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REVIEW

A Review of Microbiota and Irritable Bowel Syndrome: Future in Therapies

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ABSTRACT

Irritable bowel syndrome (IBS), one of the most frequent digestive disorders, is characterized by chronic and recurrent abdominal pain and altered bowel habit. The origin seems to be multifactorial and is still not well defined for the different subtypes. Genetic, epigenetic and sex-related modifications of the functioning of the nervous and immune-endocrine supersystems and regulation of brain-gut physiology and bile acid production and absorption are certainly involved. Acquired predisposition may act in conjunction with infectious, toxic, dietary and life event-related factors to enhance epithelial permeability and elicit mucosal microinflammation, immune activation and dysbiosis. Notably, strong evidence supports the role of bacterial, viral and parasitic infections in triggering IBS, and targeting microbiota seems promising in view of the positive response to microbiota-related therapies in some patients. However, the lack of highly predictive diagnostic biomarkers and the complexity and heterogeneity of IBS patients make management difficult and unsatisfactory in many cases, reducing patient health-related quality of life and increasing the sanitary burden. This article reviews specific alterations and interventions

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targeting the gut microbiota in IBS, including prebiotics, probiotics, synbiotics, non-absorbable antibiotics, diets, fecal transplantation and other potential future approaches useful for the diagnosis, prevention and treatment of IBS.

Keywords: Diet; FODMAP; Irritable bowel syndrome; Microbiota; Non-absorbable antibiotic; Prebiotic; Probiotic; Synbiotic; Treatment

IRRITABLE BOWEL SYNDROME: DEFINITION, MORBIDITY, GENERAL TREATMENT OPTIONS AND INTRODUCTION TO MICROBIOME MANIPULATION

Irritable bowel syndrome (IBS) is one of the most prevalent functional gastrointestinal disorders (FGIDs), afflicting around 11% of the adult population worldwide. Due to the lack of specific and sensitive diagnostic biomarkers, IBS is still diagnosed by symptomatic criteria, namely the Rome criteria (Rome IV in its current version) [1]. IBS is characterized by abdominal pain and changes in stool consistency and frequency along with other common manifestations including abdominal distention, bloating or flatulence. Based on the predominant bowel habit, patients are stratified into four subtypes: IBS with predominant constipation (IBS-C); IBS with predominant diarrhea (IBS-D); mixed IBS (IBS-M); unsubtyped IBS.

Although IBS's origin remains unsettled, growing evidence indicates that factors including food, bile acids, antibiotics and infections, sex and psychosocial events are all implicated [2]. These factors, acting in genetically and epigenetically predisposed individuals [3], may drive alterations in the gut epithelial barrier, increasing intestinal permeability, which, via activation of local and brain immune and neuroendocrine responses and changes in the microbiota, can induce abnormal secretory and sensorimotor outputs in the gut [4–6] that relate to symptom duration and severity. Not less important is the clear association with other gastrointestinal disorders, mainly functional dyspepsia, and with other chronic pain disorders and psychiatric conditions such as fibromyalgia, migraine, pelvic pain, anxiety or depression [4, 7]. Despite the availability of a great variety of therapeutic options, treatment satisfaction is suboptimal for both the patient and doctor [8, 9]. A relevant implication of associated comorbidities and treatment dissatisfaction is a marked reduction in quality of life and growing social, sanitary and economic burden worldwide. On average, IBS patients miss 2 days of work/-month, and work productivity is diminished 9 days/month [10]. In the USA, indirect costs can reach up to 20 billion dollars/year with annual costs of 7000–10,000 dollars/patient (2500 dollars more than controls annually) mainly leading by absenteeism, presenteeism and affected daily activity impairment [10]. Moreover, IBS is associated with 3.6 million physician visits per year [11], and health care costs are approximately 50% higher than for matched controls who do not have IBS and are similar to the costs of migraine and asthma patients [12]. Therefore, a pressing issue is to achieve a deeper understanding of its physiopathology to improve the therapeutic strategies and armamentarium. In this line, it is worth mentioning the advent of a new class of drugs, such as linaclotide for IBS-C or eluxadoline for IBS-D, intended to treat bowel habit and pain at the same time. However, we are still lacking approaches that may be effective for changing the natural history of the disease.

One such approach could be targeting the microbiome in IBS. IBS patients display several qualitative and quantitative alterations of the fecal microbiota [13, 14], and there is strong evidence supporting the role of bacterial, viral and parasitic infections in triggering IBS [15]. Some IBS patients respond well to certain non-absorbable antibiotics [16] and prebiotic/probiotic administration [17, 18], and improvement after fecal transplantation is being analyzed [19, 20]. Therefore, the role of the intestinal microbiota emerges as an essential feature in developing future therapeutic approaches in IBS.

METHODOLOGY

A search for studies published before December 2017 was performed in the PubMed database.

The literature search was performed in each section of the article for the explained topic, and the bibliographies of all identified relevant studies were used to perform a recursive search to find original and additional references. Information was found looking for the terms "irritable bowel syndrome," "microbiota," "metagenome," "treatment," "prebiotic," "probiotic," "synbiotic," "postbiotic," "FODMAP," "meta-analysis," "randomized," "clinical," "bifidobacterium," "bifidobacteria," "lactobacillus," "firmicutes," "bacteroidetes," "methane," "methanogen," "diet," "genetic manipulation," "fecal transplantation," "bacteriophage," "phage therapy," "fungi" and "archeabiotics" and mainly focusing on the literature that describes effects on microbiota, clinical studies and therapeutic effects in IBS. These terms were combined with the AND operator. The search was restricted to articles in English. Conference abstract books were hand-searched to identify potentially eligible studies published only in abstract form. All authors participated in the bibliographic search. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

THE MICROBIOME IN IBS

A growing body of evidence indicates dysbiosis as a hallmark of IBS (Table 1). Despite divergences between studies, there is good evidence that the microbiota is a predominant factor in the IBS pathophysiology. In general, data suggest that there is a relative abundance of proinflammatory bacterial species including *Enterobacteriaceae*, with a corresponding reduction in *Lactobacillus* and *Bifidobacterium* [21]. A decreased percentage of *Lactobacillus* [22–24] and *Bifidobacterium* [23, 25–28] genera has also been described in the IBS microbiota. *Lactobacillus* and *Bifidobacterium* genera can interact with other bacterial species or the host to modulate the microbiota and the immune system. Several species of *Lactobacillus* and *Bifidobacterium* genera can secrete bacteriocins, compounds that exert, in vitro, a bactericidal effect against pathogens such as the Salmonella genus or Listeria monocytogenes species [29]. Moreover, *Lactobacillus* and *Bifidobacterium* genera can modulate the host immune system through the development of a tolerogenic response via dendritic cells by interacting with CD209 [30]. Additionally, the *Bifidobacterium* genus, *Clostridiales* order, *Ruminococcaceae* and *Erysipelotrichaceae* families, all short chain fatty acids (SCFAs) producers, have been found in lower proportions in IBS patients [31, 32]. The opposite results have also been described in three recent studies that found an increase in the *Lactobacillus* genus or *Lactobacillales* order in IBS-D [33–35]. At the genus level, other alterations have been described in IBS, such as an increase in *Veillonella* [23, 33, 34] or *Ruminococcus* [23, 26, 36, 37] or a decrease in *Faecalibacterium* [26, 38].

The *Firmicutes*/*Bacteroidetes* ratio is a rough indicator of bacterial population shifts, and both a higher [26, 33, 39, 40] and lower ratio of *Firmicutes*/*Bacteroidetes* [31, 41] has been described in IBS. Several hypotheses may explain these differences, such as technical differences

Table 1 Summary of dysbiosis findings in IBS

Taxon	Percentage in IBS	Citations
Enterobacteriaceae	Higher	[38]
Lactobacillus	Lower	[22–24]
Lactobacillus genus or *Lactobacillales* order	Higher	[33–35]
Bifidobacterium	Lower	[23, 25–28]
Firmicutes/Bacteroides	Higher	[26, 33, 39, 40]
Firmicutes/Bacteroides	Lower	[31, 41]
Clostridiales		[31]
Ruminococcaceae or *Ruminococcus*	Higher	[23, 26, 31, 36, 37]
Erysipelotrichaceae		[31]
Methanogens	Lower	[39, 45]
Veillonella	Higher	[23, 33, 34]
Faecalibacterium	Lower	[26, 38]

between 16 s variable regions or DNA extraction methods [31, 42], low number of subjects, differences in predominance of IBS subtypes [39] or even IBS severity [39, 43]. However, the usefulness of this ratio may be limited to specific microbiota manipulations since both *Firmicutes* and *Bacteroidetes* belong to a higher taxonomic level (i.e., the phylum level for *Homo sapiens* is *Chordata*). An improvement in the genus-species analysis through new metagenomic bioinformatic strategies is required to identify microbiota changes as a consequence of manipulation and treatment.

An interesting finding is the association of methane production and IBS, with lower levels in IBS-D and higher levels in IBS-C [39, 44, 45]. Methane production is limited to methanogens from the *Archaea* kingdom that convert H_2 to produce methane. In the human microbiota, the *Methanobacteriales* order is the most common methane producer. Methane has been related to slower intestinal transit [46, 47] and also to anti-inflammatory effects. The increased production of methane in constipated patients could be related to microbial overgrowth because *Methanobacteriales* detection is associated with microbial richness within the enterotype *Clostridiales*, which is further associated with slower transit [39, 48, 49]. In fact, IBS symptom severity correlates with all microbial richness, exhaled methane, presence of methanogens and enterotypes enriched with *Clostridiales* or *Prevotella* species. Despite the strong association with clinical significance, this microbiota signature cannot yet be explained by genetic factors, differences in diet or the use of medications.

To better determine the role the microbiota plays in the IBS pathophysiology, it is important to identify the interaction between factors that influence the IBS severity and bacterial composition. For instance, sex has been associated with microbiota diversity and functional richness (clusters of orthologous groups) level in a population-based study [50]. Women showed higher richness in clusters of orthologous groups, an effect that was not found in IBS studies, despite differences in enterotype proportions between sexes [39]. Psychiatric comorbidity may also be associated with IBS dysbiosis, as transplantation of IBS-D microbiota to mice can alter anxiety levels [51]. Therefore, sex and psychiatric comorbidities may be essential variables to explain the underlying and specific microbial changes in IBS.

THERAPEUTIC OPTIONS IN MANAGING THE INTESTINAL MICROBIOME IN IBS

While it is not clear whether quantitative (small intestinal bacterial overgrowth) and qualitative (dysbiosis) alterations in the intestinal microbiota in IBS precede or are merely a consequence of disturbed local gut microenvironmental conditions, the use of specific interventions to modulate gut microbiota is being tested as a new tool to implement in IBS management. This is based on several facts [52]: some critical IBS features such as visceral colonic hypersensitivity can be transferred from IBS patients to germ-free rats by fecal transplant [53]; gastrointestinal infections increase the overall relative risk of developing IBS by a factor of 4.23, depending on the germ involved [15]; randomized placebo-controlled trials with non-absorbable antibiotics such as rifixamin may benefit IBS patients [16]; some pro-/prebiotics can alleviate IBS symptoms, though more evidence is needed [18]; dietary interventions known to modify the intestinal microbiota have also been shown to be effective in randomized placebo-controlled trials [54]. Preliminary observations suggest improvement of symptoms after fecal microbiota transplantation [55].

Pre-, Pro- and Synbiotics

The current definition of probiotics was formulated in 2002 by the Food and Agriculture Organization of the United Nations and World Health Organization experts [56] and maintained by the International Scientific Association for Probiotics and Prebiotics in 2013 [57]. It states that probiotics are "live strains of strictly selected microorganisms which, when

administered in adequate amounts, confer a health benefit on the host." Prebiotics have been defined since 2007 as a nonviable food component that confers a health benefit on the host associated with modulation of the microbiota [58]. Finally, synbiotics refer to the combination of synergistically acting probiotics and prebiotics [59], where a selected component introduced to the gastrointestinal tract should selectively stimulate growth and/or activate the metabolism of a physiologic intestinal microbiota, thus having a beneficial effect on the host's health [60]. The term should be reserved for those products in which a prebiotic component selectively favors a probiotic microorganism [61].

Prebiotics

Prebiotics may be classified as disaccharides, such as lactulose, oligosaccharides including fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS), isomalto-oligosaccharides, xylo-oligosaccharides, transgalacto-oligosaccharides (TGOS) and soybean oligosaccharides, and polysaccharides, such as the fructan inulin, reflux starch, cellulose, hemicellulose or pectin [62]. Natural sources of prebiotics are cereals, fruit, green vegetables and plants including bananas, asparagus, artichokes, berries, tomatoes, garlic, onions, legumes, chicory, linseed, oats, barley and wheat [63]. Some artificially produced prebiotics are lactulose, GOS, FOS, malto-oligosaccharides, cyclodextrins and lactosaccharose.

Prebiotics are resistant to enzymatic and chemical digestion until they reach the large intestine, where fermentation by non-pathogenic colonic bacteria promotes generation of microbial metabolic end products as SCFAs, particularly acetate, butyrate and propionate, which bind 'metabolite-sensing' G-protein-coupled receptors such as GPR43, GPR41 and GPR109A [64]. These receptors develop key roles in the promotion of gut homeostasis and the regulation of inflammatory responses influencing Treg and dendritic cell biology, epithelial integrity, IgA antibody responses and gene transcription such as the formation of mucin, antimicrobial peptides and tight junctions [62, 65]. In addition, microbial metabolic end products are an energy source for the epithelium, muscle and brain, decrease the pH leading to decreased bile acid solubility in the colon, increase mineral absorption, decrease ammonia absorption, stimulate absorption of water and sodium, increase colonic blood flow and oxygen uptake and regulate the host metabolism, affecting cholesterol production, liver lipogenesis or satiety [65]. Notably, prebiotics such as inulin-type fructans and short-chain FOS may also induce other microbiota-independent benefits for the host such as potent immunomodulatory effects [58] and direct promotion of barrier integrity [59].

Prebiotics have great potential for modifying individual strains and species of the gut microbiota. For instance, prebiotic GOS can be specifically digested by Bifidobacteria [66], promoting the growth of *Bacteroides*, lactobacilli and especially *Bifidobacterium* [67]. Table 2 lists some of the more common prebiotics and the bacteria whose growth is specifically favoured. A more extensive description of the prebiotic bacterial specificity is reviewed in [67].

Few randomized control trials have been performed in IBS patients. Two studies did not show any improvement [68, 69]. However, two other studies observed symptom improvement. Silk et al. used a prebiotic mixture of TGOS (3.5–7 g/day) in a randomized, single-blinded, placebo-controlled, crossover study of patients with IBS (23 IBS-D, 12 IBS-C and 9 IBS-M) [70]. Patients who received the prebiotic mixture experienced significant improvements in stool consistency, flatulence, bloating, composite symptom score and subjective global assessment compared with baseline after 4 weeks of treatment ($P < 0.05$, for all vs. baseline). The prebiotic mixture significantly increased fecal levels of *Bifidobacterium* after 4 weeks of treatment compared with placebo ($P < 0.005$). Increased bifidobacteria by prebiotic administration was observed in other studies [71–73] and, in consequence, can increase SCFAs production with the effects previously described [65]. In the same study, lower proportions of the *Clostridium perfringens* subgroup *histolyticum* and *Bacteroides/Prevotella* spp were observed after a 7 g/day TGOS, but increased proportions of *E. rectale/C. coccoides* after 3.5 g/day TGOS.

Table 2 Specificity of prebiotic treatment

Prebiotic	Dose (g/day)	Duration	Studied species	Detection method	Affected taxon	Citation
AX	10	10 days	Total anaerobes, aerobes, bifidobacteria, eubacteria, *Bacteroides* spp., *Clostridium* spp., *Veillonella*, *Lactobacillus*, *Streptococci*, *Staphylococci*, yeasts and molds, *Enterobacteriaceae*	Specific agar cultures	No differences	[154]
scFOS	4	2 Weeks	Anaerobes, *bifidobacterium* and *lactobacillus*	Specific agar cultures	Increased bifidobacteria and lactobacilli	[155]
Inulin and FOS	15	45 days	Anaerobes, total aerobes, coliforms, gram-positive cocci, bifidobacteria, *Bacteroides*, *Fusobacteria*, lactobacilli and *Clostridia*,	Specific agar cultures	Increased predominance of bifidobacteria	[59]
FOS	12.5	12 days	Anaerobes and bifidobacteria	Specific agar cultures	Increased bifidobacteria	[156]
FOS	4	42 days	Anaerobes, enterobacteria and bifidobacteria	Specific agar cultures	Increased bifidobacteria	[157]
Inulin and lactose	20–40	19 days	Anaerobes, bifidobacteria, lactobacilli and *Bacteroides* spp	Specific agar cultures	Increased bifidobacteria, decreases enterococci and *Fusobacteria*	[158]
GOS	15		Lactic acid bacteria and bifidobacteria	Specific agar cultures	Increased fecal lactic acid bacteria	[159]
Inulin	34	64 days	Total and bifidobacteria	FISH	Increased bifidobacteria	[160]
scFOS	2,5–20	14 days	Anaerobes and bifidobacteria	Specific agar cultures	Increased bifidobacteria	[161]
FOS	8	5 weeks	Anaerobes, *Bacteroides*, lactobacilli, Coliforms, *Clostridium perfringens*, bifidobacteria	Specific agar cultures	Increased bifidobacteria	[162]
FOS	5	3 weeks	Total anaerobes, total aerobes, *Bacteroides*, bifidobacteria, coliforms	Specific agar cultures	Increased bifidobacteria and *Bacteroides*	[163]
Inulin	8	2 weeks	Bifidobacteria, *Bacteroides*, *Clostridia* (*Clostridium perfringens/histolyticum* sub.grp.) and lactobacilli/enterococci	FISH	Increased bifidobacteria	[164]
FOS	7	42 days	Bifidobacteria, *Bacteroides*, *Clostridia* (*Clostridium perfringens/histolyticum* sub.grp.) and *Lactobacillus-Enterococcus* spp.	FISH	Increased bifidobacteria	[165]
scFOS	8	3 weeks	*Enterobacteriacea*e, bifidobacteria, lactobacilli, *Clostridium perfringens*, *Bacteroides* and *Enterococci*	Specific agar cultures	Increased bifidobacteria	[166]
Inulin	9	2 weeks	Total bacteria, bifidobacteria, *E. rectale/C. coccoides*, *Bacteroides*, eubacteria	FISH, DGGE	Increased bifidobacteria	[167]
GOS and FOS	0.4 and 0.8	28 days	Bifidobacteria, lactobacilli, *Bacteroides*, *Clostridium* species, *Escherichia coli, Enterobacter*, *Citrobacter*, *Proteus*, *Klebsiella* and *Candida*	Specific agar cultures	Growth of bifidobacteria and lactobacilli	[168]
Inulin	20 g Nutricia inulin (%?)	3 weeks	Total aerobes, enterobacteria, *Enterococcus*, *Pseudomonas* sp., total anaerobes, total *Bacteroides*, *Bacteroides* fragilis, *Clostridia*, lactobacilli, bifidobacteria, yeast and fungi	Specific agar cultures	Decreased *Bacteroides fragilis*	[169]
scFOS or GOS	10	6 weeks	Total anaerobes, *Bifidobacterium*, *Bacteroides*, *Lactobacillus* and enterobacteria	Specific agar cultures	Increased fecal bifidobacteria	[170]

Table 2 continued

Prebiotic	Dose (g/day)	Duration	Studied species	Detection method	Affected taxon	Citation
FOS and inulin	2,8 to 3,4	2 weeks	Total anaerobes, *Bifidobacterium* and *Bacteroides*, *Clostridium difficile*, lactobacilli, enterococci, *Veillonella* by culture. *Bifidobacterium* genus, *Atopobium* cluster and *Coriobacterium*, *Escherichia coli*, *Bacteroides distasonis*, B. *fragilis*, *Clostridium histolyticum*, *C. lituseburense*, C. *coccoides* and *Eubacterium rectale*, *Streptococcus–Lactococcus*, *Lactobacillus* and *Enterococcus* by FISH	Specific agar cultures and FISH	Increased bacteria	[171]
Low and high SOS (LSO and HSO)	1.5 or 3	30 days	Total bacteria and bifidobacteria	Specific agar cultures	Increased bacteria with both LSO and HSO; increased bifidobacteria only with HSO	[172]
scFOS	8	4 weeks	Total anaerobes, *Bifidobacterium*, *Clostridium* spp. and enterobacteria	Specific agar cultures	Increased fecal bifidobacteria	[173]
XOS	3.8	3 weeks	*Bifidobacterium*, *C. perfringens*	Specific agar cultures	Increased bifidobacteria	[174]
Inulin	7.7 then 15.4	3 weeks	Bacteria, *Clostridium coccoides/Eubacterium rectale*, *Bacteroides/Prevotella* (*Bacteroides fragilis* group and *Bacteroides distasonis*), *Faecalibacterium prausnitzii*, bifidobacteria, *Atopobium*, *Clostridium histolyticum*, *Clostridium lituseburense* by FISH. *Enterobacteriaceae*, lactobacilli, enterococci and *Clostridium perfringens* and yeasts by specific culture	FISH and specific agar cultures	Increased bifidobacteria and decreased *Bacteroides*	[175]
Inulin	5–8	2 weeks	*Bacteroides/Prevotella*, *Bifidobacterium* genus, *Clostridium perfringens histolyticum* subgroup and *Lactobacillus/Enterococcus*	FISH	Increased bifidobacteria	[176]
GOS, FOS	03-ene	3 months	Bifidobacteria, *Clostridia* and *E.coli*	FISH	Increased *Bifidobacterium*; decreased *E. coli* and *Clostridium*	[177]
Inulin/FOS	10	4 weeks	V3 profiles. Specifically, *Bifidobacterium* by qPCR	DGGE and qPCR	Increased bifidobacteria	[178]
GOS	3.6–7	7 days	*Bifidobacterium* genus, *Clostridium perfringens/histolyticum* subgroup, *Bacteroides–Prevotella* and *Lactobacillus/Enterococcus* spp	FISH	Bifidogenic effect	[179]
GOS, FOS	6 g/l ratio 9:1	27 weeks	*Bifidobacterium*, *Clostridium histolyticum/Clostridium lituseburense*, *E. coli*	FISH	Increased *Bifidobacterium*; decreased *Clostridium*	[180]
FOS and inulin	11.1:3.6	6 weeks	*Bifidobacterium*	qPCR	'Nearly significant" increased *Bifidobacterium*	[181]
AXOS	10	21 days	Total bacteria, *Bifidobacterium* spp., *Bifidobacterium adolescentis*, *Lactobacillus* spp., *Roseburia–Eubacterium rectale*, enterobacteria	qPCR	Increased bifidobacteria; decreased lactobacilli	[182]
FOS and inulin	6.8 ± 1.5	2 weeks	Bifidobacteria, lactobacilli and enterococci, *Bacteroides* and *Clostridia coccoides–Eubacterium rectale*	FISH	No differences	[183]
FOS and inulin	Not indicated	1–2 weeks	Bifidobacteria, lactobacilli, *Clostridia*, *Bacteroides* and *Faecalibacterium prausnitzii*	FISH	Decreased *F. prausnitzii*	[184]
β-GOS (Bimuno™)	5.5	5–10 weeks	*Bifidobacterium* spp., *Bacteroides* spp., *Atopobium* cluster, *Lactobacillus/Enterococcus* spp., *Fecalibacterium prausnitzii* cluster, *Roseburia/Eubacterium rectale* group, *Clostridium coccoides/E. rectale* group, *Clostridium histolyticum* group, *E. coli*, *Desulfovibrio* spp.	FISH	Increased bifidobacteria and *Bacteroides*. *Atopobium* cluster increased in the follow-up	[72]
GOS	Escalating from 1.5 to 15	36 days	16 s rRNA gene v1-v2 amplicon	454 Genome Sequencer FLX Titanium	Increased *Bifidobacterium*, *Faecalibacterium* and *Lactobacillus*	[185]
Inulin/FOS	16	3 months	1100 Intestinal bacterial phylotypes	Human Intestinal Tract Chip (HITChip) and qPCR	Increased *Bifidobacterium*, *Faecalibacterium prausnitzii*, *Lactobacillus* spp.; decreased *Bacteroides intestinalis* and *vulgatus*.	[186]

Table 2 continued

Prebiotic	Dose (g/day)	Duration	Studied species	Detection method	Affected taxon	Citation
GOS	10	4 weeks	16 s rRNA Gene v1-v2 amplicon	Illumina MiSeq	Increased *Bifidobacteriaceae*; decreased *lachnospiracae*, *Ruminococcaceae*, *Peptostreptococcaceae*, *Erysipelotrichacae*, *Porphyromonadaceae*	[187]
FOS and GOS		2 weeks	16 s rRNA gene v4 amplicon	Ion Torrent	FOS increased *Bifidobacterium*; FOS decreased abundance of *Phascolarctobacterium*, *Enterobacter*, *Turicibacter*, *Coprococcus* and *Salmonella*. GOS increased *Bifidobacterium*; GOS decreased *Ruminococcus*, *Dehalobacterium*, *Synergistes* and *Holdemania*.	[188]
Inulin	8	16 weeks	16 s rRNA gene v3-v4 amplicon	Illumina MiSeq	Increased *Bifidobacterium* spp (*Bifidobacterium adolescentis* and *Bifidobacterium longum*); decreased *Clostridium cluster XI*, *Faecalibacterium prausnitzii*, *Bacteroides vulgatus*, *Ruminococcus gauvreauii* (all differences before correction)	[189]
FOS and inulin	16	9 weeks	16 s rRNA gene v3-v4 amplicon	Illumina MiSeq	Increased *Bifidobacterium*	[190]
Inulin	12	4 weeks	16 s rRNA gene v4 amplicon	Illumina MiSeq	Increased *Bifidobacterium* and anaerostipes; decreased *Bilophila*	[191]

Interestingly, *Bifidobacterium* has several mechanisms to effectively compete with *Clostridium perfringens* as specific growth in the presence of FOS, secretion of antimicrobial peptides and induction of low environmental pH [74, 75]. Different clinical responses were also found between doses, with the low dose being more effective the low dose. In a randomized, double-blind study of healthy individuals with mild functional bowel symptoms, Paineau et al. showed that regular consumption of FOS (5 g/day) reduced the frequency and intensity of digestive symptoms and improved intestinal discomfort and quality of life compared with placebo after 6 weeks [76].

Because bifidobacteria concentrations have been found to be reduced in IBS compared with healthy controls, it seems reasonable, logical and safe to use prebiotics to enhance the growth of bifidobacteria and other beneficial bacteria to improve symptoms in these patients. However, based on available evidence, general use cannot be recommended in patients with IBS [18, 77]. More controlled studies are needed to understand the type and dose of the prebiotic and the benefit/harm derived from their use in IBS.

Probiotics

Consistent with the known IBS pathophysiology, probiotics, principally those containing *Lactobacillus* sp. and *Bifidobacterium* sp. [78], theoretically might be able to induce beneficial modulation of altered gut microbiota: reducing the number of competing pathogens by both production of antimicrobial substances and interfering in intestinal mucosal adhesion [18, 79–81], modulating the metabolism of biliary salts [82] and reducing low-grade inflammation by cytokine and Toll-like receptor modulation [83], immune activation, intestinal permeability by tight junction complex regulation [83], visceral hypersensitivity, gastrointestinal dysmotility [14, 84] and even brain activity and depression [85]. Proposed mechanisms of action are extensively reviewed in [83]. However, interpreting results from probiotic studies in IBS is challenging because of enrollment of patients with different IBS subtypes and the use of multiple probiotic strains and doses

across studies, which may obscure the beneficial effects of individual strains within that species.

Several recent meta-analyses assessed the role of probiotics in the IBS population. Ford et al. found 35 randomized-controlled trials (RCTs) eligible for inclusion. The relative risk (RR) of IBS symptoms persisting with probiotics vs. placebo was 0.79 (95% CI 0.70–0.89) and the number needed to treat was 7. Probiotics had beneficial effects on global IBS, abdominal pain, bloating and flatulence scores. Some combinations of probiotics were superior to individual species or strains, although no specific combination was superior to another. Adverse events were more common with probiotics (16.5%) compared with placebo (13.8%). The pooled RR of any adverse event in patients taking probiotics versus placebo was 1.21 (95% CI 1.02–1.44), with a number needed to harm of 35. [18]. Didari et al. analyzed 15 RCTs to show that probiotics were better than placebo in reducing overall symptoms and abdominal pain in IBS after 8–10 weeks of therapy [81]. Interestingly, probiotics also improved mucosal barrier function in pediatric and IBS-D adult patients, particularly in females. A third meta-analysis included 21 RCTs [86]. Probiotic therapy was associated with more improvement than placebo in overall symptom response (RR: 1.82, 95% CI 1.27–2.60) and quality of life, but not in individual IBS symptoms. In this meta-analysis, single probiotics, a low dose and short treatment duration were more effective than other combinations. Single probiotics for IBS were also analyzed by Ford et al. with variable results [18]: six trials of *Lactobacillus* (RR of persistence of symptoms = 0.75; 95% CI 0.54–1.04), two RCTs of *Bifidobacterium* (RR of persistence of symptoms = 0.71; 95% CI 0.44–1.16), two RCTs of *Escherichia* (RR of persistence of symptoms = 0.86; 95% CI 0.79–0.93) and one RCT of *Streptococcus* (RR of persistence of symptoms = 0.79; 95% CI 0.79–0.89). Other RCTs have evaluated different formulas, such as a combination of *Bifidobacterium*, *Lactobacillus* and *Streptococcus* [87] or a single-strain probiotic containing *Bacillus coagulans* in combination with simethicone [88], showing improvement in pain, bloating and overall IBS symptom scores and in bloating, respectively, though the last trial did not include a treatment arm of only simethicone. Moreover, some focused meta-analyses investigated the role of *Saccharomyces boulardii* [89] and *B. infantis* [90] in adults, *Lactobacillus rhamnosus* GG in children [91] and *Lactobacillus* species and strains in both children and adults [92] with IBS. *S. boulardii* induced a significant improvement of bowel frequency, but even this result was replicated in animal stress and viral infection models, and the mechanism is not known [93, 94]. *B. infantis* alone did not have an impact on abdominal pain, bloating/distention or bowel habit satisfaction though patients who received composite probiotics containing *B. infantis* had significantly reduced abdominal pain (standardized mean difference (SMD), 0.22; 95% CI, 0.03–0.41) and bloating/distention (SMD, 0.30; 95% CI, 0.04–0.56). *B. infantis* effects could be partially associated with the cytokine normalization in IBS [95], but more studies are needed in this direction. *L. rhamnosus* reduced the intensity and frequency of abdominal pain, and *Lactobacillus* achieved a significant RR of clinical improvement of 7.69 overall. *L. rhamnosus* showed a strong adherence and production of antimicrobial peptides competing effectively with pathogenic bacteria. Moreover, it can enhance TLR2 in epithelial cells in vitro [83]. Very recent meta-analyses found *Saccharomyces cerevisiae* CNCM I-3856GI modestly effective in decreasing IBS symptoms in adults only during supplementation [96]. This benefit was also observed in some (but not all) studies in children regarding the frequency and intensity of abdominal pain, for example, with a combination of three Bifidobacterial species or *L. reuteri* DSM 17938 [97, 98].

Overall, pooled conclusions of all these studies indicate that probiotics are effective treatments for IBS, although which individual species and strains are the most beneficial remains unclear. Therefore, further evidence is required to ascertain the benefits of the use of probiotics in dealing with particular IBS symptoms.

Synbiotics

Relatively few randomized controlled trials have examined the effect of symbiotics on outcomes

in IBS. Min et al. analyzed composite yogurt enriched with acacia fiber and *Bifidobacterium lactis* vs. a placebo yoghurt drink in 130 IBS patients [99]. There was a significant benefit for IBS symptoms and bowel habit satisfaction in both IBS-D and IBS-C. Tsuchiya et al. used a combination of *L. acidophilus*, *L. helveticus* and *Bifidobacterium* species in a vitamin and phyloextract-enriched medium for 12 weeks compared versus a heat-inactivated symbiotic; 80% of patients with IBS reported the preparation as effective when compared with baseline and control IBS severity scores after 6 weeks ($P < 0.01$) [100]. Further RCTs by Rogha et al. [101] and Saneian et al. [102] showed significantly higher improvement of abdominal pain and diarrhea over placebo in adult and children with IBS, respectively, when taking a symbiotic preparation containing *Bacillus coagulans* and FOS with placebo in 12-week follow-up studies. However, dropout rates were 41% in the treatment group, mainly because of adverse events in the study by Rogha. Šmid et al. randomized 76 IBS-C patients (test = 33, control = 43) to receive a synbiotic fermented milk containing *Lactobacillus acidophilus* La-5® and *Bifidobacterium* BB-12 or placebo (heat-treated fermented milk without probiotic bacteria and dietary fibers) [103]. On average, an 18% improvement in the total IBS-QoL score was reported as well as significant improvements in bloating severity and satisfaction with bowel movements although there were no statistically significant differences between the synbiotic group and the placebo group. Abbas et al. demonstrated a significant reduction in proinflammatory cytokines interleukin-8 and tumor necrosis factor-α, and an increase in the anti-inflammatory cytokine interleukin-10, but no difference in overall symptom severity scores or quality of life in 72 IBS-D randomized to 6 weeks of *Saccharomyces boulardii* or placebo in combination with ispaghula husk [104]. Finally, Baştürk et al. found that *Bifidobacterium lactis* B94 with inulin was superior to inulin alone in improving belching, bloating and constipation in IBS children [105]. Despite promising evidence, more data from RCTs are needed to support the benefits of synbiotics in managing IBS.

Non-absorbable Antibiotics

Although the mode of action of non-absorbable antibiotics in IBS is unclear, relief of symptoms is thought to derive from both the reduction of the gastrointestinal bacterial load and changes in bacterial composition [14] and also by modulating intestinal permeability and fecal microbiome [106]. Neomycin produced a 50% improvement in global IBS symptoms compared with placebo, but also induced rapid bacterial resistance [14]. However, the best studied is the nonsystemic, broad-spectrum antibiotic rifaximin. Rifaximin has shown efficacy in several small-scale studies of IBS as well as three large-scale, phase 3, double-blind, placebo-controlled, multicenter trials (TARGET 1–3). In TARGET 1 and TARGET 2, patients affected by mild to moderate IBS without constipation ($N = 1258$) received either rifaximin 550 mg or placebo three times daily for 2 weeks, followed by 10 weeks of follow-up without medication. Significantly more patients in the rifaximin group than in the placebo group had adequate relief of global IBS symptoms during the first 4 weeks after treatment. The percentage of patients with adequate relief decreased over time in both groups, but remained higher for patients treated with rifaximin compared with patients receiving placebo during all 3 months in both studies [107]. The incidence of adverse events was similar in the rifaximin and placebo groups. A meta-analysis of five trials including TARGET 1 and 2 showed that NNT was 10.2 for global improvement of IBS (OR (odds ratio) 1.57, 95% CI 1.22–2.01) and 10.1 for relief of bloating (OR 1.55, 95% CI 1.23–1.96) [107]. Most recently, the randomized, placebo-controlled TARGET 3 study ($N = 2579$) indicated that the durability of benefit in patients with IBS-D responding to a 2-week course of rifaximin was 50% at 10 weeks and 10% at 20 weeks [108]. Rifaximin produced significant improvements in core symptoms of IBS-D in patients treated with up to three 2-week courses of therapy. With second repeat treatment, the most significant benefit was the relief of urgency and bloating, with borderline benefit on abdominal pain ($P = 0.055$) and stool consistency ($P = 0.08$) [109, 110]. Although not

indicated for IBS-C, rifaximin (400 mg 3 times daily for 7–10 days) has been evaluated in this population in two small, double-blind trials. In one trial, rifaximin plus neomycin significantly improved severity of constipation and symptoms of bloating and straining for up to 4 weeks compared with neomycin plus placebo [111]. In the other trial, rifaximin significantly decreased bloating, abdominal pain, abdominal distension and flatulence compared with placebo [112]. Overall, data suggest that rifaximin is a relatively safe therapeutic option for patients with IBS-D. Multiple mechanisms of action of rifaximin were proposed including change in motility or alteration on host immune response at the cytokine level, but the main proposed mechanism is the alteration of gut microbiota, focusing in small intestine bacterial overgrowth [113].

Dietary Interventions

Dietary intervention can be useful because many IBS patients relate their symptoms with the ingestion of certain foods, mainly carbohydrates and fat [114]. There is growing evidence indicating that fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) may result in bloating, pain and other IBS symptoms in approximately 70% of IBS patients [54, 115–117]. The proposed mechanisms include increasing water retention in the small intestine through the osmotic effects of FODMAPs and rapid fermentation by colonic bacteria, leading to production of gas and SCFAs with luminal distension and stimulation of abnormal motility [118–120]. Other studies show that serum levels of proinflammatory IL-6 and IL-8, as well as levels of fecal *Actinobacteria*, *Bifidobacterium* and *Faecalibacterium prausnitzii*, total SCFAs and n-butyric acid, decreased significantly on the low FODMAP diet compared with baseline [121]. A recent study from Bennet et al. may also help to understand the possible mode of action of a low-FODMAP diet [122]. Responders to low-FODMAP, but not traditional dietary intervention were discriminated from non-responders before and after intervention based on bacterial abundance and fecal bacterial profiles. While a traditional IBS diet was not associated with significant reduction of investigated bacteria, a low FODMAP diet was associated with reduced *Bifidobacterium* and *Actinobacteria* in patients, correlating with lactose consumption.

A meta-analysis from Marsh et al. collected information from 6 RCTs of 3–6 weeks duration including 182 patients on low FODMAP and 172 controls [123]. The analysis showed an improvement in IBS severity and IBS quality of life scores and the odds ratio for severity of abdominal pain based on four trials was 1.81 (95% CI of 1.13–2.88). In a second recent meta-analysis, Altobelli et al. collected information from three RCTs on the effect of low FODMAPs compared with habitual diet from three papers comparing low and moderate/high FODMAPs and six cohort studies [124]. The results showed that in the RCTs, the patients receiving a low-FODMAP diet experienced a statistically significant pain and bloating reduction compared with those receiving a traditional diet; regarding stool consistency, there was no significant difference between treatments. A significant reduction in abdominal pain and bloating was described by patients receiving a low-FODMAP diet compared with those receiving a high-FODMAP diet. In cohort studies, pain and bloating were significantly reduced after treatment compared with the baseline diet. These beneficial results were corroborated by Staudacher et al. recently, although it is not clear whether changes resulted from collective FODMAP restriction or removal of a single component, such as lactose [125].

When interpreting the effect of a low-FODMAP diet on IBS, it should be emphasized that studies comparing its efficacy versus proper dietary advice for IBS (British National Institute for Health and Care Excellence, NICE diet) did not show a clear-cut advantage over the low-FODMAP diet [116, 126, 127]; overall, the IBS dietary algorithm has been simplified to first-line (healthy eating, provided by any healthcare professional) and second-line (low FODMAP, provided by dietitian) dietary advice [128].

In general, the low FODMAP still presents short- and long-term limitations, including a high level of restriction that may be required in

individual patients, the need for monitoring by an expert dietitian, potential for developing nutritional deficiencies, potential for changes in gut microbiota, lack of predictors of response as well as relative efficacy compared with other dietary, psychologic or pharmacologic interventions for IBS [129]. Nevertheless, a recent prospective study in the UK showed that a low-FODMAP diet can be effective and nutritionally adequate up to 18 months after initial dietitian-led education [130]. More studies are necessary to understand the effects of low-FODMAP diet in IBS patients.

FUTURE CONSIDERATIONS AND POTENTIAL TREATMENTS IN MANAGING IBS MICROBIOME

Although our knowledge about microbiota manipulation is limited at this moment, the future is open to new possibilities and perspectives:

Genetic Engineering of Bacteria and Personalized Microbiota Manipulation

This approach is a close reality [131]. A phase I trial with transgenic *Lactococcus lactis* expressing mature human interleukin-10 instead of thymidylate synthase in 10 patients with Crohn's disease was performed, showing improvement in clinical scores of these patients [132]. Also, the development of an *Escherichia coli* to sense and kill *Pseudomonas aeruginosa* in infections in animal models opens the possibility to specifically attack some species [133]. However, limited studies have been performed because of safety issues associated with genetically modified organisms. For instance, although there are biocontainment mechanisms that can be used as thymineless death in bacteria without horizontal gene transfer [134], synthetic protein design [135] and gene circuit engineering [136], the risk of contamination of natural ecosystems and potential transmission between humans is still a major safety concern [131].

Personalized microbiota manipulation emerges as a future therapeutic option but because efficacy depends not only on microbial characteristics but also on the host genetic and epigenetic background [137], deeper knowledge of human and microbial genetics is needed to implement this approach.

Fecal Transplantation

Strong support for dysbiosis having a role in the pathophysiology of IBS has raised the hypothesis that a healthy microbiota could be restored by fecal microbiota transplantation and improve IBS symptoms [138]. Fecal transplantation is a field that moves quickly, even with oral fecal administration using capsules, being not inferior to colonoscopy-administered transplantation [139]. However, until recently only a few uncontrolled small studies were found to report improvement. The first randomized, double-blind, placebo-controlled trial of fecal microbiota transplantation in moderate-to-severe IBS-D and IBS-M has been published in 2017 [20]. The results show a significant effect of active treatment (fresh or frozen transplant) on IBS severity after 3 months but not at 12 months, and no serious adverse effects were reported. Although these results require further confirmation in larger study groups, fecal transplantation opens new questions because filtered feces may have the same effect as whole fecal material transplantation [140]. This could be due to two main factors, bacteriophages and postbiotics, both being able to pass through the filters.

Bacteriophage Therapy

Phages are the main ecological microbial regulators [141]. Their use as therapeutic agents has several advantages such as the high specificity of bacterial taxa, bacterial co-adaptation implicating less resistances and easy and cheap production. However, there are still important drawbacks, mainly legal and ethical issues related to the possibility of inducing septic/toxic shock. The limited knowledge of this biologic "dark matter" opens really interesting questions and opportunities in the future, in both

microbial biology-ecology and bacterial manipulation [142].

Postbiotics

Postbiotics are new formulations containing non-viable bacterial products or purified metabolic byproducts from probiotic microorganisms that have biologic activity and a defined benefit to the host, as opposed to live bacteria in probiotics [143]. Postbiotic interventions have been used in animal models of autism, colitis, cardiovascular disease, recurrent obesity, asthma, type I diabetes and central nervous system inflammation [144]. For example, ex vivo culture with the probiotic *Lactobacillus plantarum* NCIMB8826 elicited an undesired immune response, but the culture media protected against *Salmonella*-mediated tumor necrosis factor secretion from intestinal mucosal explants [145]. The use of postbiotics would theoretically bypass adverse effects promoted by unknown processes triggered by probiotic formulations or potential pathogens delivered via fecal transplant. In the future, more knowledge on the role and production of postbiotics will expand current approaches to manipulate intestinal microbiota in gastrointestinal disorders in a safer way.

New Probiotics

The supplementation with "archeabiotics" or soil-based probiotics can be an interesting approach for FGIDs, particularly for the low methane-related disorders [146]. Another developing possibility is to manipulate the mycobioma, composed mainly by *Saccharomyces*, *Malassezia* and *Candida* [147], because mycobiotic dysbiosis has been associated with hepatitis B, cystic fibrosis, inflammatory bowel disease [148] and recently IBS [149]. However, current knowledge on the role of these taxa and their interactions with microbiota remains unexplored.

Drug-mediated Manipulation of the Gut Microbiome

Population-based metagenomic analysis investigated proton-pump inhibitors [50]. Proton-pump inhibitors induced changes in phylum *Actinobacteria* and the families *Lachnospiraceae*, *Erysipelotrichaceae* and *Bifidobacteriaceae* [150]. Metformin, laxatives, statins and dexamethasone can also affect the microbiota composition [50, 151–153].

CONCLUSION

There is strong and growing evidence supporting the role of dysbiosis in the pathophysiology of IBS. The use of probiotics, prebiotics, symbiotics and dietary manipulation of gut microbiota to treat IBS is increasingly common, and though insufficient knowledge about types, formulations, indications and doses is currently available, promising results have been highlighted by recent meta-analyses. A variety of future therapeutic options is being explored and analyzed, including fecal transplant, but further evidence coming from larger and well-controlled studies is needed.

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