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Microbiota-gut-brain axis: towards a microbiota-centred approach for irritable bowel syndrome

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Abstract

Irritable Bowel Syndrome (IBS) is a highly prevalent Disorder of the Gut-Brain Interaction (DGBI). Despite years of research, the mechanisms of IBS pathogenesis are not yet fully understood, but a key role is played by the gut-brain axis, whose alteration may lead to visceral hypersensitivity and altered motility. In recent years, advancements in research on the gut microbiota have shifted the understanding of the underlying pathophysiological mechanisms in IBS, with increasing attention to the role of the microbiota. In IBS patients, studies showed an altered gut microbial composition, with elevated levels of Clostridia and *Escherichia coli*, while Bacteroidia, *Lactobacillus* spp., and *Bifidobacterium* spp. were diminished. Moreover, an increased Firmicutes/Bacteroidetes ratio and a lower microbial diversity was commonly observed in many IBS patients. The complex interplay between the gut microbiota and the gut-brain axis is leading to the intriguing concept of a microbiota-gut-brain axis. Evidence for microbiota-altering interventions is still heterogeneous, with a described role of antibiotics, probiotics, prebiotics, while interventions such as Faecal Microbiota Transplantation (FMT) remain used primarily in research settings. A knowledge gap still exists about the microbiota profile of the ideal donor in FMT for IBS patients. Finally, the recent advancements in artificial intelligence offer new possibilities to improve diagnosis of IBS and efficacy of microbiota altering interventions to improve symptoms. Today, there is a need for gastroenterologists to develop expertise in this field and to collaborate with specialist of microbiota to manage this complex disease. Microbiota tests are increasingly used by patients, and personalized medicine will require gastroenterologists to adopt microbiota modulation strategies with the help of an expert microbiologist.

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Introduction

Irritable Bowel Syndrome (IBS) is a chronic and multifactorial Functional Gastrointestinal Disorder (FGID) characterized by recurrent abdominal discomfort and changes in bowel habits.[1] IBS is currently categorized as a Disorder of the Gut-Brain Interaction (DGBI). According to a recent global survey by the Rome Foundation IBS (diagnosed according to Rome-IV criteria), it affects an estimated 4% of the global population, with substantially higher rates among women than men (Odds Ratio 1.7).[2] Moreover, its global prevalence has significantly risen in the latest years also in non-Western countries. IBS significantly impairs the quality of life, often leading to avoidance behaviours, social withdrawal, and decreased work productivity.[3–5]

Diagnosis of IBS is clinical and made according to Rome-IV diagnostic criteria: patients must present with recurrent abdominal pain on average at least 1 day/week, associated with two or more criteria; a. related to defecation, b. a change in stool frequency, c. a change in stool appearance. These criteria must be fulfilled for the past 3 months with symptoms onset at least 6 months before diagnosis.[6]

Despite years of inquiry, the pathophysiology of IBS remains uncertain, but with a key role of gut-brain axis alteration leading to visceral hypersensitivity, altered motility and modified Central Nervous System (CNS) processing.[1] However, the last decade has seen significant progress in understanding its key mechanisms, largely due to increased research focus on the role of gut microbiota and the concept of dysbiosis in IBS. Factors traditionally linked to IBS development such as psychological stressors, dietary habits, and changes in environment could in theory all trigger changes in gut microbiota composition.[7] Moreover, an etiologic link between infectious enteritis and the development of post-infection IBS (PI-IBS) has been demonstrated in many studies: more than 10% of individuals experiencing infectious enteritis subsequently manifest IBS, with a relative risk in this cohort quadrupled compared to controls.[8,9]

Microbiota could be the underlying unifying element explaining key pathophysiological alterations well described and studied in IBS such as visceral hypersensitivity, impaired intestinal barrier function, altered intestinal secretion, activation of the mucosal immune system with low-grade inflammatory response.[10]

This is supported not only by the known role of acute infectious events in PI-IBS development, but also by multiple evidence that gut microbiota-modifying treatments (e.g., prebiotics, probiotics, antibiotics) can improve IBS symptoms without side effects.[11]

The human gut microbiota

The gastrointestinal tract anatomical and functional division into stomach, small intestine and large intestine corresponds to a specific diversity of the respective microbiota, which is composed of both symbiotic and pathogenic microorganisms. Five major genera dominate the gastric environment: *Prevotella, Streptococcus*, *Veillonella*, *Rothia* and *Haemophilus*.[12] Along small intestine bacterial density progressively increases from 10^3 - 10^4 CFU/mL in the duodenum to 10^7 CFU/mL in the ileum along with a shift from predominantly aerobic species to anaerobes and Gram-negative bacteria in the terminal portion of the ileum.[13] In the large intestine bacterial density reach 10^{12} CFU/mL with a significant shift towards an anaerobic population and two prevalent phyla: Firmicutes and Bacteroidetes. The ratio of these two phyla evolves with age and may be altered in various pathophysiological conditions.[14,15]

During the first years of life gut microbiota is shaped significantly with exposure to different factors such as environmental stress, diet (e.g., breastfeeding, fibre consumption), antibiotics. Mode of delivery plays a pivotal role in initial colonization of the gut, with an abundance of *Lactobacillus* and *Prevotella* species in infant delivered through vaginal canal, rather than an abundance of *Staphylococcus* and *Corynebacterium* species in infant delivered with Caesarean section.[16]

Along with age the composition of microbiota changes significantly and after the age of 3-5 years it becomes stable and adult-like.[17] During life gut microbiota shows a certain degree of resilience to endogenous and external stimuli unless there is no radical shift in long-term dietary habits, prolonged antibiotics treatment or stress.[17,18]

Gut microbiota influences several aspects of host immune response development. Intestinal bacteria presence influences positively the number of goblet cells in intestinal epithelial barrier and has a major role in determining mucus layer thickness and composition, thereby defining the mucus-microbiota layer. This concept highlights how the role of the microbiota in the balance between health and disease involves not only the microorganisms themselves, but also the surrounding matrix. Within this matrix, mainly composed of mucus, microbes live, proliferate and release by-products of their metabolism as well as nanovesicles, which exert bioactive actions both within the microbial community and towards the host.[19]

Moreover, microbial colonization represents a major step for the correct development of lymphoid structures (e.g., Peyer's patches, mesenteric lymph nodes and splenic white pulp).

The various array of enzymes produced by colonic bacteria has a key role in human metabolism: i) indigestible dietary fibres are fermented by bacteria producing Short-Chain Fatty Acids (SCFAs), gases and small amounts of organic acids which in turn can be used by human cells as energy source;[20,21] ii) protein catabolism by various bacteria results in production of Gamma-Aminobutyric Acid (GABA), serotonin, dopamine, histamine and others neurotransmitters;[22] iii) the 5% of conjugated bile acids that escapes distal ileum reabsorption is deconjugated by bacteria-produced bile salt hydrolase resulting in secondary bile acids that can be absorbed passively in the colon and act as a signalling molecule.[23]

Animal model studies showed how gut microbiota can modulate host immune cells differentiation; for example *Bacteroides fragilis* induces differentiation of CD4+ T cells into T_{reg} cells via its symbiosis factor Polysaccharide A (PSA), thus eliciting an anti-inflammatory mechanism,[24] with recent *in vitro* studies confirming the effect of PSA in humans.[25] Moreover, also bacteria from Gram-positive class Clostridia can induce T_{reg} cell population expansion by inducing production of transforming growth factor-β (TGF-β).[26–28]

Gut microbiota also can modulate innate immune response through alteration of intestinal barrier permeability: treatment with *Lactobacillus plantarum* DSM 2648 and *Escherichia coli* Nissle 1917 showed *in vitro* capability of tight junction expression upregulation.[29,30]

How to perform gut microbiota analysis

In the last decade technological improvement has produced a wide range of tools to analyze human gut microbiota composition and function both in healthy and diseased subjects (namely 16S rRNA based sequencing techniques and metagenomic analysis).[31] This variety of techniques generated the need for standards to make results comparable across studies. In this regards the International Human Microbiome Standards project analysed major factors that affect the analysis of the microbial community such as stool sample collection, storage, and DNA/RNA extraction protocols. Stool sample processing should be minimal with no role for the addition of RNAse inhibitors, while the use of cell-wall destruction methods such as bead-beating (physical method) or adding muralytic agents (chemical method) has proven crucial to proper detection of Gram-positive bacteria.[32,33] A recent article analysed differences between 21 different DNA extraction methods, further emphasizing the effect of different techniques on the outcome of metagenome analysis.[34]

Besides differences in protocols for handling the sample, a broad distinction for culture-independent microbiota analysis can be made between 16s rRNA techniques and metagenomics analysis. Techniques based on 16s rRNA gene rely on the fact that it includes both preserved region which can be used for amplification thanks to targeted primers and hypervariable (V1-V9) regions that allow us to distinguish at family and genus levels among different gut bacteria.[35]

The advent of high-throughput sequencing technique (Next Generation Sequencing, NGS) drastically reduced sequencing cost and time.[36] Metagenomic analysis involves untargeted sequencing of total DNA and comparison with genomic databases, enabling the gut microbiota profiling at strain level.[37,38] In addition to taxonomy surveys the use of metagenomics makes also possible functional analysis of microbiota using dedicated databases such as the Kyoto Encyclopedia of Genes and Genomes (KEGG) or the

Clusters of Orthologous Genes (COG).[39] Moreover, in recent years there has been an ever-growing interest in the use of metabolomic analysis via mass spectrometry, providing a deeper understanding of the function of microbial-derived molecules in the gut ecosystem.[40]

The microbiota-gut-brain axis

The gastrointestinal tract is functionally connected to the CNS through the Enteric Nervous System (ENS) which is composed by millions of neuronal cells located both in myenteric and submucosal plexuses. Many studies described the possible mechanism of communication between gut microbiota, CNS and ENS: i) production of microbial-derived intermediates (e.g. SCFAs, tryptophan metabolites, secondary bile acids);[41-43] ii) regulation of intestinal barrier and tight junction integrity;[29,30,44] iii) modulation of the enteric sensory afferents, in particular interactions with vagus nerve endings;[45] iv) mucosal immune regulation.

This intricate, bidirectional relationship is core to the concept of a microbiota-gut-brain axis central to the pathophysiology of both gastrointestinal tract and other systems diseases (e.g. cardiovascular disease, neurological degenerative conditions, and psychiatric disorders).[46,47]

The role of SCFAs has been studied mainly on animals, with evidence about its direct effect on systemic inflammation. SCFAs regulate production of inflammatory cytokines such as Tumor Necrosis Factor (TNF) through neutrophils inhibition; moreover they can modulate T cells differentiation and proliferation.[42] Studies in human subjects are still scarce with a systematic review showing only two studies in which SCFAs administration reduced serum markers of systemic inflammation.[48] Moreover, gut bacteria produced SCFAs seem to modulate secretion of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) by enteroendocrine cells.[49] The essential aminoacid tryptophan (Trp) follows different metabolic pathways, with production of three main metabolites along the gastrointestinal tract: serotonin, kynurenic acid with its downstream products, and indoles. The metabolism of each of these products can be regulated by gut microbiota; in particular, Trp direct transformation into indoles is performed only by some human commensal species and affects intestinal permeability and host immunity.[50]

Recent studies also challenged the classical understanding of the intestinal wall introducing the concept of the muco-microbiotic (MuMi) layer, a dynamic morphofunctional structure composed of mucus, microbial communities, and soluble mediators such as nanovesicles. The MuMi layer plays a key role not only in local homeostasis but also in systemic signaling, including communication with the CNS through Extracellular Vesicles (EVs). These EVs, of both human and bacterial origin, can reach distant organs via the bloodstream and may contribute to immune modulation, neuroinflammatory priming, and gut-brain axis signaling.[51,52]

Microbiota alterations in IBS

In IBS patients a lower microbial diversity is usually observed; currently, no specific patognomonic dysbiosis has been found.[53] When comparing the α-diversity of IBS patients and healthy controls, the first one shows a significant decrease. More robust evidence come from a meta-analysis comprehensive of 16 articles with 777 IBS patients. This study highlighted some constant changes in IBS faecal microbiota including an increase in Firmicutes, decrease of Bacteroidetes, with overall increase in Firmicutes/Bacteroidetes ratio, as well as an increase in Clostridia and Clostridiales, decrease in Bacteroidia and Bacteroidales.[54] In another recent meta-analysis of 23 articles IBS patients showed lower faecal *Lactobacillus* spp. and *Bifidobacterium* spp., higher *Escherichia coli*, with no difference in *Bacteroides* spp. and *Enterococcus* spp. numbers compared to healthy subjects.[55] Other studies observed among IBS patients an increase in the numbers of bacteria from the families Enterobacteriaceae and Lactobacillaceae, and of genus *Bacteroides* along with a decrease of Clostridiales, genus *Faecalibacterium* and genus *Bifidobacterium*.[56]

Major microbiota alterations in the gut of IBS patients are reported in Figure 1.

Recent studies shifted their approach from taxonomic only to a multi-omics one, interfering function through microbial gene content (metagenomics) or microbiota metabolites (metabolomics). Multi-omics analysis showed a modification in IBS patients of distinct metabolites including increased tyramine and decreased gentisate and hydro cinnamate, while metatranscriptomics use high-

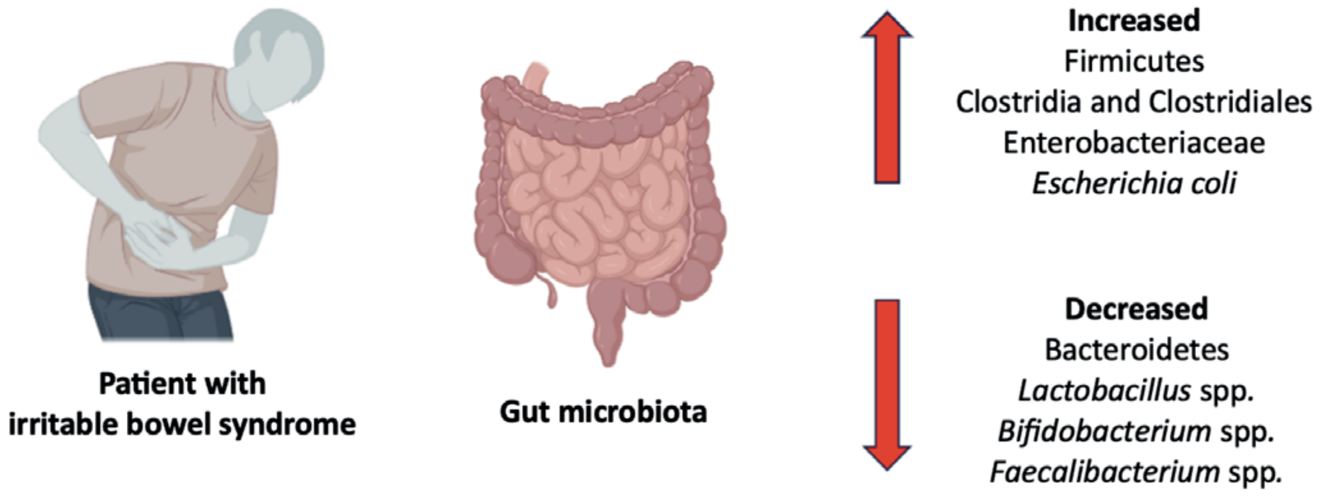

Figure 1. Changes in faecal microbiota of patients with irritable bowel syndrome.[54,56,57,59,60]

lights transcriptional upregulation of enzymes involved in fructose metabolism, glucan metabolism and succinate pathway.[57] However, the evidence is still limited. There is also a significant heterogeneity both in patient selection criteria and IBS diagnosis modalities.

Microbiota and metabolic activity alterations in IBS phenotypes

Besides differences between IBS patients and controls, many studies explored the possible differences between IBS phenotypes, mainly IBS-D and IBS-C, without finding a significant difference in gut microbiota composition.[54,58,59] However, it is fundamental to consider that differences in composition alone may not help in distinguishing functional IBS phenotypes.

In the study by Jacobs *et al.* they confirmed no significant difference in IBS subtypes taxonomic composition but on the opposite they found a significant difference in metabolic activity of gut microbiota between IBS-D and IBS-C. IBS-D was characterized by an increase in levels of cholate and isoursodeoxycholate. Furthermore, they found an upregulation of both carbohydrate metabolism and amino-acids catabolism into energy sources. This evidence may support the role of restrictive diets, such as low Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols (FODMAPs) diet, to reduce increased fermentable carbohydrates metabolic pathway.[57] Functional groups-based studies confirmed in IBS-C an increase in the population level of Enterobacteriaceae, along with a decrease of lactic acid bacteria (such as bifidobacteria and lactobacilli) and an increase of lactate-utilizing Sulphate-Reducing Bacteria (SRB). No comparison was made in this study with other IBS subtypes.[60]

Microbiota manipulation strategies for IBS treatment

With the increasing evidence regarding the microbiota-gut-brain axis, there has been a significant focus on understanding how to intervene on microbiota in order to treat IBS symptoms, with interest in the use of probiotics, prebiotics, antibiotics, and Faecal Microbiota Transplantation (FMT).[61–63] According to the World Health Organization (WHO) and the International Scientific Association for Probiotics and Prebiotics (ISAPP) probiotics can be defined as live microorganisms which when administered in adequate amounts confer a health benefit on the host.[64] Given the amount of evidence regarding dysbiosis in IBS patients, many studies examined the role of probiotics to improve patients' symptoms and attempt to restore eubiosis. Data on the use of probiotics in the treatment of IBS is vast but not univocal as there's great heterogeneity in the kind of microorganisms administered, their association with concomitant medications and the assessment of outcomes in IBS patients, that still relies purely on patients reported symptoms gathered through standardized questionnaires.[65] A meta-analysis by Ford *et al.* found evidence regarding the use of combination probiotics (containing different bacteria species) in reducing global IBS symptoms and abdominal pain, with data also supporting the role of specific strains such as *Lactobacillus plantarum* DSM 9843*, E. coli* DSM1752*, Streptococcus faecium* and *Bifidobacterium infantis*.[66]

A recent study conducted by the team led by Barbaro *et al.* confirmed that the probiotic formulation containing *Lactobacillus rhamnosus* LR32, *Bifidobacterium longum* BB536, and *Bifidobacterium lactis* BL04 mitigates the increased intestinal barrier permeability associated with IBS.[67] This effect is mediated by the targeted regulation of key Tight Junction (TJ) protein expression, critical structures for maintaining the integrity and functionality of the intestinal mucosa. Studies using the same probiotic combination showed also reduced intestinal inflammation, up-regulation of TJ proteins and modulation of the crosstalk among the intestinal epithelium, macrophages and mast cells thereby contributing to the preservation of epithelial integrity following pro-inflammatory stimulation with Lipopolysaccharide (LPS).[68–70] All subjects underwent colon biopsy, and the mucosal mediators spontaneously released from the tissue samples were analysed. Treatment with probiotics demonstrated a significant capacity to counteract the increased intestinal permeability induced by the IBS supernatants, with a particularly pronounced effect in the IBS-D and IBS-M subtypes, which are typically characterized by more marked alterations in paracellular permeability.[67] A recent work by Santonocito *et al.* demonstrated that a probiotic combination containing *Lactobacillus salivarius* LS33, *Lactobacillus acidophilus* LA14, and *Bifidobacterium bifidum* BGN4 in patients with IBS-D modulated the interaction between the microbiota, gut, and brain through the regulation of tryptophan metabolism, leading to an increase in its metabolic derivatives, such as serotonin and kynurenine.[71] Most common probiotics used in IBS management are reported in Table 1.

In addition to the scientific evidence supporting the role of probiotics in relieving IBS symptoms they have high patients' preference as they are perceived lacking any side effects usually associated with other medications such as tricyclic antidepressants.[72] Another interesting strategy in managing IBS through microbiota manipulation could be the supplementation of prebiotics, which are defined as a group of substances metabolized by gut microbiota. Fermentation of Fructo-Oligosaccharides (FOS), Galacto-Oligosaccharides (GOS), and Trans-Galacto-Oligosaccharides (TOS) results in SCFAs production and has shown to induce growth of specific strains of bacteria.[73,74] However, there is a lack of Randomized-Control Trials (RCTs) on the role of oligosaccharides in IBS. Two RCTs on the use of FOS versus placebo in IBS patients (the first one 20 g dose, the second one 2.5 g) found no difference between the two treatment groups in symptoms relief; however, it should be noted that the study by Azpiroz *et al.* was underpowered to detect a difference, while the study by Olesen *et*

Table 1. Currently used probiotics with evidence of efficacy in the management of irritable bowel syndrome.[102–110]

Bifidobacterium bifidum, Bifidobacterium animalis lactis, Bifidobacterium longum
Enterococcus faecium
Escherichia coli
Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus plantarum, Lactobacillus rhamnosus
Saccharomyces boulardii

al. provided no sample size analysis.[75,76] In contrast an RCT on TOS by Silk *et al.* observed after 4 weeks treatment a significant reduction in symptoms scores.[77]

Although being capable of modifying to some degree gut microbiota composition and function, limited interventions such prebiotics, probiotics or non-adsorbable antibiotics do not appear to bypass the resilience of pathological or dysbiotic microbiota. On the other hand, FMT may represent a possible therapeutic possibility to induce a stable shift in gut microbiota.[78]

Role of non-microbiota related factors in IBS

While microbiota-directed therapies hold promise for managing IBS by targeting gut dysbiosis, a comprehensive approach necessitates the integral inclusion of exercise, diet, and neuromodulators. Regular physical activity has demonstrated benefits in reducing IBS symptoms,[79,80] potentially by modulating the gut microbiota, improving gut motility, and alleviating stress.[81] Dietary interventions, such as the low-FODMAP diet or personalized elimination diets, play a crucial role in identifying and mitigating symptom-triggering foods.[82,83]

Recent evidence suggests that a significant portion of individuals with IBS experience acute mucosal reactions to specific foods, observed as identified as fluorescein leakage and cell shedding on Confocal Laser Endomicroscopy (CLE), an advanced and innovative diagnostic endoscopic imaging technology that provides real-time, high-resolution cellular-level visualization of the gastrointestinal epithelium.[84] Notably, more than 70% of these patients reported feeling better when they avoided these specific foods.[85] This implies that localized immune system activity and problems with the gut's protective barrier might play a role in causing IBS symptoms. Therefore, CLE could be used into personalized dietary management for difficult-to-treat IBS.[86]

Furthermore, a considerable proportion of patients with IBS report experiencing symptoms following wheat intake. Recognizing the potential causes as celiac disease, wheat allergy, wheat sensitive IBS, and non-celiac gluten/wheat sensitivity, is therefore critical for correct diagnosis, thereby preventing patient dissatisfaction, unnecessary testing, and inaccurate or delayed identification of the underlying issue. While a gluten-free diet is recommended for celiac patients, for patients with symptoms similar to those of functional diseases (wheat sensitive IBS) there is evidence that a low-FODMAP diet should be the first dietary option, together with the other treatment of IBS (e.g., microbiota-directed therapy).[87] Furthermore, neuromodulators (e.g. Amitriptyline), acting along the brain-gut axis, can address visceral hypersensitivity, modify gut motility and the associated psychological comorbidities like anxiety and depression, thereby offering significant symptom relief.[88,89]

In those patients with associated psychological comorbidities, it could be considered to integrate the psychological therapies into patient management. Cognitive Behavioural Therapy (CBT), relaxation therapy, multi-component psychological therapy, hypnotherapy, and dynamic psychotherapy were all beneficial when data from two or more RCTs were pooled in a meta-analysis.[90] Moreover, mindfulness-based approaches directly address this dysregulation.[91,92] CBT, for instance, equips patients with coping mechanisms to manage stress and modify negative thought patterns that can trigger or worsen IBS symptoms. By targeting the psychological distress associated with IBS, these therapies can lead to a reduction in both the frequency and severity of physical symptoms, ultimately improving quality of life and overall well-being of patients with IBS.[93]

Future perspectives: new strategies and targets for microbiota altering interventions

The long-term goal would be to develop treatments that can modulate this microbiota-gut-brain axis to reduce visceral sensitization, improve intestinal motility, alleviate gastrointestinal symptoms and improve patients' quality of life without the side-effects that may be associated with traditional drug therapies.[39] A significant gap of knowledge on the role of FMT in IBS still exists and represents future possible opportunities for research. Selection of well-defined donor with a normal dysbiosis index and favourable specific microbial signature seems to be possible to achieve an effective treatment for patients with IBS. Current available studies show that a single FMT may result in significantly fewer IBS symptoms, and an overall improved quality of life both at 2 and 3 years after the transplantation.[78,94–96]

Recent studies have explored the role of integrating the capabilities of Artificial Intelligence (AI) with the process of diagnosis and therapy in IBS. A systematic review analysed 6 observational studies finding that machine learning models trained on faecal microbiota profiles could predict IBS patients with variable accuracy (from 54% to 98%), with one study reporting 98% sensitivity and specificity.[97,98] A pilot-study by Karakan *et al.* compared standard IBS diet versus an AI personalized diet in patients with IBS-M. Only the AI personalized diet group showed a change in IBS Symptom Severity Score (SSS) from severe to moderate in 78% of the patients. Moreover, a statistically significant increase of both *Faecalibacterium* spp. and *Propionibacterium* spp. was observed in the personalized diet group.[99] A 2024 multicentric randomized controlled trial of 121 patients also confirmed that AI-assisted personalized diet reduced significantly both IBS-SSS and IBS-Quality of Life (IBS-QOL) scores for all subtypes, with additional shift of microbiota diversity compared to traditional FODMAP diet.[100]

Besides new technological and research advancements in IBS and microbiota-gut-brain axis, the complexity of the subject calls for a radical shift in gastroenterologist's approach: IBS will be required to have an increasingly global, but also specific and in-depth understanding of the mechanisms underlying this gastrointestinal condition, which requires an integrated vision and multidisciplinary practice between gastroenterology, molecular biology, microbiology and genetics.[101] Health care professionals will not only have to be updated on research advances but also develop specific skills in the management of microbiome-based therapies, an area that is constantly evolving.

Conclusions

Despite emerging evidence, there are still many open questions and challenges to be addressed regarding the exact mechanism through which the microbiota influences the brain and behaviour of the individual. Interaction with genetic, epigenetic and environmental factors, and the complexity of interactions between the different microorganisms of the microbiota make it difficult to obtain definitive answers as the response to treatment can vary greatly from patient to patient.

The selection of the most effective probiotic strains and species, microbiological dosages, dosage of administration, immune response and symptomatic subjectivity are variables that are difficult to control as they have a high inter-individual variability.

However, the microbiota-gut-brain axis field offers promising opportunities for new treatments and prevention strategies for a range of both physical and mental disorders. Future directions will also need to be aimed at reducing the risk of ineffective treatment or unwanted side effects. New technologies such as AI could also offer tools to account for individual variation and improve dietary interventions efficacy.

Finally, the multidisciplinary and interdisciplinary approach involving gastroenterologists, microbiologists and clinical psychologists is crucial to face the future challenges in the world of functional pathologies, including IBS. Professional collaboration between experts from different fields, including research on the gut microbiome and DGBI, could accelerate the identification of the pathophysiological mechanisms intrinsic to the disease, deepen the understanding of genetic, epigenetic and environmental factors, and foster the development of more targeted, effective and innovative therapeutic strategies for the management of the disease.

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