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.
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,” “fimicutes,” “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].

| 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 H2 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 rifaximin 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 microflora, 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), isomalt-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.
| 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] |
| xFOS     | 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, Porphyromonas, 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 Enterobacteriaceae | [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] |
| xFOS     | 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/butyrificum sub.gp.) and lactobacilli/enterococci | FISH | Increased bifidobacteria | [164] |
| FOS      | 7            | 42 days  | Bifidobacteria, Bacteroides, Clostridia (Clostridium perfringens/butyrificum sub.gp.) and Lactobacillus/Enterococcus spp | FISH | Increased bifidobacteria | [165] |
| xFOS     | 8            | 3 weeks  | Enterobacteriaceae, 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, Enterobacteriaceae | 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 imulin (%) | 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] |
| xFOS 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 3.6   | 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. lactobacillus*, *C. cocoides* and *Eubacterium rectale*, *Streptococcus-Lactococcus*, *Lactobacillus* and *Enterococcus* by FISH | Specific agar cultures and FISH          | Increased bacteria                                                                                   | [171]     |
| Low and high SOS   | 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]     |
| sFOS               | 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  | 3 weeks  | *Bacteroides*, *Clostridium acetate*, *Eubacterium rectale*, *Bacteroides*/*Prevotella* (*Bacteroides* fragilis group and *Bacteroides* distasonis), *Fecalibacterium prausnitzii*, bifidobacteria, *Atopobium*, *Clostridium histolyticum*, *Clostridium lituseburense* by FISH, *Enterobacteriaceae*, lactobacilli, enterococci, *Veillonella* by culture, *Bacteroides* distasonis, *B. fragilis*, *Clostridium histolyticum*, *C. lituseburense*, *C. coccoides* and *Eubacterium rectale*, *Lactobacillus*, *Enterococcus* by FISH | Specific agar cultures and FISH          | 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           | 0.5–1.0      | 3 months | *Bifidobacteria*, *Clostridium* and *E. coli*                                  | FISH                                    | Increased *Bifidobacterium*; decreased *E. coli* and *Clostridium*                                 | [177]     |
| Inulin/FOS         | 6 g/l ratio  | 27 weeks | *Bifidobacterium*, *Clostridium histolyticum*, *Clostridium lituseburense*, *E. coli* | FISH                                    | Increased *Bifidobacterium*; decreased *Clostridium*                                                | [178]     |
| 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 *Clostridium* *cocoides*-*Eubacterium* *rectale* | FISH                                    | No differences                                                                                      | [183]     |
| FOS and inulin     | Not indicated| 1–2 weeks | *Bifidobacteria*, lactobacilli, *Clostridium*, *Bacteroides* and *Fecalibacterium* *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* *cocoides*/*E. rectale* group, *Clostridium lituseburense* group, *E. coli*, *Desulfovibrio* spp. | FISH                                    | Increased bifidobacteria and *Bacteroides*, *Atopobium* cluster increased in the follow-up           | [72]      |
| GOS                 | Escalating   | 36 days  | 16s rRNA gene v1-v2 amplicon                                                   | 454 Genome Sequencer FLX Titanium        | Increased *Bifidobacterium*, *Fecalibacterium* and *Lactobacillus*                                | [185]     |
| Inulin/FOS         | 16           | 3 months | 1100 Intestinal bacterial phylotypes                                            | Human Intestinal Tract Chip (HITChip) and qPCR | Increased *Bifidobacterium*, *Fecalibacterium prausnitzii*, *Lactobacillus* spp.; decreased *Bacteroides* intestinalis and *vulgatus*. | [186]     |
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. 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 synbiotics 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 phytoextract-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 symbiotic 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 symbiotic 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].
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 mycobiota, 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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**REFERENCES**

1. Drossman DA, Hasler WL. Rome IV—functional GI disorders: disorders of gut–brain interaction. Gastroenterology. 2016;150:1257–61.

2. Barbara G, Feinle-Bisset C, Ghoshal UC, Quigley EM, Santos J, Vanner S, et al. The intestinal microenvironment and functional gastrointestinal disorders. Gastroenterology. 2016;150(6):1305–18.

3. Gazouli M, Wouters MM, Kapur-Pojskic´ L, Bengtson M-B, Friedman E, Nikčević G, et al. Lessons learned—resolving the enigma of genetic factors in IBS. Nat Rev Gastroenterol Hepatol. 2016;13(2):77.

4. Enck P, Aziz Q, Barbara G, Farmer AD, Fukudo S, Mayer EA, et al. Irritable bowel syndrome. Nat Rev Dis Primer. 2016;2:16014.

5. Ohman L, Simrén M. Pathogenesis of IBS: role of inflammation, immunity and neuroimmune interactions. Nat Rev Gastroenterol Hepatol. 2010;7:163–73.

6. Ford AC, Lacy BE, Talley NJ. Irritable bowel syndrome. N Engl J Med. 2017;376:2566–78.

7. Doulberis M, Saleh C, Beyenburg S. Is there an association between migraine and gastrointestinal disorders? J Clin Neurol Seoul Korea. 2017;13:215–26.

8. Moayyedi P, Mearin F, Azpiroz F, Andresen V, Barbara G, Corsetti M, et al. Irritable bowel syndrome diagnosis and management: a simplified algorithm for clinical practice. United Eur Gastroenterol J. 2017;5:773–88.

9. Lacy BE. Diagnosis and treatment of diarrhea-predominant irritable bowel syndrome. Int J Gen Med. 2016;9:7–17.

10. Buono JL, Carson RT, Flores NM. Health-related quality of life, work productivity, and indirect costs among patients with irritable bowel syndrome with diarrhea. Health Qual Life Outcomes. 2017;15:35.

11. Sandler RS, Everhart JE, Donowitz M, Adams E, Cronin K, Goodman C, et al. The burden of selected digestive diseases in the United States. Gastroenterology. 2002;122:1500–11.

12. Longstreth GF, Wilson A, Knight K, Wong J, Chiou C-F, Barghout V, et al. Irritable bowel syndrome, health care use, and costs: a U.S. managed care perspective. Am J Gastroenterol. 2003;98:600–7.

13. Dupont HL. Review article: evidence for the role of gut microbiota in irritable bowel syndrome and its potential influence on therapeutic targets. Aliment Pharmacol Ther. 2014;39:1033–42.

14. Distrutti E, Monaldi L, Ricci P, Fiorucci S. Gut microbiota role in irritable bowel syndrome: new therapeutic strategies. World J Gastroenterol. 2016;22:2219–41.

15. Klem F, Wadhwa A, Prokop LJ, Sundt WJ, Farrugia G, Camilleri M, et al. Prevalence, risk factors, and outcomes of irritable bowel syndrome after infectious enteritis: a systematic review and meta-analysis. Gastroenterology. 2017;152(1042–1054):e1.

16. Pimentel M, Lembo A, Chey WD, Zakko S, Ringel Y, Yu J, et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. N Engl J Med. 2011;364:22–32.

17. Moraes-Filho JP, Quigley EMM. The intestinal microbiota and the role of probiotics in irritable bowel syndrome: a review. Arq Gastroenterol. 2015;52:331–8.

18. Ford AC, Quigley EMM, Lacy BE, Lembo AJ, Saito YA, Schiller LR, et al. Efficacy of prebiotics, probiotics, and synbiotics in irritable bowel syndrome and chronic idiopathic constipation: systematic
review and meta-analysis. Am J Gastroenterol. 2014;109:1547–61 (quiz 1546, 1562).

19. Pinn DM, Aroniadis OC, Brandt LJ. Is fecal microbiota transplantation the answer for irritable bowel syndrome? A single-center experience. Am J Gastroenterol. 2014;109:1831–2.

20. Johnsen PH, Hilpösch F, Cavanagh JP, Leikanger IS, Kolstad C, Valde PC, 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. 2017;3(1):17–24.

21. Zhuang X, Xiong L, Li L, Li M, Chen M. Alterations of gut microbiota in patients with irritable bowel syndrome: a systematic review and meta-analysis. J Gastroenterol Hepatol. 2017;32:28–38.

22. Balsari A, Cecarelli A, Dubini F, Fesce E, Poli G. The fecal microbial population in the irritable bowel syndrome. Microbiologia. 1982;5:185–94.

23. Malinen E, Rinttilä T, Kajander K, Mättö J, Kassinen A, Krogus L, et al. Analysis of the fecal microbiota of irritable bowel syndrome patients and healthy controls with real-time PCR. Am J Gastroenterol. 2005;100:373–82.

24. Carroll IM, Chang Y-H, Park J, Sartor RB, Ringel Y. Luminal and mucosal-associated intestinal microbiota in patients with diarrhea-predominant irritable bowel syndrome. Gut Pathog. 2010;2:19.

25. Kerckhoffs APM, Samsom M, van der Rest ME, de Vogel J, Knol J, Ben-Amor K, et al. Lower Bifidobacteria counts in both duodenal mucosa-associated and fecal microbiota in irritable bowel syndrome patients. World J Gastroenterol WJG. 2009;15:2887–92.

26. Rajilić-Stojanović M, Biagi E, Heilig HGHJ, Kajander K, Kekkonen RA, Tims S, et al. Global and deep molecular analysis of microbiota signatures in fecal samples from patients with irritable bowel syndrome. Gastroenterology. 2011;141:1792–801.

27. Duboc H, Rainteau D, Rajca S, Humbert L, Farabos D, Maubert M, et al. Increase in fecal primary bile acids and dysbiosis in patients with diarrhea-predominant irritable bowel syndrome. Neurogastroenterol. 2012;24(513–20):e246–7.

28. Parkes GC, Rayment NB, Hudspith BN, Petrovska L, Lomer MC, Brostoff J, et al. Distinct microbial populations exist in the mucosa-associated microbiota of sub-groups of irritable bowel syndrome. Neurogastroenterol. 2012;24:31–9.

29. Angelakis E, Merhej V, Raoult D. Related actions of probiotics and antibiotics on gut microbiota and weight modification. Lancet Infect Dis. 2013;13:889–99.

30. Pace F, Pace M, Quartarone G. Probiotics in digestive diseases: focus on Lactobacillus GG. Minerva Gastroenterol Dietol. 2015;61:273–92.

31. Pozuelo M, Panda S, Santiago A, Mendez S, Accarino A, Santos J, et al. Reduction of butyrate- and methane-producing microorganisms in patients with irritable bowel syndrome. Sci Rep. 2015;5:12693.

32. Załeński A, Banaszkiewicz A, Walkowiak J. Butyric acid in irritable bowel syndrome. Prz Gastroenterol. 2013;8:350–3.

33. 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;22:512.

34. Rigsbee L, Agans R, Shankar V, Kenche H, Khnis HJ, Michail S, et al. Quantitative profiling of gut microbiota of children with diarrhea-predominant irritable bowel syndrome. Am J Gastroenterol. 2012;107:1740–51.

35. Labus JS, Hollister EB, Jacobs J, Kirbach K, Oezguen N, Gupta A, et al. Differences in gut microbial composition correlate with regional brain volumes in irritable bowel syndrome. Microbiome. 2017;5:49.

36. Saulnier DM, Riehle K, Mistretta T-A, Diaz M-A, Mandal D, Raza S, et al. Gastrointestinal microbiome signatures of pediatric patients with irritable bowel syndrome. Gastroenterology. 2011;141:1782–91.

37. Lyra A, Rinttilä T, Nikkilä J, Krogus-Kurikka L, Kajander K, Malinen E, et al. Diarrhoea-predominant irritable bowel syndrome distinguishable by 16S rRNA gene phytophyletotype quantification. World J Gastroenterol. 2009;15:5936–45.

38. Carroll IM, Ringel-Kulka T, Siddle JP, Ringel Y. Alterations in composition and diversity of the intestinal microbiota in patients with diarrhea-predominant irritable bowel syndrome. Gastroenterology. 2012;141(5):1230–42.
40. Jeffery IB, O’Toole PW, Öhman L, Claesson MJ, Deane J, Quigley EMM, et al. An irritable bowel syndrome subtype defined by species-specific alterations in faecal microbiota. Gut. 2012;61:997–1006.

41. Jalanka-Tuovinen J, Salojärvi J, Salonen A, Immonen O, Garsed K, Kelly FM, et al. Faecal microbiota composition and host-microbe cross-talk following gastroenteritis and in postinfectious irritable bowel syndrome. Gut. 2014;63:1737–45.

42. Lozupone CA, Stombaugh J, Gonzalez A, Ackermann G, Wendel D, Vázquez-Baeza Y, et al. Metaanalyses of studies of the human microbiota. Genome Res. 2013;23:1704–14.

43. Mavrangelos C, Campaniello MA, Andrews JM, Bampton PA, Hughes PA. Longitudinal analysis indicates symptom severity influences immune profile in irritable bowel syndrome. Gut. 2017;67:398–9.

44. Pimentel M, Chow EJ, Lin HC. Normalization of lactulose breath testing correlates with symptom improvement in irritable bowel syndrome: a double-blind, randomized, placebo-controlled study. Am J Gastroenterol. 2003;98:412–9.

45. Kim G, Deepinder F, Morales W, Hwang L, Weitsman S, Chang C, et al. Methanobrevibacter smithii is the predominant methanogen in patients with constipation-predominant IBS and methane on breath. Dig Dis Sci. 2012;57:3213–8.

46. Pimentel M, Lin HC, Enayati P, van den Burg B, Lee H-R, Chen JH, et al. Methane, a gas produced by enteric bacteria, slows intestinal transit and augments small intestinal contractile activity. Am J Physiol Gastrointest Liver Physiol. 2006;290:G1089–95.

47. Jahng J, Jung IS, Choi EJ, Conklin JL, Park H. The effects of methane and hydrogen gases produced by enteric bacteria on ileal motility and colonic transit time. Neurogastroenterol. 2012;24(185–90):e92.

48. Vanpeputte D, Falony G, Vieira-Silva S, Tito RY, Joossens M, Raes J. Stool consistency is strongly associated with gut microbiota richness and composition, enterotypes and bacterial growth rates. Gut. 2016;65:57–62.

49. Falony G, Joossens M, Vieira-Silva S, Wang J, Darzi Y, Faust K, et al. Population-level analysis of gut microbiome variation. Science. 2016;352:560–4.

50. Zhernakova A, Kurilshikov A, Bonder MJ, Tigchelaar EF, Schirmer M, Vatanen T, et al. Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity. Science. 2016;352:565–9.
63. Crittenden R, Playne MJ. Prebiotics. In: Lee YK, Salminen S, editors. Handb probiotics prebiotics (internet). Wiley Inc.; 2008. 533–81. http://onlinelibrary.wiley.com/doi/10.1002/9780470432624.ch7/summary. Accessed 18 Oct 2017.

64. Alvarez-Curto E, Milligan G. Metabolism meets immunity: the role of free fatty acid receptors in the immune system. Biochem Pharmacol. 2016;114:3–13.

65. Rivière A, Selak M, Lantin D, Leroy F, De Vuyst L. Bifidobacteria and butyrate-producing colon bacteria: importance and strategies for their stimulation in the human gut. Front Microbiol (internet). 2016. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4923077/. 22 Jan 2018.

66. Wilson B, Whelan K. Prebiotic inulin-type fructans and galacto-oligosaccharides: definition, specificity, function, and application in gastrointestinal disorders. J Gastroenterol Hepatol. 2017;32(Suppl 1):64–8.

67. Roberfroid M, Gibson GR, Hoyles L, McCartney AL, Rastall R, Rowland I, et al. Prebiotic effects: metabolic and health benefits. Br J Nutr. 2010;104(Suppl 2):S1–63.

68. Hunter JO, Tuffnell Q, Lee AJ. Controlled trial of oligofructose in the management of irritable bowel syndrome. J Nutr. 1999;129:1451S–3S.

69. Olesen M, Gudmand-Hoyer E. Efficacy, safety, and tolerability of short-chain fructooligosaccharides in the treatment of irritable bowel syndrome. Am J Clin Nutr. 2008;99:311–8.

70. Silk DBA, Davis A, Vulevic J, Tzortzis G, Gibson GR. Clinical trial: the effects of a trans-galactooligosaccharide prebiotic on faecal microbiota and symptoms in irritable bowel syndrome. Aliment Pharmacol Ther. 2009;29:508–18.

71. Vogt L, Meyer D, Pullens G, Faas M, Smelt M, Venema K, et al. Immunological properties of inulin-type fructans. Crit Rev Food Sci Nutr. 2015;55:41–36.

72. Vulevic J, Juric A, Walton GE, Claus SP, Tzortzis G, Toward RE, et al. Influence of galacto-oligosaccharide mixture (B-GOS) on gut microbiota, immune parameters, and metabolomics in elderly persons. Br J Nutr. 2015;114:586–95.

73. Mego M, Manichanh C, Accarino A, Campos D, Pozuelo M, Varela E, et al. Metabolic adaptation of colon microbiota to galactooligosaccharides: a proof-of-concept-study. Aliment Pharmacol Ther. 2017;45:670–80.

74. Gibson GR, Wang X. Bifidogenic properties of different types of fructo-oligosaccharides. Food Microbiol. 1994;11:491–8.

75. Gibson GR, Wang X. Regulatory effects of bifidobacteria on the growth of other colonic bacteria. J Appl Bacteriol. 1994;77:412–20.

76. Paineau D, Payen F, Panserieu S, Coulombier G, Sobaszek A, Lartigau I, et al. The effects of regular consumption of short-chain fructo-oligosaccharides on digestive comfort of subjects with minor functional bowel disorders. Br J Nutr. 2008;99:311–8.

77. Ford AC, Moayyedi P, Lacy BE, Lembo AJ, Saito YA, Schiller LR, et al. American College of Gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. Am J Gastroenterol. 2014;109(Suppl 1):S2–26 (quiz S27).

78. Wrighton KH. Mucosal immunology: probiotic induction of tolerogenic T cells in the gut. Nat Rev Immunol. 2017;17:592.

79. Simrén M, Barbara G, Flint HJ, Spiegel BMR, Spiller RC, Vanner S, et al. Intestinal microbiota in functional bowel disorders: a Rome foundation report. Gut. 2013;62:159–76.

80. Mayer EA, Savidge T, Shulman RJ. Brain gut microbiome interactions and functional bowel disorders. Gastroenterology. 2014;146:1500–12.

81. Didari T, Mozaffari S, Nikfar S, Abdollahi M. Effectiveness of probiotics in irritable bowel syndrome: updated systematic review with meta-analysis. World J Gastroenterol. 2015;21:3072–84.

82. Joyce SA, MacSharry J, Casey PG, Kinsella M, Murphy EF, Shanahan F, et al. Regulation of host weight gain and lipid metabolism by bacterial bile acid modification in the gut. Proc Natl Acad Sci USA. 2014;111:7421–6.

83. Bermudez-Brito M, Plaza-Díaz J, Muñoz-Quezada S, Gómez-Llorente C, Gil A. Probiotic mechanisms of action. Ann Nutr Metab. 2012;61:160–74.

84. Curró D, Janiro G, Pecere S, Bibbò S, Cammarota G. Probiotics, fibre and herbal medicinal products for functional and inflammatory bowel disorders. Br J Pharmacol. 2017;174:1426–49.

85. Pinto-Sanchez MI, Hall GB, Ghajar K, Nardelli A, Bolino C, Lau JT, et al. Probiotic Bifidobacterium longum NCC3001 reduces depression scores and alters brain activity: a pilot study in patients with irritable bowel syndrome. Gastroenterology. 2017;153(448–459):e8.

86. Zhang Y, Li L, Guo C, Mu D, Feng R, Zuo X, et al. Effects of probiotic type, dose and treatment duration on irritable bowel syndrome diagnosed by Rome III criteria: a meta-analysis. BMC Gastroenterol. 2016;16:62.
87. Jafari E, Vaheedi H, Merat S, Momtahen S, Riahi A. Therapeutic effects, tolerability and safety of a multi-strain probiotic in Iranian adults with irritable bowel syndrome and bloating. Arch Iran Med. 2014;17:466–70.

88. Urgesi R, Casale C, Pistelli R, Rapaccini GL, de Vitis J. A randomized double-blind placebo-controlled clinical trial on efficacy and safety of association of simethicone and Bacillus coagulans (Colinox®) in patients with irritable bowel syndrome. Eur Rev Med Pharmacol Sci. 2014;18:1344–53.

89. McFarland LV. Systematic review and meta-analysis of Saccharomyces boulardii in adult patients. World J Gastroenterol. 2010;16:2202–22.

90. Yuan F, Ni H, Asche CV, Kim M, Walayat S, Ren J. Efficacy of Bifidobacterium infantis 35624 in patients with irritable bowel syndrome: a meta-analysis. Curr Med Res Opin. 2017;33:1191–7.

91. Horvath A, Dziechciarz P, Szajewska H. Meta-analysis: Lactobacillus rhamnosus GG for abdominal pain-related functional gastrointestinal disorders in childhood. Aliment Pharmacol Ther. 2011;33:1302–10.

92. Tiequn B, Guanqun C, Shuo Z. Therapeutic effects of Lactobacillus in treating irritable bowel syndrome: a meta-analysis. Intern Med Tokyo Jpn. 2015;54:243–9.

93. West C, Stanisz AM, Wong A, Kunze WA. Effects of Saccharomyces cerevisiae or boulardii yeasts on acute stress induced intestinal dysmotility. World J Gastroenterol. 2016;22:10532–44.

94. Brun P, Scarpa M, Marchiori C, Sarasin G, Caputi V, Porzionato A, et al. Saccharomyces boulardii CNCM I-745 supplementation reduces gastrointestinal dysfunction in an animal model of IBS. PLoS ONE. 2017;12:e0181863.

95. O'Mahony L, McCarthy J, Kelly P, Hurley G, Luo F, Chen K, et al. Lactobacillus and Bifidobacterium in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. Gastroenterology. 2005;128:541–51.

96. Cayzene-Decherf A, Pélerin F, Leuillet S, Douillard B, Housez B, Cazaubiel M, et al. Saccharomyces cerevisiae CNCM I-3856 in irritable bowel syndrome: an individual subject meta-analysis. World J Gastroenterol. 2017;23:336–44.

97. Giannetti E, Maglione M, Alessandrella A, Strisciuglio C, De Giovanni D, Campanozzi A, et al. A mixture of 3 bifidobacteria decreases abdominal pain and improves the quality of life in children with irritable bowel syndrome: a multicenter, randomized, double-blind, placebo-controlled, crossover trial. J Clin Gastroenterol. 2017;51:e5–10.

98. Weizman Z, Abu-Abed J, Binsztk M. Lactobacillus reuteri DSM 17938 for the management of functional abdominal pain in childhood: a randomized, double-blind, placebo-controlled trial. J Pediatr. 2016;174(160–164):e1.

99. Min YW, Park SU, Jang YS, Kim Y-H, Rhee P-L, Ko SH, et al. Effect of composite yogurt enriched with acacia fiber and Bifidobacterium lactis. World J Gastroenterol. 2012;18:4563–9.

100. Tsuchiya J, Barreto R, Okura R, Kawakita S, Fesse E, Marotta F. Single-blind follow-up study on the effectiveness of a symbiotic preparation in irritable bowel syndrome. Chin J Dig Dis. 2004;5:169–74.

101. Rogha M, Esfahani MZ, Zargarzadeh AH. The efficacy of a symbiotic containing Bacillus coagulans in treatment of irritable bowel syndrome: a randomized placebo-controlled trial. Gastroenterol Hepatol Bed Bench. 2014;7:156–63.

102. Saneian H, Pourmoghaddas Z, Roodafs H, Ghomrannaei A. Symbiotic containing Bacillus coagulans and fructo-oligosaccharides for functional abdominal pain in children. Gastroenterol Hepatol Bed Bench. 2015;8:56–65.

103. Šmid A, Strniša L, Bajc K, Vujič-Podlipč B, Bogovič Matijašič B, Rogelj I. Randomized clinical trial: the effect of fermented milk with the probiotic cultures Lactobacillus acidophilus La-5® and Bifidobacterium BB-12® and Beneo dietary fibres on health-related quality of life and the symptoms of irritable bowel syndrome in adults. J Funct Foods. 2016;24:549–57.

104. Abbas Z, Yakoob J, Jafri W, Ahmad Z, Azam Z, Usman MW, et al. Cytokine and clinical response to Saccharomyces boulardii therapy in diarrhea-dominant irritable bowel syndrome: a randomized trial. Eur J Gastroenterol Hepatol. 2014;26:630–9.

105. Baştürk A, Artan R, Yılmaz A. Efficacy of symbiotic, probiotic, and prebiotic treatments for irritable bowel syndrome in children: a randomized controlled trial. Turk J Gastroenterol Off J Turk Soc Gastroenterol. 2016;27:439–43.

106. Acosta A, Camilleri M, Shin A, Linker Nord S, O’Neill J, Gray AV, et al. Effects of rifaximin on transit, permeability, fecal microbiome, and organic acid excretion in irritable bowel syndrome. Clin Transl Gastroenterol. 2016;7:e173.

107. Menees SB, Maneerattannaporn M, Kim HM, Chey WD. The efficacy and safety of rifaximin for the irritable bowel syndrome: a systematic review and meta-analysis. Am J Gastroenterol. 2012;107:28–35 (quiz 36).
108. Pimentel M, Chang L, Lembo A, Barrett AC, Yu J, Bortey E, et al. Mo1279 durability of benefit in IBS-D patients responding to a 2-week course of rifaximin: results from TARGET 3. Gastroenterology. 2015;148:S-658–9.

109. Chey WD, Chang L, Lembo A, Aggarwal K, Bortey E, Paterson C, et al. 313 Effects of rifaximin on urgency, bloating, and abdominal pain in patients with IBS-D: a randomized, controlled, repeat treatment study. Gastroenterology. 2015;148:S-69.

110. Chang L, Pimentel M, Lembo A, Barrett AC, Yu J, Bortey E, et al. Mo1261 characterizing the effect of rifaximin on individual symptoms of IBS-D: findings from the open-label phase of TARGET 3. Gastroenterology. 2015;148:S-653.

111. Pimentel M, Chang C, Chua KS, Mirocha J, DiBaise J, Rao S, et al. Antibiotic treatment of constipation-predominant irritable bowel syndrome. Dig Dis Sci. 2014;59:1278–85.

112. Di Stefano M, Tana P, Mengoli C, Miceli E, Pagani E, Corazza GR. Colonic hypersensitivity is a major determinant of the efficacy of bloating treatment in constipation-predominant irritable bowel syndrome. Intern Emerg Med. 2011;6:403–11.

113. Pimentel M. Review article: potential mechanisms of action of rifaximin in the management of irritable bowel syndrome with diarrhoea. Aliment Pharmacol Ther. 2016;43(Suppl 1):37–49.

114. Böhn L, Störsrud S, Törnbloom H, Bengtsson U, Simrén M. Self-reported food-related gastrointestinal symptoms in IBS are common and associated with more severe symptoms and reduced quality of life. Am J Gastroenterol. 2013;108:634–41.

115. Staudacher HM, Lomer MCE, Anderson JL, Barrett JS, Muir JG, Irving PM, et al. Fermentable carbohydrate restriction reduces luminal bifidobacteria and gastrointestinal symptoms in patients with irritable bowel syndrome. J Nutr. 2012;142:1510–8.

116. Böhn L, Störsrud S, Liljebo T, Collin L, Lindfors P, Törnbloom H, et al. Diet low in FODMAPs reduces symptoms of irritable bowel syndrome as well as traditional dietary advice: a randomized controlled trial. Gastroenterology. 2015;149(1399–1407):e2.

117. Biesiekierski JR, Newnham ED, Irving PM, Barrett JS, Haines M, Doecke JD, et al. Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial. Am J Gastroenterol. 2011;106:508–14 (quiz 515).

118. Gibson PR, Varney J, Malakar S, Muir JG. Food components and irritable bowel syndrome. Gastroenterology. 2015;148(1158–1174):e4.

119. Valeur J, Røseth AG, Knudsen T, Malmstrøm GH, Fiennes JT, Midtvedt T, et al. Fecal fermentation in irritable bowel syndrome: influence of dietary restriction of fermentable oligosaccharides, disaccharides, monosaccharides and polyols. Digestion. 2016;94:50–6.

120. Halmos EP, Christophersen CT, Bird AR, Shepherd SJ, Gibson PR, Muir JG. Diets that differ in their FODMAP content alter the colonic luminal microenvironment. Gut. 2014;64:93–100.

121. Hustoft TN, Hausken T, Ystad SO, Valeur J, Brokstad K, Hatlebakk JG, et al. Effects of varying dietary content of fermentable short-chain carbohydrates on symptoms, fecal microenvironment, and cytokine profiles in patients with irritable bowel syndrome. Neurogastroenterol. 2017;29:e12969.

122. Bennet SMP, Böhn L, Störsrud S, Liljebo T, Collin L, Lindfors P, et al. Multivariate modelling of faecal bacterial profiles of patients with IBS predicts responsiveness to a diet low in FODMAPs. Gut. 2017. https://doi.org/10.1136/gutjnl-2016-313128

123. Marsh A, Eslick MG, Eslick GD. Does a diet low in FODMAPs reduce symptoms associated with functional gastrointestinal disorders? A comprehensive systematic review and meta-analysis. Eur J Nutr. 2016;55:897–906.

124. Aitoﬁllo E, Del Negro V, Angeletti PM, Latella G. Low-FODMAP diet improves irritable bowel syndrome symptoms: a meta-analysis. Nutrients. 2017;9(9):940.

125. Staudacher HM, Lomer MCE, Farquharson FM, Louis P, Fava F, Franciosi E, et al. A diet low in FODMAPs reduces symptoms in patients with irritable bowel syndrome and a probiotic restores Bifidobacterium species: a randomized controlled trial. Gastroenterology. 2017;153:936–47.

126. Eswaran SL, Chey WD, Han-Markey T, Ball S, Jackson KA, randomized controlled trial comparing the low FODMAP Diet vs. modified NICE guidelines in US Adults with IBS-D. Am J Gastroenterol. 2016;111:1824–32.

127. Whigham L, Joyce T, Harper G, Irving PM, Staudacher HM, Whelan K, et al. Clinical effectiveness and economic costs of group versus one-to-one education for short-chain fermentable carbohydrate restriction (low FODMAP diet) in the management of irritable bowel syndrome. J Hum Nutr Diet Off J Br Diet Assoc. 2015;28:687–96.

128. McKenzie YA, Bowyer RK, Leach H, Gulia P, Horobin J, O’Sullivan NA, et al. British dietetic association systematic review and evidence-based practice guidelines for the dietary management of
irritable bowel syndrome in adults (2016 update). J Hum Nutr Diet Off J Br Diet Assoc. 2016;29:549–75.

129. Molina-Infante J, Serra J, Fernandez-Bañares F, Mearin F. The low-FODMAP diet for irritable bowel syndrome: lights and shadows. Gastroenterol Hepatol. 2016;39:55–65.

130. O’Keeffe M, Jansen C, Martin L, Williams M, Seemark L, Staudacher HM, et al. Long-term impact of the low-FODMAP diet on gastrointestinal symptoms, dietary intake, patient acceptability, and healthcare utilization in irritable bowel syndrome. Neurogastroenterol. 2017;30. https://doi.org/10.1111/nmo.13154

131. Ma B, Pan Q, Peppelenbosch MP. Genetically engineered bacteria for treating human disease. Trends Pharmacol Sci. 2017;38:763–4.

132. Braat H, Rottiers P, Hommes DW, Huyghebaert N, Remaut E, Remon J-P, et al. A phase I trial with transgenic bacteria expressing interleukin-10 in Crohn’s disease. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc. 2006;4:754–9.

133. Hwang IY, Koh E, Wong A, March JC, Bentley WE, Lee YS, et al. Engineered probiotic Escherichia coli can eliminate and prevent Pseudomonas aeruginosa gut infection in animal models. Nat Commun. 2017;8:15028.

134. Wegmann U, Carvalho AL, Stocks M, Carding SR. Use of genetically modified bacteria for drug delivery in humans: revisiting the safety aspect. Sci Rep. 2017;7:2294.

135. Mandell DJ, Lajoie MJ, Mee MT, Takeuchi R, Kuznetsov G, Norville JE, et al. Biocontainment of genetically modified organisms by synthetic protein design. Nature. 2015;518:55–60.

136. Brophy JAN, Voigt CA. Principles of genetic circuit design. Nat Methods. 2014;11:508–20.

137. Kurilshikov A, Wijmenga C, Fu J, Zhnernakova A. Host genetics and gut microbiome: challenges and perspectives. Trends Immunol. 2017;38:633–47.

138. Cammarota G, Pecere S, Ianiro G, Masucci L, Curró D. Principles of DNA-based gut microbiota assessment and therapeutic efficacy of fecal microbiota transplantation in gastrointestinal diseases. Dig Dis Basel Switz. 2016;34:279–85.

139. Kao D, Roach B, Silva M, Beck P, Rioux K, Kaplan GG, et al. Effect of oral capsule- vs colonoscopy-delivered fecal microbiota transplantation on recurrent clostridium difficile infection: a randomized clinical trial. JAMA. 2017;318:1985–93.

140. Ott SJ, Waetzig GH, Rehman A, Moltzau-Anderson J, Bharti R, Grasis JA, et al. Efficacy of sterile fecal filtrate transfer for treating patients with clostridium difficile infection. Gastroenterology. 2017;152(799–811):e7.

141. Navarro F, Muniesa M. Phages in the human body. Front Microbiol. 2017;8:566.

142. Fischetti VA, Nelson D, Schuch R. Reinventing phage therapy: are the parts greater than the sum? Nat Biotechnol. 2006;24:1508–11.

143. Tsilingiri K, Rescigno M. Postbiotics: what else? Benef Microbes. 2013;4:101–7.

144. Thaiss CA, Elinav E. The remedy within: will the microbiome fulfill its therapeutic promise? J Mol Med Berl Ger. 2017;95:1021–7.

145. Tsilingiri K, Barbosa T, Penna G, Caprioli F, Sonzogni A, Viale G, et al. Probiotic and postbiotic activity in health and disease: comparison on a novel polarised ex vivo organ culture model. Gut. 2012;61:1007–15.

146. Brugère J-F, Borrel G, Gaci N, Tottey W, O’Toole PW, Malpuech-Brugère C. Archaebiotics: proposed therapeutic use of archaea to prevent trimethylaminuria and cardiovascular disease. Gut Microbes. 2014;5:5–10.

147. Nash AK, Auchtung TA, Wong MC, Smith DP, Gesell JR, Ross MC, et al. The gut mycobiome of the Human Microbiome Project healthy cohort. Microbiome. 2017;5:153.

148. Cui L, Morris A, Ghedin E. The human mycobiome in health and disease. Genome Med. 2013;5:63.

149. Botschuijver S, Roeselers G, Welting O, Heinsbroek SEM, et al. Intestinal fungal dysbiosis is associated with visceral hypersensitivity in patients with irritable bowel syndrome and rats. Gastroenterology. 2017;153:1026–39.

150. Revelles KR, Ryan CN, Chan L, Cosimi RA, Haynes WL. Proton pump inhibitor use associated with changes in gut microbiota composition. Gut. 2017. https://doi.org/10.1136/gutjnl-2017-315306.

151. Wu H, Esteve E, Tremaroli V, Khan MT, Caesar R, Manneräs-Holm L, et al. Metformin alters the gut microbiome of individuals with treatment-naive type 2 diabetes, contributing to the therapeutic effects of the drug. Nat Med. 2017;23:850–8.

152. Gottlieb K, Wacher V, Sliman J, Pimentel M. Review article: inhibition of methanogenic archaea by statins as a targeted management strategy for constipation and related disorders. Aliment Pharmacol Ther. 2016;43:197–212.
153. Wu T, Yang L, Jiang J, Ni Y, Zhu J, Zheng X, et al. Chronic glucocorticoid treatment induced circadian clock disorder leads to lipid metabolism and gut microbiota alterations in rats. Life Sci. 2017;192:173–82.

154. Sugawara M, Sato Y, Yokoyama S, Mitsuoka T. Effect of corn fiber residue supplementation on fecal properties, flora, ammonia, and bacterial enzyme activities in healthy humans. J Nutr Sci Vitaminol (Tokyo). 1991;37:109–16.

155. Williams CH, Witherly SA, Buddington RK. Influence of dietary neosugar on selected bacterial groups of the human faecal microbiota. Microb Ecol Health Dis. 1994;7:91–7.

156. Bouhnik Y, Fleurie B, Riottot M, Bisetti N, Gailing MF, Guibert A, et al. Effects of fructo-oligosaccharides ingestion on fecal bifidobacteria and selected metabolic indexes of colon carcinogenesis in healthy humans. Nutr Cancer. 1996;26:21–9.

157. Buddington RK, Williams CH, Chen SC, Witherly SA. Dietary supplement of neosugar alters the fecal flora and decreases activities of some reductive enzymes in human subjects. Am J Clin Nutr. 1996;63:709–16.

158. Kleessen B, Sykura B, Zunft HJ, Blaut M. Effects of inulin and lactose on fecal microflora, microbial activity, and bowel habit in elderly constipated persons. Am J Clin Nutr. 1997;65:1397–402.

159. Teuri U, Korpela R, Saxelin M, Montonen L, Salmi- nen S. Increased fecal frequency and gastrointestinal symptoms following ingestion of galacto-oligosaccharide-containing yogurt. J Nutr Sci Vitaminol (Tokyo). 1998;44:465–71.

160. Kruse HP, Kleessen B, Blaut M. Effects of inulin on faecal bifidobacteria in human subjects. Br J Nutr. 1999;82:375–82.

161. Bouhnik Y, Vahedi K, Achour L, Attar A, Salfati J, Pochart P, et al. The capacity of nondigestible carbohydrates to stimulate fecal bifidobacteria in healthy elderly persons. Am J Clin Nutr. 1997;65:1397–402.

162. Schneider SM, Girard-Pipau F, Anty R, van der Linde EGM, Philipsen-Geerling BJ, Knol J, et al. Effects of total enteral nutrition supplemented with a multi-fibre mix on faecal short-chain fatty acids and microbiota. Clin Nutr Edinb Scotl. 2006;25:82–90.

163. Bang MH, Chio OS, Kim WK. Soyoligosaccharide increases fecal bifidobacteria counts, short-chain fatty acids, and fecal lipid concentrations in young Korean women. J Med Food. 2007;10:366–70.

164. Tuohy KM, Finlay RK, Wynne AG, Gibson GR. A human volunteer study on the prebiotic effects of hp-inulin—faecal bacteria enumerated using fluorescent in situ hybridisation (FISH). Anaerobe. 2001;7:113–8.
chicory inulin in bakery products affect faecal microbiota of healthy volunteers. Br J Nutr. 2007;98:540–9.

176. Kolida S, Gibson GR. Prebiotic capacity of inulin-type fructans. J Nutr. 2007;137:2503S–6S.

177. Costalos C, Kapiki A, Apostolou M, Papathoma E. The effect of a prebiotic supplemented formula on growth and stool microbiology of term infants. Early Hum Dev. 2008;84:45–9.

178. de Preter V, Vanhoutte T, Huys G, Swings J, Rutgeerts P, Verbeke K. Baseline microbiota activity and initial bifidobacteria counts influence responses to prebiotic dosing in healthy subjects. Aliment Pharmacol Ther. 2008;27:504–13.

179. Depeint F, Tzortzis G, Vulevic J, I’Anson K, Gibson GR. Prebiotic evaluation of a novel galactooligosaccharide mixture produced by the enzymatic activity of Bifidobacterium bifidum NCIMB 41171, in healthy humans: a randomized, double-blind, crossover, placebo-controlled intervention study. Am J Clin Nutr. 2008;87:785–91.

180. Scholtens PAMJ, Alliet P, Raes M, Kroes H, Boehm G, et al. Fecal secretory immunoglobulin A is increased in healthy infants who receive a formula with short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides. J Nutr. 2008;138:1141–7.

181. Wierdsma NJ, van Bodegraven AA, Uitdehaag BMJ, Arjaans W, Savelkoul PHM, Kruijzena HM, et al. Fructo-oligosaccharides and fibre in enteral nutrition has a beneficial influence on microbiota and gastrointestinal quality of life. Scand J Gastroenterol. 2009;44:804–12.

182. Cloetens L, Broekaert WF, Delaedt Y, Ollevier F, Courtin CM, Delcour JA, et al. Tolerance of arabinoxylan-oligosaccharides and their prebiotic activity in healthy subjects: a randomised, placebo-controlled cross-over study. Br J Nutr. 2010;103:703–13.

183. Majid HBA, Cole J, Sherry T, Beale R, Ervine M, Reid C, et al. Tu2042 a multi-centre, randomised, double-blind, controlled trial determining the effect of additional fructo-oligosaccharides on fecal microbiota and short-chain fatty acids among critical care patients receiving enteral nutrition. Gastroenterology. 2012;142:909.

184. Majid HA, Emery PW, Whelan K. Faecal microbiota and short-chain fatty acids in patients receiving enteral nutrition with standard or fructo-oligosaccharides and fibre-enriched formulas. J Hum Nutr Diet Off J Br Diet Assoc. 2011;24:260–8.

185. Azcarate-Peril MA, Ritter AJ, Savaiano D, Monteagudo-Mera A, Anderson C, Magness ST, et al. Impact of short-chain galactooligosaccharides on the gut microbiome of lactose-intolerant individuals. Proc Natl Acad Sci USA. 2017;114:E367–75.

186. Dewulf EM, Cani PD, Claus SP, Fuentes S, Puylaert PGB, Neyrinck AM, et al. Insight into the prebiotic concept: lessons from an exploratory, double blind intervention study with inulin-type fructans in obese women. Gut. 2013;62:1112–21.

187. Gonai M, Shigeisha A, Kigawa I, Kurasaki K, Chonan O, Matsuki T, et al. Galacto-oligosaccharides ameliorate dysbiotic Bifidobacteriaceae decline in Japanese patients with type 2 diabetes. Benef Microbes. 2017;8:105–16.

188. Liu F, Li P, Chen M, Luo Y, Prabhakar M, Zheng H, et al. Fructooligosaccharide (FOS) and galactooligosaccharide (GOS) increase Bifidobacterium but reduce butyrate producing bacteria with adverse glycemic metabolism in healthy young population. Sci Rep. 2017;7:11789.

189. Nicolucci AC, Humé MP, Martinez I, Mayengbam S, Walter J, Reimer RA. Prebiotics reduce body fat and alter intestinal microbiota in children who are overweight or with obesity. Gastroenterology. 2017;153:711–22.

190. Reimer RA, Willis HJ, Tunnicliffe JM, Park H, Madsen KL, Soto-Vaca A. Inulin-type fructans and whey protein both modulate appetite but only fructans alter gut microbiota in adults with obesity: a randomized controlled trial. Mol Nutr Food Res. 2017;61. https://doi.org/10.1002/mnfr.201700484.

191. Vandeputte D, Falony G, Vieira-Silva S, Wang J, Sailer M, Theis S, et al. Prebiotic inulin-type fructans induce specific changes in the human gut microbiota. Gut. 2017;66:1968–74.