Adverse events in fecal microbiota transplantation: a systematic review and meta-analysis

Eliot A. Rapoport, Muhammad Baig, Srinivas R. Puli
University of Illinois College of Medicine at Peoria, Peoria, IL, USA

Abstract

Background Fecal microbiota transplantation (FMT) is a highly efficacious procedure used most commonly for the treatment of recurrent Clostridioides difficile infection (CDI). Despite the high value of incorporating FMT into practice, there remain concerns about its safety. To the best of our knowledge, there has not been an updated meta-analysis reporting pooled rates of adverse events in FMT for CDI.

Methods A search for studies of FMT in patients with CDI was performed with the rate of serious adverse events (SAEs) related to FMT evaluated as the primary outcome. Secondary outcomes included SAEs unrelated to FMT and minor adverse events associated with FMT. A pooled analysis was then performed.

Results Initial search identified 378 reference articles. Data were extracted from the 61 of these studies that met the inclusion criteria, comprising 5099 patients. Pooled analysis showed that SAEs related to FMT developed in less than 1% of patients. The pooled rate of SAEs not related to FMT was higher at 2.9%. The pooled rate of minor adverse events also showed infrequent self-limited gastrointestinal and systemic discomfort.

Conclusions This meta-analysis supports FMT as a safe option for treating recurrent CDI. Future randomized trials are needed to improve our current understanding of FMT safety and further examine the improvements in the quality of life of patients treated with FMT compared to standard therapy of antibiotics.

Keywords Fecal microbiota transplantation, Clostridioides difficile, adverse events

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Introduction

Clostridioides difficile infection (CDI) has emerged as a significant cause of human morbidity and mortality [1]. It is now estimated that CDI has an incidence up to 32.6 per 100,000 person-years, with a direct care cost of $4.8 billion per year in the USA alone [2]. This gram-positive, spore-forming anaerobe is the most common cause of pseudomembranous colitis—a condition characterized by intractable diarrhea with the formation of intestinal pseudomembranes of cellular material in the colon [3]. As a result of these physical characteristics, as well as the development of multidrug resistance, the challenge of effectively treating CDI continues to grow [1].

Given the prevalence and increasing antibiotic resistance of CDI, fecal microbiota transplantation (FMT) is emerging as an exciting alternative to antibiotic therapies in preventing recurrent and complicated CDI. Since its initial implementation, the frequency of use has grown significantly. Current guidelines recommend FMT for patients with multiple recurrences of antibiotic-treated CDI [4]. Accurate study of FMT is challenging, given the heterogeneity of administration protocols. One issue that arises is the variation in stool preparation—studies have described usage of both fresh and frozen stool, various sources of stool (family, pooled, or standardized preparation), and inconsistent donor and stool screening protocols [5,6]. An additional challenge has been the quality of these studies; many of the randomized controlled trials that have compared FMT...
Materials and methods

Search methodology

A literature search was conducted using the electronic database engines MEDLINE through PubMed, Ovid, Cochrane Library (Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews) and EMBASE, from January 1st 2015 to January 1st 2021, to identify published articles and reports addressing the use of FMT in patients with CDI. The combinations of keywords used were (“Enterococcalis, Pseudomembranous”[Mesh] OR “CDI”) AND (“Fecal Microbiota Transplantation”[Mesh] OR “FMT”). The reference list of all eligible studies was reviewed to identify additional studies. The retrieved studies were carefully examined to exclude potential duplicates or overlapping data. Titles and abstracts selected from the initial search were scanned, and the full papers of potentially eligible studies were reviewed.

Study eligibility

Published studies were eligible for inclusion if they reported the use of FMT for the management of CDI. Articles were excluded if they were not written in English or did not have English translations, if they included a pediatric population or studied FMT for non-CDI indications, or if no outcomes were reported. In studies using multiple modalities for the management of CDI, data from the cohort of patients who underwent FMT were collected and analyzed. Two reviewers (ER, MB) independently performed study selection according to eligibility criteria. Disagreements were resolved by discussion or a third reviewer. The agreement between reviewers for the collected data gave a Cohen κ value of 1.0.

Data extraction

The following data were independently abstracted onto a standardized form: study characteristics (primary author, time period of study, year of publication, and country of the population studied), study design, baseline characteristics of the study population (the numbers of patients enrolled, participant demographics, route of FMT), the intervention details and outcomes (adverse events). Risk of bias was rated for each study by 2 authors independently, using the Cochrane criteria for randomized controlled trials [19].

Outcome definition

The primary outcome of interest was the rate of serious adverse events (SAEs) (NCI Common Terminology Criteria for Adverse Events grade 3-5) related to FMT. The rate of SAEs determined to be unrelated to FMT, minor adverse events (grades 1-2) and the rate of specific SAEs were evaluated as a secondary outcome.

Statistical analysis

This meta-analysis was performed by calculating pooled proportions. First, the individual study proportions were transformed into a quantity using the Freeman-Tukey variant of the arcsine square root transformed proportion. The pooled proportion is calculated as the back-transform of the weighted mean of the transformed proportions, using inverse arcsine variance weights for the fixed effects model and DerSimonian-Laird weights for the random effects model [20]. Forest plots were drawn to show the point estimates in each study in relation to the summary pooled estimate. The width of the point estimates in the Forest plots indicates the weight assigned to that study. The heterogeneity among studies was tested using the F statistic and Cochran Q test based upon inverse variance weights [20]. F values of 0-39% were considered as nonsignificant heterogeneity, 40-75% as moderate heterogeneity, and 76-100% as considerable heterogeneity. If the P-value is >0.10, it rejects the null hypothesis that the studies are heterogeneous. The effect of publication and selection bias on the summary estimates was tested using the Harbord-Egger bias indicator [21].

Results

A total of 378 studies were found using the above search criteria. After removing duplicated studies, studies that did
not describe adverse events, studies that focused primarily on pediatric populations, and studies for non-CDI indications, remained (Table 1) [22-82]. A Preferred Reporting Items for Systematic Reviews and Meta-analysis flow diagram for the

| Study [ref.] | Study design | Number of patients | Average patient age | Percent female | Percent immuno suppressed | Percent with active inflammatory bowel disease | Number of transplants via upper GI route | Number of transplants via lower GI route |
|-------------|--------------|--------------------|---------------------|----------------|---------------------------|-----------------------------------------------|------------------------------------------|------------------------------------------|
| Ianiro et al 2018 [22] | Randomized Controlled Trial | 56 | 74.5 | 70 | 0 | 0 | 84 | 0 | 84 |
| Hvas et al 2019 [23] | Randomized Controlled Trial | 24 | 68 | 83 | 17 | 21 | 24 | 5 | 19 |
| Jiang et al 2018 [24] | Randomized Controlled Trial | 65 | 65 | 71 | NR | NR | 65 | 31 | 34 |
| Kao et al 2017 [25] | Randomized Controlled Trial | 116 | 58 | 68 | 15 | 5 | 116 | 57 | 59 |
| Hota et al 2017 [26] | Randomized Controlled Trial | 16 | 78 | 69 | 0 | 0 | 16 | 0 | 16 |
| Friedman-Korn et al 2018 [27] | Randomized Controlled Trial | 11 | 78 | 45 | 0 | 0 | 11 | 7 | 4 |
| Camacho-Ortiz et al 2017 [28] | Randomized Controlled Trial | 7 | 40 | 43 | 29 | 0 | 10 | 9 | 1 |
| Jiang et al 2017 [29] | Randomized Controlled Trial | 72 | 67 | 72 | NR | NR | 72 | 0 | 72 |
| Webb et al 2016 [30] | Case Series | 7 | 43 | 43 | 100 | 0 | 8 | 1 | 7 |
| Lee et al 2016 [31] | Randomized Controlled Trial | 219 | 73 | 67 | 11 | 3 | 350 | 0 | 219 |
| Orenstein et al 2015 [32] | Case Series | 31 | 66.8 | 74 | 0 | 0 | 46 | 0 | 46 |
| Lagier et al 2015 [33] | Case Series | 19 | 84 | NR | 0 | 0 | 33 | NR | NR |
| Cammarota et al 2015 [34] | Randomized Controlled Trial | 20 | 71 | 60 | 0 | 0 | 29 | 0 | 29 |
| Kelly et al 2016 [35] | Randomized Controlled Trial | 46 | 51 | 80 | 0 | 0 | 56 | 0 | 56 |
| Staley et al 2017 [36] | Prospective Cohort Study | 49 | 62 | 88 | 0 | 0 | 49 | 49 | 0 |
| Quera et al 2018 [37] | Case Series | 8 | 50 | 75 | 0 | 13 | 8 | 7 | 1 |
| Ponte et al 2018 [38] | Case Series | 28 | 79 | 64 | 0 | 0 | 34 | 24 | 4 |
| Girotra et al 2016 [39] | Case Series | 29 | 80 | 79 | NR | NR | 35 | 35 | 35 |
| Alghamdi et al 2019 [40] | Case Series | 29 | 65 | 83 | 3 | 10 | 31 | 9 | 20 |
| Allegretti et al 2019 [41] | Case Series | 37 | 37.6 | 57 | NR | NR | 40 | NR | NR |

(Contd...)
| Study [ref.] | Study design | Number of patients | Average patient age | Percent female | Percent immuno suppressed | Percent with active inflammatory bowel disease | Number of transplants | Number of transplants via upper GI route | Number of transplants via lower GI route |
|--------------|--------------|--------------------|---------------------|---------------|--------------------------|-----------------------------------------------|-----------------------|------------------------------------------|------------------------------------------|
| Abdallah et al 2019 [42] | Retrospective Cohort Study | 59 | 57 | 73 | 22 | 19 | 61 | 0 | 59 |
| Bobilev et al 2019 [43] | Randomized Controlled Trial | 25 | NR | NR | 0 | 0 | 25 | 25 | 0 |
| Cheng et al 2019 [44] | Case Series | 69 | 61.9 | 52 | 32 | 19 | 80 | 65 | 4 |
| Gjini et al 2019 [45] | Retrospective Cohort Study | 139 | 61.5 | 53 | NR | NR | 139 | 45 | 94 |
| Loudin et al 2019 [46] | Retrospective Cohort Study | 30 | 63.3 | 77 | 23 | 7 | 30 | 30 | 0 |
| Khanna et al 2019 [47] | Randomized Controlled Trial | 30 | NR | NR | NR | NR | 30 | 40 | 0 |
| Tirumanisetty et al 2019 [48] | Retrospective Cohort Study | 30 | 66 | 63 | NR | NR | 30 | 0 | 30 |
| Hassoun et al 2018 [49] | Prospective Cohort Study | 35 | 77 | 60 | NR | NR | 36 | 13 | 23 |
| Shin et al 2018 [50] | Case Series | 27 | NR | NR | NR | NR | 27 | NR | NR |
| Cheng et al 2018 [51] | Retrospective Cohort Study | 94 | 56.3 | 50 | 100 | 17 | 131 | NR | 107 |
| Stein et al 2018 [52] | Prospective Single Arm Trial | 8 | 69 | 50 | 0 | 0 | 9 | 9 | 0 |
| Juul et al 2018 [53] | Randomized Controlled Trial Multicenter | 9 | NR | NR | NR | NR | 9 | NR | NR |
| Allegretti et al 2018 [54] | Retrospective Cohort Study | 47 | 61 | 66 | NR | NR | 47 | 47 | 0 |
| Tabbaa et al 2018 [55] | Case series | 77 | NR | NR | NR | NR | 80 | NR | NR |
| Ng et al 2017 [56] | Randomized Controlled Trial | 15 | NR | NR | NR | NR | 15 | 15 | 0 |
| Tseng et al 2017 [57] | Retrospective Cohort Study | 234 | 62 | NR | NR | NR | 234 | 0 | 234 |
| Mosby et al 2017 [58] | Prospective Cohort trial | 41 | 65 | NR | NR | NR | 41 | 4 | 37 |
| Mamo et al 2017 [59] | Case Series | 137 | NR | NR | NR | NR | 137 | NR | NR |
| Dupont et al 2017 [60] | Randomized Controlled Trial | 54 | 71 | 69 | NR | NR | 71 | 71 | 0 |
| Ulmer et al 2017 [61] | Prospective Cohort Study | 46 | 56 | 67 | NR | NR | 46 | NR | NR |
| Mitchell et al 2017 [62] | Retrospective Cohort Study | 20 | NR | NR | NR | NR | 20 | 10 | 10 |
| Habib et al 2017 [63] | Retrospective Cohort Study | 37 | 63 | NR | 11 | 0 | 52 | 3 | 49 |

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Primary outcome

In pooled analysis, the overall rate of SAEs related to FMT was 0.65% (95%CI 0.45-0.89; P<0.001). A forest plot diagram of this pooled analysis is shown in Fig. 2. Publication bias calculated using the Harbord-Egger bias indicator gave a value of 1.10 (95%CI 0.26-1.94; P=0.02), indicating no publication bias. Fig. 3 is a funnel plot assessing the publication bias for the same variable.
Secondary outcomes

Rate of individual SAEs

Sepsis or sepsis-like conditions were reported in 0.19% (95%CI 0.09-0.31), aspiration pneumonia in 0.27% (95%CI 0.15-0.43), and bowel perforation was noted after 0.20% (95%CI 0.09-0.34) of FMTs. The pooled rate of SAEs not related to FMT was 2.91% (95%CI 2.47-3.39).

Rate of minor adverse events

Among minor adverse events, constipation was reported in 1.03% (95%CI 0.77-1.33), abdominal pain in 1.66% (95%CI 1.33-2.03), nausea in 0.92% (95%CI 0.67-1.20), vomiting in 0.34% (95%CI 0.20-0.52), flatulence in 0.70% (95%CI 0.49-0.94), and febrile episodes were noted after 0.33% (95%CI 0.19-0.50) of FMTs.

Discussion

FMT is rapidly gaining acceptance as a treatment for CDI. In an episode of CDI, major dysbiosis is commonly seen, with suppression of native Bacteroidetes and Firmicutes species and an increase in Proteobacteria [84]. FMT has been shown to restore this balance, with evidence that the composition of an FMT recipient’s microbiome retains similarity to the donor’s for months to years [85]. With the complexity of the microbiota being transplanted, several mechanisms have been observed. The first consists of direct competition of the transplanted microorganisms—through both resource competition and production of antimicrobial peptides [85]. Additionally, FMT restores a normal balance of bile acid metabolization in the gut, a process demonstrated to affect cellular signaling and spore germination [84,85]. Finally, it has been suggested that the protection FMT offers the mucosal barrier of the colon plays a role in favorably altering the immune system’s response to CDI [85].

A wealth of randomized clinical trials supports the effectiveness of FMT for recurrent CDI. This progress is vital, given the heavy disease burden CDI carries and the major risks associated with uncontrolled CDI [4,7,8]. Antimicrobial success rate in recurrent CDI is low, only about 35%, and surgery has very poor outcomes, with mortality up to 50% [86,87]. FMT involves the infusion of stool from a healthy donor to an infected patient with the goal of restoring a healthy microbiome, and exists as an exciting alternate approach for treatment that utilizes a novel and exciting mechanism [85]. However, there is still hesitancy regarding
Figure 2: Forest plot. Individual study proportions and the pooled estimate of the rate of serious adverse events related to fecal microbiota transplantation (random effect).
### Table 2 Outcomes of reviewed studies

| Study [ref.] | Number of patients | Number of transplants | Related serious adverse events (per transplant) | Related serious adverse events (per person) | Specific serious adverse event | Minor adverse events (per person) |
|--------------|--------------------|-----------------------|-----------------------------------------------|---------------------------------------------|--------------------------------|---------------------------------|
| Ianiro et al 2018 [22] | 56 | 84 | 0 | 0 | | 1.393 |
| Hvas et al 2019 [23] | 24 | 24 | 0.083 | 0.083 | Sepsis, bacterial overgrowth | 1.042 |
| Jiang et al 2018 [24] | 65 | 65 | 0 | 0 | | 3.615 |
| Kao et al 2017 [25] | 116 | 116 | 0 | 0 | | 0.112 |
| Hota et al 2017 [26] | 16 | 16 | 0 | 0 | | 5.750 |
| Friedman-Korn et al 2018 [27] | 11 | 11 | 0.182 | 0.182 | Aspiration leading to death; propofol toxicity leading to pneumonia | 0.000 |
| Camacho-Ortiz et al 2017 [28] | 7 | 10 | 0 | 0 | | 0.000 |
| Jiang et al 2017 [29] | 72 | 72 | 0 | 0 | | 2.778 |
| Webb et al 2016 [30] | 7 | 8 | 0 | 0 | | 0.857 |
| Lee et al 2016 [31] | 219 | 350 | 0 | 0 | | 2.078 |
| Orenstein et al 2015 [32] | 31 | 46 | 0 | 0 | | 6.065 |
| Lagier et al 2015 [33] | 19 | 33 | 0.03 | 0.053 | Acute cardiac insufficiency | 1.316 |
| Cammarota et al 2015 [34] | 20 | 29 | 0 | 0 | | 2.150 |
| Kelly et al 2016 [35] | 46 | 56 | 0 | 0 | | 0.022 |
| Staley et al 2017 [36] | 49 | 49 | 0 | 0 | | 0.265 |
| Quera et al 2018 [37] | 8 | 8 | 0.125 | 0.125 | Bacteremia in a patient with Crohn's | 0.250 |
| Ponte et al 2018 [38] | 28 | 34 | 0 | 0 | | 0.000 |
| Girotra et al 2016 [39] | 29 | 35 | 0 | 0 | | 0.172 |
| Alghamdi et al 2019 [40] | 29 | 31 | 0 | 0 | | 0.000 |
| Allegretti et al 2019 [41] | 37 | 40 | 0 | 0 | | NR |
| Abdallah et al 2019 [42] | 59 | 61 | 0 | 0 | | NR |
| Bobilev et al 2019 [43] | 25 | 25 | 0 | 0 | | 0.520 |

(Contd...)
Table 2 (Continued)

| Study [ref.] | Number of patients | Number of transplants | Related serious adverse events (per transplant) | Related serious adverse events (per person) | Specific serious adverse event | Minor adverse events (per person) |
|--------------|---------------------|-----------------------|-------------------------------------------------|-------------------------------------------|-------------------------------|----------------------------------|
| Cheng et al 2019 [44] | 69                  | 80                    | 0.038                                           | 0.043                                     | Not specified                 | 0.319                           |
| Gjini et al 2019 [45] | 139                 | 139                   | 0                                               | 0                                         |                               | 0.137                           |
| Loudin et al 2019 [46] | 30                  | 30                    | 0                                               | 0                                         |                               | 0.867                           |
| Khanna et al 2019 [47] | 30                  | 30                    | 0                                               | 0                                         |                               | NR                              |
| Tirumanisetty et al 2019 [48] | 30                 | 30                    | 0                                               | 0                                         |                               | 0.067                           |
| Hassoun et al 2018 [49] | 35                  | 36                    | 0                                               | 0                                         |                               | NR                              |
| Shin et al 2018 [50] | 27                  | 27                    | 0.111                                           | 0.111                                     | Aspiration                    | 0.111                           |
| Cheng et al 2018 [51] | 94                  | 131                   | 0.046                                           | 0.064                                     | Diarrhea ×3; Crohn's flare    | 0.191                           |
| Stein et al 2018 [52] | 8                   | 9                     | 0                                               | 0                                         |                               | 0.750                           |
| Juul et al 2018 [53] | 9                   | 9                     | 0                                               | 0                                         |                               | NR                              |
| Allegretti et al 2018 [54] | 47                 | 47                    | 0                                               | 0                                         |                               | NR                              |
| Tabbaa et al 2018 [55] | 77                  | 80                    | 0.088                                           | 0.091                                     | Colectomy secondary to toxic megacolon ×1; Inflammatory bowel flares ×6 | 0.649                           |
| Ng et al 2017 [56] | 15                  | 15                    | 0                                               | 0                                         |                               | NR                              |
| Tseng et al 2017 [57] | 234                 | 234                   | 0.004                                           | 0.004                                     | Colonic perforation           | NR                              |
| Mosby et al 2017 [58] | 41                  | 41                    | 0                                               | 0                                         |                               | 0.488                           |
| Mamo et al 2017 [59] | 137                 | 137                   | 0                                               | 0                                         |                               | NR                              |
| Dupont et al 2017 [60] | 54                  | 71                    | 0                                               | 0                                         |                               | 0.000                           |
| Ulmer et al 2017 [61] | 46                  | 46                    | 0                                               | 0                                         |                               | 0.022                           |
| Mitchell et al 2017 [62] | 20                 | 20                    | 0                                               | 0                                         |                               | 1.200                           |
| Habib et al 2017 [63] | 37                  | 52                    | 0                                               | 0                                         |                               | 0.000                           |
| Fischer et al 2017 [64] | 47                  | 64                    | 0.016                                           | 0.021                                     | Aspiration                    | NR                              |

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the implementation of FMT in the standard of care [15-18]. Our analysis seeks to further explore the safety of FMT, to ensure patients and physicians have an optimal data-driven approach to considering FMT.

To our knowledge, this is the largest published systematic review with a meta-analysis of adverse events for FMT in CDI, and it offers several advantages compared to the previously published literature. This meta-analysis establishes that FMT is safe when used for CDI, with significant adverse events noted in less than 1% of the patients. This knowledge is invaluable in aiding decision making for patients and physicians and supports FMT as an excellent alternative option to standard therapy with antibiotics—especially for recurrent CDI. The majority of the significant adverse events noted in our review were unrelated...
to the FMT itself, which is unsurprising given that FMT is often administered in patients with severe, treatment-refractory CDI with multiple baseline medical comorbidities. Additionally, a relatively high percentage of the included patients were immunosuppressed, which could account for exaggeration of negative sequelae. Finally, minor adverse events, including nausea, vomiting, abdominal pain and constipation, were also noted very rarely, with an individual pooled rate of less than 2%, lower than previously reported [10,14].

The primary challenge faced by our review was the determination of SAE causality. The process for determining whether or not to attribute an adverse event to FMT was based on each study’s own standards. An area that highlights this difficulty is the unclear causality of inflammatory bowel disease flares and FMT. While some studies listed this as a sequela of FMT, others ruled it to be unrelated. An additional challenge was the mild inconsistency in several of the measured outcomes. This can probably be attributed to the heterogeneous patient populations and study protocols. Similarly, the average duration of follow up varied widely, as did symptom reporting. Missing data on demographics, method of stool transplantation, volume and amount of stool, and relationships of donor and recipients were also common [6].

This study, despite its limitations, demonstrated that FMT is a largely safe procedure. As the understanding of the effects of the fecal microbiome expands, causal relationships with new adverse events and long-term sequelae of FMT may continue to be discovered. Nevertheless, our current knowledge of both related and unrelated SAEs indicates that FMT should be a therapy strongly considered for patients with recurrent CDI.

This meta-analysis supports FMT as a safe option for treating recurrent CDI. While the short-term safety of fecal microbiota transplantation for treating recurrent CDI is promising from our meta-analysis, the potential long-term consequences of altering a patient’s gut microbiota are not fully known. Future randomized trials are needed to improve our current understanding of FMT safety and further clarify the improvements in the quality of life of patients treated with FMT compared to standard antibiotic therapy.

Figure 3 Bias assessment plot of publication bias in reporting serious adverse events in fecal microbiota transplantation

Summary Box

What is already known:

- Fecal microbiota transplantation (FMT) is a highly efficacious procedure used in the treatment of recurrent Clostridioides difficile infection
- A residual concern in the integration of FMT is concerns about the safety of the procedure
- Published studies have struggled with heterogeneous protocols that display various durations of follow up

What the new findings are:

- Our analysis shows a very low pooled rate of significant adverse events related to FMT, in total less than 1%, despite a significant portion of patients being immunocompromised or having underlying gastrointestinal conditions
- The pooled rate of minor adverse events was also relatively rare, and were most commonly diarrhea, constipation, abdominal pain, nausea and vomiting
- Further high-quality randomized control trials are necessary to evaluate the longer-term safety of FMT and its impact on quality of life

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References

1. Spigaglia P. Recent advances in the understanding of antibiotic resistance in Clostridium difficile infection. Ther Adv Infect Dis 2016;3:23-42.
2. Depestel DD, Aronoff DM. Epidemiology of Clostridium difficile infection. J Pharm Pract 2013;26:464-475.
3. Czepiel J, Dróźdz M, Pituch H, et al. Clostridium difficile infection: review. Eur J Clin Microbiol Infect Dis 2019;38:1211-1221.
4. McDonald LC, Gording DN, Johnson S, et al. Clinical Practice Guidelines for Clostridioides 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:e1-e48.
5. Tan X, Johnson S. Fecal microbiota transplantation (FMT) for C. difficile infection, just say 'No'. Anaerobe 2019;60:102092.
6. Lai CY, Sung J, Cheng F, et al. Systematic review with meta-analysis: review of donor features, procedures and outcomes in 168 clinical studies of faecal microbiota transplantation. Aliment Pharmacol Ther 2019;49:354-363.
7. Khan MY, Dirweesh A, Khurshid T, Siddiqui WJ. Comparing fecal microbiota transplantation to standard-of-care treatment for recurrent *Clostridium difficile* infection: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol* 2018;30:1309-1317.

8. Quraishi MN, Widlak M, Bhatla 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.

9. Tariq R, Pardi DS, Bartlett MG, Khanna S. Low cure rates in controlled trials of fecal microbiota transplantation for recurrent *Clostridium difficile* infection: a systematic review and meta-analysis. *Clin Infect Dis* 2019;68:1351-1358.

10. Wang S, Xu M, Wang W, et al. Systematic review: adverse events of fecal microbiota transplantation. *PloS One* 2016;11:e0161174.

11. Li YT, Cai HF, Wang ZH, Xu J, Fang JY. Systematic review with meta-analysis: long-term outcomes of faecal microbiota transplantation for *Clostridium difficile* infection. *Aliment Pharmacol Ther* 2016;43:445-457.

12. Alhifany AA, Almutairi AR, Almangour TA, et al. Comparing the efficacy and safety of faecal microbiota transplantation with bezlotoxumab in reducing the risk of recurrent *Clostridium difficile* infections: a systematic review and Bayesian network meta-analysis of randomised controlled trials. *BMJ Open* 2019;9:e031145.

13. Ali FS, Soin S, Abu-Shieh H, Sundararajan N. Mo1959 – a meta-analysis of the safety and efficacy of faecal microbiota transplantation for the treatment of *Clostridium difficile* infection in solid organ transplant recipients. *Gastroenterology* 2019;156:S-901.

14. Kim S. The safety and effectiveness of faecal microbiota transplantation: systematic review and meta-analysis. *Value Health* 2018;21:S41-S42.

15. Kahn SA, Vachon A, Rodriguez D, et al. Patient perceptions of fecal microbiota transplantation for ulcerative colitis. *Inflamm Bowel Dis* 2013;19:1506-1513.

16. Gundling F, Roggenbrod S, Schleifer S, Sohn M, Schepp W. Patient perception and approval of faecal microbiota transplantation (FMT) as an alternative treatment option for obesity. *Obes Sci Pract* 2019;5:68-74.

17. Madar PC, Petre O, Baban A, Dumitrascu DL. Medical students' perception on fecal microbiota transplantation. *BMC Med Educ* 2019;19:368.

18. Gill M, Blacketer C, Chitti F, et al. Physician and patient perceptions of fecal microbiota transplant for recurrent or refractory *Clostridoides difficile* in the first 6 years of a central stool bank. *JGH Open* 2020;4:950-957.

19. Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 [Internet]; 2021 [updated February; cited Dec 5, 2021]. Available from: https://training.cochrane.org/handbook [Accessed 28 January 2022].

20. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-188.

21. Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Stat Med* 2006;25:3433-3457.

22. Ianiro 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;48:152-159.

23. Hvas CL, Dahl Jørgensen SM, Jørgensen SP, et al. Fecal microbiota transplantation is superior to fidaxomycin for treatment of recurrent *Clostridium difficile* infection. *Gastroenterology* 2019;156:1324-1332.e3.

24. Jiang Z, 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.

25. 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.

26. Hota SS, Sales V, Tomlinson G, et al. Oral vancomycin followed by fecal transplantation versus tapering oral vancomycin treatment for recurrent *Clostridium difficile* infection: an open-label, randomized controlled trial. *Clin Infect Dis* 2017;64:265-271.

27. Friedman-Korn T, Livovsky DM, Maharshak N, et al. Fecal transplantation for treatment of *Clostridium difficile* infection in elderly and debilitated patients. *Dig Dis Sci* 2018;63:198-203.

28. Camacho-Ortiz A, Gutiérrez-Delgado EM, García-Maczoorro JF, et al. Randomized clinical trial to evaluate the effect of fecal microbiota transplant for initial *Clostridium difficile* infection in intestinal microbiome. *PloS One* 2017;12:e0189768.

29. Jiang ZD, Ajami NJ, Petrocosino JF, et al. Randomised clinical trial: faecal microbiota transplantation for recurrent *Clostridium difficile* infection - fresh, or frozen, or lyophilised microbiota from a small pool of healthy donors delivered by colonoscopy. *Aliment Pharmacol Ther* 2017;45:899-908.

30. Webb BJ, Brunner A, Ford CD, Gazdik MA, Petersen FB, Hoda D. Fecal microbiota transplantation for recurrent *Clostridium difficile* infection in hematopoietic stem cell transplant recipients. *Transpl Infect Dis* 2016;18:628-233.

31. Lee CH, Steiner T, Petrof EO, et al. Frozen vs fresh fecal microbiota transplantation and clinical resolution of diarrhea in patients with recurrent *Clostridium difficile* infection: a randomized clinical trial. *JAMA* 2016;315:142-149.

32. Orenstein R, Dubberke E, Hardi R, et al. Safety and durability of RBX2660 (microbiota suspension) for recurrent *Clostridium difficile* infection: results of the PUNCH CD study. *Clin Infect Dis* 2016;62:596-602.

33. Lagier J-, Delord M, Million M, et al. Dramatic reduction in *Clostridium difficile* ribotype 027-associated mortality with early fecal transplantation by the nasogastric route: a preliminary report. *Eur J Clin Microbiol Infect Dis* 2015;34:1597-6101.

34. Cammarota G, Masucci L, Ianigo 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;41:835-843.

35. 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;165:609-916.

36. Staley C, Hamilton MJ, Vaughn BP, et al. Successful resolution of recurrent *Clostridium difficile* infection using freeze-dried, encapsulated fecal microbiota. *Gastroenterology* 2017;152:S343-S344.

37. Quera R, Ibáñez P, Simian D, Rivera D, Acuña G, Espinoza R. Fecal microbiota transplantation through colonoscopy for *Clostridium difficile* recurrent infection. Report of eight cases. *Rev Med Chil* 2018;146:823-830.

38. Ponte A, Pinho R, Mota M, et al. Fecal microbiota transplantation in refractory or recurrent *Clostridium difficile* infection: a real-life experience in a non-academic center. *Rev Esp Enferm Dig* 2018;110:311-315.

39. Girotra M, Garg S, Anand R, Song Y, Dutta SK. Fecal microbiota transplantation for recurrent *Clostridium difficile* infection in the elderly: long-term outcomes and microbiota changes. *Am J Gastroenterol* 2019;114:2307-2315.

40. Alghamdi AA, Tabb D. Fecal microbiota transplantation after oral vancomycin for recurrent *Clostridium difficile* infection. * Infect Dis Clin Pract* 2019;27:356-359.
41. Allegretti JR, Mullish B, Hurtado J, et al. Short chain fatty acid profiles are altered by fecal microbiota transplantation for the treatment of inflammatory bowel disease and recurrent *Clostridiales* difficile infection. *Am J Gastroenterol* 2019;114:S484-S485.

42. Abdallah M, Abdalla A, Wiedel N, Baloun R, Gilberg J, Fecal microbiota transplantation for recurrent *Clostridiales* difficile infection: Efficacy and predictors of success. *Am J Gastroenterol* 2019;114:S78.

43. Bobilev D, Vaiikus L, DePetrillo P, et al. VE303, a live biotherapeutic product for prevention of recurrent *Clostridiales* difficile (C. difficile) infection. Preliminary results of a phase 1, open-label healthy volunteers study of oral VE303 after vancomycin. *Gastroenterology* 2019;156:S-900.

44. Cheng Y, Alhaffar D, Saha S, et al. Fecal microbiota transplantation is safe and effective for the treatment of *Clostridiales* difficile infection in patients with liver cirrhosis. *Gastroenterology* 2019;156:S-899.

45. Gjini P, Bybnick D, Green P. Constipation is a complication of oral encapsulated fecal microbial transplantation. *Gastroenterology* 2019;156:S-900.

46. Louden M, Hakki M. Institutional experience with capsule fecal microbiota transplantation for recurrent *Clostridiales* difficile infection. *Gastroenterology* 2019;156:S-904.

47. Khanna S, Pardi DS, Gerdin GN, et al. Durable freedom from *Clostridiales* difficile infection recurrence and microbiome restoration during six-month follow-up for a phase 1 clinical trial of RBX7455? An investigational room temperature-stable, oral microbiota-based therapeutic. *Gastroenterology* 2019;156:S-1158.

48. Tirumaniisetty P, Disalle M, Chodos A. Volume of fecal filtrate for fecal microbial transplantation does not affect the *Clostridiales* difficile infection cure rate. *Gastroenterology* 2019;156:S-910.

49. Hassoun A, Edwards J. Evaluation of fecal microbial transplantation (FMT) in elderly patients with recurrent *Clostridiales* difficile infection (CDI). *Open Forum Infect Dis* 2018;5:S336.

50. Shin Y, Bang B, Kwon K. Fecal microbiota transplantation for refractory and recurrent C. difficile. *Helicobacter* 2018;23:101-102.

51. Cheng Y, Phelps EL, Ganipini V, et al. Fecal microbiota transplantation for the treatment of *Clostridiales* difficile infection is efficacious and safe in solid organ transplant recipients. *Gastroenterology* 2018;154:S-1044.

52. Stein DJ, Harrington K, Bader H, et al. Oral freeze-dried fecal microbiota capsule treatment is effective for recurrent and refractory C. difficile infection. *Gastroenterology* 2018;154:S-856.

53. Juul FE, Skadal H, Ólens MN, et al. Fecal microbiota transplantation versus antibiotics for primary *Clostridiales* difficile infection – a multicenter randomized proof-of-concept trial. *Gastroenterology* 2018;154:S-10.

54. Allegretti JR, Fischer M, Shu E, et al. Fecal microbiota transplantation capsules with targeted colonic versus gastric delivery in recurrent C. difficile infection: a comparative analysis of high and low doses. *Gastroenterology* 2018;154:S-1050.

55. Tabbaa O, Rastogi P, Alukal J, Laster J, Mattar M. Long-term safety and efficacy of fecal microbiota transplantation in the treatment of *Clostridiales* difficile infection in patients with and without inflammatory bowel disease: A tertiary care center's experience. *Gastroenterology* 2018;154:S78-S79.

56. Ng SCC, Wong SH, Lui RN, et al. Vancomycin followed by fecal microbiota transplantation versus vancomycin for initial *Clostridiales* difficile infection: An open-label randomised controlled trial. *United Eur Gastroenterol J* 2017;9:A314.

57. Tseng AS, Crowell M, Orenstein B, Patron RL, DiBase J. Older patient age is associated with similar safety but higher relapse after fecal microbiota transplantation for recurrent *Clostridiales* difficile infection. *Am J Gastroenterol* 2017;112:551.

58. Mosby D, Mcgraw P, Duffalo C, et al. Factors affecting effectiveness of fecal microbiota transplant. *Open Forum Infect Dis* 2017;4:S386.

59. Mamo Y, Woodworth M, Tchinenko K, Dhure T, Kraft C. Durability and long-term clinical outcomes of fecal microbiota transplant (FMT) treatment in patients with recurrent *C. difficile* infection. *Open Forum Infect Dis* 2017;4:S384-S385.

60. Dupont H, Jiang ZD, Alexander A, et al. Lyophilized fecal microbiota transplantation capsules for recurrent *Clostridiales* difficile infection. *Open Forum Infect Dis* 2017;4:S381.

61. Ulmer L, Verma A, Brock J, Iyer R. Fecal microbiota transplant for C. difficile colitis from thawed frozen stool and “real world” experience in a community hospital over two years. *Gastroenterology* 2017;152:S341.

62. Mitchell SW, DeZoye PA, Leis S, et al. Adverse effects of liquid vs. encapsulated lyophilized fullspectrum microbiota for the treatment of *Clostridiales* difficile infection. *Gastroenterology* 2017;152:S346-S347.

63. Habib I, Hug N, Madanna V. Standardized openbiome product as a treatment for *Clostridiales* difficile infections: a single center experience. *Gastroenterology* 2017;152:S951.

64. Fischer M, Khan M, Phelps EL, et al. Fecal microbiota transplantation is safe and effective for the treatment of *Clostridiales* difficile infection in solid organ transplant recipients. *Gastroenterology* 2017;152:S1005.

65. El-Nachef N, Piceno YM, Kassam Z, et al. Fecal microbiota transplantation is safe and effective in chronic pouchitis patients. *Gastroenterology* 2017;152:S1009.

66. Cicerone C, Bruno G, Lamonaca I, Trancassini M, Corazziari ES. Fecal microbiota transplantation for recurrent *Clostridiales* difficile infection: Transplant protocol by retention enema and preliminary results. *Dig Liver Dis* 2017;49:e175.

67. Hefazi M, Patnaik MM, Hogan WJ, Litzow MR, Pardi DS, Khanna S. Safety and efficacy of fecal microbiota transplantation for recurrent *Clostridiales* difficile infection in patients with hematologic malignancies. *Blood* 2016;128:3599.

68. Rezk AN, Stewart D, West S, Miao C, Khara HS, Komar M. Outcomes, safety and predictors of failure of fecal microbiota transplantation for refractory *Clostridiales* difficile infection. *Am J Gastroenterol* 2016;111:S82-583.

69. Le L, El-Nachef N. Fecal microbiota transplantation in solid organ transplant and hematopoietic stem cell transplant patients with recurrent or refractory *Clostridiales* difficile infection: A case series. *Am J Gastroenterol* 2016;111:S615.

70. Ianiro G, Masucci I, Nagel D, et al. Repeat fecal microbiota transplantation by colonoscopy for *Clostridiales* difficile-associated pseudomembranous colitis: results from a prospective, single-centre cohort. *United Eur Gastroenterol J* 2016;4:A654.

71. Curry S, Bogdanovich T, Pakstis D, Schwartz M, Binion D. Fecal microbiota transplantation for treatment of recurrent *Clostridiales* difficile infections using recipient-directed donors sero- matched for latent viruses: The University of Pittsburgh Medical Center (UPMC) experience. *Open Forum Infect Dis* 2016;3(Suppl 1):1208.

72. Pennell B, Hussain C, Theodoropoulos N, et al. Safety and efficacy of fecal microbiota transplants for the treatment of *Clostridiales* difficile at a tertiary care academic medical center. *Open Forum Infect Dis* 2016;3(Suppl 1):1208.

73. Zeitler K, Joshi R, Montero J. Alrabaa S. Fecal microbiota transplantation outcomes in immunocompetent and immunocompromised patients: A single center experience. *Open Forum Infect Dis* 2016;3(Suppl 1):2111.

74. Osman M, O’Brien K, Stoltzer Z, et al. Safety and efficacy of fecal microbiota transplantation for recurrent *Clostridiales* difficile infection from an international public stool bank: Results from a 2050-patient multicenter cohort. *Open Forum Infect Dis* 2016;3(Suppl 1):2120.

75. Van Beurden YH, De Groot PF, Van Nood E, Nieuwdorp M,
Keller JJ, Goorhuis A. Complications and long term follow-up of fecal microbiota transplantation for treatment of recurrent *Clostridium difficile* infection. *Gastroenterology* 2016;150:S544.

76. Ramsauer B, König C, Sabelhaus T, Ockenga J, Otte J-M. Fecal microbiota transplantation in relapsing *Clostridium difficile* colitis. *MMW Fortschr Med* 2016;158(Suppl 4):17-20.

77. Greenberg SA, Youngster I, Cohen NA, et al. Five years of fecal microbiota transplantation - an update of the Israeli experience. *World J Gastroenterol* 2018;24:5403-5414.

78. 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. *Inflamm Bowel Dis* 2016;22:2402-2409.

79. 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.

80. Peri R, Aguilar RC, Tüffers K, et al. The impact of technical and clinical factors on fecal microbiota transfer outcomes for the treatment of recurrent *Clostridioides difficile* infections in Germany. *United European Gastroenterol J* 2019;7:716-722.

81. Aroniadis OC, Brandt LJ, Greenberg A, et al. Long-term follow-up study of fecal microbiota transplantation for severe and/or complicated *Clostridium difficile* infection: a multicenter experience. *J Clin Gastroenterol* 2016;50:398-402.

82. Cohen NA, Livovsky DM, Yaakovovitch S, et al. A Retrospective comparison of fecal microbial transplantation methods for recurrent *Clostridium difficile* infection. *Isr Med Assoc J* 2016;18:594-599.

83. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.

84. Weingarden AR, Chen C, Bobr A, et al. Microbiota transplantation restores normal fecal bile acid composition in recurrent *Clostridium difficile* infection. *Am J Physiol Gastrointest Liver Physiol* 2014;306:G310-G319.

85. Khoruts A, Sadowsky MJ. Understanding the mechanisms of faecal microbiota transplantation. *Nat Rev Gastroenterol Hepatol* 2016;13:508-516.

86. Longo WE, Mazuski JE, Virgo KS, Lee P, Bahadursingh AN, Johnson FE. Outcome after colectomy for *Clostridium difficile* colitis. *Dis Colon Rectum* 2004;47:1620-1626.

87. Cornely OA, Miller MA, Louie TJ, Crook DW, Gorbach SL. Treatment of first recurrence of *Clostridium difficile* infection: fidaxomicin versus vancomycin. *Clin Infect Dis* 2012;55(Suppl 2):S154-S161.