Treatment of Recurrent *Clostridioides difficile* Infection Using Fecal Microbiota Transplantation in Iranian Patients with Underlying Inflammatory Bowel Disease

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Purpose: Fecal microbiota transplantation (FMT) is an effective treatment option for patients with recurrent *Clostridioides difficile* infection (rCDI). However, there is a paucity of evidence regarding its efficacy and safety in patients with rCDI and concurrent inflammatory bowel disease (IBD). Here, we present a single-center experience of FMT for treatment of rCDI in Iranian patients with IBD.

Patients and Methods: Eight patients with established IBD (7 with ulcerative colitis and 1 with Crohn’s disease) who underwent at least one FMT via colonoscopy for treatment of rCDI were enrolled in this study. Demographics, pre-FMT and post-FMT IBD activity, efficacy for rCDI and adverse events (AEs) were assessed during a 6-month follow-up period. All patients had experienced 3 episodes of rCDI and were refractory to conventional therapies with metronidazole and vancomycin. Primary cure and secondary cure rates were assessed after FMT treatments.

Results: A total of 10 FMTs were performed via colonoscopy in 8 patients (6/8; 75% men) with a median age of 35 years (range: 22–60). Two patients received a second FMT. Overall, the primary and secondary cure rates were 75% and 100%, respectively. Two patients developed CPE-producing *Clostridium perfringens* diagnoses after second FMTs. There were no other AEs, and no patient experienced IBD flare.

Conclusion: We demonstrated that FMT appears to be an effective, safe and rational therapeutic alternative for resolution of rCDI in patients with underlying IBD. Furthermore, we suggest implementing the CPE-producing *C. perfringens* testing in the screening of FMT donors.

Keywords: fecal microbiota transplantation, recurrent *Clostridioides difficile* infection, inflammatory bowel disease, FMT, rCDI, IBD, Iran

Introduction

*Clostridioides difficile* infection (CDI) is the most common cause of nosocomial diarrhea and is implicated in 20–30% of all cases of antibiotic-associated diarrhea (AAD).\(^1,2\) The incidence of CDI is increasing in both adult and pediatric populations, and it is considered as a major concern in healthcare settings worldwide.\(^3–5\)

CDI is typically associated with consumption of antimicrobial agents that alter the normal composition of gut microbiota, thereby leading to the overgrowth of *C. difficile* and its toxin production.\(^6\) Patients with inflammatory bowel disease...
(IBD), particularly ulcerative colitis (UC), are at increased risk of CDI, and the incidence of CDI in the IBD population is reported to be 2.5 to 8-fold greater than in patients without IBD.﻿,9 This complex association is the result of several factors, including the intestinal dysbiosis of patients with IBD (typically, characterized by a reduction in overall biodiversity and perturbed microbial functions), use of immunosuppressive medications and antimicrobial drugs, frequent contacts with the healthcare environment, and systemic comorbidities.﻿,11 The initial treatment for CDI includes cessation of the precipitating antibiotics, when possible, and antibiotics with activity against C. difficile, mainly vancomycin.﻿ Recurrence occurs in 15% to 30% of patients after treatment of a first CDI episode, with risk of further recurrence rising after each subsequent recurrent CDI (rCDI) episode, impacting quality of life and resulting in high morbidity.﻿

It is well established that normal intestinal microbiota can confer protection against the invasion of non-native bacteria and the expansion of pathobionts, particularly through colonization resistance mechanisms and stimulation of the innate or adaptive immune system.﻿ The microbiota promotes direct colonization resistance by competition for nutrients and space as well as production of bactericidal molecules and inhibitory metabolites.﻿ Furthermore, bacteria in the distal gut convert primary bile acids to secondary bile acids, which inhibit C. difficile germination and growth.﻿ Fecal microbiota transplantation (FMT), which is the process of introducing intestinal microbial communities from a healthy donor into a recipient, normalizes the composition and functionality of gut microbiota and has become increasingly utilized as a highly successful rescue treatment for patients with rCDI.﻿,19,21 Furthermore, increasing evidence has suggested that FMT may be a promising treatment option for IBD by effectively correcting underlying dysbiosis to induce clinical remission.﻿,20,21 However, only a few studies have been performed to assess the efficacy of FMT in rCDI patients with concurrent IBD.﻿,22,23 In this study, we present a single-center experience on the use of FMT to treat rCDI in patients with IBD. Also, we aimed to assess FMT safety, efficacy, and its primary and secondary cure rates in patients with rCDI and concurrent IBD.

**Methods**

**Definitions**

CDI diagnosis was made based on the presence of unexplained and new-onset diarrhea (≥3 unformed stools in 24 consecutive hours) and a positive laboratory test for toxin-producing C. difficile.﻿,24 rCDI was defined as at least three episodes of mild-to-moderate CDI and failure of completion of a 6- to 8-week course of therapy (taper with vancomycin) or at least two episodes of severe CDI leading to increased hospitalization and significant morbidity.﻿,25,26 IBD was diagnosed based on clinical, endoscopic and histopathologic findings, and the disease activity for patients with UC and Crohn’s disease (CD) was determined using the Mayo clinical disease activity score and the Crohn’s disease activity index (CDAI), respectively.﻿,27,28 The primary cure was defined as the resolution of CDI clinical symptoms following initial FMT with no recurrence in the subsequent 8 weeks. The secondary cure was defined as the resolution of clinical symptoms subsequent to repeat FMT after failure of the initial FMT.

**Study Design**

Patients with IBD and rCDI were enrolled between November 2018 and April 2019 at two teaching hospitals in Tehran. The treatment protocol for FMT in patients with rCDI was approved by the Institutional Ethical Review Committee of Research Institute for Gastroenterology and Liver Diseases (RIGLD) at Shahid Beheshti University of Medical Sciences (Project No. IR.SBMU.RIGLD. REC.1396.185), and the study was also conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all eligible subjects or their legal representative prior to participation in this study.

Possible adverse events (AEs) related to FMT were described in the consent process including vomiting, transient fever, belching, abdominal discomfort, bloating, flatulence, diarrhea, constipation, colonoscopic perforation and bleeding, side effects related to sedation, and possible transmission of infectious agents including unknown risks.﻿

**Study Population**

Consecutive patients aged ≥18 years were invited to participate as candidates for the FMT procedure if they had at least three or more documented episodes of CDI. All patients completed at least 10 days of vancomycin therapy for the most recent CDI, which was continued until 2 to 3 days before the procedure. All patients were evaluated by a multidisciplinary team consisting of a gastroenterologist, an infectious disease specialist and an expert microbiologist. Patients were excluded if they had a history of chronic diarrheal disease, positive pregnancy test,
prolonged compromised immunity because of recent chemotherapy, advanced human immunodeficiency virus (HIV), and other causes of severe immunodeficiency.

Donor Identification and Screening
Donors were usually identified by the patients and included adult (≥18) healthy family members or friends. A detailed medical history and lifestyle habits were obtained from each donor through a specific questionnaire, and donors were initially screened about possible risk factors for potentially transmissible diseases. Donors were excluded if they reported antibiotic use within the preceding 3 months, actively smoked, were obese with body mass index (BMI) >30, had history of incarceration, tattoo or body piercing within the preceding 3 months, used illicit drugs, engaged in high-risk sexual behavior, traveled within 6 months to areas with endemic diarrheal illnesses, were currently infected with any communicable disease, had known chronic gastrointestinal (GI) disease including diarrhea, constipation, IBD, irritable bowel syndrome (IBS), GI malignancy or polyposis, liver disease, and for other conditions including chronic kidney disease, autoimmune disease, chronic pain syndrome, metabolic syndrome, diabetes, immunodeficiency, allergies or atopy. Prospective donors underwent laboratory testing including complete blood count (CBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serological testing for syphilis, HIV, hepatitis A, B and C, and rotavirus. Donor stools were screened for enteropathogens including Salmonella spp., Shigella spp., Yersinia enterocolitica, Yersinia pseudotuberculosis, Campylobacter spp., ova, cysts and parasites, Giardia, Cryptosporidium, and Isospora. Donor stool was also tested for C. difficile toxins A and B by enzyme-linked immunosorbent assay (ELISA), and cultured for C. difficile, and C. perfringens. PCR testing was also performed to detect C. difficile toxins (tcdA and tcdB) and C. perfringens enterotoxin (cpe).

Donor and Recipient Preparation
A flowchart summary of the FMT procedure is depicted in Supplementary Figure 1. Donors took a single dose of osmotic laxative (magnesium hydroxide) in the night before the stool donation. All patients were maintained on vancomycin until 48 hours before the procedure and the baseline IBD immunosuppressive regimen was continued afterwards, with the addition of prednisolone 10 mg/day for 3 months. Patients were given a bowel purge preparation (polyethylene glycol) the day before the procedure.

Preparation of Stool Sample and FMT Procedure
Fresh stools were collected by the donor on the day of procedure and immediately transported to the laboratory and processed within 6 h of the collection. Approximately 50 g of donor stool was diluted in 300 mL of sterile, physiological saline (0.9% w/v of NaCl) and homogenized by a lab blender (Stomacher® 400 Circulator). After homogenization, the slurry was filtered through gauze to eliminate the undigested particulate matter in the fecal suspension. Fecal suspension was immediately transported on ice to endoscopy units in 50 mL sterile bottles. A total of 300 mL of the fecal suspension was instilled via the colonoscope working channel into the terminal ileum or cecum. After FMT, patients were transferred to the recovery unit and encouraged to retain the stool for at least 4 h. Two weeks after procedure they submitted stool specimens for C. difficile testing.

FMT Follow-Up
Telephone follow-up was performed by a laboratory specialist approximately for one week after FMT to record any solicited adverse events (AEs). All patients were seen in the clinic for follow-up 2 and 8 weeks after transplantation, where they were assessed for infectious and GI symptoms, including consistency and frequency of stool, and underwent physical examination. Finally, all patients were contacted by telephone by a study representative 6 months after the last transplantation to record any AEs, new medical conditions or changes in medical conditions or medications since the last study contact.

Statistical Analysis
All statistical analyses were performed using SPSS version 21.0 (SPSS, Inc, Chicago IL, USA). Outcomes before and after treatment were compared using the chi-square test. A P-value <0.05 was considered to be statistically significant.

Results
Study Patient Characteristics
Eight eligible patients were identified from two medical facilities. The demographics and baseline clinical data of the patients with IBD who received at least one FMT for rCDI are presented in Supplementary Table 1. With regard to IBD, 7 patients had UC and one patient had CD. The median age of the patients was 35 years (range 22 to 60
years). Most of the patients (7/8, 88%) underwent FMT as outpatients; however, one patient was hospitalized at the time of FMT. Of the 8 patients who completed the study, 2 (25%) were women and 6 (75%) were men and all had experienced 3 previous episodes of CDI despite treatment with courses of metronidazole and vancomycin prior to FMT. A total of 10 FMT procedures were performed in these patients; 6 patients received a single FMT and 2 patients opted to undergo a second FMT due to failure of primary one. Various treatment regimens were attempted before initial FMT, including oral vancomycin given in a standard manner or in a pulsed with or without the use of proton pump inhibitor (PPI) and immunosuppressive medications (Supplementary Table 1 and Table 1).

Donor Characteristics
A total of 8 individual donors were selected, with one donor per recipient. In 6 cases (75%), the donor was related to the recipient, and in 2 cases (25%) was unrelated (friend and son-in-law). The median age of the donors was 38 years (range 25 to 58 years). In one case, donor stool was obtained from a friend of the patient. In total, 5 of the 8 donors resided in the same household as the recipient. All donors were negative for the blood and stool screening panels.

Pre-FMT Data
The mean duration of symptoms before FMT (average number of prior CDI episodes) was 8 ± 5 months (range, 3–17 months). Diarrhea was reported as mild, moderate, and severe in 50, 12.5, and 37.5% of the patients, respectively. The majority of patients (6/8, 75%) reported abdominal pain in association with their bouts of CDI, and the average of BMI was 21.95 kg/m² (range, 18.30–29.60 kg/m²).

Post-FMT Data, Outcomes and Safety
Clinical symptoms commonly associated with FMT resolved in 75%, and 100% of the patients after first and second FMTs, respectively (Table 2). Diarrhea resolved in 75% of the patients within an average of 3 days after first FMT (range, 2–3 days). Resolution of abdominal pain and diarrhea occurred in 75% of the recipients after first FMT, and the mean number of days between FMT and resolution of abdominal pain was 5 days (range 2–6 days). Laboratory findings showed that FMT therapy led to a significant reduction of CRP, ESR and normalization of the clinical score of IBD patients in all treated subjects based on the disease activity index (Table 2). Overall, the primary FMT was successful in 6 patients (75%), and the secondary cure rate after FMT was 100%.

Two (25%) patients did not report improvement in abdominal pain and diarrhea after initial FMT. Weight increased or remained the same in 62.5% and 37.5% of the patients, respectively. Although there was no statistical difference in the body weight between Pre- and Post-FMT (P-value = 0.24), a considerable increase in body weight after FMT treatment was observed (mean, 23.29 kg/m²; range, 18.70–29.90 kg/m²). All patients were tested for toxigenic (TcdA+/TcdB–) C. difficile two weeks after FMT, and 6 patients had negative results based on stool culture and PCR. No severe AEs

| Table 1 Pre-FMT Data |
|----------------------------------|
| Total number of study patients   | 8 |
| Men                              | 6 (75%) |
| Women                            | 2 (25%) |
| Mean age (years)                 | 37 ± 14.26 (range 22–60) |
| Status at time of FMT            |
| Hospitalized                     | 1 (12.5%) |
| Homebound                        | 7 (87.5%) |
| Duration of symptoms (months)    | 8 ± 5 (3–17) |
| Diarrhea                         |
| Mild (<3 BM/24 hrs)              | 4 (50%) |
| Moderate (3–6 BM/24 hrs)         | 1 (12.5%) |
| Severe (>6 BM/24 hrs)            | 3 (37.5%) |
| Abdominal pain                   | 6 (75%) |
| Leucocyte count (per mm³)        |
| Median                           | 10,500 |
| Range                            | 4000–14,400 |
| CRP                              | 13.75 ± 2.1 |
| ESR                              | 25.5 ± 2.9 |
| BMI                              |
| Mean                             | 21.95 |
| Range                            | 18.30–29.60 |
| Antibiotic used to treat CDI     |
| Previous tapered metronidazole therapy | 2 (25%) |
| Previous tapered vancomycin therapy | 8 (100%) |
| Additional medications           |
| Proton pump inhibitor            | 2 (25%) |
| H2-blocker                       | 1 (12.5%) |
| Failure to resolve CDI within 2 weeks | 2 (25%) |

Abbreviations: BM, bowel movement; BMI, body mass index; CDI, Clostridiales difficile infection; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FMT, fecal microbiota transplantation.
definitely related to the FMT was observed during the FMT procedure or within the follow-up period. One patient developed a low-grade fever (38.5°C) which resolved after 4 days, and two continued to have diarrhea and abdominal discomfort and tested positive for non-toxigenic (TcdA/-TcdB-) C. difficile after first FMT. For these two patients, who continued to experience diarrhea, a second FMT was performed two weeks later via colonoscopy using stool from the same donor as the one used in their first FMT. At follow-up 2 months later, these patients presented with clinical improvement but continued to have watery diarrhea. Both of them were negative for CDI, but became positive for Clostridium perfringens (C. perfringens) type A strains producing the enterotoxin (CPE) according to stool culture and PCR (Figure S1). In these patients, diarrhea had resolved by their 1-month follow-up and they experienced no AEs attributable to FMT.

### Discussion

Manipulation of intestinal microbiota by transplant of donor feces has emerged as a remarkably effective and safe alternative treatment for rCDI unresponsive to standard antibiotic therapies, with high cure rates. Additionally, FMT has been proposed for a variety of other disorders associated with dysbiosis of intestinal microbiota, such as the metabolic syndrome, IBD, IBS, autoimmune diseases, neurodevelopmental disorders, and allergic diseases. In this brief report, we describe a single-center experience of using FMT for rCDI in patients with established IBD. To our knowledge, this is the first report using FMT for resolution of rCDI in Iranian IBD patients.

Patients with IBD are at increased risk of developing CDI and having worse short- and long-term outcomes, including longer hospital stay, and higher rates of colectomy and death. Patients with IBD who present with a disease flare precipitated by CDI, are usually treated with prolonged pulsed and tapered courses of oral vancomycin. Indeed, specific antibiotics used to treat CDI can perturb the composition of gut microbiota and may predispose patients to further relapses. Thus, patients with CDI and underlying IBD have an altered intestinal microbial composition, which can be normalized using FMT.

Here we studied the efficacy of FMT by colonoscopy in 8 patients with IBD and multiple rCDI. Cure rate after first FMT was 75% and increased to 100% after a second FMT, comparable to cure rates reported in the literature. Several case series and reports have reported similar cure rates of 91–100% in patients treated for CDI via FMT procedure. Fischer et al reported a cure rate of 79% after a single FMT by colonoscopy which increased to 88% after two FMTs in patients with rCDI or refractory CDI and concurrent IBD. Despite the high cure rate of primary FMT (91%), Brandt et al demonstrated that one FMT was not sufficient to completely restore the normal population of intestinal microbiota particularly at the biodiversity level.

Our results support the conclusions of previous studies that FMT is generally effective in achieving resolution of rCDI in IBD patients. However, other studies have suggested a substantial risk of clinically significant flares and progression, including rectal abscess/fistula despite resolution of rCDI in a patient with IBD who underwent FMT through colonoscopy. These observations suggest that patients with IBD have an altered gut microbiome that results in impaired intestinal barrier function and dysregulated immune response, allowing recurrence of CDI in some of the patients. Thus, it should be noticed that the clinical outcomes after FMT may vary in patients with IBD based on concurrent rCDI, severity, subtype, diseases activity, methods of preparation of fecal microbiota and the delivery way of FMT.
We demonstrated that FMT was not only effective, but also safe in the patients studied. No severe FMT-related AEs were observed in this study. However, CPE-producing \(C.\) perfringens was isolated from stool culture of two patients who continued to have watery diarrhea, post FMT. \(C.\) perfringens is a common environmental bacterium and a major cause of human GI disease, which usually can produce CPE that is responsible for diarrhea and food poisoning.\(^{47,48}\) In theory, it is possible to transmit potentially harmful microbiota from donors to FMT recipients. Although the role of \(C.\) perfringens has presented as an important cause of AAD in hospitalized patients, it is not clear whether \(C.\) perfringens was transmitted by the donor, or whether \(C.\) perfringens spores were acquired through environmental exposures (eg, the healthcare setting). Nevertheless, with the fast-growing appeal to use FMT as a therapeutic modality for rCDI, IBD and other disorders related to an altered gut microbiota, safety evaluations for FMT and assessment of its potential AEs are extremely important. The causality between AEs and FMT is affected by many factors, including the disease status of recipients, donors, administration route and FMT protocol. In a recently published systematic review on AEs attributable to FMT, the total incidence rate of AEs was 28.5\% and among them, 5 kinds were definitely and 38 kinds were probably related to FMT.\(^{49}\) Additionally, the incidence of severe infection attributable to FMT was 2.5\% (27/1089), in which 8 cases were probably or possibly related to FMT, including 2 viral infections (cytomegalovirus and norovirus), 2 bacteremia (Escherichia coli, Proteus mirabilis, Citrobacter koseri, and Enterococcus faecium), and the remaining 4 were infections caused by unknown pathogens.\(^{50-52}\)

**Conclusions**

We demonstrate that FMT is a highly effective and safe approach for eradicating rCDI in patients with IBD. Nevertheless, the limited sample size, lack of characterization of microbiota composition before and after FMT, and single-center experience limit the generalizability of our findings. Furthermore, based on our experience we suggest testing CPE-producing \(C.\) perfringens in the donor screening panel of FMT. In conclusion, although FMT seemed to be safe and effective for IBD patients with rCDI, there are important caveats that need to be addressed including standardized donor screening, selection of patients, and evaluating the relatedness of IBD flare post-FMT. Patients with IBD should be counselled prior to FMT to ensure they fully understand the potential risks, benefits, and alternatives to FMT.

**Author Contributions**

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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**Disclosure**

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**References**

1. Bishara J, Peled N, Pitlik S, Samra Z. Mortality of patients with antibiotic-associated diarrhoea: the impact of Clostridium difficile. \*J Hosp Infect. 2008;68(4):308–314. doi:10.1016/j.jhin.2008.01.033*

2. Azimirad M, Knutova M, Balai H, et al. Coexistence of Clostridiodes difficile and Staphylococcus aureus in gut of Iranian outpatients with underlying inflammatory bowel disease. \*Anaerobe. 2019;102113.\*

3. Bauer MP, Notermans DW, Van Benthem BH, et al. \*Clostridium difficile infection in Europe: a hospital-based survey. Lancet. 2011;377(9759):63–73. doi:10.1016/S0140-6736(10)61266-4*

4. Sammons JS, Toltzis P. Recent trends in the epidemiology and treatment of \(C.\) difficile infection in children. \*Curr Opin Pediatr. 2013;25(1):116–121. doi:10.1097/MOP.0b013e32835bf0c0*

5. Azimirad M, Knutova M, Yadegar A, et al. \*Clostridiodes difficile ribotypes 001 and 126 were predominant in Tehran healthcare settings from 2004 to 2018: a 14-year-long cross-sectional study. Emerg Microbes Infect. 2020;9(1):1432–1443. doi:10.1080/22221751.2020.1780949*
6. Schaeffer H, Breitbreuke A. Clostridium difficile – from colonization to infection. Front Microbiol. 2018;9:646. doi:10.3389/fmicb.2018.00646

7. Goodhand JR, Alazawi W, Rampton DS. Systematic review: Clostridium difficile and inflammatory bowel disease. Aliment Pharmacol Ther. 2011;33(4):426–441. doi:10.1111/j.1365-2036.2010.04548.x

8. Fischer M, Kao D, Kelly C, et al. Fecal microbiota transplantation is safe and efficacious for recurrent or refractory Clostridium difficile infection in patients with inflammatory bowel disease. JBD. 2016;22(10):2402–2409.

9. Ghomam-Mostafaei FS, Yedegar A, Aghdaei HA, et al. Anti-TNF containing regimens may be associated with increased risk of Clostridioides difficile infection in patients with underlying inflammatory bowel disease. Curr Res Trans Med. 2020;S2452-3186(20)30028-3.

10. Morgan XC, Tickle TL, Sokol H, et al. Dysfunction of the intestinal microbiome in inflammatory bowel disease and treatment. Genome Biol. 2012;13(9):R79. doi:10.1186/gb-2012-13-9-r79

11. Nguyen GC, Kaplan GG, Harris ML, Brant SR. A national survey of the prevalence and impact of Clostridium difficile infection among hospitalized inflammatory bowel disease patients. Am J Gastroenterol. 2008;103(6):1443. doi:10.1111/j.1572-0241.2007.01780.x

12. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018;66(7):e1–e48.

13. De Leon LM, Watson JB, Kelly CR. Transient flare of ulcerative colitis after fecal microbiota transplantation for recurrent Clostridium difficile infection. Clin Gastroenterol Hepatol. 2013;11(8):1036–1038. doi:10.1016/j.cgh.2013.04.045

14. Pickard JM, Zeng MY, Caruso R, Núñez G. Gut microbiota: role in pathogen colonization, immune responses, and inflammatory disease. Immunol Rev. 2017;279(1):70–89.

15. Tavoukjian V. Fecal microbiota transplantation for the decolonisation of antibiotic-resistant bacteria in the gut: a systematic review and meta-analysis. J Hosp Infect. 2019;102(2):174–188

16. Weingarden AR, Dosa P, DeWinter E, et al. Changes in colonic bile acid composition following fecal microbiota transplantation are sufficient to control Clostridium difficile germination and growth. PLoS One. 2016;11(1):e0147210. doi:10.1371/journal.pone.0147210

17. Cammarota G, Masucci L, Janiro G, et al. Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent Clostridium difficile infection. Aliment Pharmacol Ther. 2015;41(9):835–843. doi:10.1111/apt.13144

18. Krajićek E, Fischer M, Allegretti JR, Kelly CR. Nuts and bolts of fecal microbiota transplantation. Clin Gastroenterol Hepatol. 2019;17(2):345–352. doi:10.1016/j.cgh.2018.09.029

19. Van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent Clostridium difficile. N Engl J Med. 2013;368(5):407–415. doi:10.1056/NEJMoa1205037

20. Levy AN, Allegretti JR. Insights into the role of fecal microbiota transplantation for the treatment of inflammatory bowel disease. Therap Adv Gastroenterol. 2019;12:1756284819836893. doi:10.1177/1756284819836893

21. Costello SP, Soo W, Bryant RV, Jairath V, Hart AL, Andrews JM. Systematic review with meta-analysis: faecal microbiota transplantation for the induction of remission for active ulcerative colitis. Aliment Pharmacol Ther. 2017;46(3):213–224. doi:10.1111/apt.14173

22. Dehlinolf-Lambertson E, Hall BK, Jorgensen SM, et al. Cost savings following faecal microbiota transplantation for recurrent Clostridium difficile infection. Therap Adv Gastroenterol. 2019;12:1756284819843002. doi:10.1177/1756284819843002

23. Chin SM, Sawk J, Mahabamunuge J, Kaplan JL, Hohmann EL, Khalili H. Fecal microbiota transplantation for recurrent Clostridium difficile infection in patients with inflammatory bowel disease: a single-center experience. Clin Gastroenterol Hepatol. 2017;15(4):597–599. doi:10.1016/j.cgh.2016.11.028

24. Debast SB, Bauer MP, Kuijper EJ. European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for Clostridium difficile infection. Clin Microbiol Infect. 2014;20:1–26. doi:10.1111/1469-0691.12418

25. Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. Am J Gastroenterol. 2013;108(4):478. doi:10.1038/ajg.2013.4

26. Moore T, Rodriguez A, Bakken JS. Fecal microbiota transplantation: a practical update for the infectious disease specialist. Clin Infect Dis. 2013;58(4):541–545. doi:10.1093/cid/cit950

27. Rubin DT, Ananthakrishnan AN, Siegel CA, Sawyer BG, Long MD. ACG clinical guideline: ulcerative colitis in adults. AJG. 2019;114(3):384–413. doi:10.14309/ajg.0000000000000152

28. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG clinical guideline: management of Crohn’s disease in adults. AJG. 2018;113(4):481–517. doi:10.1038/ajg.2018.27

29. Kelly CR, Kahn S, Kashyp P, et al. Update on fecal microbiota transplantation 2015: indications, methodologies, mechanisms, and outlook. Gastroenterol. 2015;149(1):223–237. doi:10.1053/j.gastro.2015.05.008

30. Brandt LJ, Aroniadis OC, Mellow M, et al. Long-term follow-up of colonoscopic fecal microbiota transplant for recurrent Clostridium difficile infection. AJG. 2012;107(7):1079. doi:10.1038/ajg.2012.60

31. Brandt LJ, Aroniadis OC. An overview of fecal microbiota transplantation: techniques, indications, and outcomes. Gastrointest Endosc. 2013;78(2):240–249. doi:10.1016/j.gie.2013.03.1329

32. Vermeire S, Joossens M, Verbeke K, et al. Donor species richness determines faecal microbiota transplantation success in inflammatory bowel disease. JCC. 2015;10(4):387–394.

33. Kelly CR, Khoruts A, Staley C, et al. Effect of fecal microbiota transplantation on recurrence in multiply recurrent Clostridium difficile infection: a randomized trial. Ann Intern Med. 2016;165(9):609. doi:10.7326/M16-0271

34. Ianigo G, Masucci L, Quaranta G, et al. Randomised clinical trial: faecal microbiota transplantation by colonoscopy plus vancomycin for the treatment of severe refractory Clostridium difficile infection-single versus multiple infusions. Aliment Pharmacol Ther. 2018;48(2):152–159. doi:10.1111/apt.14816

35. Ianigo G, Valerio L, Masucci L, et al. Predictors of failure after single faecal microbiota transplantation in patients with recurrent Clostridium difficile infection: results from a 3-year, single-centre cohort study. Clin Microbiol Infect. 2017;23(5):e337–e337. e333. doi:10.1016/j.cmi.2017.05.005

36. Ianigo G, Maida M, Barisch J, et al. Efficacy of different faecal microbiota transplantation protocols for Clostridium difficile infection: a systematic review and meta-analysis. United European Gastroenterol J. 2018;6(8):1232–1244. doi:10.1111/1751-5535.13188

37. Ianigo G, Eusebi LH, Black CJ, Gasbarrini A, Cammarota G, Ford AC. Systematic review with meta-analysis: efficacy of faecal microbiota transplantation for the treatment of irritable bowel syndrome. Aliment Pharmacol Ther. 2019;50(3):240–248. doi:10.1111/apt.15330

38. Nitzen O, Elias M, Chazan B, Raz R, Saliba W. Clostridium difficile and inflammatory bowel disease: role in pathogenesis and implications in treatment. WJG. 2013;19(43):7577. doi:10.3748/wjg.v19.i43.7577

39. Agrawal M, Aroniadis OC, Brandt LJ, et al. The long-term efficacy and safety of fecal microbiota transplant for recurrent, severe, and complicated Clostridium difficile infection in 146 elderly individuals. J Clin Gastroenterol. 2016;50(5):403–407.
40. Newman KM, Rank KM, Vaughn BP, Khoruts A. Treatment of recurrent *Clostridium difficile* infection using fecal microbiota transplantation in patients with inflammatory bowel disease. *Gut Microbes*. 2017;8(3):303–309. doi:10.1080/19490976.2017.1279377

41. Kelly CR, de Leon L, Jasutkar N. Fecal microbiota transplantation for relapsing *Clostridium difficile* infection in 26 patients: methodology and results. *J Clin Gastroenterol*. 2012;46(2):145–149. doi:10.1097/MCG.0b013e318234570b

42. Aas J, Gessert CE, Bakken JS. Recurrent *Clostridium difficile* colitis: case series involving 18 patients treated with donor stool administered via a nasogastric tube. *Clin Infect Dis*. 2003;36(5):580–585. doi:10.1086/376767

43. Rohlike F, Surawicz CM, Stollman N. Fecal flora reconstitution for recurrent *Clostridium difficile* infection: results and methodology. *J Clin Gastroenterol*. 2010;44(8):567–570. doi:10.1097/MCG.0b013e3181dadb10

44. Khoruts A, Rank KM, Newman KM, et al. Inflammatory bowel disease affects the outcome of fecal microbiota transplantation for recurrent *Clostridium difficile* infection. *Clin Gastroenterol Hepatol*. 2016;14(10):1433–1438. doi:10.1016/j.cgh.2016.02.018

45. Moayyedi P, Surette MG, Kim PT, et al. Fecal microbiota transplantation induces remission in patients with active ulcerative colitis in a randomized controlled trial. *Gastroenterol*. 2015;149(1):102–109.e106. doi:10.1053/j.gastro.2015.04.001

46. Ding X, Li Q, Li P, et al. Long-term safety and efficacy of fecal microbiota transplant in active ulcerative colitis. *Drug Saf*. 2019;42(7):869–880. doi:10.1007/s40264-019-00809-2

47. Azimirad M, Gholami F, Yadegar A, et al. Prevalence and characterization of *Clostridium perfringens* toxigenotypes among patients with antibiotic-associated diarrhea in Iran. *Sci Rep*. 2019;9(1):7792. doi:10.1038/s41598-019-44281-5

48. Azimirad M, Yadegar A, Asadzadeh Aghdaei H, Kelly CR. Enterotoxigenic *Clostridium perfringens* Infection as an adverse event after faecal microbiota transplantation in two patients with ulcerative colitis and recurrent *Clostridium difficile* infection: a neglected agent in donor screening. *JCC*. 2019.

49. Wang S, Xu M, Wang W, et al. Systematic review: adverse events of fecal microbiota transplantation. *PLoS One*. 2016;11(8):e0161174. doi:10.1371/journal.pone.0161174

50. Hohmann EL, Ananthakrishnan AN, Deshpande V. Case 25-2014: a 37-year-old man with ulcerative colitis and bloody diarrhea. *N Engl J Med*. 2014;371(7):668–675. doi:10.1056/NEJMcp1400842

51. Schwartz M, Gluck M, Koon S. Norovirus gastroenteritis after fecal microbiota transplantation for treatment of *Clostridium difficile* infection despite asymptomatic donors and lack of sick contacts. *Am J Gastroenterol*. 2013;108(8):1367. doi:10.1038/ajg.2013.164

52. Quera R, Espinoza R, Estay C, Rivera D. Bacteremia as an adverse event of fecal microbiota transplantation in a patient with Crohn’s disease and recurrent *Clostridium difficile* infection. *JCC*. 2014;8(3):252–253.