | IBD | ≤84 |
| Crohn's flare | 1 | IBD | ≤84 |
| Pertussis | 1 | IBD | ≤30 |
| Nausea | 1 | IBD | 30 |
| Minor mucosal tear during colonoscopy used to administer FMT | 1 | SOT | 0 |

AE, adverse event; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; FMT, fecal microbiota transplantation; IBD, inflammatory bowel disease; SOT, solid organ transplant; UC, ulcerative colitis.

[a]Serious Adverse Events: death, hospitalization, or life-threatening event.