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REVIEW

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Current status of fecal microbiota transplantation for irritable bowel syndrome

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Abstract

Background: Irritable bowel syndrome (IBS) is a common gastrointestinal functional disorder. Although IBS is a benign condition, it reduces the quality of life considerably. While there is currently no effective treatment for this disorder, fecal microbiota transplantation (FMT) seems to be promising.

Purpose: The aim of this review was to analysis possible factors affecting the success or failure of the randomized controlled trials (RCTs) of FMT for IBS and highlighting the gaps in our knowledge that need to be filled and of sketching a possible model for successful FMT in IBS patients.

Methods: A systematic search was conducted of literature published in English from January 2015 to December 2020 using the keywords: fecal microbiota transplantation, randomized trials, and IBS.

Key Results: Seven randomized controlled trials (RCTs) on the efficacy of FMT for IBS were found in the literature. Four of the seven RCTs found various positive effects, while the other three did not find any effect.

Conclusions and Inferences: The efficacy of FMT for IBS appears to be donor-dependent. The effective (super) donor would need to have a favorable microbiota signature, and 11 clinical criteria that are known to be associated with a favorable microbiota have been suggested for selecting FMT donors for IBS. Comparing the microbiota of the effective donors with those of healthy subjects would reveal the favorable microbiota signature required for a super-donor. However, the studies reviewed were not designed to compare efficacy of different donor types. The dose of the fecal transplant is also an important factor influencing the outcome of FMT for IBS. However, further studies designed to test the effect of fecal transplant dose are needed to answer this question. Administering the fecal transplant to either the small or large intestine seems to be effective, but the optimal route of administration remains to be determined. Moreover, whether single or repeated FMT is more effective is also still unclear. A 1-year follow-up of IBS patients who received FMT showed that adverse events of abdominal pain, diarrhea, and constipation were both mild and self-limiting.

KEYWORDS
fecal transplant, microbiota, short-chain fatty acids, super-donor, therapy

Key Points

- FMT is a promising treatment for IBS. The outcome of FMT is a donor-dependent and a careful selection is needed for a successful FMT.
- The dose of the fecal transplant is important to the efficacy of FMT. Doses lower than 30 g did not show any effect seems to be effective.
- The optimal route of administering the fecal transplant to either the small or large intestine is still unclear. Moreover, whether single or repeated FMT is more effective remains to be determined.
- The adverse events of FMT were both mild and self-limiting in form of abdominal pain, diarrhea, and constipation.

1 | INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic disorder affecting 11.2% of the world's population, with the highest prevalence in South America and the lowest prevalence in South Asia.[1,2] IBS is a benign disorder that is not associated with increased mortality, and it does not develop into a serious disease.[3] However, IBS reduces the quality of life of the affected patients considerably.[1] There is no effective treatment for IBS, with the available treatments being directed at symptom relief.[4]

The etiology of IBS is unknown, but the intestinal microbiota seems to play a pivotal role in its pathophysiology.[1] The intestinal bacterial profile in IBS patients differs from that in healthy subjects.[5-12] IBS patients have also a lower diversity of gut bacteria (dysbiosis) than healthy subjects.[5-10] Fecal microbiota transplantation (FMT) has been applied to IBS patients in seven randomized controlled trials (RCTs),[13-19] four of which showed a positive effect [13,15,18,19] while the other three showed no effect.[14,16,17] At first sight, it appears to be challenging to compare these RCTs due to variations in the criteria used to select the donors and patients, in the dose of the fecal transplant used, and in the FMT protocols. Furthermore, different measurements were used to assess efficacy of FMT in these RCTs. Thus, in the RCT of El-Salhy et al, the efficacy of FMT was measured by both IBS-symptom severity system (BS-SSS) and the rigorous requirements of the European Medicines Agency and (EMA) and the Food and Drug Administration (FDA) using a composite responder endpoint.[20,21] While reduction in IBS-SSS score was used 5 RCTs to measure the efficacy of FMT,[13,14,16-18] relief of general IBS symptoms and abdominal bloating was used in one RCT.[19] Recommendations for consideration in future FMT studies in IBS concerning several topics of investigation have been suggested for improving the outcome of FMT in IBS.[22,23]

Benech and Sokol considered that the application of FMT in gastrointestinal disorders represents the start of a new era.[24] All RCTs on FMT for IBS (regardless of their outcomes) provide crucial information that can be used to improve the efficacy of FMT in IBS patients. Hence, the present review includes an analysis of possible factors affecting the success or failure of these RCTs, with the aim of highlighting the gaps in our knowledge that need to be filled and of sketching a possible model for successful FMT in IBS patients.

2 | DONOR SELECTION

The response to FMT in inflammatory bowel disease (IBD) appears to be donor-dependent, with variations in the study outcomes explainable by differences between the donors.[5,25] This situation has led to the term super-donor being coined to describe a donor that induces desirable effects in recipients.[5] Since there are no clear criteria for the super-donor, predicting the clinical efficacy of the donor before FMT is impossible. Attempts to overcome this obstacle have led to suggestions that donors' feces should be pooled in order to increase the likelihood of patients receiving effective feces.[26] However, applying this approach did not increase the response rate to FMT, which is probably because the feces of the super-donor would be diluted and consequently the recipients would not receive a sufficient dose from the super-donor.[27]

The donors in all of the RCTs done on IBS patients were healthy and had a normal body mass index (BMI).[13-19] The super-donor for the IBS patients was selected based either on clinical efficacy in a pilot trial or on clinical criteria and the fecal microbiota profile.[15,17,19,28] The RCT of Holvoet and colleagues used two donors who were effective in a pilot trial.[19,28] Another RCT selected two donors who had the highest fecal abundance of the butyryl-CoA CoA transferase gene.[17] El-Salhy et al used both clinical criteria and the fecal bacterial profile when choosing a single donor.[15] The basis for choosing the clinical criteria and identifying the bacterial signature of their donor is explained below.

In the absence of clear criteria for a super-donor, El-Salhy and colleagues considered the factors that are known to affect the gut microbiota negatively or positively, and attempted to select a donor having the positive factors and lacking the negative factors. The factors that have negative effects on the gut microbiota and reduce the bacterial diversity include aging (>50 years), smoking/smoking cessation, being born by cesarean section and/or being formula-fed, frequent treatment with antibiotics, and regular intake of non-antibiotic drugs.[6,29-37] On the other hand, regular exercise and consuming a sport-specific diet are associated with a favorable gut microbiota.[38-40] Furthermore, since the intestinal microbiota is affected by the genetic composition, the super-donor should not be a first-degree relative of any recipient, since genetic similarity may be associated with similarities in the fecal microbiota.[41,42] Applying these criteria resulted in the chosen donor

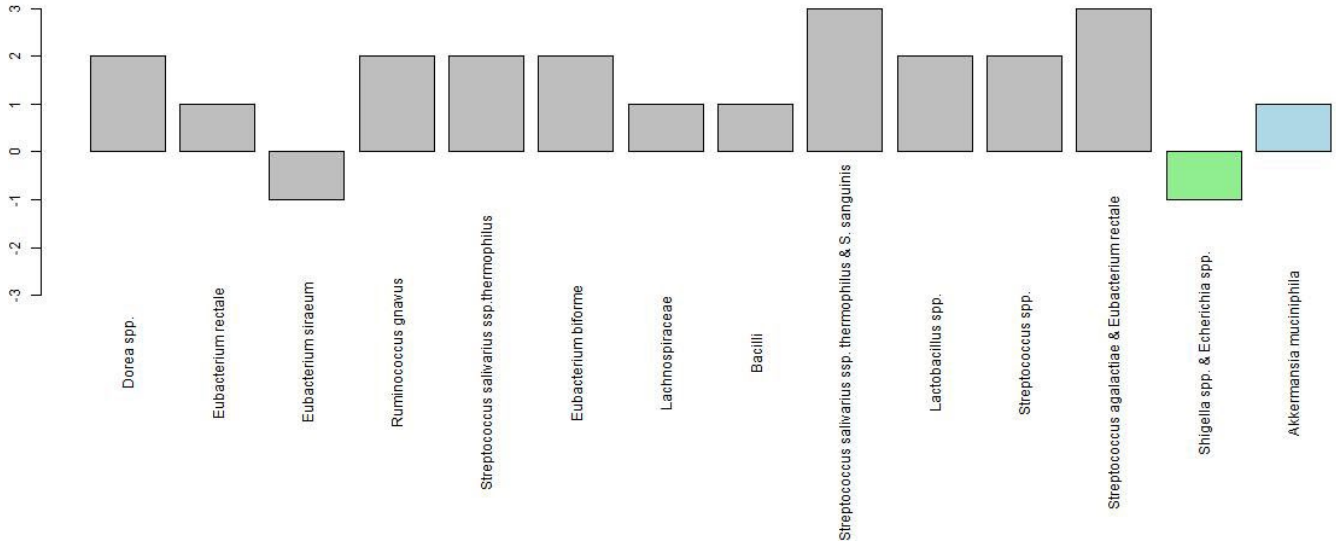

FIGURE 1 The super-donor bacterial profile deviated from the expected normal abundance in 14 of the 39 bacteria markers. The deviating bacteria belong to the typical commensal bacteria species that do not contribute to dysbiosis. Twelve of these bacteria belong to the phylum Firmicutes (gray), one to the phylum Proteobacteria (light green), and one to the phylum Verrucomicrobia (light blue). Reproduced from El-Salhy et al[15] with permission from the authors and publisher.

being healthy with a normal BMI, a young male (37 years old), born via a vaginal delivery, breastfed, and a non-smoker, not taking any medication, having been treated only a few times with antibiotics, and regularly performing physical exercise. The donor's diet was within the normal range of those consumed by 35 healthy subjects as measured by the MoBa Food Frequency Questionnaire, but he consumed also a sport-specific diet that was richer in protein, fiber, minerals, and vitamins than average.[43] The donor was not related to any of the recipients.[15] Moreover, an examination of the fecal microbiota of this donor showed that he was normobiotic (ie, having a high microbial diversity), but deviated from the normal abundance of 165 healthy subjects in 14 of 39 tested bacteria markers. Twelve of the bacteria were in the phylum Firmicutes, with one each in the phyla Proteobacteria and Verrucomicrobia (Figure 1).[15] The bacterial signature (deviation) included an abundance of *Streptococcus*, *Dorea*, *Lactobacillus*, and *Ruminococcaceae* spp. These four genera of bacteria have been reported to constitute favorable bacteria for a donor.[5,28,44,45]

Holvoet et al observed that the fecal bacterial composition of one of the two donors they used was stable over time, and that donor was more effective than the second donor whose fecal bacterial composition varied over time.[19] Based on these observations, those authors concluded that next to a high bacterial diversity, stability of the bacterial composition over time is also an important factor when selecting an effective donor.[19] It is noteworthy that the fecal bacterial composition of the super-donor used in the RCT of El-Salhy et al was stable over the 18-month period during which he donated his feces (Figure 2).[15]

Pooling the feces from different donors resulted in no response or only a transient improvement.[13,14] Thus, pooling donor feces in IBS (like in IBD) is not recommended.

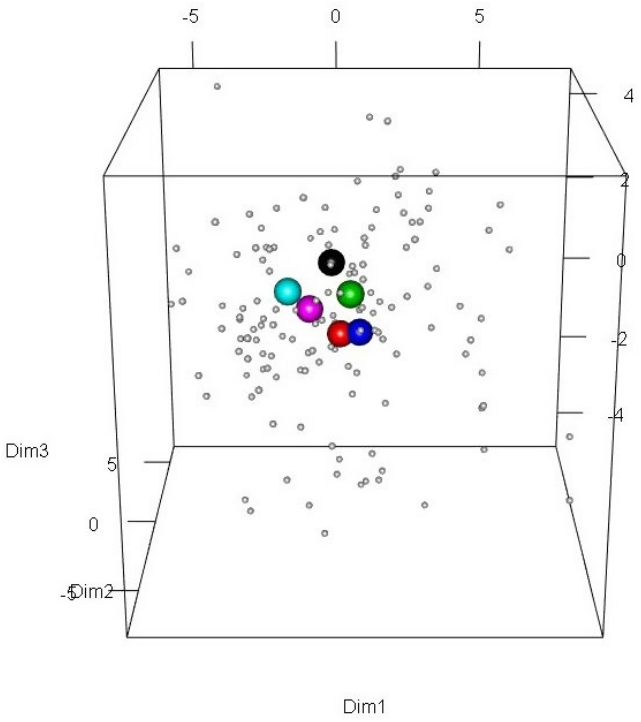

FIGURE 2 Scaled PCA plot of fecal samples from the super-donor and patients before transplantation. The patient samples are indicated by small gray circles. The super-donor samples are indicated by the larger circles of different colors that indicate the sampling times: black, 3 months; red, 6 months; green, 9 months; blue, 12 months; light blue, 15 months; and pink, 18 months. All of the super-donor samples are grouped closely together and remain in very similar positions over time. Reproduced from El-Salhy et al.[15] with permission from the authors and publisher.

The donor in the RCT of Lahtinen et al was a healthy young adult male with a normal BMI who was born via a vaginal delivery, had not taken antibiotics during the previous year, and was not using any permanent medications.[18] Thus, 6 of the 11 clinical criteria for an effective donor described by El-Salhy et al were fulfilled[15]; the remaining criteria are breastfeeding, not smoking, regularly performing exercise, consuming a sport-specific diet rich in proteins, fibers, minerals and vitamins, and not being genetic related to the recipients. While the RCT of Lahtinen and colleagues resulted in a transient improvement of symptoms after 12 weeks, that of El-Salhy and colleagues—using the same transplant dose (30 g)—resulted in a lasting effect in most patients at 1 year after FMT.[15,18,46] It is difficult to speculate as to which of the five factors was responsible for the difference in the outcomes between these two RCTs. However, the donor's diet in the RCT of El-Salhy et al might have been a major factor, since dietary modifications and nutritional supplements influence the intestinal microbiota.[47]

The selection of donors in the two RCTs that produced the most positive effects of FMT in IBS patients was based either on clinical efficacy in a pilot trial or on the donor's specific characteristics associated with a favorable microbiota signature.[15,19] The later approach is to be preferred, since accumulating data on the microbiota signature of the effective (super) donors would make it possible to standardize FMT and construct feces banks in order to develop a tailored microbial consortia.[48] This would also allow the identification of the beneficial microbiota of the donors and their probable reconstitution in the laboratory.[48] To identify the presence of a favorable signature in a donor, their bacterial profile should be compared with that of healthy subjects.

Donor-recipient compatibility should also be considered when a donor is selected for FMT, in terms of the gut microbiota, immune profile, and genetic composition, since these factors may affect the clinical outcome.[24] It is worthy of note that in the successful RCTs of FMT for IBS male donors were used,[15,18,19] whether the sex of the donor plays a role in the outcome of FMT for IBS patients remains to be determined.

3 | PATIENT SELECTION

The patients included in the FMT RCTs in IBS fulfilled the Rome III criteria for the diagnosis of IBS, with the exception of those in the RCT of El-Salhy et al fulfilling the Rome IV criteria.[13-19] Patients with IBS-D and IBS-M were investigated in four of the RCTs,[13,16,18,19] and those with IBS-D, IBS-C, and IBS-M were included in the other three.[14,15,17] Furthermore, different subsets of IBS patients were included in three RCTs.[15,17,19] The patients included in the RCT of El-Salhy et al had undergone a 12-hour classroom course of "living with IBS" lasting 2 days, which resulted in slight symptom improvement. They also had moderate-to-severe IBS symptoms despite adhering to a diet consistent with the NICE (National Institute for Health and Care Excellence)-modified diet for at least 3 months.[15] Only IBS patients with low amounts of fecal butyrate-producing bacteria were included in the RCT of Holster et al.[17] Refractory IBS patients with severe bloating who had failed to respond to at least three conventional therapies for IBS were included in the study of Holvoet et al.[19] Such restriction to subsets of IBS patients indicates the need for caution when attempting to draw general conclusions from these RCTs that apply to the entire IBS population.

4 | DOSAGE, ROUTE OF ADMINISTRATION, AND FORM OF THE FECAL TRANSPLANT

Increasing the dose of the fecal transplant from 30 g to 60 g increased the response to FMT in IBS patients, suggesting the presence of a dose-dependent response similar to that described previously in *Clostridium difficile* infection (CDI), where using >50 g of feces resulted in a higher efficacy rate (Figure 3).[15,49] Moreover, 70% of the patients that did not respond to a 30-g fecal transplant responded when they received a 60-g fecal transplant (Figure 4).[50] Five of the FMT RCTs for IBS used a dose of at least 30 g.[13-15,17,18] For two studies, the dose was either lower than 30 g or not specified.[16,19] The efficacy of single versus repeated transplantation requires further investigation.

Administering the fecal transplant to either the small or large intestine seems to be effective.[13,15,17-19] However, the placebo effect was higher in patients who received the fecal transplant into the large intestine via the working channel of a colonoscope (43%–44%) than in those received the fecal transplant into the small intestine via the working channel of a gastroscope or a nasojejunal probe (23.6%–26%).[13,15,17-19] The higher placebo response in those studies that used colonoscopy to administer the fecal transplant could be explained by the procedure itself, since colonoscopy requires bowel preparation and is often painful and takes more time than when using a gastroscope or nasojejunal probe, and the bowel cleansing required for colonoscopy has a positive effect on IBS symptoms.[51] Whether there is a difference in the efficacy of FMT administered to the small or large intestine remains to be determined in future studies.

Administering a fecal transplant via capsules was not effective in IBS.[14,16] This is unfortunate given the ease of administration using this method and it being more acceptable to the patients. The lack of response in the RCTs that used capsules to administer donor fecal transplants could be due to other factors, such as the selected donors, a low transplant dose, and/or pooling of the donors.[14,16] The capsule administration route for fecal transplants has been successful in CDI. [46] Further studies exploring the effectiveness of administrating fecal transplant in capsule form to IBS patients are needed.

Frozen feces samples of donors appear to be effective in FMT for IBS, with storage at either −80°C or −20°C being equally efficacious.[13,15,18,52-54] This observation avoids the logistical problems associated with using fresh donor' feces and facilitates the use of FMT in the clinic. Moreover, it makes it possible to establish feces banks for the routine clinical use of FMT.

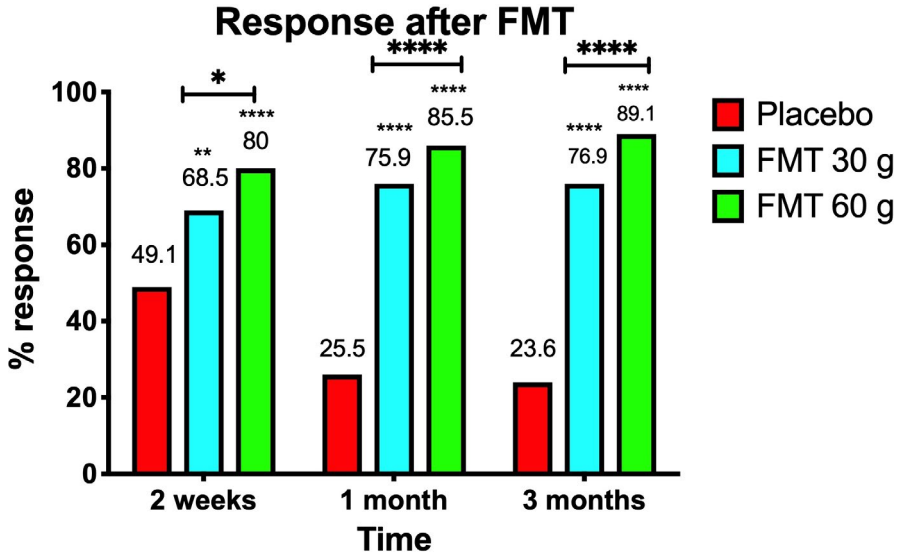

FIGURE 3 Responses of IBS patients to placebo, 30-g FMT and 60-g FMT at different intervals after transplantation. **, $p<0.001$; ****, $p<0.0001$ compared with placebo. *$p < 0.001$; ***$p < 0.0001$ for 30-g FMT compared with 60-g FMT. Reproduced from El-Salhy et al[15] with permission from the authors and publisher.

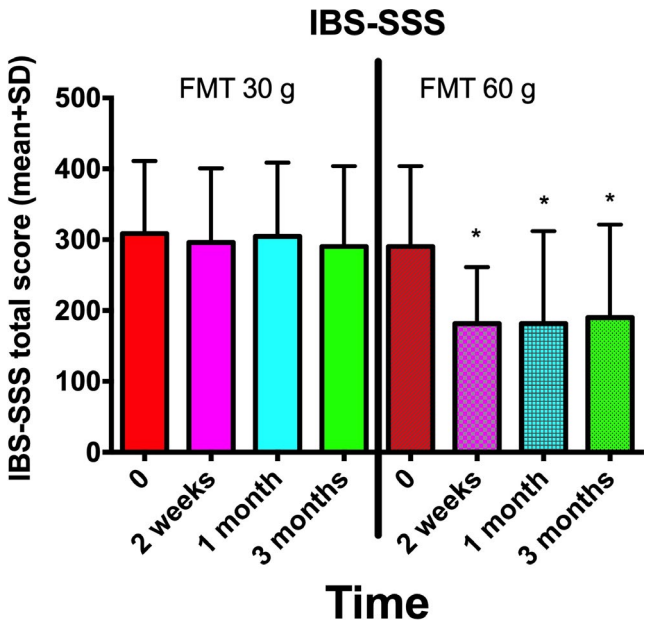

FIGURE 4 The IBS-SSS total score of patients who did not respond to a 30-g transplant and received a 60-g transplant at 3–4 months after the first transplant. *$p < 0.05$ compared to baseline. Reproduced from El-Salhy et al[48] with permission from the authors and publisher.

5 | SAFETY ISSUES OF FMT FOR IBS

The adverse events reported in FMT for IBS patients after a 1-year observation time are summarized in Table 1. These adverse events were mild, self-limiting, and only occurred during the first few days after FMT. Patients treated with FMT experienced more adverse events in the form of abdominal pain, cramping, tenderness, diarrhea, and constipation than did those in the placebo group (Table 1). Moreover, a 52-year-old man and a 55-year-old woman developed diverticulitis at 2 and 3 months after FMT, respectively. However, these two patients had known diverticulosis and experienced several diverticulitis attacks before FMT, and so it is difficult to establish whether these new attacks were causally connected to FMT.

Two patients were recently reported to have developed serious adverse events after FMT for other indications than IBS, which resulted in one fatality.[55,56] These events have started a discussion about safety issues around FMT for IBS, especially considering that IBS is a benign gastrointestinal condition.[48,57,58] The two patients involved in these events were immunosuppressed 69 and 73 years old with advanced liver cirrhosis and myelodysplastic syndrome. They received fecal capsules derived from a donor who had an antibiotic-resistant *Escherichia coli* strain.[55,56] It has been suggested that screening of FMT donors should include testing the donor feces for extended-spectrum-beta-lactase-producing *E. coli* and SARS-CoV-2, in order to reduce the risks of infection by known agents.[58] Furthermore, it has been suggested that the selection of IBS patients for FMT should be restricted to those without systemic disease, immune deficiency, treatment with immune-modulating medication, or severe illness in order to further reduce the risks.[58]

6 | POSSIBLE MECHANISMS UNDERLYING THE EFFECTS OF FMT

While it is too early to definitively identify the mechanisms underlying the positive effects of FMT, several observations have been made that may shed light on such mechanisms. The fecal levels of total short-chain fatty acids (SCFAs) increased in IBS patients after 1 month and remained elevated at 1 year following FMT.[46,59] SCFAs regulate intestinal motility and the secretion and absorption of water and electrolytes.[60,61] These effects of SCFAs seem to be caused by increasing the secretion and up-regulating the gene expression of peptide YY,[62,63] which is a mediator of the ileal brake that stimulates the absorption of water and electrolytes in the large intestine.[60,64,65]

The fecal level of the SCFA butyric acid was increased in IBS patients after 1 month and remained elevated at 1 year after FMT.[46,59]

TABLE 1 Adverse events reported following fecal microbiota transplantation (FMT) in patients with irritable bowel syndrome

	Nausea		Abdominal pain		Diarrhea		Constipation		Bloating/ flatulence		Diverticulitis	
Study	Placebo	FMT	Placebo	FMT	Placebo	FMT	Placebo	FMT	Placebo	FMT	Placebo	FMT
Johnsen et al (2018)[13]	0	0	7	2	0	0	0	0	0	0	0	0
Halkjær et al (2018)[14]	27	35	19	27	0	23*	0	12	4	19	0	0
Holster et al (2019)[17]	25	0	38	38	25	25	0	13	38	38	0	0
Aroniadis et al (2019)[16]	8	4	10	8	6	17	0	0	0	0	0	0
El-Salhy et al (2020)[15]	16	16	0	21***	4	24***	2	22***	0	0	0	2
Lahtinen et al (2020)[18,54]	0	0	0	0	4	17	0	0	8	13	0	0

Note: Values are percentages.

*$p < 0.05$,; ***$p < 0.001$ compared to placebo.

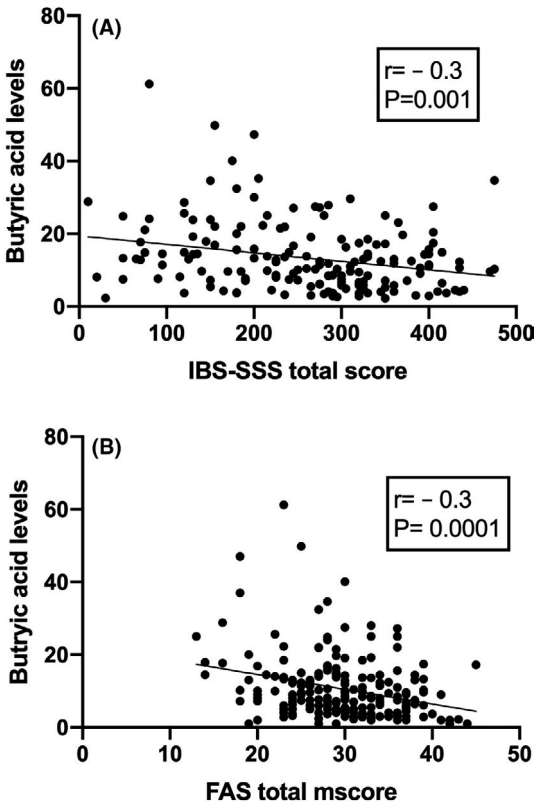

FIGURE 5 Correlation between butyric acid levels and IBs-SSS total scores (A) and FAS total score (B). Reproduced from El-Salhy et al[62] with permission from the authors and publisher.

This increase could be explained by the increased levels of butyrate-producing *Eubacterium* and *Lactobacillus* spp.[15,65-67] Butyrate is an important source of energy for colonic epithelial cells, and it affects the immune response, modulates the oxidative stress of the host, and decreases intestinal-cell permeability and intestinal motility.[61,64] Moreover, butyrate modulates colonic hypersensitivity, and treatment with butyrate reduces abdominal pain in patients with IBS.[68-70] Interestingly, following FMT in IBS patients, the levels of butyric acid were found to be correlated inversely with the total score of both the IBS-symptom severity system (IBS-SSS) and Fatigue Assessment Scale (FAS) (Figure 5).

Increased levels of the branched SCFAs isobutyric and isovaleric acids were observed in IBS patients at 1 year of FMT, suggesting a shift in microbial fermentation from a saccharolytic to a proteolytic pattern, which might be of pathophysiological relevance.[46,71] Moreover, the level of the straight SCFA acetic acid decreased significantly at 1 year after FMT,[46] which could be important given that acetic acid induces visceral hypersensitivity in rodents.[72]

7 | CONCLUSION AND PERSPECTIVE

FMT appears to be a promising treatment for IBS. The outcome of FMT is donor-dependent, indicating the need for care when selecting donors. Clinical criteria that are associated with a favorable microbiota signature have been proposed. However, it is not yet clear whether some of these criteria are more important than others or whether all of the criteria should be satisfied in an effective (super) donor. Future studies should test the reliability of these criteria and also compare the microbial signatures between the donor and healthy subjects.

The dose of the fecal transplant is important to the efficacy of FMT, with doses lower than 30 g not showing any effect. Administering the fecal transplant to either the small or large intestine is effective, but further studies are needed to establish which route is optimal. Whether the effectiveness differs between single and repeated FMT also remains to be determined.

CONFLICT OF INTEREST

The authors have nothing to disclose.

AUTHOR CONTRIBUTIONS

M.E.S. collected, analyzed and interpreted the data, and drafted the manuscript. T.H. and J.G.H. contributed to data interpretation and critically revised the manuscript for important intellectual content.

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REFERENCES

1. El-Salhy M. Recent developments in the pathophysiology of irritable bowel syndrome. *World J Gastroenterol*. 2015;21:7621-7636.
2. Canavan C, West J, Card T. The epidemiology of irritable bowel syndrome. *Clin Epidemiol*. 2014;6:71-80.
3. El-Salhy M. Irritable bowel syndrome: diagnosis and pathogenesis. *World J Gastroenterol*. 2012;18:5151-5163.
4. El-Salhy M. Recent advances in the diagnosis of irritable bowel syndrome. *Exp Rev Gastroenterol Hepatol*. 2015;9:1161-1174.
5. Wilson BC, Vatanen T, Cutfield WS, O'Sullivan JM. The super-donor phenomenon in fecal microbiota transplantation. *Front Cell Infect Microbiol*. 2019;9:2.
6. Maier L, Pruteanu M, Kuhn M, et al. Extensive impact of non-antibiotic drugs on human gut bacteria. *Nature*. 2018;555(7698):623-628.
7. El-Salhy M, Mazzawi T. Fecal microbiota transplantation for managing irritable bowel syndrome. *Exp Rev Gastroenterol Hepatol*. 2018;12(5):439-445.
8. Casén C, Vebø HC, Sekelja M, et al. Deviations in human gut microbiota: a novel diagnostic test for determining dysbiosis in patients with IBS or IBD. *Aliment Pharmacol Ther*. 2015;42(1):71-83.
9. Enck P, Mazurak N. Dysbiosis in functional bowel disorders. *Ann Nutr Metab*. 2018;72(4):296-306.
10. El-Salhy M, Hatlebakk JG, Hausken T. Diet in irritable bowel syndrome (IBS): Interaction with gut microbiota and gut hormones. *Nutrients*. 2019;11(8):1824.
11. Pozuelo M, Panda S, Santiago A, et al. Reduction of butyrate- and methane-producing microorganisms in patients with Irritable Bowel Syndrome. *Sci Rep*. 2015;5:12693.
12. Chong PP, Chin VK, Looi CY, Wong WF, Madhavan P, Yong VC. The microbiome and irritable bowel syndrome - a review on the pathophysiology, current research and future therapy. *Front Microbiol*. 2019;10:1136.
13. Johnsen PH, Hilpusch 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.
14. 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.
15. El-Salhy M, Hatlebakk JG, Gilja OH, Bråthen Kristoffersen A, Hausken T. Efficacy of faecal microbiota transplantation for patients with irritable bowel syndrome in a randomised, double-blind, placebo-controlled study. *Gut*. 2020;69(5):859-867.
16. Aroniadis OC, Brandt LJ, Oneto C, et al. Faecal microbiota transplantation for diarrhoea-predominant irritable bowel syndrome: a double-blind, randomised, placebo-controlled trial. *Lancet Gastroenterol Hepatol*. 2019;4(9):675-685.
17. Holster S, Lindqvist CM, Repsilber D, et al. The effect of allogenic versus autologous fecal microbiota transfer on symptoms, visceral perception and fecal and mucosal microbiota in irritable bowel syndrome: a randomized controlled study. *Clin Transl Gastroenterol*. 2019;10(4):e00034.
18. Lahtinen P, Jalanka J, Hartikainen A, et al. Randomised clinical trial: faecal microbiota transplantation versus autologous placebo administered via colonoscopy in irritable bowel syndrome. *Aliment Pharmacol Ther*. 2020;51(12):1321-1331.
19. Holvoet T, Joossens M, Vázquez-Castellanos JF, et al. Fecal microbiota transplantation reduces symptoms in some patients with irritable bowel syndrome with predominant abdominal bloating: short- and long-term results from a placebo-controlled randomized trial. *Gastroenterology*. 2021;160(1):145-157.e8. https://doi.org/10.1053/j.gastro.2020.07.013
20. Agency EM. Guideline on the evaluation of medicinal products for the treatment of irritable bowel syndrome. https://wwwemaeuropaeu/en/documents/scientific-guideline/guideline-evaluation-medicinal-products-treatment-irritable-bowel-syndrome-revision-1_enpdf. 2014:1-18.
21. (CDER). USDoHaHSFaDACfDEaR. Guidance for industry:irritable bowel syndrome-clinical evalution of drugs for treatment. Available at: http://wwwfdagov/downloads/Drugs/Guidances/UCM205269pdf. 2012.
22. Segal JP, Mullish BH, Quraishi MN, Iqbal TH. Letter: faecal microbiota transplantation for IBS. *Aliment Pharmacol Ther*. 2020;52(3):556-557.
23. Ianiro G, Porcari S, Ford AC, Gasbarrini A, Cammarota G. Letter: faecal microbiota transplantation for irritable bowel syndrome-room for improvement. *Aliment Pharmacol Ther*. 2020;52(5):923-924.
24. Benech N, Sokol H. Fecal microbiota transplantation in gastrointestinal disorders: time for precision medicine. *Genome Med*. 2020;12(1):58.
25. Moayyedi P, Surette MG, Kim PT, et al. Fecal microbiota transplantation induces remission in patients with active ulcerative colitis in a randomized controlled trial. *Gastroenterology*. 2015;149(1):102-109.e6.
26. Kazerouni A, Wein LM. Exploring the efficacy of pooled stools in fecal microbiota transplantation for microbiota-associated chronic diseases. *PLoS One*. 2017;12(1):e0163956.
27. Paramsothy S, Kamm MA, Kaakoush NO, et al. Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. *Lancet*. 2017;389(10075):1218-1228.
28. Holvoet T, Joossens M, Wang J, et al. Assessment of faecal microbial transfer in irritable bowel syndrome with severe bloating. *Gut*. 2017;66:980-982.
29. Capurso G, Lahner E. The interaction between smoking, alcohol and the gut microbiome. *Best Pract Res Clin Gastroenterol*. 2017;31(5):579-588.
30. Biedermann L, Brulisauer K, Zeitz J, et al. Smoking cessation alters intestinal microbiota: insights from quantitative investigations on human fecal samples using FISH. *Inflamm Bowel Dis*. 2014;20(9):1496-1501.
31. Korpela K, Dikareva E, Hanski E, Kolho KL, de Vos WM, Salonen A. Cohort profile: Finnish Health and Early Life Microbiota (HELMi) longitudinal birth cohort. *BMJ open*. 2019;9(6):e028500.
32. Yeung OY, Ng YF, Chiou J, Wong MS. A pilot study to determine the gut microbiota of Hong Kong infants fed with breast-milk and/or infant formula (P11-101-19). *Curr Dev Nutr*. 2019;3(suppl 1):11-101. https://doi.org/10.1093/cdn/nzz048.P11-101-19
33. Jakobsson HE, Abrahamsson TR, Jenmalm MC, et al. Decreased gut microbiota diversity, delayed Bacteroidetes colonisation and reduced Th1 responses in infants delivered by caesarean section. *Gut*. 2014;63(4):559-566.
34. Rutayisire E, Huang K, Liu Y, Tao F. The mode of delivery affects the diversity and colonization pattern of the gut microbiota during the first year of infants' life: a systematic review. *BMC Gastroenterol*. 2016;16(1):86.
35. Ianiro G, Tilg H, Gasbarrini A. Antibiotics as deep modulators of gut microbiota: between good and evil. *Gut*. 2016;65(11):1906-1915.
36. Modi SR, Collins JJ, Relman DA. Antibiotics and the gut microbiota. *J Clin Invest*. 2014;124(10):4212-4218.
37. Bibbò S, Settanni CR, Porcari S, et al. Fecal microbiota transplantation: screening and selection to choose the optimal donor. *J Clin Med*. 2020;9(6):1757.

38. Murtaza N, Burke LM, Vlahovich N, et al. The effects of dietary pattern during intensified training on stool microbiota of elite race walkers. *Nutrients*. 2019;11(2):261.
39. Dalton A, Mermier C, Zuhl M. Exercise influence on the microbiome-gut-brain axis. *Gut Microbes*. 2019;10(5):555-568.
40. Motiani KK, Collado MC, Eskelinen JJ, et al. Exercise training modulates gut microbiota profile and improves endotoxemia. *Med Sci Sports Exerc*. 2020;52(1):94-104.
41. Pinn DM, Aroniadis OC, Brandt LJ. Is fecal microbiota transplantation (FMT) an effective treatment for patients with functional gastrointestinal disorders (FGID)? *Neurogastroenterol Motil*. 2015;27:19-29.
42. Pinn DM, Aroniadis OC, Brandt LJ. Is fecal microbiota transplantation the answer for irritable bowel syndrome? A single-center experience. *Am J Gastroenterol*. 2014;109:1831-1832.
43. Ostgaard H, Hausken T, Gundersen D, El-Salhy M. Diet and effects of diet management on quality of life and symptoms in patients with irritable bowel syndrome. *Mol Med Report*. 2012;5:1382-1390.
44. Bull MJ, Plummer NT. Part 2: treatments for chronic gastrointestinal disease and gut dysbiosis. *Integr Med (Encinitas)*. 2015;14(1):25-33.
45. Chong CYL, Bloomfield FH, O'Sullivan JM. Factors affecting gastrointestinal microbiome development in neonates. *Nutrients*. 2018;10(3):274.
46. El-Salhy M, Kristoffersen AB, Valeur J, et al. Long-term effects of faecal microbiota transplantation (FMT) in patients with irritable bowel syndrome. *Neurogastroenterol Motil*. 2020;Submitted.
47. Dimidi E, Whelan K. Food supplements and diet as treatment options in irritable bowel syndrome. *Neurogastroenterol Motil*. 2020;32(8):e13951.
48. Barbara G, Ianiro G. Faecal microbial transplantation in IBS: ready for prime time? *Gut*. 2020;69(5):795-796.
49. Ianiro G, Maida M, Burisch J, et al. Efficacy of different faecal microbiota transplantation protocols for Clostridium difficile infection: A systematic review and meta-analysis. *United European Gastroenterol J*. 2018;6(8):1232-1244.
50. El-Salhy M, Hausken T, Hatlebakk JG. Increasing the Dose and/or Repeating Faecal Microbiota Transplantation (FMT) Increases the Response in Patients with Irritable Bowel Syndrome (IBS). *Nutrients*. 2019;11(6):1415.
51. Chen QY, Tian HL, Yang B, et al. Effect of intestinal preparation on the efficacy and safety of fecal microbiota transplantation treatment. *Zhonghua Wei Chang Wai Ke Za Zhi*. 2020;23(Z1):48-55.
52. Satokari R, Mattila E, Kainulainen V, Arkkila PE. Simple faecal preparation and efficacy of frozen inoculum in faecal microbiota transplantation for recurrent Clostridium difficile infection–an observational cohort study. *Aliment Pharmacol Ther*. 2015;41(1):46-53.
53. Mattila E, Uusitalo-Seppälä R, Wuorela M, et al. Fecal transplantation, through colonoscopy, is effective therapy for recurrent Clostridium difficile infection. *Gastroenterology*. 2012;142(3):490-496.
54. Lahtinen P, Jalanka J, Hartikainen A, et al. Letter: faecal microbiota transplantation for irritable bowel syndrome-room for improvement. Authors' reply. *Aliment Pharmacol Ther*. 2020;52(5):925-926.
55. DeFilipp Z, Bloom PP, Torres Soto M, et al. Drug-resistant *E. coli* bacteremia transmitted by fecal microbiota transplant. *N Engl J Med*. 2019;381(21):2043-2050.
56. Blaser MJ. Fecal microbiota transplantation for dysbiosis - predictable risks. *N Engl J Med*. 2019;381(21):2064-2066.
57. Camilleri M. FMT in IBS: a call for caution. *Gut*. 2020.70(2):431. https://doi.org/10.1136/gutjnl-2020-321529
58. El-Salhy M. FMT in IBS: how cautious should we be? *Gut*. 2020. https://doi.org/10.1136/gutjnl-2020-322038
59. El-Salhy M, Valeur J, Hausken T, Gunnar HJ. Changes in fecal short-chain fatty acids following fecal microbiota transplantation in patients with irritable bowel syndrome. *Neurogastroenterol Motil*. 2021;33(2):e13983.
60. Soret R, Chevalier J, De Coppet P, et al. Short-chain fatty acids regulate the enteric neurons and control gastrointestinal motility in rats. *Gastroenterology*. 2010;138:1772-1782.
61. Hamer HM, Jonkers D, Venema K, Vanhoutvin S, Troost FJ, Brummer RJ. Review article: the role of butyrate on colonic function. *Aliment Pharmacol Ther*. 2008;27:104-119.
62. Zhou J, Martin RJ, Tulley RT, et al. Dietary resistant starch upregulates total GLP-1 and PYY in a sustained day-long manner through fermentation in rodents. *Am J Physiol Endocrinol Metab*. 2008;295:E1160-1166.
63. Karaki S, Mitsui R, Hayashi H, et al. Short-chain fatty acid receptor, GPR43, is expressed by enteroendocrine cells and mucosal mast cells in rat intestine. *Cell Tissue Res*. 2006;324:353-360.
64. El-Salhy M, Hatlebakk JG, Hausken T. Possible role of peptide YY (PYY) in the pathophysiology of irritable bowel syndrome (IBS). *Neuropeptides*. 2020;79:101973.
65. Hamer HM, Jonkers DM, Bast A, et al. Butyrate modulates oxidative stress in the colonic mucosa of healthy humans. *Clin Nutr*. 2009;28:88-93.
66. Zaleski A, Banaszkiewicz A, Walkowiak J. Butyric acid in irritable bowel syndrome. *Przeglad Gastroenterol*. 2013;8(6):350-353.
67. Cremon C, Guglielmetti S, Gargari G, et al. Effect of Lactobacillus paracasei CNCM I-1572 on symptoms, gut microbiota, short chain fatty acids, and immune activation in patients with irritable bowel syndrome: A pilot randomized clinical trial. *United European Gastroenterol J*. 2018;6(4):604-613.
68. Zhang J, Song L, Wang Y, et al. Beneficial effect of butyrate-producing Lachnospiraceae on stress-induced visceral hypersensitivity in rats. *J Gastroenterol Hepatol*. 2019;34(8):1368-1376.
69. Long X, Li M, Li LX, et al. Butyrate promotes visceral hypersensitivity in an IBS-like model via enteric glial cell-derived nerve growth factor. *Neurogastroenterol Motil*. 2018;30(4):e13227.
70. Banasiewicz T, Krokowicz L, Stojcev Z, et al. Microencapsulated sodium butyrate reduces the frequency of abdominal pain in patients with irritable bowel syndrome. *Colorectal Dis*. 2013;15(2):204-209.
71. Tana C, Umesaki Y, Imaoka A, Handa T, Kanazawa M, Fukudo S. Altered profiles of intestinal microbiota and organic acids may be the origin of symptoms in irritable bowel syndrome. *Neurogastroenterol Motil*. 2010;22(5):512-519, e114–515.
72. Winston J, Shenoy M, Medley D, Naniwadekar A, Pasricha PJ. The vanilloid receptor initiates and maintains colonic hypersensitivity induced by neonatal colon irritation in rats. *Gastroenterology*. 2007;132(2):615-627.

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