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MICROBIOME IN IRRITABLE BOWEL SYNDROME: ADVANCES IN THE FIELD – A SCOPING REVIEW

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Abstract – *Objective:* The pathogenesis of irritable bowel syndrome is still not clearly understood. Brain-gut-microbiota disbalances might play an important role in irritable bowel syndrome (IBS) development. The aim of this scoping review was to summarize the latest scientific data regarding the role of microbiota in IBS pathogenesis.
Materials and Methods: PubMed was electronically searched for all observational and interventional studies, as well as systematic reviews and meta-analyses evaluating microbiota in IBS, within the interval of one year starting from March 2022 till March 2023.
Results: Compared to healthy controls, IBS subjects were observed to have an increase in *Enterobacteriaceae, Ruminococcus, Clostridium, Dorea species* and a decrease of *Lactobacillus, Bifidobacterium*, and *Faecalibacterium species*.
Conclusions: IBS with diarrhea predominance share similarities in the microbial profile with IBS patients with mixed bowel habits.

Keywords: Irritable bowel syndrome (IBS), Diarrhea, Constipation, Microbiome, Microbiota, Bloating.

INTRODUCTION

Two distinct ecosystems interact and form the intestinal microbiota[1,2]. One ecosystem is represented by fecal (luminal) bacteria, which are either dispersed in liquid feces or bound to food particles. The other ecosystem is represented by mucosa-associated bacteria, which are bound to a mucus layer adjacent to the intestinal epithelium[1,2]. The luminal microbiota constitutes most of the gastrointestinal tract microbiota and is responsible for gut homeostasis.

The composition of the human microbiota varies from one individual to another and is constantly evolving. Mode of delivery, host genotype, diet, environment, acute diarrheal illnesses, antibiotic treatment, and stress influence the composition of the microbiota. Moreover, the microbiome composition tends to vary between different geographical regions and populations[2]. On the other hand, bacteria produce metabolites and chemicals, which influence host functions, providing protective effects against pathogens and having a role in the development and activation of the immune system[3].

The Gram-positive aerobes and facultative anaerobes are predominant in the jejunum and proximal ileum. The distal ileum hosts bacteria like those found in the colon. In adults, there is a preponderance of beneficial bacteria from *Firmicutes* and *Bacteroidetes* phylum, while *Proteobacteria* (*Entero-*

bacteriaceae) phylum is present only in small amounts. Early in life, *Actinobacteria* is the predominant phylum, with the predominance of *Bifidobacteria*. The balance of this microbial ecosystem is called eubiosis[4]. The ratio between the species of these phylum changes during life and in diseases.

Irritable bowel syndrome (IBS), one of the most common disorders of gut-brain interaction, affects many people worldwide. It is characterized by abdominal pain and altered bowel habits in the absence of obvious anatomic or physiologic abnormalities[2], with an important impact on the global healthcare systems and quality of life of IBS patients. The pathogenic mechanisms responsible for IBS are not fully understood. Genetic susceptibility, stress, environmental factors, dysfunctional brain-gut-microbiome axis, visceral hypersensitivity, altered gut motility, mucosal barrier dysfunction, mucosal immune hyperactivity, and increased epithelial permeability are interacting in the complex pathogenesis of IBS. Changes in the microbiota might influence the brain-gut axis, visceral hypersensitivity, and epithelial barrier dysfunction[2]. An imbalance in the microbial community in or on the body is called dysbiosis, representing one of the most active research fields for IBS pathogenesis.

Previous scholars reported an increase in potentially harmful bacteria and a decrease in beneficial bacteria, with consequences on symptom development[2].

In 2010, Codling et al[5] found lower colonization of gut microbiota in IBS patients compared with healthy controls, based on molecular analysis. In 2011, Rajilic-Stojanovic et al[6] reported that in IBS patients, there was an increased ratio of *Firmicutes* to *Bacteroidetes*, an increase in numbers of *Dorea, Ruminococcus*, and *Clostridium* spp., and a decrease in the number of *Bacteroidetes*, *Bifidobacterium,* and *Faecalibacterium* spp. In 2012, Jeffery et al[7] reported similar results, reporting an increase of *Firmicutes*-associated taxa and a depletion of *Bacteroidetes*-related taxa. Contrary results were reported by Ng et al[8], who found an increase in *Bacteroides spp*. in IBS patients. In 2017, on larger cohorts of IBS patients and healthy controls, Tap et al[9] found that IBS symptom severity was negatively associated with microbial richness, exhaled CH4, presence of methanogens, and enterotypes enriched with *Clostridiales* or *Prevotella* species.

Compared with healthy controls, IBS patients showed lower fecal *Lactobacillus* and *Bifidobacterium* levels, in addition to higher *Escherichia coli* and *Enterobacter* levels[2,10]. The *Enterobacteriaceae* family (phylum *Proteobacteria*) is considered a potentially harmful taxon because it contains bacteria like *Escherichia, Shigella, Campylobacter,* and *Salmonella,* which are associated with enteric infections and with IL-6 and IL-8, known as proinflammatory cytokines[10]. Among beneficial bacteria, *Faecalibacterium prausnitzii* is decreased in IBS patients[3,11]. This microbe produces butyrate, mediates the expression of IL-17, has anti-inflammatory properties[12], and increases the gastrointestinal barrier's integrity[13].

This scoping review resumes the last data published on the topic of microbiota and IBS in the last year (from March 2022 to March 2023).

MATERIALS AND METHODS

Search Methods for Identification of Studies

PubMed was electronically searched for all observational and interventional studies, as well as systematic reviews and meta-analyses evaluating microbiota in IBS. The literature search included studies published within the interval of one year, starting from March 2022 till March 2023. Our search restrictions were limited to observational and interventional studies, as well as review articles. We used the terms "microbiota", "microbiome", and "IBS".

Data Collection and Extraction Process

Two authors (T.S.B. and L.C.) independently assessed the titles and abstracts obtained from the electronic search to determine their suitability and eligibility. The two reviewers individually conducted a comprehensive evaluation of the full texts of eligible articles. Data extraction from articles that met the inclusion and exclusion criteria was carried out independently by both reviewers. In case of any disagreements during the search and data extraction, a consensus was reached through mutual agreement.

Selection of Studies

Inclusion criteria of articles: (1) Published observational cohort population-based/hospital-based, case-control studies, interventional studies, systematic reviews, and meta-analyses examining the association between the microbiome and IBS; (2) IBS diagnosis according to the ROME criteria; (3) microbiota evaluation according to each study criteria; (4) studies conducted on humans; and (5) studies published in English, German or Romanian languages.

Exclusion criteria of articles: (1) case reports, conference abstracts, literature reviews, and abstracts published without a full article.

Figure 1 shows the search strategy using the PRISMA flow diagram.

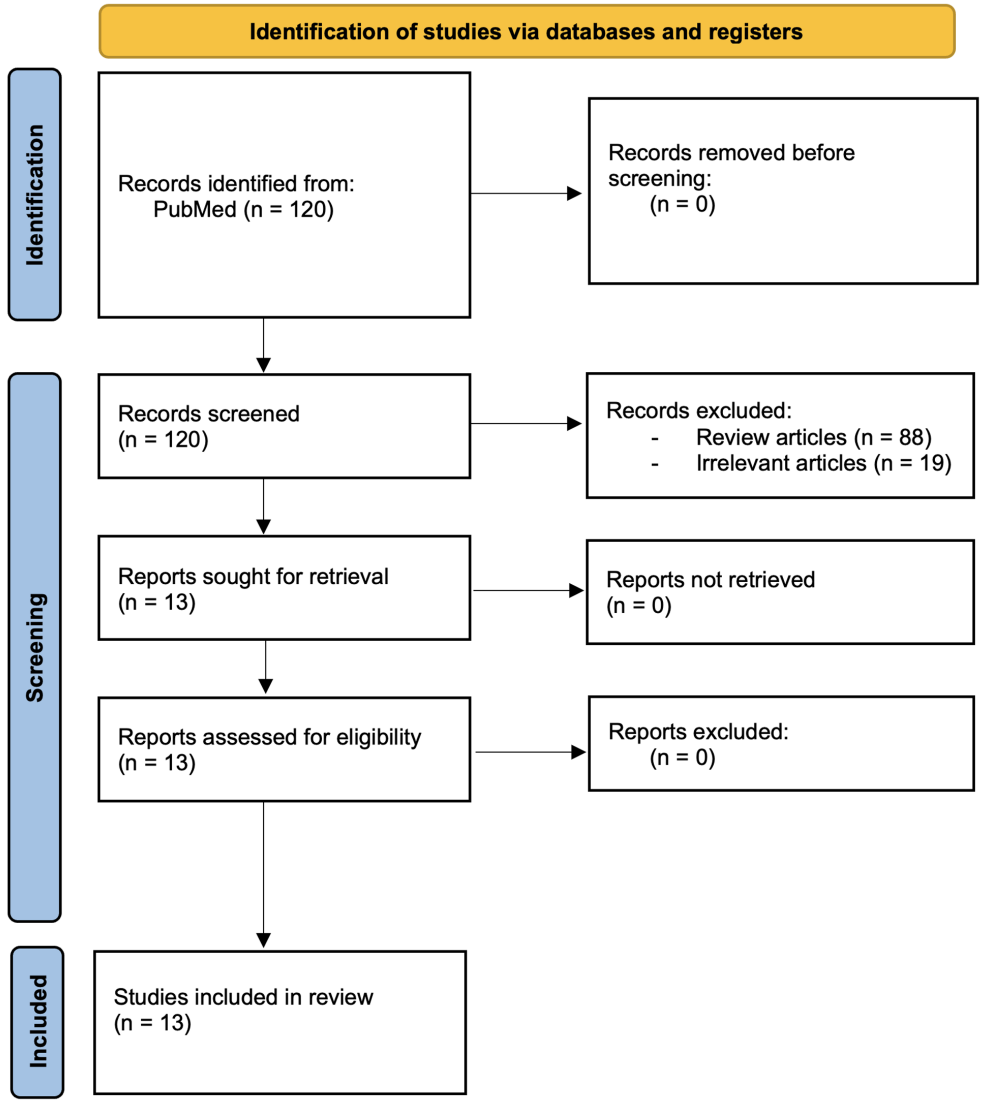

Figure 1. PRISMA flow diagram describing the identification, screening, and inclusion processes.

RESULTS

Recent studies compared IBS patients with controls, while others explored the possibility of influencing the microbiota, and consequently the IBS symptoms, by changing diet, administering probiotics, food supplements or using fecal microbiota transplantation (FMT). Figure 2 summarizes the microbiota diversity alterations according to different IBS subtypes.

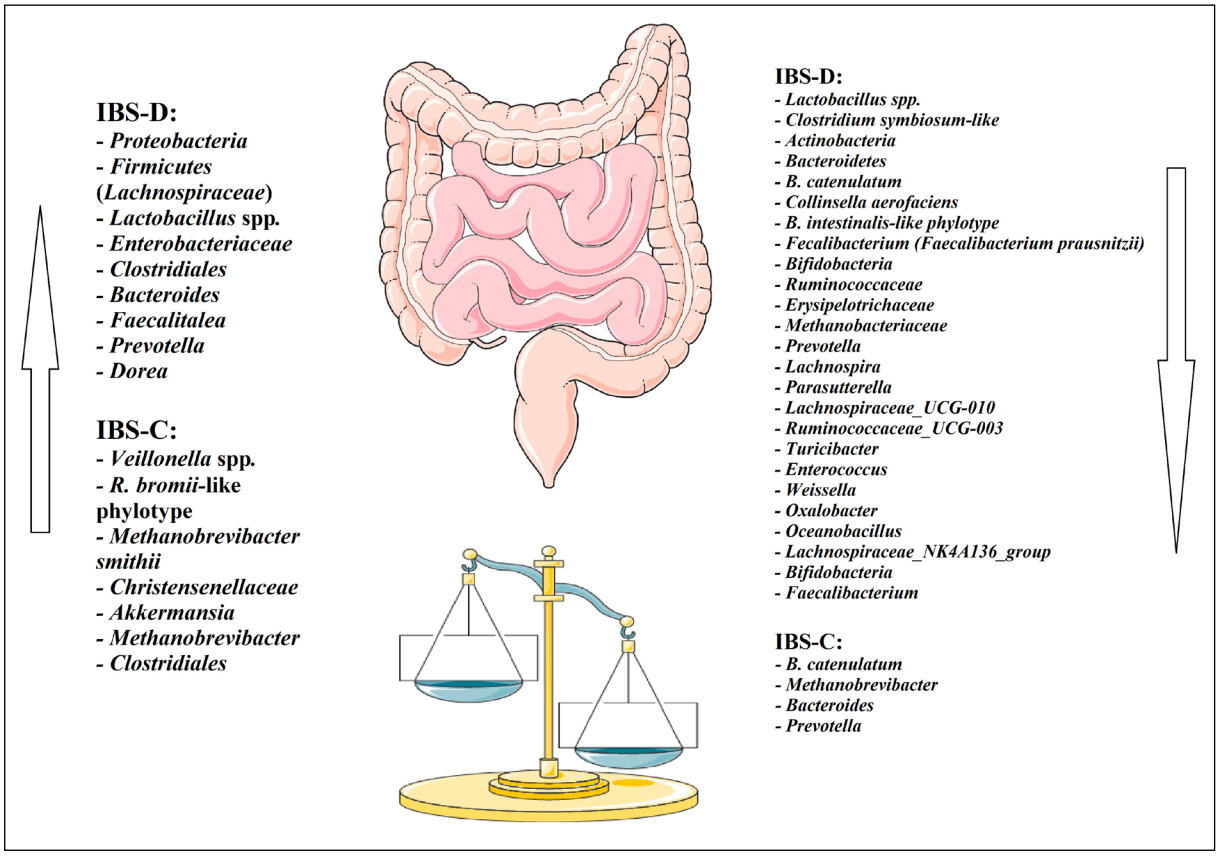

Figure 2. Microbiota diversity alterations according to different IBS subtypes. (The Figure was partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license).

Recent evidence found that *Streptococcus, Bacillus, Enterocloster, Sphingobacterium*, *and Holdemania* were increased in IBS-D and IBS-C patients, while *Faecalibacterium, Ruminococcus, Oscillibacter, Coprococcus, Acetivibrio, Lachnospira*, or *Acidaminococus* were depleted in both IBS subtypes. The influence of different diets (traditional dietary advice, GFD, and low FODMAP) on microbiota in IBS patients found no changes in the dysbiosis index.

Table 1 summarizes the characteristics of the studies included in this review and the main results reported regarding microbiota in IBS patients.

DISCUSSION

Recent Evidence for Microbiota and IBS Interaction

In a study that compared IBS patients (*n*=60) with healthy controls (*n*=20), the authors reported lower levels of intestinal *Lactobacillus* and *Bifidobacterium*, and higher levels of *Enterococcus and Enterobacter* in the study group[13]. *Bifidobacterium* (phylum *Actinobacteria*) supports the growth of the intestinal mucosa by producing nutrients, inhibiting the growth of harmful intestinal bacteria, and reducing the production of toxins. Similarly, *Lactobacillus* (phylum *Firmicutes*) is a beneficial bacterium that affects cell phagocytosis, the production of cytokines that strengthen the immune system, and the inhibition of harmful bacteria[3].

A large study analyzed the 16 s-rRNA data from 354 IBS patients and 354 healthy controls. In IBS samples, several potentially harmful microbes with enriched abundance were identified: *Enterobacteriaceae* (phylum *Proteobacteria*), *Moraxellaceae*, and *Sphingobacteriaceae*. The genera *Streptococcus* (species *oralis*, *mitis*, and *suis*), *Bacillus, Enterocloster, Sphingobacterium, Holdemania*, and *Acinetobacter* were abundant in IBS patients compared to controls. Bacteria from the phyla *Firmicutes, Euryarchaeota, Cyanobacteria, Acidobacteria*, and *Lentisphaerae* were less abundant

TABLE 1. CHARACTERISTICS OF THE STUDIES INCLUDED IN THIS REVIEW, AND THE MAIN RESULTS REPORTED REGARDING MICROBIOTA IN IBS PATIENTS.

Article	Aim of the study	Subjects	Main findings regarding the microbiota composition and its variation
Microbiota composition in IBS			
Chen H et al[14], 2023, China	– Analysis of microbiota composition at different taxonomic levels in patients with IBS compared to controls, using 16 s-rRNA sequencing data from GMrepo database	354 IBS patients 354 HC	– Abundant bacteria in IBS patients: *Enterobacteriaceae, Moraxellaceae, Sphingobacteriaceae,* and *genera Streptococcus (oralis, mitis and suis), Bacillus, Enterocloster, Sphingobacterium, Holdemania, Acinetobacter* – Less abundant in IBS were phyla Firmicutes, *Euryarchaeota, Cyanobacteria, Acidobacteria and Lentisphaerae* – Depleted in IBS - genra *Faecalibacterium* and *Bifidobacterium* – Changes based on IBS subtype. – Depleted in IBS-C and enriched in IBS-D: genra *Haemophilus*, *Peptoniphilus* and *Roseburia* – Enriched in IBS-C and depleted in IBS-D: *Anaerofilum*
Yao C et al[18], 2023, China	– The gut microbiota composition in IBS-D compared to HC, using 16S rDNA sequencing from stool samples	120 IBS-D patients 63 HC	– The richness of gut microbiota in IBS-D was significantly lower than that of HCs – The beta diversity was lower in IBS-D compared to HC but not diversity – Potential biomarkers of IBS-D: *Prevotella, Clostridiales,* and *Roseburia* – Potential biomarkers of HC: *Veillonellaceae, Bacteroides coprocola* and *Bifidobacteriales* – *Dorea genus* was associated with increased gas production and is increased in IBS-D
Diet and food supplements studies			
Algera JP et al[21], 2022, Sweden	– Influence of GFD on gut micro-environment – Double-blind, randomized, placebo-controlled, cross-over trial – Fecal samples were analyzed for bacterial profiles using 16S rRNA analysis), using 48 DNA probes – Fecal metabolites were analyzed using LC–MS analysis	20 IBS patients 18 HC	– No changes in β-diversity (variation of microbial abundances) between the interventions, were observed in IBS patients and HC – GFD influenced fecal microbiota and metabolites differently in true responders and non-responders. – GFD changes the fecal microbiota and fecal metabolite profiles of IBS patients, especially in responders to a GFD
Rej A et al[22], 2022, United Kingdom	– Patients randomized to TDA, LFD, or GFD – Stool samples analyzed with GAmap Dysbiosis Test – DI was calculated before and after intervention – A score >2 indicated dysbiosis (bacteria composition differing from a healthy normobiotic reference range)	101 IBS patients TDA = 35, LFD = 33, GFD = 33) – 55 paired stool samples were analyzed	– Changes in stool DI was similar across the diets (22%–29% showed reduced dysbiosis, 35%–39% no change, 35%–40% increased dysbiosis) – GFD decreased the following bacteria: *Actinobacteria, Parabacteroides johnsonii, Eubacterium rectale, Ruminococcus albus, R. bromii* – LFD decreased the abundance of *Actinobacteria* and *Bacteroides fragilis* – LFD increased *Alistipes*, *Parabacteroides johnsonii, Clostridium methylpentosum, Lachnospiraceae* – TDA decrease *Dorea spp* abundance – No significant changes in functional bacterial profiles – Baseline stool DI did not predict response to diet
Nilholm C et al[26] 2022, Sweden	– The effects of The 4-week SSRD on the gut microbiota and circulating micro-RNA	105 IBS patients randomized to SSRD (n=80) or habitual diet (n=25	– The most dominant phyla in both groups before and after the SSRD trial were Bacteroidetes and Firmicutes – SSRD decreased the abundance of *Bacteroidetes* – SSRD increased the abundance of *Proteobacteria, Lentisphaere, Cyanobacteria* – After SSRD several genera increased: *Eubacterium eligens, Lachnospiraceae* UCG-001, *Victivallis*, and *Lachnospira* – After SSRD the following genera decreased: *Marvinbryantia*, DTU089 (Ruminoccocaceae family), *Enterorhabdus*, and *Olsenella, Acidaminococcus, Slackia, Catenibacterium* – Alfa diversity remained unaffected. – Beta diversity significantly changed in the intervention group. – Dietary intervention did not change micro-RNA expression – The decrease in *Bacteroidetes* corelated with reduced gastrointestinal symptoms

Continued

TABLE 1 *(CONTINUED)*. CHARACTERISTICS OF THE STUDIES INCLUDED IN THIS REVIEW, AND THE MAIN RESULTS REPORTED REGARDING MICROBIOTA IN IBS PATIENTS.

Article	Aim of the study	Subjects	Main findings regarding the microbiota composition and its variation
Diet and food supplements studies			
Ivashkin VT et al[29] 2022, Russia	– Randomized double-blind placebo-controlled trial – Aim - to assess the efficacy and safety of a food supplement containing peppermint oil 240 mg (40% menthol, 1.5% limonene) and 50mg ginger oil (14% gingerol) – Secondary outcomes were the change in the number of SCFA producing bacteria, and the composition of intestinal microbiota using 16S rRNA gene sequencing	59 IBS patients, 28 patients in intervention group, 30 patients in placebo group	– The microbiota composition was different from the beginning between the two groups – After intervention, *Oscillibacter* was more prevalent in intervention group, and *Veillonella*, *Collinsella* and *Gemmiger* in control group – the differences however were similar with the baseline evaluation – The abundance of *Fusobacterium* correlated positively with the severity of IBS (FRD = 0.02) – Other bacterial families correlated with IBS severity, but they did not pass the FDR adjustment threshold (FDR > 0.05)
Ricci C et al[32], 2022, Italy	– Interventional, prospective, multicentric, randomized, double blind placebo-controlled trial – Aim: to assess the efficacy of LAGS (BIOintestil®) in IBS – Assessment of gut microbiota (from stool samples) and inflammatory cytokines (from blood samples)	56 IBS patients – Rome III criteria 27 - placebo group 29 - LAGS group 2 to 4 capsules/day (depending on body wight) once daily for 4 weeks/ placebo capsules	– The gut microbiota profile was dominated by *phylum Firmicutes* (69%), followed by *Actinobacteria* (15.3%) *Bacteroidetes* (8.4%) and *Verrucomicrobia* (5.1%). – Dominant families were: *Lachnospiraceae*, *Ruminococcaceae*, *Bifidobacteriaceae*, and *Coriobacteriaceae* – In LAGS group there was a trend of decrease of *Erysipelotrichaceae* family and *Clostridiaceae*, and a significant decrease in genus of *Ruminococcaceae*, and *Oscillospira* (associated with IBS-C) – In LAGS group there was a trend towards an increase in the relative abundance of *Faecalibacterium* (produces SCFA) – Placebo group: ↑ levels of the *Streptococcaceae*, *Enterobacteriaceae* families and ↓ of *Ruminococcus* (*Lachnospiraceae* family) – Alfa diversity decreased but did not reach statistical significance in both treatment groups – Beta diversity was similar in both groups
Anderle K et al[33]. 2022, Austria	– Randomized, placebo-controlled, double-blind pilot study – Primary outcome - to assess the efficacy of PCT in IBS-D patients (measured as proportion of responders) – Secondary outcomes: microbiome data, symptoms questionnaires and biomarkers	30 IBS-D patients based on Rome IV criteria – 12-week treatment – 14 patients (2g three times a day) – 16 – placebo group	– Microbiota diversity mildly increased in the intervention group compared to placebo – Beta diversity also increased in in the intervention group, but not in the placebo group
Intestinal microbiota and IBS severity (see also the study of Ivashkin et al. and Nilholm et al.)			
Ji M et al[34], 2022, China	– Observational study – Investigated the correlation between intestinal microbiota and IBS severity	60 IBS patients 20 HC	– Patients with IBS had lower levels of *Lactobacillus* and *Bifidobacterium* – *Enterococcus* and *Enterobacter* were higher in IBS compared to controls – The levels of *Lactobacillus* and *Bifidobacterium* were lower in patients with severe IBS compared to moderate IBS (negatively corelated with severity) – Patients with severe IBS had higher levels of *Enterococcus* and *Enterobacter*; the level of these microbes correlated positively with disease severity – The same differences were observed when the levels of these bacteria were compared between moderate and mild IBS patients

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TABLE 1 *(CONTINUED)*. CHARACTERISTICS OF THE STUDIES INCLUDED IN THIS REVIEW, AND THE MAIN RESULTS REPORTED REGARDING MICROBIOTA IN IBS PATIENTS.

Article	Aim of the study	Subjects	Main findings regarding the microbiota composition and its variation
Probiotics and IBS			
Jung K et al[37], 2022, Korea	– Double-blind, randomized, placebo-controlled trial – Assessed the efficacy of GTB1 in IBS-D (abdominal discomfort, bowel habits, fecal microbiome, and quality of life in patients were assessed)	– 27 IBS-D patients randomized 2:1 – 18 patients GTB1 group – 9 patients placebo group – treatment: two capsules at 5x109CFU GTB1TM/ capsule or placebo for 4 weeks	– *Firmicutes, Actinobacteriota* and *Bacteroidetes* were the dominant phyla – In GTB1 group after 1-week Firmicutes increased in abundance, while *Bacteroidetes* decreased – *Lactobacillus* significantly increased after 4 weeks in GTB1 group compared to placebo, in parallel with an improvement of diarrhea – The relative abundance of *Bacteroides* significantly decreased in GTB1 group after 1 week compared to placebo – The decrease in *Bacteroides* corelated with decreased diarrhea frequency – GTB1 significantly reduced the severity of symptoms and improved quality of life
Fecal microbiota transplantation and IBS			
El Salhy M et al[40], 2022, Norway	– Evaluated the differences in FMT response, symptom reduction, quality of life, dysbiosis and bacterial profile between patients with severe and moderate IBS – Stool analysis at baseline and at 1 month after FMT – Fecal bacterial profile and DI were determined, using 16S rRNA gene PCR DNA amplification – FMT was administered to the distal duodenum via a gastroscope	– 164 IBS patients – Randomized 1:1:1 into placebo (own feces – n=55), 30-g (donor feces), and 60-g (donor feces) groups – Patients that received FMT (both 30g and 60g) represent the treatment group, n=109	– DIs in the active treatment group decreased 1 month after FMT, and did not in the placebo group – DIs did not differ between severe and moderate IBS at baseline, nor at 1 month after FMT – Patients with severe IBS had lower levels of Eubacterium rectale compared to moderate IBS patients at 1 month after FMT – Eubacterium sireum significantly decreased 1 month after FMT – Eubacterium rectale correlated negatively with IBS severity score, and Eubacterium siraeum correlated positively with IBS severity score.
El Salhy M et al[41], 2022, Norway	– Evaluated the factors affecting FMT response – See above the other details	– 109 IBS patients that were in the treatment group in the study presented above, were split in responders and non-responders	– Response rate was lower in males – DIs did not differ between responders and non-responders at baseline and at 3 months after FMT – At baseline, responders had higher levels of *Alistipes*, *Bacteroides fragilis*, *Streptococcus salivarius ssp. thermophilus*, and *Streptococcus sanguinis*, and lower levels of *Actinobacteria*, *Bacteroides* pectinophilus, and Akkermansia muciniphila – After FMT, these bacterial differences disappeared, except for *Alistipes* – Although *Alistipes* significantly increased after FMT in non-responders, it did not reach the levels of the responders – Non-responders to FMT had lower fecal levels of *Alistipes* at baseline, compared to responders
Hamazaki M et al[42], 2022, Japan	– Evaluated the efficacy (using IBS symptom index), side effects, and microbiome changes of FMT in IBS patients – Diversity and microbiome were evaluated before and 12 weeks after FMT – V3-V4 regions of the 16S rRNA gene were analyzed	– 17 IBS patients refractory to other treatments	– 10 patients were responders to FMT – Alfa diversity index increased after FMT (at 4 weeks and at 12 weeks) – Alfa diversity increased in the responder group at 12 weeks after FMT, compared to baseline, and did not change in nonresponders – Relative abundance of *Neisseria* and *Akkermansia* increased, and *Desulfovibrio* and *Delftia* decreased in the responder group, 12 weeks after FMT – *Atopobium* and *Veillonella* decreased after 12 weeks in nonresponders

DI, dysbiosis index; FDR, false discovery rate (ratio of the number of false positive results to the number of total positive test results); FMT, Fecal microbiota transplantation; GFD, gluten free diet; GTB1, *Lactiplantibacillus* (formerly *Lactobacillus*) *plantarum* Apsulloc 331261; HC, healthy controls; IBS, irritable bowel syndrome; LAGS, low-absorbable geraniol food supplement; LFD, low FODMAP diet; PCT, Purified clinoptilolite-tuff (brand name G-PUR®); SSRD, starch- and sucrose-reduced diet; TDA, traditional dietary advice.

in IBS patients. Two important genera depleted in IBS were *Faecalibacterium* and *Bifidobacterium*. Among *Faecalibacterium* genra, *F. prausnitzii* seems to play a major role in the interaction between other commensally beneficial microorganisms. *Bifidobacterium* species (*B. longum, B. breve,* and *B. adolescentis*) are also interconnected, and they influence each other's growth. The authors suggested the potential use of probiotics containing these beneficial bacteria in the treatment of IBS[14].

Fecal and Mucosal Microbiota in IBS-D and IBS-C

The dysbiosis in diarrhea-predominant IBS (IBS-D) is responsible for at least some of the symptoms. Studies in IBS-D patients reported a decrease in *Bifidobacterium* and *Lactobacillus*, and an increase in *Escherichia coli* (*Proteobacteria*), *Clostridiales* (*Firmicutes*), and other pathogens. *Bifidobacteria* transform carbohydrates into short-chain fatty acids (SCFAs), which acidify the luminal environment and inhibit the adherence of pathogens like *E. Coli* and *Salmonella*[15]. *Faecalibacterium prausnitzii* is another beneficial bacterium that was found in reduced concentrations in patients with IBS-D. It produces butyrate and contributes to maintaining the mucosal integrity, and reduces the adhesion and colonization of pathogens in the intestinal tract. Pathogen bacteria produce toxins, colonize the submucosa, followed by activation of intestinal inflammation and increased permeability, which are responsible for abdominal pain, diarrhea, and abdominal distention[3]. Patients with IBS-D and abdominal distention and bloating have an increased abundance of *Clostridium coccoides* and *Bacteroides thetaiotaomicron*[16,17]. *Dorea* genus was associated with increased gas production and is increased in IBS-D[18].

Chen et al[14] reported no difference in microbial composition, at the phylum level, between IBS-D and IBS-C. However, they found differences when the results were compared with those of healthy individuals. The genra with increased abundance proportions both in IBS-D and IBS-C were *Streptococcus, Bacillus, Enterocloster, Sphingobacterium and Holdemania.* The genra that were depleted in both IBS subtypes were: *Faecalibacterium, Ruminococcus, Oscillibacter, Coprococcus* and others like *Acetivibrio, Lachnospira* or *Acidaminococus*[14].

Another study on patients with IBS-D reported as potential biomarkers of IBS-D the following: *Prevotella, Clostridiales,* and *Roseburia*. The biomarkers of healthy controls were *Veillonellaceae*, *Bacteroides coprocola*, and *Bifidobacteriales*[18].

Only a few genra were different between IBS-C and IBS-D patients. The genera of *Haemophilus, Peptoniphilus*, and *Roseburia* were depleted in IBS-C, and were enriched in IBS-D, while *Anaerofilum* was enriched in IBS-C but depleted in IBS-D. In addition, this study found no significant difference in the abundance of *Lactobacillaceae* family between IBS patients and controls[14].

Diet, Food Supplements, and IBS

Gut microbiota is closely related to diet, which acts as a prebiotic, favoring the growth of certain types of bacteria. Bacterial fermentation of nutrients influences the differentiation of stem cells[14] and might exacerbate some IBS symptoms[19,20]. In this context, restrictive diets might have beneficial effects[19].

A gluten-free diet (GFD) was found to influence the composition of the gut microbiota and fecal metabolites. These changes seem more evident in responders to a GFD than in non-responders. The study conducted by Algera et al[21] was supported by Bray-Curtis dissimilarity indices that estimated the β-diversity.

One recent study randomized 101 patients to 3 dietary interventions for a period of 4 weeks: traditional dietary advice (TDA), GFD, or low FODMAP diet. A dysbiosis index was determined for each stool sample based on a different bacteria composition compared to a healthy normobiotic reference range. There were no changes in the dysbiosis index between the 3 dietary groups. The authors also analyzed some functional bacterial profiles and their changes after diet: the levels of butyrate-producing bacteria, the levels of gut mucosa-protective bacteria, the levels of *F. prausnitzii*, the imbalance between gut barrier protective and potentially harmful bacteria, and the levels of proinflammatory bacteria. None of the three diets influenced the levels of these bacterial profiles. However, the abundance of the following species was decreased after a GFD, compared to baseline: *Actinobacteria* (phylum *Actinobacteria*), *Parabacteroides johnsonii* (phylum *Bacteroidetes*), *Eubacterium rectale, Ruminococcus albus,* and *R. bromii* (phylum *Firmicutes*)[22]. Following a Low FODMAP diet, the following species were

increased: *Alistipes, Parabacteroides johnsonii* (phylum *Bacteroidetes*), *Clostridium methylpentosum, Lachnospiraceae* (phylum *Firmicutes*), and the abundance of *Actinobacteria* and *Bacteroides fragilis* was decreased[22]. After TDA, there was a decrease in *Dorea* spp. (*Firmicutes* phylum) abundance, but no other changes in the abundance of bacterial species were noted[22].

Some patients with IBS have functional variants of the sucrase-isomaltase gene with reduced enzymatic activity and, consequently, insufficient starch and sucrose digestion[23]. Unabsorbed carbohydrates are fermented by intestinal bacteria and can be responsible for symptoms like diarrhea, bloating, flatulence, and abdominal pain. In addition, a diet rich in sugar increases the production of pro-inflammatory cytokines and increases inflammation[24]. A recent paper reported that a reduced intake of starch and sucrose for 4 weeks improved gastrointestinal symptoms in IBS patients[25]. Based on these preliminary observations, a recent randomized study[26] was conducted on 105 IBS patients who were randomized to a 4-week starch- and sucrose-reduced diet (SSRD) or to a control group. Patients were advised to avoid sweets, regular soda, processed foods, and cereals, but other carbohydrates from fruits, legumes, and vegetables, low in starch and sucrose, and whole grains were allowed. Stool samples and blood micro-RNA were analyzed. The authors analyzed the richness and evenness of microbiota in the two groups, before and after intervention. The beta diversity shifted significantly in the intervention group after 4 weeks, but not in controls. Beta diversity correlated with decreased carbohydrates, disaccharides, and starch intake. *Bacteroidetes* and *Firmicutes* were the dominant phyla in both IBS groups[26]. After the 4-week SSRD, the abundance of *Proteobacteria*, *Lentisphaere*, and *Cyanobacteria* increased, while *Bacteroidetes* decreased; a tendency of decrease in *Actinobacteria* was also noted[26].

Similarly, previous studies reported that a low FODMAP diet and a Mediterranean diet were associated with decreased *Actinobateria*[27]. The abundance of *Proteobacteria* correlated inversely with the intake of carbohydrates, disaccharides, and starch, while *Bacteroidetes* correlated positively with carbohydrates and starch[26]. These data confirm that diet influences the microbiome composition, and in order to decrease harmful bacteria like *Bacteroidetes*, patients with IBS should follow the recommendation to avoid sweets[28].

Ivashkin et al[29] administered for 30 days a food supplement containing menthol, for its antispasmodic and analgesic effect, D-limonene with a role in mucus barrier recovery, and gingerol, with antispasmodic and prokinetic effects. A total of 59 IBS subjects were randomized in a double-blinded manner. The symptoms alteration and the changes in the number of SCFA-producing bacteria, together with the qualitative and quantitative composition of intestinal microbiota, using 16S rRNA gene sequencing, were analyzed[29]. SCFA regulates the expression of tight contact proteins, T-lymphocytes, and cytokines involved in the permeability of the intestinal barrier[30]. In this study, the differences in the number of SCFA-producing bacteria were not different between the active and the control groups. There was a great variability regarding the bacterial composition between the two groups from the beginning of the study, and these differences remained after the intervention, *Oscillibacter* genra being predominant in the active group, before and after the intervention[29]. These results confirmed previous observations regarding the correlations between these bacteria and IBS severity[31] and showed that this supplement did not significantly change the microbial composition.

Geraniol, a component of essential oil, has well-known anti-inflammatory and antimicrobial properties and has eubiotic activity in gut microbiota in IBS patients[32]. Ricci et al[32] reported the effect of geraniol in IBS patients in a randomized double-blind clinical trial. Geraniol was effective in treating overall IBS symptoms, together with an improvement in the gut microbiota profile, especially for the IBS mixed subtype.

Clinoptilolite, a mineral from the group of natural zeolites, characterized by high absorptive capacity, was used in a randomized control trial in IBS-D patients. Positive effects were noted on the number of days with diarrhea; also, a minor increase in microbiota diversity was observed in the treated group compared to placebo[33].

Intestinal Microbiota and IBS Severity

Ji et al[34] reported that the levels of Lactobacillus and Bifidobacterium negatively correlated with IBS severity, while the higher the disease severity, the higher the levels of *Enterococcus* and *Enterobacter*. In addition, serum D-lactate and diamine oxidase (DAO) levels were higher in the IBS group compared to controls and increased with IBS severity[34]. Another study reported that after a 4-week

SSRD, there was a decrease in *Bacteroidetes* that correlated with IBS symptom improvement[26]. Ivashkin et al[29] reported that *Fusobacterium, Streptococcaceae, Coriobacteriaceae,* and *Veillonellaceae* positively correlated with IBS severity, while *Acidaminococcaceae* and *Enterobacteriaceae* abundance was negatively correlated with IBS severity.

Probiotics and IBS

One of the most documented probiotics in IBS is *Lactobacillus plantarum* 299v. It was reported to increase the microbiota diversity and promote intestinal barrier integrity[35]. Several studies confirmed its efficacy on abdominal pain, bloating, stool frequency, and consistency, irrespective of the IBS subtype.

Previous studies on animal models showed a good survivability of *Lactiplantibacillus* (formerly *Lactobacillus*) *plantarum* Apsulloc 331261 (GTB1), a high acid and bile salt tolerance and therefore the premises to successfully colonize the small intestine. GTB1 has good intestinal cell adhesion and anti-inflammatory efficacy and modulates the gut microbiota[36]. A recent double-blind, randomized, placebo-controlled trial evaluated the efficacy of GTB1 in 27 IBS-D patients compared to placebo[37]. In the GTB1 group, abdominal pain and severity of abdominal bloating significantly decreased after 4 weeks, and these improvements were maintained at 2 weeks follow-up. The frequency of symptoms, including the number of bowel movements per week, also decreased in the treatment group but not in the placebo group. The relative abundance of *Lactobacillus* significantly increased in the GTB1 group, while the relative abundance of Bacteroides significantly decreased after one week of ingestion. These changes in the microbiota correlated with a decreased frequency of diarrhea[37].

Fecal microbiota transplantation and IBS

The role of FMT for IBS treatment is still controversial. Despite several RCTs showing good effects of FMT in IBS patients, 2 meta-analyses found now benefit of FMT compared to controls on IBS-symptom severity score (IBS-SSS) or IBS-QOL[38,39].

A recent study showed a better response to FMT in severe IBS compared to moderate IBS. After FMT, patients with severe IBS had higher levels of *Eubacterium siraeum*, and lower levels of *Eubacterium rectale* than patients with moderate IBS[40]. The same group of authors investigated the possible factors that might predict the clinical response to FMT in IBS patients. The fecal bacterial profile and dysbiosis index were determined using 16S rRNA gene PCR DNA amplification. Male sex and those with low baseline fecal *Alistipes* levels were unlikely to respond to FMT treatment[41].

A recent study from Japan reported the beneficial effects of FMT in refractory IBS patients. The authors evaluated the IBS severity index and Bristol Stool Form Scale and compared the diversity and microbiome before and 12 weeks after FMT. The relative abundance of *Neisseria* and *Akkermansia* increased, and *Desulfovibrio* and *Delftia* decreased in the responder group after FMT[42].

CONCLUSIONS

Recent evidence found that *Streptococcus, Bacillus, Enterocloster, Sphingobacterium*, and *Holdemania* were increased in IBS-D and IBS-C patients, while *Faecalibacterium, Ruminococcus, Oscillibacter, Coprococcus, Acetivibrio, Lachnospira*, or *Acidaminococus* were depleted in both IBS subtypes. The influence of different diets (traditional dietary advice, GFD, and low FODMAP) on microbiota in IBS patients found no changes in the dysbiosis index. In contrast with previous meta-analyses regarding the effect of FMT on IBS patients, recent papers argue for its beneficial effect.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest

The authors declare that they have no conflict of interest to declare.

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Authors' Contributions

T.S.B. and D.L.D. had the idea for the manuscript. T.S.B. and L.C. independently applied the search strategy and performed the study selection. T.S.B. and A.I. performed the data extraction. T.S.B. and L.C. drafted the manuscript. A.I. and D.L.D. contributed to the writing of the manuscript. T.S.B., L.C., A.I., D.L.D. made substantial contributions to the conception and critically revised the manuscript for important intellectual content. All authors revised the final manuscript and approved the final version.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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