

Fecal Microbiome Transplantation for Recurrent CDI: Treatment Efficacy and Safety with Oral Capsules

Tadas Urbonas^{1,2}, Dalius Petrauskas¹, Vytautas Kiudelis^{1,2}, Laimas Jonaitis^{1,2}, Jurgita Skieceviciene², Rolandas Gedgaudas^{1,2}, Edita Kiudeliene^{1,2}, Irena Valantiene¹, Romanas Zyklus¹, Greta Varkalaite², Ruta Inciuraite², Elzbieta Trapenske², Ugne Kulokiene², Paulius Jonaitis^{1,2}, Rima Ramonaite², Justina Velickiene², Aida Zvirbliene¹, Egidijus Morkunas^{1,2}, Irma Kuliaviene¹, Jolanta Sumskiene¹, Kestutis Adamonis¹, Andrius Macas³, Kristina Kupcinskiene³, Laura Lukosiene³, Dainius Janciauskas⁴, Lina Poskiene⁴, Astra Vitkauskienė⁵, Gianluca Ianiro⁶, Antonio Gasbarrini⁶, Gediminas Kiudelis^{1,2}, Juozas Kupcinkas^{1,2}

1) Department of Gastroenterology, Lithuanian University of Health Sciences, Kaunas, Lithuania;
2) Institute for Digestive Research, Lithuanian University of Health Sciences, Kaunas, Lithuania;
3) Department of Anesthesiology, Lithuanian University of Health Sciences, Kaunas, Lithuania;
4) Department of Patology, Lithuanian University of Health Sciences, Kaunas, Lithuania;
5) Department of Laboratory Medicine, Lithuanian University of Health Sciences, Kaunas, Lithuania;
6) Digestive Disease Center, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica Del Sacro Cuore, Rome, Italy

Address for correspondence:

Juozas Kupcinkas
Department of Gastroenterology, Lithuanian University of Health Sciences, Kaunas, Lithuania
juozas.kupcinkas@lsmu.lt

Received: 09.11.2024

Accepted: 15.01.2025

ABSTRACT

Background & Aims: Fecal microbiota transplantation is an effective treatment method for recurrent *Clostridioides difficile* infection. Widely used enteric tube and colonoscopy methods demonstrate excellent efficacy and safety results. Recent data suggest that new fecal microbiota transplantation methods using oral capsules may provide a less invasive approach. In this study, we aimed to compare primary fecal microbiota transplantation efficacy as well as short- and long-term safety of two different administration routes: oral capsules and enteric tube.

Methods: This retrospective study included 60 consecutive patients who underwent fecal microbiota transplantation for recurrent *Clostridioides difficile* infection. Thirty participants received 50 oral capsules containing frozen material for a single day and 30 patients received fecal microbiota transplantation via nasoenteric tube. All patients received standard treatment with oral vancomycin 500 mg q.i.d. for at least five days before the procedure. After intervention, patients were followed up for at least six months. Data on *Clostridioides difficile* infection recurrences and health status were collected and analyzed.

Results: The oral capsules group consisted of 30 patients. Among them, 22 (73.3%) participants experienced resolution of symptoms after a single fecal microbiota transplantation, while eight (26.7%) patients developed recurrent diarrhea within eight weeks. The other 30 patients received treatment via nasoenteric tube. Among them, 24 (80%) patients were cured after a single fecal microbiota transplantation, while six (20%) experienced recurrent disease within eight weeks. The primary efficacy did not show significant differences between the two groups ($p=0.85$). Throughout the follow-up period, no serious adverse events or fecal microbiota transplantation related deaths were reported in both groups.

Conclusions: Fecal microbiota transplantation with frozen oral capsules is a safe, less invasive method with comparable efficacy to nasoenteric administration route.

Key words: fecal microbiome transplantation – recurrent *Clostridioides difficile* infection – treatment efficacy – safety – oral capsules.

Abbreviations: *C. difficile*: *Clostridioides difficile*; CDI: *C. difficile* infection; FMT: fecal microbiota transplantation; rCDI: recurrent *C. difficile* infection; SAE: serious adverse event.

INTRODUCTION

Clostridioides difficile (*C. difficile*) is an anaerobic, gram-positive, spore-forming, toxin-producing bacillus transmitted through fecal-oral route. It is an enteric pathogen causing from mild to severe enterocolitis and considered as the most often cause of health care associated infectious diarrhea [1]. First and mild episodes of *C. difficile*

infection (CDI) are managed with antibiotic therapies – with metronidazole, vancomycin, and fidaxomicin currently being recommended by clinical guidelines [2, 3]. Monoclonal antibody Bezlotoxumab has displayed promising results in preventing recurrent disease [4]. However, it is currently recommended exclusively for patients with an elevated risk of recurrence and has limited efficacy [2]. In recent years, fecal microbiota transplantation (FMT) has proved its efficacy and safety as a treatment modality for recurrent and refractory CDI infection [5-7]. According to published systematic reviews and meta-analyses, the efficacy of FMT for recurrent *C. difficile* infection (rCDI) ranges from 85% to 90% [8-11]. Current guidelines endorse FMT as a recommended intervention for cases of second or subsequent

CDI occurrences, while emerging data shows the potential viability of early FMT interventions [12]. The transplantation of gut microbiota can be facilitated through both upper and lower gastrointestinal pathways. The initial approach involved the administration of FMT via the lower endoscopic route, yielding remarkable efficacy rates from 90% [12, 13]. Subsequently, upper gastrointestinal techniques have emerged, demonstrating commendable efficacy levels in the range of approximately 80% [14, 15]. Despite the satisfactory outcomes observed in colonoscopy and enteric tube efficacy and safety results, less invasive FMT methods such as oral capsules began to evolve. Data from several studies showed promising efficacy results with oral capsules [16-19]. In this study, we aimed to compare the effectiveness of FMT for rCDI using orally administered frozen capsules vs nasoenteric route of administration. We hypothesized that a less invasive FMT delivery method may be an equally efficacious alternative to existing standard FMT methods.

METHODS

This retrospective study aimed to compare two different CDI treatment methods and included a cohort of 60 patients who underwent FMT for recurrent CDI in Lithuanian University of Health Sciences Hospital, Kauno Klinikos. All recipients were treated in our hospital or referred to our center from regional hospitals for FMT procedure from 2017 to 2021. Thirty consecutive participants received FMT via oral capsules, with each patient administering 50 oral capsules containing frozen material (50g) from a single donor over a single day. Their outcomes were compared to the other group of consecutive 30 patients who underwent FMT via nasoenteric tube from 2020 to 2021. All patients who underwent FMT were followed up for at least six months post-procedure. The study protocol was reviewed and approved by the Kaunas Regional Ethical Committee (Lithuanian University of Health Sciences, Kaunas, Lithuania, approval number P2-BE-2-31/2018). Written informed consent was obtained from all participants.

Study Population

All 60 FMT recipients were diagnosed with rCDI, which, according to guidelines, is defined as an episode of CDI occurring within 8 weeks of a previous episode and had experienced a second or subsequent rCDI episode [20, 21]. *Clostridioides difficile* infection was confirmed by recurrent diarrhea (>3 times/day) and ELISA test by detecting enterotoxins A and B in patients' feces (Simple 2a-bdiff /stick 2a-bdiff, Operon®, Spain). The study population received sufficient treatment with oral vancomycin 500 mg q.i.d for at least five days prior to the FMT procedure in both nasoenteric and capsules groups. *Clostridioides difficile* infection diagnostics and treatment are standardized in our center, as published earlier [22]. None of these patients had bowel lavage before FMT.

Donor Preparation

The donor screening protocol was conducted according to the screening design outlined in previously published guidelines [23, 24], updated according to newly published data [25] and is routine screening protocol in our center [22]. Three volunteer donors contributed fecal material for our study. These

volunteers were in good health, under the age of 35, with no identifiable risk factors or contraindications for stool donation. The donors had no familial relationship with the patients. Prior to donating fecal material, the donors confirmed they had not undergone antibiotic therapy for at least six months leading up to the donation. Furthermore, they had not experienced any significant infectious diseases in the three months before or during their participation in the fecal donation process. Donors underwent a microbiological screening, which included testing their blood for hepatitis A, B, and C viruses, human immunodeficiency virus, *Epstein Barr virus*, *Cytomegalovirus*, and *Treponema pallidum*. Stool samples were examined for common pathogenic agents such as *C. difficile*, enteric pathogens like *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *Norovirus*, *Giardia lamblia*, and *Cryptosporidium parvum*, as well as various protozoa and helminths. Additionally, the donor feces were assessed for multi-drug-resistant bacteria, including extended-spectrum beta-lactamase producing *Enterobacteriaceae* (ESBL), *vancomycin-resistant enterococci* (VRE), *carbapenem-resistant Enterobacteriaceae* (CRE), and *methicillin-resistant Staphylococcus aureus* (MRSA). All FMT recipients received feces from a single donor, and the feces were donated at different time points.

Patient Preparation

Prior to FMT, all patients received CDI treatment with oral antibiotics (vancomycin, or metronidazole as an alternative) for at least 10 days. A minority of the patients treated in regional hospitals received metronidazole. To standardize treatment and ensure proper engraftment, all patients were additionally treated with oral vancomycin 500 mg q.i.d. for a minimum of five days before the procedure. Recipients received two doses of oral omeprazole (40 mg): one in the evening before and another in the morning of FMT administration day. Vancomycin was discontinued at least 24 hours prior to FMT. Patients in both groups did not undergo bowel preparation before the FMT procedure.

Preparation of Stool

Feces were collected in special disposable containers. Each patient in both groups received 50g of donor feces. The donor feces were mixed with isotonic 0.9% NaCl solution using a blender and mixed for five to eight minutes. After blending, the material is filtered twice. The prepared fecal material is then mixed with glycerol and deep-frozen at -80°C temperature. For enteric tube preparation, an additional 0.9% NaCl isotonic solution was added up to a total volume of 500 ml. The prepared FMT suspension was then transferred to the special bag, which was later attached to an 8 Fr nasoenteric tube (Kangaroo™ Nasogastric Feeding Tube, Cardinal Health, USA) [22]. For oral capsules, deep-frozen feces were used. Unfrozen fecal material was centrifuged twice, and sediments with supernatant were filled into capsules (DRcaps® capsules, Lonza Group, Switzerland).

FMT procedure

Oral capsules group

Fecal microbiota transplantation was administered via oral capsules, with each patient ingesting 50 frozen capsules obtained from a single donor within a single day. The FMT

material was administered over two-three hours. To mitigate the risk of potential regurgitation and aspiration of donor feces, patients were positioned upright at a 45° angle during the procedure. Medical staff attended to patients during the procedure and at 30-minute intervals for six hours following the FMT, to monitor recipients and address any potential complications associated with the procedure.

Enteric tube group

Following our successful experience FMT was performed via nasoenteric tube for 30 patients, with the tube inserted into the descending duodenum during upper gastrointestinal endoscopy [22]. To minimize the risk of aspiration and ensure proper placement of the tube within the duodenum, an abdominal X-ray was conducted for all patient's post-endoscopy to confirm correct positioning. The transplantation material was infused while patients were in a supine position at a 45° angle. To prevent aspiration of the infused material, patients were required to maintain this 45° upright position for a minimum of four hours following transplantation.

To oversee recipients and mitigate potential complications associated with FMT, medical staff provided continuous attendance during the procedure and at 30-minute intervals for six hours post-FMT. Following the delivery of FMT, the nasoenteric tube was rinsed with 20 ml of water prior to removal.

Evaluation of Outcomes

Resolved diarrhea was considered a positive response to FMT therapy (20,21,26). Primary non-responders were defined as patients who experienced treatment failure within the first week of FMT, characterized by persistent diarrhea post-FMT. Resolution of CDI was defined as the absence of diarrhea for a period of eight weeks [20, 21]. After a successful FMT,

asymptomatic patients did not undergo stool testing for *C. difficile*, as per guidelines [23].

RESULTS

Primary efficacy in capsules group was 73.3% compared to 80% in nasoenteric group. No difference between groups was found between age ($p=0.97$), gender distribution (males $p=0.82$, females $p=0.66$), polymorbidity ($p=0.79$), number of inflammatory bowel disease (IBD) ($p=1$) and immunosuppressed patients ($p=1$) as shown in Table I. In the oral capsules group after the first FMT procedure, 22 patients achieved clinical remission, resulting in a primary cure rate of 73.3% compared to 24 patients with resolved symptoms in enteric tube group. However, 14 patients (eight and six respectively) experienced recurrent diarrhea within eight weeks. Non-responders were repeatedly treated with oral vancomycin 500 mg q.i.d. for a minimum of five days and received FMT with the same modalities.

More than half of the FMT recipients, comprising 17 in the capsules group and 19 in the enteric tube group, were polymorbid, indicating they had at least two chronic illnesses prior to contracting CDI. No significant differences between the groups were observed ($p=0.79$).

An equal number of patients (eight in both groups) were immunosuppressed – were using glucocorticoids, anti-TNF, azathioprine, tacrolimus for conditions not related to CDI and continued using medication after FMT. Twelve patients (six in both groups) had earlier been diagnosed with IBD. We did not observe IBD flares in our patient's cohort.

Throughout the follow-up period, no serious adverse events or FMT-related deaths were observed. Minor side effects such as bloating, nausea, abdominal discomfort, and diarrhea occurred shortly after FMT, but all symptoms were resolved within a few hours, and no additional medical attention was required.

Table I. Patient baseline characteristics comparison

	FMT by capsules n = 30	FMT by nasoenteric tube n = 30	p
Symptoms resolution after 1st FMT, n (%)	22 (73.3)	24 (80)	0.85
Recurrent disease, n (%)	8 (26.7)	6 (20)	0.77
SAE, n (%)	0 (0)	0 (0)	1
Age, mean (SD)	66.03 (20.69)	66.23 (17.89)	0.97
Males, n (%)	14 (47)	12 (40)	0.82
Females, n (%)	16 (53)	18 (60)	0.66
Polymorbidity, n (%)	17 (56.7)	19 (63)	0.79
IBD, n (%)	6 (20)	6 (20)	1
Ulcerative colitis, n (%)	4 (13.33)	5 (16.67)	1
Crohn's disease, n (%)	2 (6.67)	1 (3.33)	1
Immunosuppressed, n (%)	8* (26.67)	8** (26.67)	1
Glucocorticoids, n (%)	5 (16.67)	8 (26.67)	0.55
Immunosuppressant, n (%)	2 (6.67)	5 (16.67)	0.43
Biological therapy, n (%)	4 (13.33)	0 (0)	0.12

*3 patients received more than 1 immunosuppressant drug, **5 patients received more than 1 immunosuppressant drug. SAE: serious adverse events; IBD: inflammatory bowel disease. The Fisher Exact Test was used for statistical analysis.

DISCUSSION

Fecal microbiota transplantation using orally administered capsules has demonstrated significant efficacy in the treatment of recurrent CDI and is a guideline-recommended modality for centers with expertise [27]. Additionally, this approach is characterized by its safety and reduced invasiveness in the restoration of the normal gut microbiota. A meta-analysis by Osman et al. [16] and Ramai et al. [28] evaluated FMT effectiveness with different procedure modalities. Fecal microbiota transplantation via colonoscopy remains the dominating method with the highest reported cure rate, from 81% up to 94.8%. Nevertheless, FMT by oral capsules provided sufficient efficacy with a reported cure rate from 71% to 92.2% after consecutive FMTs [16, 18, 28]. Other smaller studies had shown cure rate ranging from 70-88% after single FMT [29, 30]. This study offers comparable efficacy findings following a single FMT. However, it implies that the utilization of sequential FMTs, particularly when administered via easily ingested oral capsules, may enhance cure rates [31, 32]. A mid-study published meta-analysis on PPI use did not identify an impact on FMT efficacy. However, it remained the standard of care within our center. Any potential negative effects of PPI use on CDI recurrence were associated with chronic PPI use. Therefore, we decided to adhere to the initial protocol [33, 34].

Beran et al. [35] conducted a comprehensive meta-analysis encompassing a cohort of 4327 patients who had undergone FMT as a therapeutic intervention for recurrent or refractory CDI. This study investigated plausible patient-specific, disease-related, and treatment-associated determinants contributing to the likelihood of FMT failure. The authors successfully pinpointed a constellation of pertinent risk factors, including advanced age, severe manifestations of CDI, concurrent coexistence of IBD, inpatient status at the time of FMT, post-FMT administration of non-CDI antibiotics, suboptimal bowel preparation, and a history of prior hospitalizations associated with CDI [35]. Participants in the enteric tube and oral capsules did not undergo pre-FMT bowel preparation due to the preferential use of the upper gastrointestinal route. The results of this study suggest similar potential reasons for reduced efficacy between the oral capsule and enteric tube groups. Both groups consisted of patients of advanced age (mean (SD) age: 66.03 (20.69) vs 66.23 (17.89), respectively), with more than half being polymorbid (56.7% vs 63%), and 20% of patients in both groups having IBD as a comorbidity.

Although FMT has demonstrated high efficacy rates for rCDI, safety concerns have persisted. Numerous comprehensive meta-analyses and studies have reported an exceptionally low percentage of serious adverse events (SAEs) associated with FMT [16, 36]. Furthermore, even among high-risk patient groups with conditions such as severe or fulminant CDI, IBD, immunosuppression, or advanced age, the rate of adverse events remained within acceptable limits [37-40]. In our study, we did not observe any instances of serious or life-threatening complications linked to FMT. The absence of SAEs underscores the importance of rigorous donor screening, adherence to well-defined periprocedural protocols, and diligent patient monitoring following FMT. During this study, minor side effects were not recorded, as they usually

resolve spontaneously and may be related to comorbidities, endoscopy, prior vancomycin use, or CDI itself, and not directly caused by FMT.

It is imperative to acknowledge several notable limitations in the context of this study. Firstly, the validity of group comparisons and data analysis may be constrained due to the modest sample size and retrospective study design. Furthermore, the interpretation of CDI severity evaluation and follow-up data poses challenges, primarily arising from incomplete clinical data and substantial prevalence of comorbidities. Discriminating between complications stemming from FMT and exacerbations of pre-existing medical conditions remain a particularly intricate task within this framework. Furthermore, this study did not include a placebo group, as vancomycin monotherapy has been shown to result in symptom resolution in up to 45% of patients, as demonstrated in a published study [41]. However, the comparison of two different FMT methods remains valuable, as the placebo effect would likely influence both groups similarly. Lastly, feces from a single donor were donated over the four years of the study. We acknowledge that microbial composition may vary across multiple time points and could influence the results; however, in this study, we did not analyze data on the microbial composition of the donor feces.

CONCLUSIONS

A less invasive method of FMT with oral capsules demonstrated efficacy comparable to that of the enteric tube. The favorable safety profile of the procedure, along with its adequate primary efficacy, encourages further development of oral capsulized FMT methods.

Conflicts of interest: None to declare.

Author's contributions. T.U. and D.P. are responsible for study conception and design, data collection, analysis and interpretation of results, and manuscript preparation. All authors' contributed to the design and implementation of the research, FMT patients' preparation, FMT procedures and data collection to the analysis of the results and to the writing of the manuscript.

Acknowledgement: This project has received funding from the Research Council of Lithuania (LMTLT), agreement No: S-A-EI-3-7 and No. S-JPIAMR-23-1.

REFERENCES

1. Leffler DA, Lamont JT. Clostridium difficile infection. *N Engl J Med* 2015;372:1539-1548. doi:[10.1056/NEJMr1403772](https://doi.org/10.1056/NEJMr1403772)
2. Kelly CR, Fischer M, Allegretti JR, et al. ACG Clinical Guidelines: Prevention, Diagnosis, and Treatment of Clostridioides difficile Infections. *Am J Gastroenterol* 2021;116:1124-1147. doi:[10.14309/ajg.0000000000001278](https://doi.org/10.14309/ajg.0000000000001278)
3. Debast SB, Bauer MP, Kuijper EJ; European Society of Clinical Microbiology and Infectious Diseases. European society of clinical microbiology and infectious diseases: Update of the treatment guidance document for Clostridium difficile infection. *Clin Microbiol Infect* 2014;20 Suppl 2:1-26. doi:[10.1111/1469-0691.12418](https://doi.org/10.1111/1469-0691.12418)

4. Wilcox MH, Gerding DN, Poxton IR, et al. Bezlotoxumab for Prevention of Recurrent *Clostridium difficile* Infection. *N Engl J Med* 2017;376:305–317. doi:[10.1056/NEJMoa1602615](https://doi.org/10.1056/NEJMoa1602615)
5. Moayyedi P, Yuan Y, Baharath H, Ford AC. Faecal microbiota transplantation for *Clostridium difficile*-associated diarrhoea: a systematic review of randomised controlled trials. *Med J Aust* 2017;207:166–172. doi:[10.5694/mja17.00295](https://doi.org/10.5694/mja17.00295)
6. Fischer M, Sipe B, Cheng YW, et al. Fecal microbiota transplant in severe and severe-complicated *Clostridium difficile*: A promising treatment approach. *Gut Microbes* 2017;8:289–302. doi:[10.1080/19490976.2016.1273998](https://doi.org/10.1080/19490976.2016.1273998)
7. Kelly CR, Ihunnah C, Fischer M, et al. Fecal microbiota transplant for treatment of *clostridium difficile* infection in immunocompromised patients. *Am J Gastroenterol* 2014;109:1065–1071. doi:[10.1038/ajg.2014.133](https://doi.org/10.1038/ajg.2014.133)
8. Kassam Z, Lee CH, Yuan Y, Hunt RH. Fecal microbiota transplantation for *clostridium difficile* infection: Systematic review and meta-analysis. *Am J Gastroenterol* 2013;108:500–508. doi:[10.1038/ajg.2013.59](https://doi.org/10.1038/ajg.2013.59)
9. Cammarota G, Ianiro G, Gasbarrini A. Fecal microbiota transplantation for the treatment of *Clostridium difficile* infection: a systematic review. *J Clin Gastroenterol* 2014;48:693–702. doi:[10.1097/MCG.0000000000000046](https://doi.org/10.1097/MCG.0000000000000046)
10. Lessa FC, Mu Y, Bamberg WM, et al. Burden of *Clostridium difficile* Infection in the United States. *N Engl J Med* 2015;372:825–834. doi:[10.1056/NEJMoa1408913](https://doi.org/10.1056/NEJMoa1408913)
11. Mattila E, Uusitalo-Seppälä R, Wuorela M, et al. Fecal transplantation, through colonoscopy, is effective therapy for recurrent *Clostridium difficile* infection. *Gastroenterology* 2012;142:490–496. doi:[10.1053/j.gastro.2011.11.037](https://doi.org/10.1053/j.gastro.2011.11.037)
12. 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;50:403–407. doi:[10.1097/MCG.0000000000000410](https://doi.org/10.1097/MCG.0000000000000410)
13. Zainah H, Hassan M, Shiekh-Sroujeh L, Hassan S, Alangaden G, Ramesh M. Intestinal microbiota transplantation, a simple and effective treatment for severe and refractory *Clostridium difficile* infection. *Dig Dis Sci* 2015;60:181–185. doi:[10.1007/s10620-014-3296-y](https://doi.org/10.1007/s10620-014-3296-y)
14. Ianiro G, Maida M, Burisch 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;6:1232–1244. doi:[10.1177/2050640618780762](https://doi.org/10.1177/2050640618780762)
15. Quraishi MN, Widlak M, Bhala N, et al. Systematic review with meta-analysis: the efficacy of faecal microbiota transplantation for the treatment of recurrent and refractory *Clostridium difficile* infection. *Aliment Pharmacol Ther* 2017;46:479–493. doi:[10.1111/apt.14201](https://doi.org/10.1111/apt.14201)
16. Osman M, Budree S, Kelly CR, et al. Effectiveness and Safety of Fecal Microbiota Transplantation for *Clostridioides Difficile* Infection: Results From a 5344-Patient Cohort Study. *Gastroenterology* 2022;163:319–322. doi:[10.1053/j.gastro.2022.03.051](https://doi.org/10.1053/j.gastro.2022.03.051)
17. Kao D, Roach B, Silva M, et al. Effect of Oral Capsule- vs Colonoscopy-Delivered Fecal Microbiota Transplantation on Recurrent *Clostridium difficile* Infection: A Randomized Clinical Trial. *JAMA* 2017;318:1985–1993. doi:[10.1001/jama.2017.17077](https://doi.org/10.1001/jama.2017.17077)
18. Du C, Luo Y, Walsh S, Grinspan A. Oral Fecal Microbiota Transplant Capsules Are Safe and Effective for Recurrent *Clostridioides difficile* Infection: A Systematic Review and Meta-Analysis. *J Clin Gastroenterol* 2021;55:300–308. doi:[10.1097/MCG.0000000000001495](https://doi.org/10.1097/MCG.0000000000001495)
19. Reigadas E, Bouza E, Olmedo M, et al. Faecal microbiota transplantation for recurrent *Clostridioides difficile* infection: experience with lyophilized oral capsules. *J Hosp Infect* 2020;105:319–324. doi:[10.1016/j.jhin.2019.12.022](https://doi.org/10.1016/j.jhin.2019.12.022)
20. Debast SB, Bauer MP, Kuijper EJ, et al. European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for *Clostridium difficile* infection. *Clin Microbiol Infect* 2014;20 Suppl 2:1–26. doi:[10.1111/1469-0691.12418](https://doi.org/10.1111/1469-0691.12418)
21. Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment, and prevention of *clostridium difficile* infections. *Am J Gastroenterol* 2013;108:478–499. doi:[10.1038/ajg.2013.4](https://doi.org/10.1038/ajg.2013.4)
22. Urbonas T, Ianiro G, Gedgaudas R, et al. Fecal Microbiome Transplantation for Recurrent *Clostridioides difficile* Infection: Treatment Efficacy, Short and Long-term Follow-up Results from Consecutive Case Series. *J Gastrointestin Liver Dis* 2021;30:470–476. doi:[10.15403/jgld-3800](https://doi.org/10.15403/jgld-3800)
23. Cammarota G, Ianiro G, Tilg H, et al. European consensus conference on faecal microbiota transplantation in clinical practice. *Gut* 2017;66:569–580. doi:[10.1136/gutjnl-2016-313017](https://doi.org/10.1136/gutjnl-2016-313017)
24. Van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent *clostridium difficile*. *N Engl J Med* 2013;368:407–415. doi:[10.1056/NEJMoa1205037](https://doi.org/10.1056/NEJMoa1205037)
25. Cammarota G, Ianiro G, Kelly CR, et al. International consensus conference on stool banking for faecal microbiota transplantation in clinical practice. *Gut* 2019;68:2111–2121. doi:[10.1136/gutjnl-2019-319548](https://doi.org/10.1136/gutjnl-2019-319548)
26. Mullish BH, Quraishi MN, Segal JP, et al. The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridium difficile* infection and other potential indications: Joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. *Gut* 2018;67:1920–1941. doi:[10.1136/gutjnl-2018-316818](https://doi.org/10.1136/gutjnl-2018-316818)
27. Kelly CR, Fischer M, Allegretti JR, et al. ACG Clinical Guidelines: Prevention, Diagnosis, and Treatment of *Clostridioides difficile* Infections. *Am J Gastroenterol* 2021;116:1124–1147. doi:[10.14309/ajg.0000000000001278](https://doi.org/10.14309/ajg.0000000000001278)
28. Ramai D, Zakhia K, Fields PJ, et al. Fecal Microbiota Transplantation (FMT) with Colonoscopy Is Superior to Enema and Nasogastric Tube While Comparable to Capsule for the Treatment of Recurrent *Clostridioides difficile* Infection: A Systematic Review and Meta-Analysis. *Dig Dis Sci* 2021;66:369–380. doi:[10.1007/s10620-020-06185-7](https://doi.org/10.1007/s10620-020-06185-7)
29. Youngster I, Russell GH, Pindar C, Ziv-Baran T, Sauk J, Hohmann EL. Oral, capsulized, frozen fecal microbiota transplantation for relapsing *Clostridium difficile* infection. *JAMA* 2014;312:1772–1778. doi:[10.1001/jama.2014.13875](https://doi.org/10.1001/jama.2014.13875)
30. Staley C, Hamilton MJ, Vaughn BP, et al. Successful Resolution of Recurrent *Clostridium difficile* Infection using Freeze-Dried, Encapsulated Fecal Microbiota; Pragmatic Cohort Study. *Am J Gastroenterol* 2017;112:940–947. doi:[10.1038/ajg.2017.6](https://doi.org/10.1038/ajg.2017.6)
31. Jiang ZD, Jenq RR, Ajami NJ, et al. Safety and preliminary efficacy of orally administered lyophilized fecal microbiota product compared with frozen product given by enema for recurrent *Clostridium difficile* infection: A randomized clinical trial. *PLoS One* 2018;13:e0205064. doi:[10.1371/journal.pone.0205064](https://doi.org/10.1371/journal.pone.0205064)
32. Hirsch BE, Saraiya N, Poeth K, Schwartz RM, Epstein ME, Honig G. Effectiveness of fecal-derived microbiota transfer using orally administered capsules for recurrent *Clostridium difficile* infection. *BMC Infect Dis* 2015;15:191. doi:[10.1186/s12879-015-0930-z](https://doi.org/10.1186/s12879-015-0930-z)

33. Hong AS, Yu WY, Hong JM, et al. Proton pump inhibitor in upper gastrointestinal fecal microbiota transplant: A systematic review and analysis. *J Gastroenterol Hepatol* 2020;35:932–940. doi:[10.1111/jgh.14958](https://doi.org/10.1111/jgh.14958)
34. van Prehn J, Reigadas E, Vogelzang EH, et al. European Society of Clinical Microbiology and Infectious Diseases: 2021 update on the treatment guidance document for *Clostridioides difficile* infection in adults. *Clin Microbiol Infect* 2021;27 Suppl 2:S1–S21. doi:[10.1016/j.cmi.2021.09.038](https://doi.org/10.1016/j.cmi.2021.09.038)
35. Beran A, Sharma S, Ghazaleh S, et al. Predictors of Fecal Microbiota Transplant Failure in *Clostridioides difficile* Infection: An Updated Meta-analysis. *J Clin Gastroenterol* 2023;57:389–399. doi:[10.1097/MCG.0000000000001667](https://doi.org/10.1097/MCG.0000000000001667)
36. Rapoport EA, Baig M, Puli SR. Adverse events in fecal microbiota transplantation: a systematic review and meta-analysis. *Ann Gastroenterol* 2022;35:150–163. doi:[10.20524/aog.2022.0695](https://doi.org/10.20524/aog.2022.0695)
37. Tixier EN, Verheyen E, Luo Y, et al. Systematic Review with Meta-Analysis: Fecal Microbiota Transplantation for Severe or Fulminant *Clostridioides difficile*. *Dig Dis Sci* 2022;67:978–988. doi:[10.1007/s10620-021-06908-4](https://doi.org/10.1007/s10620-021-06908-4)
38. Porcari S, Baunwall SMD, Occhionero AS, et al. Fecal microbiota transplantation for recurrent *C. difficile* infection in patients with inflammatory bowel disease: A systematic review and meta-analysis. *J Autoimmun* 2023;141:103036. doi:[10.1016/j.jaut.2023.103036](https://doi.org/10.1016/j.jaut.2023.103036)
39. van Lingen EE, Baunwall S, Lieberknecht S, et al. Short- and long-term follow-up after fecal microbiota transplantation as treatment for recurrent *Clostridioides difficile* infection in patients with inflammatory bowel disease. *Therap Adv Gastroenterol* 2023;16:17562848231156285. doi:[10.1177/17562848231156285](https://doi.org/10.1177/17562848231156285)
40. Montalto M, Gallo A, Agnitelli MC, et al. Fecal microbiota transplantation for recurrent *Clostridioides difficile* infection in frail and very old patients. *J Am Geriatr Soc* 2023;71:3530–3537. doi:[10.1111/jgs.18500](https://doi.org/10.1111/jgs.18500)
41. Dubberke ER, Lee C, Orenstein R, Khanna S, Hecht G, Fraiz J. Efficacy and Safety of RBX2660 for the Prevention of Recurrent *Clostridium difficile* Infection: Results of the PUNCH CD 2 Trial. *Open Forum Infectious Diseases* 2016;3(suppl_1):1341. doi:[10.1093/ofid/ofw172.1044](https://doi.org/10.1093/ofid/ofw172.1044)