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RESEARCH ARTICLE



Fecal microbiota transplantation for recurrent *Clostridioides difficile* infection in patients with concurrent ulcerative colitis

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ABSTRACT

Treatment of recurrent *Clostridioides difficile* infection (rCDI) has emerged as an important management dilemma particularly in patients with underlying inflammatory bowel disease (IBD). Fecal microbiota transplantation (FMT) has been used as a safe and highly effective treatment option for rCDI refractory to standard antibiotic therapies. The aim of this study was to report the efficacy of FMT in Iranian rCDI patients with concurrent IBD. A total of seven consecutive patients with ulcerative colitis (UC) who had experienced 3 episodes of rCDI were enrolled in this study. All patients received at least a single FMT administered during colonoscopy by direct infusion of minimally processed donor stool. Patients were followed for a minimum of 6 months for assessment of treatment efficacy and adverse events (AEs) attributable to FMT. All 7 UC patients (100%) experienced a durable clinical response to a single FMT following 2 months after the procedure. One patient received a second FMT in which a successful resolution of rCDI was ultimately achieved. No serious AEs from FMT were noted. FMT through colonoscopy was a safe, simple and effective alternative treatment approach for rCDI in patients with underlying IBD. However, its use and efficacy should be pursued in long-term prospective controlled trials.

KEYWORDS

Clostridioides difficile infection, fecal microbiota transplantation, recurrent infection, inflammatory bowel disease, diarrhea

INTRODUCTION

Inflammatory bowel disease (IBD), is a chronic and relapsing non-specific inflammatory intestinal disease including ulcerative colitis (UC) and Crohn's disease (CD), which is hallmarked by a disturbance in the bidirectional crosstalk between gut and brain [1]. In the last two decades, the prevalence and incidence of IBD has obviously increased in the Asian countries especially in Iran [2, 3]. Although the exact etiology of IBD remains largely unclear,

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a variety of parameters such as genetic susceptibility, environmental or microbial factors and the host immune responses are involved in its pathogenesis [4].

Clostridioides (formerly *Clostridium*) *difficile* infection (CDI) is the leading identifiable cause of antibiotic-associated diarrhea (AAD), and is a major source of morbidity and mortality for hospitalized patients [5–7]. Recurrent *C. difficile* infection (rCDI) is a common complication among patients following multiple effective antibiotic therapies and accounts for 20–35% of infected individuals, and of these 40–60% will have a second recurrence [8, 9]. Patients with IBD are at particularly high risk of developing rCDI than in those without IBD, and may experience a more severe disease with greater mortality rate [5, 10]. Several factors have been suggested to affect the relationship between CDI and IBD, including the intestinal dysbiosis of the gut microbiota, long-term and frequent hospitalizations, use of immunosuppressive medications, antimicrobial therapies, and diminished nutritional status that promotes colonization of *C. difficile* [11, 12].

Fecal microbiota transplantation (FMT), which involves infusion of feces from a healthy donor into the gut of a recipient, is strongly recommended for treatment of rCDI patients when there is no response to the conventional antibiotic therapies [13]. FMT has been reported to result in primary cure rate of 91%, and secondary cure rate of 98% with negligible adverse events (AEs) in patients with rCDI who had failed multiple treatment courses of anti-CDI regimens [14, 15]. Furthermore, data obtained from a systematic review demonstrated the majority of IBD patients with CDI experienced a reduction of symptoms, cessation of IBD medications, and disease remission after FMT [16]. However, little is known about the overall efficacy and safety of FMT procedure in IBD patients, and outcomes of FMT for treatment of rCDI in this population are more diverse compared with the non-IBD population. Here, we present a single-center experience on the use of FMT in Iranian IBD patients with ≥ 3 episodes rCDI.

MATERIALS AND METHODS

Study patients and definitions

In this study, consecutive IBD patients admitted to Research Institute for Gastroenterology and Liver Diseases (RIGLD) at Taleghani hospital in Tehran, with mild-to-moderate rCDI unresponsive to antimicrobial CDI treatment regimens (≥ 3 CDI recurrences) between September 2016 and July 2018. Subjects referred to our hospital were under evaluation of an expert multidisciplinary team consisting of gastroenterologists and medical microbiology specialists involved in the patients' recruitment, to determine their eligibility for the trial and were offered the opportunity to receive FMT. In addition, patients were informed that although FMT appears safe, without any known serious attributable adverse events (AEs), a theoretical transmission risk of unidentified

infectious agents or substances existed and could result in an unexpected disease.

Patients were included in the study if they were ≥ 18 years or older at the time of FMT. Criteria for CDI diagnosis were as per the recent update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) [17]. rCDI was defined as recurrence of mild-to-moderate CDI, after initial improvement, as evidenced by the reappearance of diarrhea, usually within 6–8 weeks of completion of a course of therapy and in the absence of any other identified pathogen [18]. Written informed consents were obtained from all enrolled subjects and/or their legal guardians prior to FMT procedure. The study protocol was approved by the local Ethical Review Committee of RIGLD at Shahid Beheshti University of Medical Sciences (Project No. IR.SBMU.RIGLD.REC.1398.036).

Selection and screening of donors

Selection of donors, screening for relevant communicable diseases, and stool processing were performed as described by the Fecal Microbiota Transplantation Working Group [19]. The stool source was patient-directed donor, and was recruited from patients' family members or healthy relatives. Donors were excluded if they had taken antibiotics within the preceding 3 months; were on major immunosuppressive agents, including chemotherapeutic agents; had known or recent exposure to HIV, hepatitis B or C; had a current communicable disease; participated in high-risk sexual behaviors; used illicit drugs; had a history of incarceration; traveled within 6 months to areas with endemic diarrheal illnesses; or had history of IBD, irritable bowel syndrome (IBS) or chronic diarrhea, gastrointestinal malignancy or polyposis, autoimmune disease, diabetes, obesity, metabolic syndrome, allergies, and atopy. Donor blood was tested for HIV, hepatitis A, B, and C. Donor stool testing included *C. difficile* toxins (TcdA and TcdB), ova and parasites, *Giardia* and *Cryptosporidium*, *Isospora*, *Helicobacter pylori*, rotavirus, and recent cytomegalovirus (CMV) infection.

FMT treatment procedure

All recipients underwent a standardized clinic visit before FMT during which demographic data, disease history and characteristics were recorded using a questionnaire. Patients continued to use the antibiotics that had been prescribed for their anti-CDI treatment regimen until 48–72 h before FMT, and underwent standard bowel preparation on the day before the procedure. Fresh stool was collected by the screened patient selected donor on the day of infusion and rapidly transported to our institute, and processed within 6 h of passage. In the institute's microbiology laboratory, approximately 50–100 g of donor stool were emulsified in 300 mL of sterile saline (0.9%, NaCl) by a blender until an appropriate consistency was achieved. The fecal suspension was filtered through gauze pads to remove large particulate matters, and the suspension poured into 60 cc catheter-tipped syringes and infused via the biopsy channel of a

colonoscopy. On average, the entire infusion procedure was performed within 10 min, and the patients were monitored in the recovery room of the Endoscopy Center for 2 h after the procedures. Patients were usually given loperamide before FMT procedure and asked to retain the infused fecal slurry for 2–6 h after procedure to facilitate donor microbiota colonization.

Outcomes and follow-up

Patients undergoing FMT received follow-up clinic visits and/or phone calls at 1–5 days, 2–10 weeks, 6 months and 1–2 years after FMT to document response and need for escalation of underlying IBD therapy. Baseline and follow-up information on demographics, medications, potential AEs, recurrence of symptoms (ie, abdominal pain, frequency/consistency of bowel movements), microbiology data, IBD activity and severity based on the judgment of the treating physician, endoscopic findings, and clinical disease activity scores were collected through medical record review. A successful FMT was defined as complete resolution of diarrhea and/or negative *C. difficile* by stool culture and polymerase chain reaction (PCR) within 2 months of FMT without the need for further anti-CDI therapy. Potential AEs were screened for at each time point including fever, chills, malaise, fatigue, anorexia, abdominal pain, diarrhea, constipation, nausea and vomiting.

RESULTS

Patient characteristics

A total of seven adult IBD patients with rCDI that received an FMT between 2016 and 2018 met the inclusion criteria and were included in this study. Their mean age was 31.6 ± 5.2 years (range, 24–41 years), of which four were men and three were women (men 57.1% vs. women 42.9%). With regard to IBD, before FMT all patients had active UC (flare-up) with overall disease severity of mild-to-severe based on clinical, biological, and endoscopic evidence of disease activity. All FMT recipients were outpatients, and none were being treated from inpatient facilities. At the time of FMT, almost all patients were infected with toxigenic *C. difficile* (6/7, 85.7% A⁺B⁺ genotype and 1/7, 14.3% A⁺B⁻ genotype), and had experienced 3 episodes of CDI. The defecation history of recipients was notable for an average of 8 ± 2.2 episodes with a minimum of 5 episodes and maximum 10 episodes. Before FMT, nearly all patients had been treated with vancomycin alone or in combination with metronidazole (4/7, 57.1%) as anti-*C. difficile* antibiotics up until two days before FMT. In addition, patients were being treated with medications for IBD treatments in various combinations including mesalazine [5-aminosalicylic acid (5-ASA)] (4/7, 57.1%), azathioprine (3/7, 42.8%), methotrexate (1/7, 14.3%), and prednisolone (3/7, 42.8%) as immunosuppressive agents, and infliximab as biological therapy (4/7, 57.1%). Characteristics and demographic information for each patient, CDI history, anti-CDI and IBD therapies, pre- and

post-FMT indications, and source of donor stool at the time of FMT are summarized in Table 1.

Donor characteristics

Donors included patient-directed first-degree and third-degree relatives. None of them had gastrointestinal symptoms and all were healthy. First-degree relatives (3 fathers, 1 brother and 1 sister) accounted for 71.4% of donors, and cousins accounted for 2 of 7 donors as third-degree relatives (Table 1). No person donated stool to more than 1 recipient. All stools were freshly passed, and none was frozen or banked.

Follow-up and outcomes of FMT

The initial FMT was successful in all (100%) patients who presented a complete resolution of diarrhea and CDI negative status following 2 months after a single FMT. All recipients reported a significant decrease in the frequency of defecation ranging from 2–3 times per day after FMT. The resolution or improvement of abdominal pain, normalization of bowel function and overall IBD clinical course 2 months after FMT were occurred in all patients. FMT was administrated via colonoscopy and well tolerated in all patients. There were no procedure-related AEs, except for transient and low-grade fever and abdominal discomfort in 1 (14.3%) and 3 (42.8%) recipients, respectively (Table 1). In all patients, these symptoms resolved approximately within 24 h post-FMT. However, late *C. difficile* recurrence (or re-infection) was seen in one patient. This patient experienced symptomatic deterioration and were found to have late *C. difficile* recurrence about 18 months after first FMT. A second FMT was performed for this case, in which a successful resolution of rCDI was ultimately achieved. Moreover, one patient required surgery (total colectomy) while PCR and stool culture testing were negative for *C. difficile*.

DISCUSSION

The increased understanding of intestinal microbiota as a true and functional organ inside the body in the past decade, and its eminent impact on human health and physiology, has proposed that FMT can be exploited to several diseases, including many inflammation-related disorders such as IBD, IBS and primary sclerosing cholangitis (PSC) [20–22]. Perturbations in the number and diversity of gut microbiota can result from antibiotic exposure and also underlying conditions and lead to an altered intestinal microbiome called gut dysbiosis, which then predispose to the development of gastrointestinal diseases and even immunologic and systemic disorders [23, 24]. Approaches to modify the population of intestinal microbiota, such as probiotic and prebiotic therapies, have been used successfully in the management of CDI and IBD, although with variable efficacy [25, 26]. Recently, FMT has emerged as a microbiota-targeted therapy which can re-establish the wide diversity of



Table 1. Characteristics and outcomes of patients with IBD undergoing FMT for rCDI before and after the FMT procedure

| Pre-FMT data | | | | | | | | | | Post-FMT data | | | | |
|--------------|------------|--------|---------------------|-------------------------------|-------------------------------------|--------------------|--------------|--------------------|------------|--------------------|--------------------------|-------------------------|-----------------------|-------------------------------------|
| Patients | Age, years | Sex | No. of CDI episodes | Toxin pattern | Frequency of defecation (times/day) | IBD type/ severity | IBD therapy | Antibiotic therapy | Donor type | Outcome at 60 days | Time to recurrence, days | Time to colectomy, days | AEs | Frequency of defecation (times/day) |
| 1 | 24 | Male | 3 | A ⁺ B ⁺ | 8 | UC/ Mild | Mesalazine | Vancomycin | Cousin | Cured | None | None | None | 2 |
| 2 | 32 | Female | 3 | A ⁺ B ⁺ | 10 | UC/ Severe | Azathioprine | Metronidazole | Father | Cured | 559 | None | Abdominal pain | 3 |
| 3 | 33 | Male | 3 | A ⁺ B ⁺ | 10 | UC/ Severe | Methotrexate | Metronidazole | Cousin | Cured | None | 126 | Fever, abdominal pain | 3 |
| 4 | 41 | Male | 3 | A ⁺ B ⁺ | 8 | UC/ Severe | Mesalazine | Vancomycin | Brother | Cured | None | None | None | 2 |
| 5 | 28 | Male | 3 | A ⁺ B ⁺ | 5 | UC/ Severe | Azathioprine | Vancomycin | Sister | Cured | None | None | None | 2 |
| 6 | 31 | Female | 3 | A ⁺ B ⁻ | 10 | UC/ Severe | Prednisolone | Metronidazole | Father | Cured | None | None | None | 2 |
| 7 | 32 | Female | 3 | A ⁺ B ⁺ | 5 | UC/ Severe | Prednisolone | Vancomycin | Father | Cured | None | None | Abdominal pain | 2 |
| | | | | | | | Mesalazine | | | | | | | |
| | | | | | | | Azathioprine | | | | | | | |
| | | | | | | | Infliximab | | | | | | | |

IBD, inflammatory bowel disease; rCDI, recurrent *Clostridioides difficile* infection; FMT, fecal microbiota transplantation; UC, ulcerative colitis; AEs, adverse events.

intestinal microbiome through the infusion of donor feces into the colon, and shows remarkable promise in controlling microbiota-associated disorders, especially rCDI with concurrent IBD [20, 27, 28].

Here, we describe a single-center experience of FMT for rCDI in patients with established IBD. In this study, all patients that were considered to undergo FMT procedure had taken multiple courses of treatment with conventional antibiotic regimens that failed to clear the recurrent infection. Based on our results, the primary cure rate defined as the complete resolution of diarrhea and CDI negative status after a single FMT by colonoscopy was 100% following 2 months post-FMT. The primary cure rate observed in this study was higher than the cure rates reported in the literature for rCDI patients with (85.7%) and without underlying IBD (91%) [14, 20]. Our data are supported by several case series and reports that have quoted similar cure rates of 92–100% in patients treated for CDI with FMT [14, 29–32]. Moreover, one patient received a second FMT due to late *C. difficile* recurrence, whom ultimately had a successful resolution of rCDI. Re-exposure to antibiotic therapy may re-develop the rCDI by disrupting the established so-called healthy neomicrobiome after FMT, thereby allowing *C. difficile* to overgrowth and flourish once again in the colonic microbiome. We also found an overall improvement in IBD activity approximately among all patients, except one who underwent total colectomy while PCR and stool culture testing showed negative results for *C. difficile*. Additionally, in a recent multi-center retrospective study by Fischer and colleagues, initial FMT was successful against rCDI in 79% of IBD patients, and this rate increased further with multiple FMTs to 88% [28]. However, they found the overall improvement in IBD activity was seen in only a third of the patients. However, data obtained from a systematic review showed the use of FMT for the management of active IBD resulted in a reduction or complete resolution of symptoms in 76% patients, cessation of all IBD medications in 76% patients and ‘prolonged remission’ of active disease in 63% of patients [16]. Furthermore, in a multicenter, long-term follow-up study by Agrawal et al. from 9 geographically disparate centers in the United States, Canada and Australia, 146 elderly individuals with different types of CDI including recurrent, severe, and complicated CDI underwent FMT [33]. According to their results, the overall primary and secondary cure rates for FMT were 82.9% and 95.9%, respectively. Additionally, Kronman et al. reported a complete resolution of infection in 90% of children with median age of 5.4 years who received FMT via nasogastric tube for treatment of rCDI [34]. They proposed FMT via nasogastric tube could be considered as a safe, well tolerated, and effective therapeutic option for pediatric rCDI colitis.

There has been some controversy over the relationship between the FMT outcome and stool donor type, and yet a few studies have directly compared FMT outcomes associated with related and unrelated stool donors [31, 35]. Data extracted from a systematic review revealed slightly higher resolution rate (93%) in FMT recipients who were closely

related to their donors, either genetically (e.g., first-degree or other close relatives), or intimately (e.g., spouses and partners) compared with recipients who were not related to their stool donors (84%) [31]. Notably, it is suggested that FMT success and resolution rate is dependent on the microbial composition, abundance and diversity of the stool donor and the use of related or unrelated donors, which may lead to introduction of FMT “super-donors” phenomenon describing donors whose stool results in significantly more successful FMT outcomes than the stool of other donors [36]. However, there are also some evidence indicating that the treatment success of FMT does not depend on the donor-recipient relationship [35, 37, 38]. Furthermore, administration of precision FMTs, transplantation of a predefined mixture of bacteria, have previously been shown to be beneficial, and potentially patient preferable for disease resolution in CDI treatment as an alternative approach opposed to whole fecal transplant [39, 40]. In our study, CDI resolution rates were not affected by the relationship between the FMT recipients and donors. However, further identification and subsequent characterization of donors’ gut microbiome and their effects on FMT success rate for treatment of rCDI will inevitably advance our understanding particularly for targeted bacteriotherapy approaches of chronic inflammatory diseases such as IBD. Additionally, at this time it remains unclear whether repopulating the bowel with predefined communities of microbial species, or with microbial community structure as a whole through FMT can correct the underlying pathophysiology of IBD in rCDI patients and simultaneously circumvent the AEs associated with administering whole fecal material.

CONCLUSION

While application of FMT holds notable promise as a rational treatment option for rCDI, weak evidence and relatively paucity of information exist for its potential effectiveness in treating concurrent IBD patients. In conclusion, we demonstrate that FMT is safe and effective in treatment of rCDI patients with IBD. Nevertheless, our findings need to be validated in larger and prospective clinical trials before it can be advocated as a standard treatment alternative for this population. Additionally, future studies focusing on the IBD subtypes, disease activity, timing of FMT, long-term follow-up, and careful monitoring of IBD activity are needed to further optimize its potential benefit in this population.

Conflicts of interest: The authors declare that they have no conflicts of interest.

Author contributions: FSGM performed the microbiological screening tests and prepared the stool suspension. AY designed the study, reviewed the literature and wrote the manuscript. HAA, SS and NED performed the colonoscopic procedures. MRZ critically revised the manuscript.



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REFERENCES

- Oligschlaeger Y, Yadati T, Houben T, Condello Olivan CM, Shiri-Sverdlov R. Inflammatory bowel disease: a stressed “gut/feeling”. *Cells* 2019; 8(7).
- Taghavi SA, Safarpour AR, Hosseini SV, Noroozi H, Safarpour M, Rahimikazerooni S. Epidemiology of inflammatory bowel diseases (IBD) in Iran: a review of 740 patients in Fars Province, Southern Iran. *Ann Colorectal Res* 2013; 1(1): 17–22.
- Azimirad M, Krutova M, Balaii H, Kodori M, Shahrokh S, Azizi O, et al. Coexistence of *Clostridioides difficile* and *Staphylococcus aureus* in gut of Iranian outpatients with underlying inflammatory bowel disease. *Anaerobe* 2019; 61: 102–13.
- Zhang YZ, Li YY. Inflammatory bowel disease: pathogenesis. *World J Gastroenterol* 2014; 20(1): 91–9.
- 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.
- Azimirad M, Krutova M, Yadegar A, Shahrokh S, Olfatifar M, Aghdaei HA, et al. *Clostridioides 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; 1–39.
- Gholam-Mostafaei FS, Yadegar A, Aghdaei HA, Azimirad M, Daryani NE, Zali MR. Anti-TNF containing regimens may be associated with increased risk of *Clostridioides difficile* infection in patients with underlying inflammatory bowel disease. *Curr Res Transl Med* 2020; 68(3): 125–30.
- McFarland LV, Elmer GW, Surawicz CM. Breaking the cycle: treatment strategies for 163 cases of recurrent *Clostridium difficile* disease. *Am J Gastroenterol* 2002; 97(7): 1769.
- Hopkins RJ, Wilson RB. Treatment of recurrent *Clostridium difficile* colitis: a narrative review. *Gastroenterol Rep* 2018; 6(1): 21–8.
- Kelsen JR, Kim J, Latta D, Smathers S, McGowan KL, Zaoutis T, et al. Recurrence rate of *Clostridium difficile* infection in hospitalized pediatric patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2011; 17(1): 50–5.
- Manichanh C, Rigottier-Gois L, Bonnaud E, Gloux K, Pelletier E, Frangeul L, et al. Reduced diversity of faecal microbiota in Crohn’s disease revealed by a metagenomic approach. *Gut* 2006; 55(2): 205–11.
- Morgan XC, Tickle TL, Sokol H, Gevers D, Devaney KL, Ward DV, et al. Dysfunction of the intestinal microbiome in inflammatory bowel disease and treatment. *Genome Biol* 2012; 13(9): R79.
- Fischer M, Sipe B, Cheng YW, Phelps E, Rogers N, Sagi S, et al. Fecal microbiota transplant in severe and severe-complicated *Clostridium difficile*: a promising treatment approach. *Gut Microbes* 2017; 8(3): 289–302.
- Brandt LJ, Aroniadis OC, Mellow M, Kanatzar A, Kelly C, Park T, et al. Long-term follow-up of colonoscopic fecal microbiota transplant for recurrent *Clostridium difficile* infection. *Am J Gastroenterol* 2012; 107(7): 1079–87.
- 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. *J Crohns Colitis* 2019; 13(7): 960–1.
- Anderson JL, Edney RJ, Whelan K. Systematic review: faecal microbiota transplantation in the management of inflammatory bowel disease. *Aliment Pharmacol Ther* 2012; 36(6): 503–16.
- McDonald LC, Gerding DN, Johnson S, Bakken JS, Carroll KC, Coffin SE, 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 Official Pub Infect Dis Soc America* 2018; 66(7): e1–48.
- Surawicz CM, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH, et al. Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections. *Am J Gastroenterol*; 108(4): 478–98. quiz 499 (2013).
- Bakken JS, Borody T, Brandt LJ, Brill JV, Demarco DC, Franzos MA, et al. Treating *Clostridium difficile* infection with fecal microbiota transplantation. *Clin Gastroenterol Hepatol* 2011; 9(12): 1044–9.
- 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): 303–9.
- Xu D, Chen VL, Steiner CA, Berinstein JA, Eswaran S, Waljee AK, et al. Efficacy of fecal microbiota transplantation in irritable bowel syndrome: a systematic review and meta-analysis. *Am J Gastroenterol* 2019; 114(7): 1043–50.
- Allegretti JR, Kassam Z, Carrellas M, Mullish BH, Marchesi JR, Pechlivanis A, et al. Fecal microbiota transplantation in patients with primary sclerosing cholangitis: a pilot clinical trial. *Am J Gastroenterol* 2019; 114(7): 1071–9.
- Xu MQ, Cao HL, Wang WQ, Wang S, Cao XC, Yan F, et al. Fecal microbiota transplantation broadening its application beyond intestinal disorders. *World J Gastroenterol* 2015; 21(1): 102–11.
- Wortelboer K, Nieuwdorp M, Herrema H. Fecal microbiota transplantation beyond *Clostridioides difficile* infections. *EBioMedicine* 2019; 44: 716–29.
- Orel R, Kamhi Trop T. Intestinal microbiota, probiotics and prebiotics in inflammatory bowel disease. *World J Gastroenterol* 2014; 20(33): 11505–24.
- Mills JP, Rao K, Young VB. Probiotics for prevention of *Clostridium difficile* infection. *Curr Opin Gastroenterol* 2018; 34(1): 3–10.
- Chin SM, Sauk 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): 597–9.
28. Fischer M, Kao D, Kelly C, Kuchipudi A, Jafri S-M, Blumenkehl M, et al. Fecal microbiota transplantation is safe and efficacious for recurrent or refractory *Clostridium difficile* infection in patients with inflammatory bowel disease. Inflamm Bowel Dis 2016; 22(10): 2402–9.
29. Rohlke F, Surawicz CM, Stollman N. Fecal flora reconstitution for recurrent *Clostridium difficile* infection: results and methodology. J Clin Gastroenterol 2010; 44(8): 567–70.
30. 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): 145–9.
31. Gough E, Shaikh H, Manges AR. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent *Clostridium difficile* infection. Clin Infect Dis 2011; 53(10): 994–1002.
32. 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): 580–5.
33. Agrawal M, Aroniadis OC, Brandt LJ, Kelly C, Freeman S, Surawicz C, 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): 403–7.
34. Kronman MP, Nielson HJ, Adler AL, Giefer MJ, Wahbeh G, Singh N, et al. Fecal microbiota transplantation via nasogastric tube for recurrent *Clostridium difficile* infection in pediatric patients. J Pediatr Gastroenterol Nutr 2015; 60(1): 23–6.
35. Ramai D, Zakhia K, Ofosu A, Ofori E, Reddy M. Fecal microbiota transplantation: donor relation, fresh or frozen, delivery methods, cost-effectiveness. Ann Gastroenterol 2019; 32(1): 30–8.
36. Wilson BC, Vatanen T, Cutfield WS, O'Sullivan JM. The super-donor phenomenon in fecal microbiota transplantation. Front Cell Infect Microbiol 2019; 9(2).
37. Kassam Z, Lee CH, Yuan Y, Hunt RH. Fecal microbiota transplantation for *Clostridium difficile* infection: systematic review and meta-analysis. Am J Gastroenterol 2013; 108(4): 500.
38. Osman M, Stoltzner Z, O'Brien K, Ling K, Koelsch E, Dubois N, et al. Donor efficacy in fecal microbiota transplantation for recurrent *Clostridium difficile*: evidence from a 1,999-patient cohort. Open Forum Infect Dis 2016; 3(suppl_1).
39. Petrof EO, Gloor GB, Vanner SJ, Weese SJ, Carter D, Daigneault MC, et al. Stool substitute transplant therapy for the eradication of *Clostridium difficile* infection: 'RePOOPulating' the gut. Microbiome 2013; 1(1): 3.
40. Emanuelsson F, Claesson BE, Ljungstrom L, Tvede M, Ung KA. Faecal microbiota transplantation and bacteriotherapy for recurrent *Clostridium difficile* infection: a retrospective evaluation of 31 patients. Scand J Infect Dis 2014; 46(2): 89–97.