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SUMMARY WITH CRITICAL APPRAISAL

Lyophilized versus Frozen Fecal Microbiota Transplant for Recurrent Clostridium Difficile Infection, Inflammatory Bowel Disease, and Irritable Bowel Syndrome: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

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Abbreviations

CDI	Clostridium difficile infection
FMT	fecal microbiota transplantation
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
RCT	randomized controlled trial

Context and Policy Issues

Fecal microbiota transplant (FMT) refers to the transfer of microbes from the feces of a healthy donor into the gut of a patient through oral administration, enema, colonoscopy or other means.[1] The objective of FMT is to re-establish a healthy and diverse gut microbial environment,[1] and FMT has been used in patients with recurrent Clostridium difficile infection, inflammatory bowel disease (IBD), or irritable bowel syndrome (IBS).[2,3] From 2009 to 2015, over 20,623 adult patients were reported to have Clostridium difficile infection (CDI), according to the Canadian Nosocomial Infection Surveillance Program.[4] Approximately 233,000 Canadians are living with IBD,[3] and an estimated 18% of Canadians are living with IBS.[5] FMT is used with the aim of fostering a healthy microbial environment in the gastrointestinal tract in these populations.[1]

FMT may be administered via different preparations. Lyophilized FMT is prepared by freezing a filtered stool sample solution from a healthy donor, then freeze drying the sample through sublimation to a powder form.[6] It can be administered orally and through colonoscopy.[6,7] In contrast, frozen FMT treatment involves freezing filtered stool samples at -80°C, thawing prior to administration, then administrating orally, by enema or via colonscopy.[6,7] It is suggested that lyophilized FMT is easier to store (e.g., at standard refrigerator temperature of 4°C) and that the powder material is easier to encapsulate.[7,8]

The objective of this report is to evaluate the clinical effectiveness, cost-effectiveness and evidence-based guidelines regarding the use of lyophilized FMT versus frozen FMT for patients of all ages with recurrent CDI, IBD, and IBS.

Research Questions

1. What is the comparative clinical effectiveness of lyophilized fecal microbiota transplantation versus frozen fecal microbiota transplantation for the treatment of recurrent Clostridium difficile infection, inflammatory bowel disease, or irritable bowel syndrome?

2. What is the comparative cost-effectiveness of lyophilized fecal microbiota transplantation versus frozen fecal microbiota transplantation for the treatment of patients with recurrent Clostridium difficile infection, inflammatory bowel disease, or irritable bowel syndrome?

3. What are the evidence-based guidelines regarding lyophilized fecal microbiota transplantation for the treatment of patients with recurrent Clostridium difficile infection, inflammatory bowel disease, or irritable bowel syndrome?

Key Findings

Two randomized controlled trials were identified regarding the clinical effectiveness of lyophilized versus frozen fecal microbiota transplant for recurrent Clostridium difficile infection. Evidence of limited quality from the two studies identified no statistically significant difference in cure rates for CDI between lyophilized and frozen fecal microbiota transplant via colonoscopy, and no difference in adverse events between oral lyophilized fecal microbiota transplant and frozen fecal microbiota transplant enema. The evidence presented in this report should be interpreted with caution based on the limitations and paucity of comparative data. No relevant literature was found regarding clinical effectiveness of lyophilized versus frozen FMT for the IBD and IBS indications, or the cost-effectiveness of lyophilized versus frozen FMT for CDI, IBD and IBS. No relevant evidence-based guidelines were identified.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Medline, PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were lyophilized or frozen fecal microbiota transplant. No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and July 11, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Q1-3: Patients of all ages with recurrent Clostridium difficile infection, inflammatory bowel disease, or irritable bowel syndrome
Intervention	Q1-3: Lyophilized fecal microbiota transplantation (all routes of administration)
Comparator	Q1-2: Frozen fecal microbiota transplantation (all routes of administration) Q3: No comparator
Outcomes	Q1: Clinical effectiveness, safety, harms Q2: Cost-effectiveness Q3: Guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized trials, economic evaluations, guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1 Guidelines that mentioned the intervention of interest but did not make recommendations regarding the intervention of interest were also excluded.

Critical Appraisal of Individual Studies

The included randomized controlled trials (RCT)[6,7] were critically appraised using the Downs and Black checklist.[9] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 401 citations were identified in the literature search. Following screening of titles and abstracts, 396 citations were excluded and five potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search for full-text review. Of these potentially relevant articles, four publications were excluded for various reasons, and two randomized controlled trials (RCTs) met the inclusion criteria and were included in this report. Note that one eligible systematic review[8] was excluded because it had a single relevant primary study[6] which was also captured by the search; the primary study[6] was retained for this report because it provided the most complete information. Appendix 1 presents the PRISMA[10] flowchart of the study selection. Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

The two RCTs included in this review were published in 2018[7] and 2017.[6]

Country of Origin

The two RCTs were conducted in the United States.[6,7]

Patient Population

Jiang et al., 2018 enrolled 65 non-pregnant adults from a medical clinic in Houston, Texas, between 20 and 97 years of age with recurrent CDI.[7] The study participants were 74% females and 36% males.[7] The length of follow-up was three months.[7] Patients were excluded if they had total colectomy, incontinence, concomitant antibiotics or probiotics, non-CDI diarrhea pathogen, white blood count >15×10^9/L or absolute neutrophil count < 0.5×10^9/L, toxic megacolon, intestinal perforation, or unstable medical conditions.[7]

Jiang et al., 2017 enrolled 73 non-pregnant adults between 19 and 97 years of age who had at least three episodes of CDI in the past 12 months.[6] Patients were excluded if they

had received previous FMT.[6] Seventy-two adults were followed up for five months and one was lost to follow-up.[6] Fifty-two of the 72 participants were females; and 20 were males.[6]

Interventions and Comparators

In Jiang et al., 2018, patients were randomized to receive lyophilized oral FMT (of 100 g) or frozen FMT enema (500 mL containing 100 g of fecal microbiota).[7] Note that after randomizing the first 14 subjects, the investigator reported that three of eight patients in the lyophilized FMT group had failed treatment compared to no patients with failed treatment in the frozen FMT group at two months post-FMT.[7] Therefore, the investigator involved the study data safety monitoring board and increased the oral lyophilized product to two doses of 100 g each for subjects subsequently randomized to the lyophilized group.[7] In total, of the patients in the lyophilized group, eight patients received a single 100 g dose and 23 patients received two doses of 100 g (the patients receiving one or two doses were analyzed both separately and grouped together in the analysis).[7]

In Jiang et al., 2017, patients were randomized to receive lyophilized FMT, fresh FMT or frozen FMT via colonoscopy.[6] Note that "fresh FMT" was not of interest for the current report. The exact doses of fecal microbiota administered were not reported.[6]

Outcomes

In Jiang et al., 2018, the outcomes of interest were adverse events that included diarrhea, nausea, vomiting, abdominal cramps/pain, flatulence, fecal urgency, and constipation.[7] The secondary outcome was cure with no episodes of CDI during the two months after FMT.[7] In Jiang et al., 2017, the outcome of interest was cure of CDI at 2 months after FMT.[6]

Summary of Critical Appraisal

For both of the RCTs, the objectives of the study, the characteristics of the patients included, and the interventions of interest were described clearly.[6,7] The main outcomes to be measured and the main findings of the study were well reported.[6,7] Patients were randomized to treatment arms.[6,7] Both studies evaluated the outcomes with standard, widely used measures (e.g., cured from CDI), and applied appropriate statistical tests to assess the outcomes.[6,7] A sample size calculation was performed for the Jiang et al., 2018 study and the calculation result was used in the Jiang et al., 2017study.[6,7] Adverse events that may have resulted from the interventions were reported in both studies.[6,7] The authors of both studies declared potential conflict of interest and sources of funding.[6,7] The Jiang et al., 2017 study was double-blinded and there two groups did not differ significantly with respect to any baseline characteristics.[6] All relevant characteristics were quantified and reported.[6]

For both RCTs, it was unclear whether the participants were representative of the source population.[6,7] Some of the outcomes were patient self-reported which could introduce detection bias.[6,7] In the Jiang et al., 2018 study, demographic features were not compared statistically between groups.[7] It was unclear whether the study investigators were blinded.[7] In addition, the groups differed with respect to both the intervention and route of administration (i.e., oral lyophilized FMT versus frozen FMT via enema); because the same route of administration was not used between groups it is possible that some of the observed effects were due differences in route of administration and not due to differences in the interventions.[7] Participants were not blinded to treatment allocations which could introduce performance bias.[7] Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Summary of Findings

Appendix 4 presents a table of the main study findings and authors' conclusions.

Clinical Effectiveness of Lyophilized FMT

Two randomized controlled trials provided evidence on the clinical effectiveness of lyophilized FMT for recurrent CDI.[6,7] No studies on the clinical effectiveness of lyophilized FMT for IBD and IBS met the inclusion criteria. In the Jiang et al., 2018 RCT, the incidence of adverse events such as diarrhea were not significantly different between the oral lyophilized FMT and frozen FMT enema groups.[7] There was no statistically significant difference in safety outcomes or 2-month cure rates between patients treated with orally administered lyophilized FMT versus frozen FMT enema.[7]

The Jiang et al., 2017 RCT reported no statistically significant difference in cure rate between the groups treated with lyophilized versus frozen FMT via colonoscopy, despite the rate of cure being numerically but non-statistically significantly lower with lyophilized product.[6] Although fresh FMT was not of interest for the current report, results for this group are reported in Appendix 4.

No relevant literature was found regarding clinical effectiveness of lyophilized versus frozen FMT for the IBD and IBS indications.

Cost Effectiveness of Lyophilized FMT

No relevant cost-effectiveness evidence regarding the lyophilized FMT for the treatment of recurrent CDI, IBD, and IBS was identified; therefore, no summary can be provided

Evidence-based Guidelines

No relevant evidence-based guidelines regarding the lyophilized FMT for the treatment of recurrent CDI, IBD, and IBS were identified; therefore, no summary can be provided.

Limitations

The two randomized controlled studies were conducted by the same group of investigators in the same medical center.[6,7] It was unclear whether the participants from this medical center were representative of the CDI patient population.[6,7] There was lack of comparative statistical analysis of the baseline characteristics of the two treatment groups in Jiang et al., 2018.[7] The patients in the lyophilized FMT group were reported to be older and had a higher percentage of pre-existing ICD.[7] In the Jiang et al., 2017 study, the descriptions of the doses and frequency of different FMT interventions via colonoscopy were not reported thereby introducing a level of uncertainty about the intervention and comparators in the results.[6] There was no evidence regarding the comparative effectiveness of lyophilized FMT versus frozen FMT with respect to hospital admission, mortality, health-related quality of life, long-term safety, cost-effectiveness, or guidelines in patients with CDI. Both included studies[6,7] were conducted in the United States; it is unknown if the results are generalizable to patients with CDI in Canada given the different demographics and prevalence rates.

Conclusions and Implications for Decision or Policy Making

Two randomized controlled trials were identified regarding the comparative effectiveness of lyophilized FMT versus frozen FMT for patients with recurrent CDI.[6,7] No relevant literature was found regarding clinical effectiveness of lyophilized versus frozen FMT for the IBD and

IBS indications. The evidence, from two studies by a single group of investigators, suggested that there were no significant differences between lyophilized and frozen FMT for 2-month cure rate and adverse events.[6,7] No comparative evidence on cost-effectiveness or evidence-based guidelines were found.

The evidence presented in this report should be interpreted with caution based on the limitations and paucity of comparative data. Specifically, there were limitations related to the quality of the included primary studies, in particular related to the potential for performance and detection biases.[6,7] Further research with randomized controlled trial designs addressing lyophilized FMT versus frozen FMT may help to reduce uncertainty and inform clinical practice.

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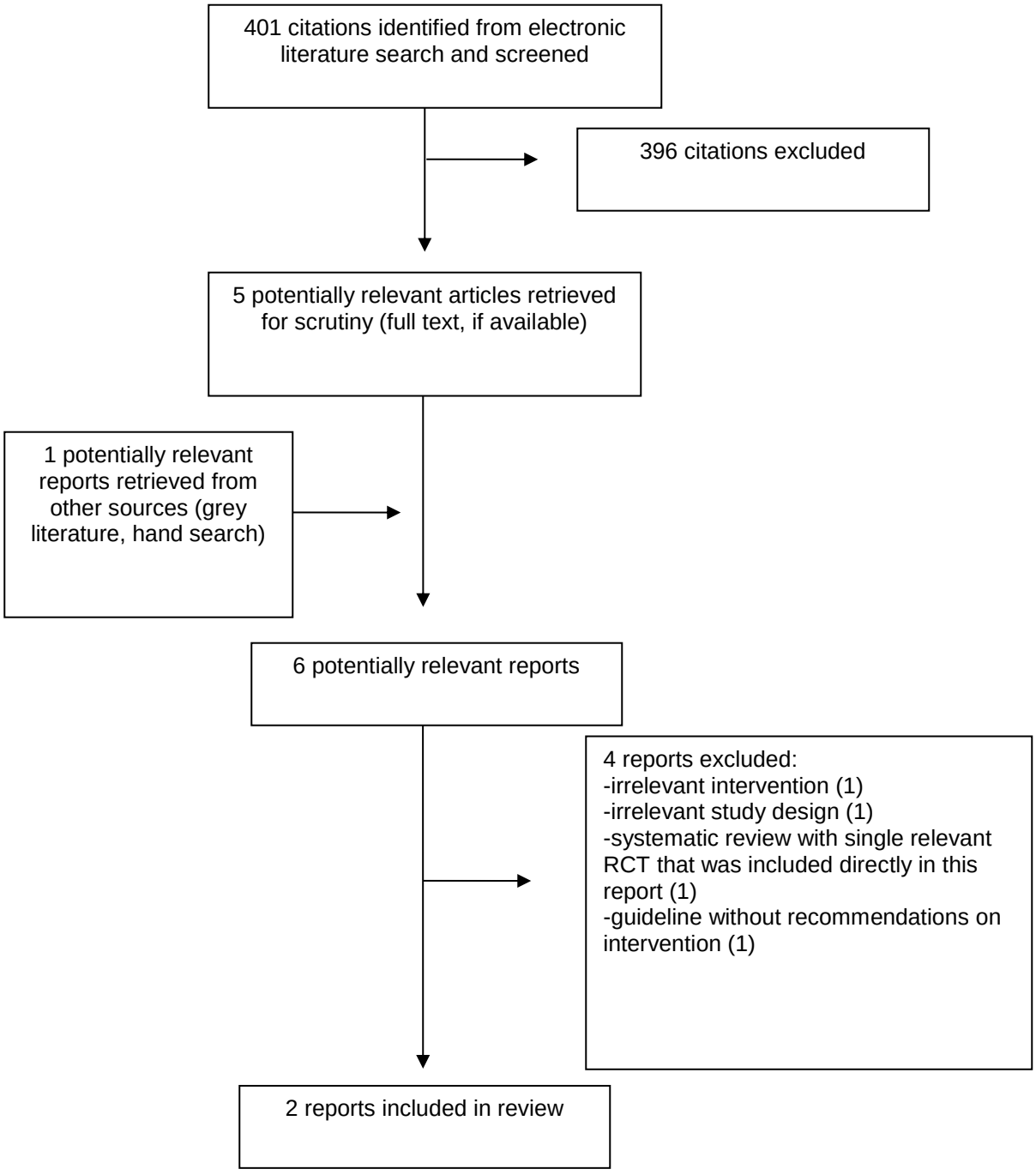
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Randomized Controlled Trials

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Jiang, 2018[7] **United States**	RCT Personnel performing the analyses were blinded to group assignment	65 non-pregnant adults with recurrent CDI (≥3 total episodes of CDI) and receipt of ≥1 course of anti-CDI antibiotics for most recent episode Age between 20 and 97 years old 74% female; 36% males	Intervention: One or two doses of 100 g of Lyophilized oral FMT (After randomizing 14 subjects, the investigator reported that 3 of 8 patients in the lyophilized FMT group had failed treatment compared to no patients with failed treatment in the frozen FMT group at 2 months post-FMT. Therefore, the investigator involved the study data safety monitoring board and increased the oral lyophilized product to 2 doses of 100 g each for subjects subsequently randomized to the lyophilized group) Comparator: 500 mL containing 100 g of frozen FMT enema	Efficacy: cure with no episodes of CDI during the two months after FMT Safety: diarrhea, nausea, vomiting, abdominal cramps/pain, flatulence, fecal urgency, constipation, other adverse events Length of follow-up: 3 months
Jiang, 2017[6] **United States**	Double-blind RCT	73 non-pregnant adults with ≥3 episodes of CDI in the past 12 months Age between 19 and 97 years old 52/72 female; 20/72 males	Intervention: Lyophilized FMT Comparators: Fresh FMT or frozen FMT via colonoscopy Doses administered NR	2-month cure of CDI after FMT Length of follow-up: 5 months for clinical response

CDI = Clostridium difficile infection; FMT = fecal microbiota transplantation; NR = not reported; RCT = randomized controlled trial.

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Randomized Controlled Trials using Downs and Black Checklist[9]

Strengths	Limitations
Jiang, 2018[7]	
• The objective of the study, the characteristics of the patients included, the interventions of interest, main outcomes to be measured, and the main findings of the study were described clearly • Study participants were recruited from the same population, using the same inclusion criteria, and over the same period • Patients were randomized to study groups • The statistical analyses used to assess the main outcomes were appropriate • The main findings were evaluated with standard widely used measures (e.g., side effects, cure) • Sample size calculations were performed a priori to determine the sample size required to adequately power the study to detect significant differences in outcomes between the treatment arms • A description of adverse events that may resulted from the intervention was reported • The authors declared potential conflicts of interest and sources of funding for the study	• It was unclear whether the participants were representative of the source population • Between-group differences in demographic features, pre-existing IBD, number of CDI episodes pre-FMT, or months since last episode of CDI were not compared statistically • The adverse effect outcomes were patient self-reported and could introduce detection bias • It was unclear whether the study was single-blinded. • The groups differed with respect to both the intervention and route of administration (i.e., oral lyophilized FMT vs. frozen FMT via enema); because the same route of administration was not used between groups it is possible that some of the observed effects were due differences in route of administration and not due to differences in the intervention. . • Participants were not blinded to treatment allocations which could introduce performance bias
Jiang, 2017[6]	
• The objective of the study, the characteristics of the patients included, the interventions of interest, main outcomes to be measured, and the main findings of the study were described clearly • Study participants were recruited from the same population, using the same inclusion criteria, and over the same period • There were no statistically significant differences in baseline characteristics between the two groups • Patients were randomized to study groups • The statistical analyses used to assess the main outcomes were appropriate • The main findings were evaluated with standard widely used measures (e.g., cure) • Sample size calculations were performed a priori to determine the sample size required to adequately power the study to detect significant differences in outcomes between the treatment arms • Participants and investigators were blinded to treatment allocations • A description of adverse events that may have resulted from the intervention was reported • The authors declared potential conflicts of interest and sources of funding for the study	• It was unclear whether the participants were representative of the source population • The adverse effect outcomes were patient self-reported and could introduce detection bias •

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

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Findings of Included Randomized Controlled Trials

Main Study Findings	Authors' Conclusion
Jiang, 2018[7]	
Lyophilized vs. Frozen FMTs **Patient-reported adverse events during the first seven days after FMT, n (%):** Diarrhea: 12 (39) vs. 10 (29); *P* = 0.28 Nausea: 13 (42) vs. 7 (21); *P* = 0.12 Vomiting: 2 (7) vs. 2 (6); *P* = 1.00 Abdominal cramps/pain: 17 (55) vs. 24 (71); *P* = 0.21 Flatulence: 8 (26) vs. 11 (32); *P* = 0.60 Fecal Urgency: 14 (45) 10 (29); *P* = 0.21 Constipation: 1 (3) vs. 3 (8); *P* = 0.62 Other AEs: 10 (32) vs. 8 (24); *P* = 0.58 **Patient-reported adverse experiences for 3 Months-Time Period after FMT, n (%):** Diarrhea: 14 (45) vs. 16 (47); *P* = 1.00 Nausea: 15 (48) vs. 12 (35); *P* = 0.32 Vomiting: 7 (22) vs. 2 (6); *P* = 0.07 Abdominal cramps/pain: 21 (68) vs. 26 (76); *P* = 0.78 Flatulence: 13 (42) vs. 15 (44); *P* = 1.00 Fecal Urgency: 22 (71) vs. 21 (62); *P* = 0.60 Constipation: 4 (13) vs. 36 (18); *P* = 0.74 Other AEs: 15 (44) vs. 18 (53); *P* = 0.81 **Cured, n (%):** Total Lyophilized groups combined: 26 (84) Lyophilized 100 g FMT product once: 5 (63) Lyophilized 100 g FMT product for 2 consecutive days (total 200 g): 21 (91) Frozen 100 g FMT product once: 30 (88)	"While the frequency of nausea was higher in subjects receiving orally administered capsules, this rate was not significantly different than that seen in the group receiving rectal instillation and rates of vomiting were low and similar in the two groups. Overall the microbiota products were safely administered with no apparent difference between orally administered lyophilized FMT versus frozen product given by enema." (p. 9) "We found that lyophilized orally administered FMT product in enteric-coated capsules was as effective in producing CDI cure as frozen product given by enema when we administered the oral product in twice the dose and given on two consecutive days." (p. 9)
Jiang, 2017[6]	
Lost to follow up = 1/73 **Clinical resolution of CDI for 2 months after FMT: N (%)** Fresh FMT: 25 (100) Frozen FMT: 20 (83) Lyophilized FMT: 18 (78) ***P*-value:** Fresh vs. frozen: 0.233 Fresh vs. lyophilized: 0.022 Frozen vs. lyophilized: 0.255	"The cure rate was highest for the group randomised to receive fresh product, 25/25 (100%) and lowest for the group of subjects randomised to receive lyophilised product, 18/23 (78%), with intermediate response seen in the group receiving frozen product, 20/24 (83%) (P = 0.041)." (p. 902) "[D]ifferences between groups receiving fresh vs. frozen did not reach significance" (p. 902) "Rates of cure were slightly less with the lyophilised product but well within the range of cures seen in the literature with fresh product." (p. 906)

CDI = Clostridium difficile infection; FMT = fecal microbiota transplantation.

Appendix 5: Additional References of Potential Interest

Evidence-based Guidelines – No Recommendations Regarding Lyophilized Fecal Microbiota Transplant

Mullish BH, Nabil Quraishi M, 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. https://gut.bmj.com/content/gutjnl/67/11/1920.full.pdf Accessed 2019 Aug 14.