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Does Fecal Microbiota Transplantation improve symptoms in adults with Irritable Bowel Syndrome?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not fecal microbiota transplantation improves symptoms in adults with Irritable Bowel Syndrome.

STUDY DESIGN: A systematic review of two randomized controlled trials and one case series published in English and after 2009.

DATA SOURCES: All three studies were collected from peer-reviewed journals. Databases searched included Cochrane Collaboration and PubMed.

OUTCOMES MEASURED: Outcomes measured included Bristol Stool Form Scale and IBS Severity Scoring System (IBS-SSS).

RESULTS: Halkjær et al. revealed that the placebo FMT had a significant effect ($p=0.008$) at reducing IBS symptom severity in comparison to the FMT three months after transplantation. Johnsen et al. found that, at three months post-FMT, the treatment group showed a statistically significant effect ($p=0.049$) at reducing symptom severity. Mizuno et al. showed that six out of the 10 patients achieved a clinical improvement in stool form four weeks following FMT.

CONCLUSIONS: Out of the three articles reviewed, two found that FMT treatment group improved symptoms and one found that the control group given the placebo had a greater effect in improving symptoms.

KEYWORDS: Fecal Microbiota Transplantation, Irritable Bowel Syndrome

INTRODUCTION

Irritable Bowel Syndrome (IBS) is an idiopathic chronic medical condition that causes changes in bowel habits and abdominal pain. It is the most commonly diagnosed gastrointestinal condition in the United States with approximately 10-15% of the population living with the condition.[1] Many suffer for years before seeking out medical care as the symptoms can be vague and often are confused with other GI conditions. A specific number of healthcare visits due to IBS could not be found, however, only 1 in 4 with IBS seek out medical care for their symptoms.[2] Even still, IBS consumes a significant amount of health care resources and dollars. Of the patients who are referred to gastroenterologist, IBS comprises 40% of the referrals.[1] The disease also carries a heavy cost burden for patients; this is evident as the direct and indirect costs combined total approximately $1.6B each year.[3]

IBS is defined as a "chronic functional disorder of the gastrointestinal (GI) tract characterized by abdominal pain and altered bowel habits in the absence of an organic disease."[4] Since it is a functional GI disorder, it is a part of a spectrum of disorders related to how the brain and gut interact and function together.[5] The exact pathophysiology is not completely understood, but potentially includes abnormal motility, visceral hypersensitivity, intestinal inflammation, and psychosocial abnormalities.[6] There are three subtypes of IBS: constipation-predominant (IBS-C), diarrhea-predominant (IBS-D), and mixed (IBS-M), which are determined based on the symptomatic presentation. There is no specific diagnostic test for IBS; instead, clinicians use a combination of subjective scales to establish this clinical diagnosis, which happens to be a diagnosis of exclusion. These scales include the ROME Criteria and Bristol Stool Form Scale. The ROME III Diagnostic Criteria requires "recurrent abdominal pain or discomfort… for at least three days/month in the last three months, associated with two or more of the following:

improvement with defecation, onset associated with a change in the frequency of stool, onset associated with a change in the form (appearance) of stool."[7] The Bristol Stool Scale specifically focuses on the visual appearance of stool which is then rated on a scale from 1-7 from constipation to diarrhea, respectively.

Because there is no single underlying etiology to "cure", traditional treatment methods focus on alleviating symptoms. For abdominal pain, SSRIs and probiotics are used. For bloating, tricyclic antidepressants, dietary modifications (such as a low FODMAPs diet), and the antibiotic rifaximin are options. For constipation, lubiprostone, laxatives, linaclotide, and polyethylene glycol are used. For diarrhea, loperamide, eluxadoline, and cholestyramine are used. Because IBS is thought to have a psychological component, behavioral therapy such as CBT are often recommended to reduce anxiety and depression. Since many patients suffer from various symptoms concurrently requiring polypharmacy, it is apparent how burdensome the use of multiple medications can be without any promise of a cure.

Health care providers, such as physicians and physician assistants, care for IBS patients in practically every specialty. It is imperative that they can not only provide symptom relief using traditional therapies, but also research up-and-coming treatment options which may provide more definitive relief and reduce pill burden.

Fecal microbiota transplantation (FMT) is the process of introducing stool from a healthy donor into the GI tract of a recipient for therapeutic purposes. The presumed effect of FMT is that the healthy gut microbiota will reestablish a homeostatic balance in the patient with impaired gut function, thus relieving symptoms. FMT has shown to be effective for *C. difficile* infections, in which a systematic review showed resolution of 92% of cases which had previously failed traditional treatment options.[8] Correction of altered gut microbiota in those ground-breaking

cases have led researchers to view FMT as a potential treatment option for IBS, where altered microbiota appears to be hallmark of the disease. Some of the treatment options currently available, such as probiotics, antibiotics, and low FODMAP diets, already aim to manipulate the gut microbiota with hopes to reestablish homeostatic balance.[9] Healthy stool has more than 100 types of microorganisms[10], and the presence of this wide range of microbiota supports the theory that FMT may reestablish proper bacterial balance in patients with IBS.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not fecal microbiota transplantation improve symptoms in adults with Irritable Bowel Syndrome.

METHODS

Articles were selected for this review by searching for the keywords "Fecal Microbiota Transplantation" and "Irritable Bowel Syndrome" in the Cochrane Collaboration and PubMed. The articles needed to evaluate Patient-Oriented Evidence that Matters (POEMs). Inclusion criteria included studies published after 2009, primary research designs, studies on humans, and studies in the English language. Exclusion criteria included studies published before 2009, studies not on humans, systematic reviews, and meta-analyses. Table 1 expands upon further inclusion and exclusion criteria for each specific study. The statistics analyzed and reported in this review include p-values, CER, EER, RBI, ABI, and NNT, with the exception of Mizuno et al.[9] which solely reports "treatment success."

Two randomized controlled trials and one case series were utilized in this review. The populations examined were adults over 18 years old diagnosed with IBS by the ROME III Criteria. The intervention in all three studies was FMT. For the control, Mizuno et al.[9] used

patient baseline, Halkjær et al.[10] used placebo capsules, and Johnsen et al.[11] used placebo colonoscopies. The outcomes measured were improvement in stool form using the Bristol Stool Form Scale and improvement in symptom severity using the IBS Severity Scoring System.

Table 1. Demographics and Characteristics

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Mizuno (2017)[9]	Case Series	10	25-57	≥20yo, IBS dx based on ROME III criteria, persistent sx despite medical therapy for at least 1yr	Pregnant, unable to give consent, severe liver/kidney dysfunction, psychiatric condition preventing endoscopy	None listed	Fecal microbiota transplantation via colonoscopy
Halkjær (2018)[10]	RCT	51	No range given Mean = 36.39	18-60yo, IBS dx based on ROME III criteria, moderate-severe disease (IBS-SSS ≥175), able to read/speak Danish, normal colonoscopy	Other GI disease, HIV/HBV/HCV, enteropathogens, GI surgery, psychiatric disorder, faecal calprotectin ≥50mg/kg, ETOH/drug abuse, meds other than routine, abnormal CBC/BMP/colonscopy, pregnant/ breastfeeding, abx/probiotic use in last 8wks	1	Fecal microbiota transplantation via 25 capsules q.a.m. PO Or Placebo capsule
Johnsen (2018)[11]	RCT	90	33-57	18-75yo, IBS dx based on ROME III criteria, moderate-severe disease (IBS-SSS ≥175), IBS-D, IBS-M	IBS-C, IBS-M with constipation dominating sx, severe cardiac/pulmonary/kidney disease, immunodeficiency, non-related abdominal pain, likely non-compliant	7	Fecal microbiota transplantation via colonoscopy Or Placebo colonoscopy

OUTCOMES MEASURED

The outcomes focused on for this selective review were improvement in stool form and improvement in symptom severity. The Bristol Stool Form Scale is a diagnostic tool used to

describe patient stool consistency in order to examine underlying gut function. The score ranges from Type 1, indicating constipation, to Type 7, indicating diarrhea. Types 3 and 4 are considered "normal". The IBS Severity Scoring System (IBS-SSS) transforms the symptoms of pain, distension, bowel dysfunction, and quality of life into objective data. The maximum score is 500, and a score ≥175 indicates moderate-to-severe disease. These two measurements allow for clinical assessment of disease severity.

RESULTS

Mizuno et al.[9] conducted a case series study examining the efficacy of FMT on 10 participants aged 25-57 years old who were diagnosed with IBS based on the ROME III criteria. The participants had persistent IBS symptoms refractory to traditional medical therapy, and all subtypes of IBS were included. The intervention was FMT using a fecal slurry created from relative donor's stool (either spouse, parent, or sibling), which was then administered to the participants via colonoscopy. All participants were included in the treatment group and received this treatment. There was no control or placebo, instead, the comparison group was patient baseline before receiving treatment. Participants were then reevaluated for improvement in stool form. Improvement to types 3-4 on the Bristol Stool Form Scale at four weeks post-FMT was considered a clinical response. No participants were lost to attrition. No adverse side effects of FMT were noted. The researchers found that FMT improved stool form in 6 out of the 10 participants, making the Treatment Success = 60%. No measure of precision or additional statistical analysis was provided in this study.[9]

Halkjær et al.[10] conducted a double-blinded, randomized controlled study of 52 participants aged 18-60 years old who were diagnosed with IBS based on ROME III criteria. All subtypes of IBS were included. The participants were randomly split 1:1 into either the control or

treatment group. The FMT was administered by consuming 25 capsules by mouth daily for 12 days. The treatment group received capsules which were created using the stool of four donors that were combined into one sample. The placebo group received identical appearing capsules filled with saline, glycerol, and food coloring. Participants were evaluated for improvement in IBS-SSS at three months, with a 50-point reduction in IBS-SSS considered a clinical response. One participant dropped out of the study, however, no reasoning for attrition was provided. The only side effect of FMT that was more significant in the treatment group versus the placebo group was diarrhea. Eight of the 22 patients who received the FMT treatment capsules showed a reduction in IBS symptoms at three months post-FMT; 19 of the 24 patients who received the placebo capsules showed a reduction (p=0.008). The NNT was -2 (Table 2). Therefore, the placebo group had a significantly greater reduction in IBS symptom severity in comparison to the treatment group (p=0.008).[10]

Table 2. Treatment Effect of FMT Using IBS-SSS at Inclusion and 3-month Visit

	CER	**EER**	**RBI**	**ABI**	**NNT**
Halkjær et al.[10]	0.792	0.364	-0.54	-0.428	-2

CER: Control Event Rate EER: Experimental Event Rate RBI: Relative Benefit Increase ABI: Absolute Benefit Increase NNT: Numbers Needed to Treat

Johnsen et al.[11] conducted a double-blinded, randomized controlled trial of 90 participants aged 33-56 years old who were diagnosed with IBS based on the ROME III criteria. Participants were split into the treatment group versus placebo group using a 2:1 ratio. The treatment group received FMT via colonoscopy delivery of the donor stool of two donors. The control group received a placebo FMT via colonoscopy delivery of the participant's own stool. Participants were evaluated for symptom improvement at three and 12 months post-FMT, where a 75-point reduction in the IBS-SSS was considered a clinical response. Four participants were excluded from the trial because they developed colitis post-FMT which could have

inappropriately impacted the results, and three participants did not show up for the FMT with no additional reasoning provided. This left 83 participants for analysis. One participant experienced an adverse side effect of FMT (vertigo and nausea). 36 of the 55 participants who received the FMT treatment showed reduction in IBS symptoms at three months post-FMT, whereas only 12 of the 28 patients who received the placebo capsules showed reduction (p=0.049). The NNT was 5 (Table 3). Overall, this showed that the active FMT treatment had a precise and statistically significant effect in improving symptoms in patients with IBS.

Table 3. Treatment Effect of FMT Using IBS-SSS at Inclusion and 3-month Visit

	CER	**EER**	**RBI**	**ABI**	**NNT**
Johnsen et al.[11]	0.43	0.65	0.51	0.22	5

CER: Control Event Rate EER: Experimental Event Rate RBI: Relative Benefit Increase ABI: Absolute Benefit Increase NNT: Numbers Needed to Treat

DISCUSSION

Altered gut microbiota is a speculated cause of IBS, but only recently has FMT been speculated as a potential cure for IBS. This systematic review analyzed how FMT might alleviate symptom severity in individuals suffering from IBS. Two of the studies, Mizuno et al.[9] and Johnsen et al.[11], found FMT to be efficacious in reducing IBS symptoms, and one of the studies, Halkjær et al.[10], found the placebo to be more effective than the FMT treatment.

Mizuno et al.[9] results showed that FMT was successful in reducing symptoms as six out of the 10 patients achieved a clinical response in stool form four weeks post-FMT. However, the clinical significance of the study is limited as it does not have a control group to compare treatment effectiveness. The duration of the study was shorter than the other two studies as the main end point was four weeks post-FMT. Also, the study was not blinded so all participants knew they were receiving active treatment which may have led to a false perception of symptom

improvement. Additionally, the generalizability is limited due to the small population size of only 10 participants, and the study was conducted in Japan. Mizuno et al.[9] was the only study in this analysis to use donor stool from relatives specific to the individual participants, instead of a combination of donor stool unrelated to the participant. This allows for more variables as the individuals are technically receiving different stool samples. Overall, given the promising results of this study, it would be beneficial for the authors of this study or additional researchers to proceed with similar treatment parameters but in a RCT design instead of a case series, which would strengthen the results by improving the aforementioned limitations.

Halkjær et al.[10] found that the placebo FMT significantly ($p=0.008$) reduced symptoms versus active FMT. Both this study and Johnsen et al.[11] followed participants for the same duration, as the primary end points were both three months. Generalizability is limited as the study was conducted in Denmark. Also, of note, this study did not screen stool for pathogens prior to FMT, whereas the other two studies did. This may have reduced efficacy and even caused adverse reactions to both the treatment and control groups. Another factor that may have affected the study is the method of administration, as this study used capsules taken by mouth while the other two used colonoscopies. It would be crucial to determine if this impacted the perceived treatment effect for the participants, so that moving forward the most efficacious delivery system can be utilized in future studies of FMT.

Johnsen et al.[11] found that FMT was effective at reducing symptoms versus the placebo treatment ($p=0.049$). However, total retention time of the FMT inside the bowel was not recorded, which potentially could influence how successful the FMT uptake was. Another variable was fresh versus frozen FMT. The researchers used a combination of storage techniques including directly transferring fresh stool as well as preserving frozen stool before transfer at a

later date. They did not record these assignments so did not conduct analysis about whether one method was more effective than the other. Also, generalizability was limited because only IBS subtypes IBS-M and IBS-D were included, therefore, the effect on IBS-C cannot be inferred.

General research regarding the safety of FMT has been gathered during studies examining the efficacy of FMT for *C. difficile* infections. However, the risks and safety of the procedure are similarly applicable as the mechanism of transplantation is the same. The most common severe risk associated with FMT is transmission of infectious diseases from the donor stool into the digestive tract of the recipient; to reduce this risk, the FDA recommends proper screening and testing of donor stool prior to transplantation.[12] As previously mentioned, Mizuno et al.[9] and Johnsen et al.[11] both screened for pathogens, whereas Halkjær et al.[10] did not. Nonetheless, none of the studies in this review had any reported side effects directly attributed to an infectious etiology as a result of the FMT.

Additionally, FMT is considered "experimental" for IBS and is not covered by most insurances, thus making it a challenge to currently study and implement FMT as a treatment option. However, FMT is now considered an indication for *C. difficile* infections after numerous studies have analyzed its efficacy and proved it a successful treatment.[13,14] Researchers are hopeful that as more studies analyze the promising effects of FMT for IBS, insurances will begin to cover it. This will make it accessible for all patients instead of solely those who can afford it, and promote the use by health care providers who will be sufficiently reimbursed for the procedure. Therefore, it is pertinent that physicians and advanced practice providers such as physician assistants stay informed on further research regarding FMT as a possible treatment option for IBS and other GI disorders.

CONCLUSION

Of the three studies analyzed, one RCT and one case study found that FMT was successful in reducing symptoms, whereas the second RCT found the placebo to reduce symptoms more than FMT. Therefore, the results of this systematic review are inconclusive as the evidence is conflicting. However, given the promising results of two of the studies, FMT appears to have potential to be an effective treatment for IBS and warrants further exploration. Future studies should aim to analyze the significance of the source of donor stool, either single-donor or multi-donor, and mechanism of transplantation, either oral capsules or colonoscopy. Researchers should closely monitor stool retention time post-transplantation, subtype of IBS the participants are diagnosed with, screening of stool to eliminate risk of infection transmission, and whether fresh or frozen stool is used. While the pathophysiology of IBS is still unknown, studies examining FMT as a treatment option have the ability to provide symptomatic relief while simultaneously learning about the potential etiology.

REFERENCE LIST

1. Wald A. Clinical manifestations and diagnosis of irritable bowel syndrome in adults. UpToDate website. Updated August 29, 2019. Accessed October 10, 2020. https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-irritable-bowel-syndrome-in-adults.
2. Irritable bowel syndrome. American College of Gastroenterology Website. Accessed October 11, 2020. https://gi.org/topics/irritable-bowel-syndrome/#tabs2.
3. Sandler RS, et al. The burden of selected digestive diseases in the United States. *Gastroenterology*. 2002;122:1500-1511. https://doi.org/10.1053/gast.2002.32978
4. Wald A. Treatment of irritable bowel syndrome in adults. UpToDate Website. Updated July 15, 2020. Accessed October 10, 2020. https://www.uptodate.com/contents/treatment-of-irritable-bowel-syndrome-in-adults.
5. Definition & facts for irritable bowel syndrome. National Institute of Diabetes and Digestive and Kidney Disease Website. Accessed October 11, 2020. https://www.niddk.nih.gov/health-information/digestive-diseases/irritable-bowel-syndrome/definition-facts.
6. McQuaid KR. Irritable bowel syndrome. In Papadakis MA, McPhee SJ, ed. *Current Medical Diagnosis & Treatment.* 2020: 659-663.
7. Lacy BE, Patel NK. Rome criteria and a diagnostic approach to irritable bowel syndrome. *J Clin Med*. 2017;6(11):99. doi:10.3390/jcm6110099.
8. Kim MO, Gluck M. Fecal microbiota transplantation: an update on clinical practice. *Clin Endosc*. 2019;52(2):137-143. doi: 10.5946/ce.2019.009.
9. Mizuno S, Masaoka T, Naganuma M, et al. Bifidobacterium-rich fecal donor may be a positive predictor for successful fecal microbiota transplantation in patients with irritable bowel syndrome. *Digestion*. 2017;96(1):29-38. doi: 10.1159/000471919.
10. Halkjær SI, Christensen AH, Lo BZS, et al. Faecal microbiota transplantation alters gut microbiota in patients with irritable bowel syndrome: Results from a randomised, double-blind placebo-controlled study. *Gut*. 2018;67(12):2107-2115. doi: 10.1136/gutjnl-2018-316434.
11. Johnsen PH, Hilpüsch F, Cavanagh JP, et al. Faecal microbiota transplantation versus placebo for moderate-to-severe irritable bowel syndrome: A double-blind, randomised, placebo-controlled, parallel-group, single-centre trial. *Lancet Gastroenterol Hepatol*. 2018;3(1):17-24. doi: 10.1016/S2468-1253(17)30338-2.
12. Borody TJ, Ramrakha S. Fecal microbiota transplantation for treatment of Clostridioides (formerly Clostridium) difficile infection. UpToDate website. Updated November 24, 2020. Accessed December 13, 2020. https://www.uptodate.com/contents/fecal-microbiota-transplantation-for-treatment-of-clostridioides-formerly-clostridium-difficile-infection.
13. Policies and procedure manual. Geisinger Health Plan website. Updated April 2020. Accessed December 13, 2020. https://www.geisinger.org/-/media/OneGeisinger/Files/Policy-PDFs/MP/251-300/MP290-Fecal-Microbiota-Transplantation.pdf?la=en.
14. Fecal bacteriotherapy. Aetna website. Updated December 11, 2020. Accessed December 13, 2020. http://www.aetna.com/cpb/medical/data/800_899/0844.html.