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Emerging role of the gut microbiome in post-infectious irritable bowel syndrome: A literature review

Vasile Valeriu Lupu, Cristina Mihaela Ghiciuc, Gabriela Stefanescu, Cristina Maria Mihai, Alina Popp, Maria Oana Sasaran, Laura Bozomitu, Iuliana Magdalena Starcea, Anca Adam Raileanu, Ancuta Lupu

Abstract

Post-infectious irritable bowel syndrome (PI-IBS) is a particular type of IBS, with symptom onset after an acute episode of infectious gastroenteritis. Despite infectious disease resolution and clearance of the inciting pathogen agent, 10% of patients will develop PI-IBS. In susceptible individuals, the exposure to pathogenic organisms leads to a marked shift in the gut microbiota with prolonged changes in host–microbiota interactions. These changes can affect the gut–brain axis and the visceral sensitivity, disrupting the intestinal barrier, altering neuromuscular function, triggering persistent low inflammation, and sustaining the onset of IBS symptoms. There is no specific treatment strategy for PI-IBS. Different drug classes can be used to treat PI-IBS similar to patients with IBS in general, guided by their clinical symptoms. This review summarizes the current evidence for microbial dysbiosis in PI-IBS and analyzes the available data regarding the role of the microbiome in mediating the central and peripheral dysfunctions that lead to IBS symptoms. It also discusses the current state of evidence on therapies targeting the microbiome in the management of PI-IBS. The results of microbial modulation strategies used in relieving IBS symptomatology are encouraging. Several

studies on PI-IBS animal models reported promising results. However, published data that describe the efficacy and safety of microbial targeted therapy in PI-IBS patients are scarce. Future research is required.

Key Words: Gut microbiome; Infectious gastroenteritis; Irritable bowel syndrome; Post infection syndrome; Pathophysiology; Inflammation

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Core Tip: Acute infectious gastroenteritis can trigger the onset of irritable bowel syndrome (IBS), leading to the development of post-infectious IBS (PI-IBS). PI-IBS is a clinical entity associated with gut dysbiosis. Alterations in the gut microbiome can affect the gut–brain axis, visceral sensitivity, intestinal barrier, intestinal secretion, gut motility, and immune activation, which in turn can cause IBS symptoms. A better understanding of PI-IBS is necessary to develop more targeted and effective treatments. Therapies targeting the microbiome, such as probiotics, antibiotics, diet, and fecal microbiota transplants, improve IBS symptoms. There is a lack of evidence of their efficiency in PI-IBS.

INTRODUCTION

Irritable bowel syndrome (IBS) is the most frequently encountered disorder of gut-brain interactions[1], with a worldwide prevalence ranging between 7% and 15% of the general population[2,3]. According to the Rome IV criteria, it is characterized by mild to severe recurrent abdominal pain and bloating associated with alterations in bowel habits in the absence of organic disease or biochemical abnormalities[4]. Due to its symptoms, IBS is thought to be a disabling disease. It generates significant healthcare costs, reduces work productivity and school attendance, and decreases the health-related quality of life of the affected individuals[5,6]. Despite being a frequent entity in current gastroenterology practice, the physiopathology of IBS is not fully understood. It is considered to be a complex multifactorial disorder affected by several factors such as age, sex, genetics, diet, psychosocial status, altered microbiota, subclinical inflammation, and hypersensitivity of the neural network[7,8]. In recent years, accumulating evidence has suggested that the alteration of the gut microbiota plays an important role in the pathophysiology of IBS, as gut microbes exert effects on the host immune system, on gut barrier function, and on the brain-gut axis[9,10].

Acute infectious gastroenteritis [bacterial-*Campylobacter* species[11], *Salmonella* species[12,13], *Escherichia coli* (*E. coli*)[14], *Shigella*[15], *Clostridium difficile* (*C. difficile*)[16], viral-norovirus[17], rotavirus[18], severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[19], and protozoal-*Giardia*[20]] has been shown to be one of the strongest risk factors for the development of post-infectious IBS (PI-IBS), a distinct condition in which IBS diagnostic criteria are met[21,22]. PI-IBS occurs after the resolution of a gastrointestinal-related infection and the clearance of the inciting pathogen, in a patient without a prior history of IBS symptoms[22,23]. IBS clinical features usually develop 6-18 mo after the infectious gastroenteritis episode[24]. PI-IBS management strategies involve nonpharmacologic and pharmacologic therapies. Current guidance relies on IBS treatment experience, as there is a lack of evidence-based recommendations for PI-IBS treatment[1]. The aim of this review is to analyze the current literature and to describe the role of the human gut microbiota on PI-IBS physiopathology. The main questions to be

answered include which long-term consequences of acute enteric infections may serve as triggers to PI-IBS and whether the acute enteric infection associated dysbiosis and its recovery can be used to predict PI-IBS development. Additionally, under discussion is whether there is a specific microbial signature associated with PI-IBS, as most studies of PI-IBS combine patients infected by varying pathogens, thus generating a considerable variability of outcomes. The gut microbiota modulation and its potential therapeutic implications in PI-IBS in terms of efficacy and safety continue to be a subject of debate and highlight the need for specific treatment protocols. A better characterization of the relationship between gut-associated dysbiosis and PI-IBS progression will lead the way to personalized medicine and the individualized management of each patient.

PI-IBS GENERAL DATA

A globally accepted definition of PI-IBS is not currently available in the literature. Most authors consider PI-IBS as a form of IBS for which the symptoms, as specified in the Rome IV criteria, appear after the resolution of an acute gastroenteritis episode in patients without any IBS symptomatology before the gastrointestinal infection[1,4]. In 2019, the Rome Foundation Working Group proposed symptomatic diagnostic criteria for PI-IBS based on the Rome IV criteria (Figure 1), as there are no sensitive and specific diagnostic markers available yet[25]. Considering the predominant bowel pattern graded on the Bristol stool scale, PI-IBS can be classified as diarrhea-predominant IBS (IBS-D), constipation-predominant (IBS-C), mixed bowel habits (IBS-M), and unclassified[1,26]. A bowel pattern is considered predominant when it is ≥ 25% of the time as either hard/lumpy (IBS-C), loose/watery (IBS-D), or both (IBS-M)[1]. PI-IBS patients are more likely than sporadic IBS patients to present a diarrhea-predominant phenotype. The association between each patient and a PI-IBS subtype is important for disease management and therapy[22].

While most pathogen agents cause self-limiting acute gastroenteritis, subsequent chronic alteration may persist in some genetically predisposed individuals[27]. According to several studies, about 1 in 10 individuals with an acute episode of gastroenteritis will

develop PI-IBS[21,28]. A 2017 meta-analysis reported that the incidence of PI-IBS more than a year after the acute episode of gastroenteritis was 14.5%[29]. Epidemiologic data of the reported incidence and prevalence vary across the literature, in part due to the methodological heterogeneity, including the criteria used to define IBS (Rome criteria I, II, III, or IV)[3,16,22]. Moreover, there is evidence that the data might be underestimated due to the high incidence of infectious gastroenteritis and the poor recall of milder episodes, as the diagnosis relies on self-reported symptom clusters[2,21,30].

Female sex, a young age, certain psychological factors before or during acute infectious gastroenteritis (anxiety, depression, somatization, and/or neuroticism), and genetic predisposition (carriers of the *TLR9*, *CDH1*, and *IL6* genes) seem to increase the risk of developing PI-IBS[29,31]. The severity of the acute infectious episode also seems to increase the probability of developing PI-IBS after the gastroenteritis resolution[29]. The risk of PI-IBS is doubled when diarrhea lasts > 7 d and is tripled when diarrhea lasts > 21 d. Other symptoms such as abdominal cramps, weight loss, and bloody stools are also associated with an elevated risk, with abdominal cramps increasing the PI-IBS risk four times. Fever is not mentioned as a risk factor[32]. Moreover, it might have a protective action, representing the host's response to the infectious injury[33]. The risk of IP-IBS remains high for at least 2 to 3 years post infection[22].

Various pathogens have been reported as related to PI-IBS development. A systematic review evaluating the prevalence and risk factors of PI-IBS after acute gastroenteritis by specific pathogens revealed the fact that the evidence indicated a similar risk for bacterial pathogens, while for viral and parasitic gastroenteritis, the data were limited[34]. However, a recent study found the incidence of PI-IBS to be higher in patients with *Campylobacter jejuni* (*C. jejuni*) gastroenteritis, compared to other etiologic agents such as bacteria, viruses, or protozoa[35]. When comparing different pathogens, protozoal enteritis shows the highest risk for PI-IBS development, followed by bacterial and then viral[33,36]. Bacterial infections seem to generate more PI-IBS cases than viral gastroenteritis probably due to the fact that the mucosal damage and inflammation caused by bacteria is often greater than that caused by viral agents[37].

There is a strong association between travelers' diarrhea and PI-IBS. Self-reports of exposure seem to result in a higher PI-IBS occurrence than laboratory-confirmed cases of travelers' diarrhea, but further studies are needed to confirm this finding[38]. Culture-confirmed infections, either bacterial or viral, seem to present an equally increased risk of PI-IBS as nonspecific gastrointestinal infections[39]. However, viral gastroenteritis is more likely to develop transient forms of PI-IBS than bacterial episodes[40]. The significant decrease in the PI-IBS prevalence from 19% to 4% one year after a viral infection may be due to the less invasive nature of the pathogen, perhaps avoiding a stronger host response[29]. During the recent pandemic, the novel coronavirus SARS-CoV-2 displayed its potential to generate gastrointestinal manifestations[41,42]. It seems that the prevalence of gastrointestinal symptoms in coronavirus disease 2019 (COVID-19) patients is around 10%, and it is following an increasing trend[43,44]. A multicenter study from 2020 reported that digestive symptoms such as diarrhea, vomiting, and abdominal pain were present in 50.5% of COVID-19 patients, while other studies concluded that the incidence of diarrhea in the same category of patients varied from 2% to 20%[41,45,46]. A recent study found an incidence of 11.6% of IBS, according to the Rome IV criteria, with symptom onset following COVID-19 infection[41]. Another group of researchers reported similar results, with 10% of the included patients with an acute episode of SARS-CoV-2 in their medical history meeting the Rome IV criteria for IBS 6 mo after the viral infection. Three percent of them had gastrointestinal symptoms during COVID-19[47]. Noviello *et al*[48] found an incidence of PI-IBS in 26.2% of patients. The risk of developing *de novo* IBS post-COVID-19 increases in patients with gastrointestinal symptoms present during the active viral infection. Similar to noninfectious IBS, the risk is higher in female patients. The presence of severe disease markers, such as an oxygen requirement and high procalcitonin levels, increases the risk of post-COVID-19 IBS[49]. Another similar study reported that patients with dyspnea at time of admission and a history of allergies and chronic treatment with proton pump inhibitors had an increased risk of developing post-COVID-19 IBS[50].

Compared to sporadic IBS, PI forms of the disease might have a better outcome[2]. The prognosis of PI-IBS appears favorable with the spontaneous and gradual resolution of symptoms in most patients[22]. However, one longitudinal follow-up study showed that 15% of patients with post-infection IBS remained symptomatic 8 years after disease onset[28].

PI-IBS PATHOPHYSIOLOGY

Available studies have failed to give a clear holistic picture on the underlying pathophysiology of PI-IBS. As IBS is a multifactorial disease, it has been hypothesized that the development of PI-IBS could result from the interplay of fecal microbiota, the immune response of the host, and the psychological factors[51], as illustrated in Figure 2. The current conceptual framework regarding the pathophysiologic mechanism for PI-BS suggests that the exposure to pathogenic organisms leads to the alteration of the gut microbiome. PI-IBS is associated with hyperplasia of enterochromaffin (EC) cells and increased counts of neutrophils, mast cells, and T cells in the colonic mucosa. It is believed that gastrointestinal infections stimulate the immune system causing low-grade inflammation leading to PI-IBS[52].

It was reported that patients with PI-IBS often present an increased visceral pain perception known as visceral hypersensitivity (VHS). The incomplete resolution of the immune response to acute infectious injury might facilitate the persistence of a microscopic inflammation of the bowel, activating and sensitizing pain-sensing nerves[53]. A persistent low-grade inflammation of the bowel is thought to trigger PI-IBS symptoms, by aberrant activation of intrinsic and extrinsic nerves. The increased numbers of immune cells and the enhanced cytokine signaling play an important role in the underlying mechanism of PI-IBS pathophysiology[54]. A group of researchers found an increased IL-1β mRNA expression in rectal tissue biopsies after an acute episode of infectious gastroenteritis. Patients with a *Campylobacter* enteritis were found to present increased EC cell numbers, intraepithelial lymphocytes, and intestinal permeability up to one year after the infectious episode[55], while patients with PI-IBS following a *Shigella*

gastroenteritis had an increased number of mast cell in the terminal ileum[56]. These cells release mediators such as histamine, IL-1β, IL-6, and TNF-α, mediators that can stimulate or sensitize visceral nociceptors and possibly generate the abdominal pain in PI-IBS[54]. Excessive secretion of IL-8 is a hallmark of *Campylobacter* pathogenesis, being initiated by the host recognition of the pathogen-associated lipooligosaccharide[57,58]. Another study on PI-IBS patients, however, found no evidence of increased inflammatory gene expression or infiltrating inflammatory cells in biopsies and no increase in cytokine levels[54]. Similarly, no difference was reported in the number of T lymphocytes or proinflammatory cytokines between PI-IBS patients and infected healthy volunteers, 3 years after a *Salmonella* infection[59]. Another study on a large cohort found similar results, with no difference in serum cytokines and mucosal cytokine expression between PI-IBS patients and healthy volunteers[60]. γδT cells are a subset of T cells involved in initiating inflammatory responses and can acquire the capacity of inducing various cytokines. A recent study of Dong *et al*[61] found that the Vδ1 γδ T cells subset from PI-IBS patients remarkably proliferated, activated, and produced abundant IL-17. In these patients, the IFN-γ level remained unchanged, as proof of the fact that the local IL-17 could participate in the intestinal pathological disorder during PI-IBS, as the major proinflammatory cytokine[61]. Furthermore, a rodent study concluded that the upregulation of A2AR increased PI-IBS by promoting the T17 polarization of CD4+ T cells[62]. In their study, Balemans *et al*[54] reported that although initiated by inflammation, the pronociceptive changes seen in PI-IBS patients were mediated by the Hrh1 receptor sensitization of TRPV1 signaling, suggesting that similar to the "standard" IBS12, Hrh1 antagonism may represent an interesting new target for treatment of PI-IBS[54]. In conclusion, the presence of low-grade inflammation is an inconsistent finding in PI-IBS, as it might be an interim event following gastroenteritis that is superseded by another more persistent change in the gut microenvironment[54].

Increased intestinal permeability was shown to be an early event in PI-IBS physiopathology, associated with low-grade inflammation[1]. Patients with PI-IBS and

high fecal proteolytic activity presented *in vivo* and *ex vivo* distal gut permeability that depended on the fecal level of proteolytic activity[63]. Following a mixed infection of enterohemorrhagic *E. coli* (EHEC) O157:H7 and *C. jejuni* during a waterborne outbreak of bacterial gastroenteritis, there was reported an increased intestinal permeability[58]. EHEC is known for its deleterious impact on the epithelial barrier[64]. *Giardia duodenalis* (*G. duodenalis*), a protozoan pathogen also implicated in promoting PI-IBS development, is well known to disturb the homeostatic barrier function through several mechanisms[65].

Viral gastroenteritis is a known risk factor for the PI onset of IBS. There are many studies describing the relation between norovirus infection and PI-IBS. As a conclusion to their study, Porter *et al*[66] suggested that dysmotility disorders may follow viral infections. A high incidence of functional gastrointestinal disorders was reported in patients who suffered from a norovirus gastroenteritis[66]. Similarly, another two studies reported an increased prevalence of PI-IBS in patients who experienced an acute episode of gastroenteritis during a confirmed norovirus outbreak[40,67]. It is thought that norovirus infection can cause epithelial barrier dysfunction, increased intestinal permeability, a reduction in the villous surface area and villous height, and a mucosal immune response with an increase in cytotoxic intraepithelial T cells, impairing the gut's sensory-motor function[67].

COVID-19, an immunologic and inflammatory response associated with low-grade inflammation and mucosal injury, caused the development of IBS features in genetically predisposed individuals. Patients with PI-IBS can present high levels of macrophages and T lymphocytes in intestinal samples, increased levels of calproctin and fecal cytokines, such as IL-8; all these were found in COVID-19 patients, as well as the presence of virus-specific IgA, together with increased blood levels of proinflammatory cytokines[68,69]. Similar to IBS, the altered intestinal permeability associated with gut dysbiosis and with an alteration of the neuromuscular function might also be involved in PI-IBS onset[67].

On the other hand, the pandemic led to a stressful situation, anxiety, and depression. These factors resulted in other diseases related to psychological stress and the nervous system similar to IBS[70,71]. Farsi *et al*[41] in their study found that psychological stress had

no significant influence on COVID-19-induced IBS symptoms[41]. However, another similar study reported that COVID-19 had adverse effects on both GI and psychological symptoms among individuals with functional dyspepsia-IBS overlap syndrome[70]. Similarly, another study concluded that the COVID-19 pandemic increased psychosocial stress and gastrointestinal symptoms in patients already known to have IBS[72]. The interaction between the gut-brain axis disturbances and genetic and psychosocial factors can contribute to IBS development[41]. Psychological stress acts as a trigger in developing IBS through its adverse effects on intestinal permeability and motility and hypersensitivity to visceral pain. Acute and chronic stressful situations lead to cortico-tropin-releasing hormone secretion, activating the hypothalamic-pituitary-adrenal axis and creating new premises for IBS onset. Stress-induced dysbiosis can modulate the neuro-immune-endocrine systems and interfere with the brain-gut axis[73,74].

PI-IBS MICROBIOME ALTERATION

Due to the bioavailability of nutrients, the human gastrointestinal tract harbors the largest concentration and diversity of microbiota of the human body. Healthy adult gastrointestinal microbiota are represented by five primary bacteria phyla: *Firmicutes* (synonym *Bacilliota*) and *Bacteroides* (synonym *Bacteroidota*) phylum predominate the microbiota, while *Actinobacteria* (synonym *Actinomycetota*), *Proteobacteria* (synonym *Pseudomonadota*), and *Verrucomicrobia* phylum are found in modest proportions[75]. The gut microbiota have a dynamic composition, influenced by many intrinsic and extrinsic factors, such as genetic inheritance, birth mode, breastfeeding duration, age, sex, diet, and drugs[75-77]. The alteration of the healthy microbial structure leads to dysbiosis, resulting in various gastrointestinal disorders, systemic metabolic diseases, and neurological impairments[75].

During an acute infectious gastroenteritis, there is a decline in the gut's microbial diversity[78]. There are several mechanisms explaining the disruption of the indigenous microbiota. One would be directly throughout pathogen agent-microbiota interaction. Secondly, the alteration of the microbiota might occur *via* the host's mucosal immune

response, or there is the possibility of a combination of the two presented mechanisms[27,79]. In rodents, *Salmonella enterica* serovar typhimurium was shown to induce the loss of 95% of the total bacterial numbers of the intestinal tract, 7 d after the infectious episode[80]. *G. duodenalis* and *C. jejuni* can directly alter the composition of human gut microbiota[81]. Aside from the predominance of the etiologic bacterial pathogen, certain native taxa of the gut microbiome such as *Streptococci, Fusobacteria,* and *Campylobacter*, can also increase their numbers throughout the acute episode but also in the weeks following the bacterial infection[82,83].

Immediately after acute gastroenteritis with *Vibrio cholerae* (*V. cholerae*), increased levels of *V. cholerae*, *Streptococcus, Fusobacterium,* and *Campylobacter* species were found during a 16S rRNA gene polymerase chain reaction (PCR) analysis of the infected patients' stool samples. Two months after the first assessment, there was a decrease in *V. cholerae*, *Streptococcus, Fusobacterium,* and *Campylobacter* species, while *Ruminococcus obeum, Collinsella aerofasciens, Ruminococcus torques, Eubacterium rectale,* and *Faecalibacterium prausnitzii* increased their levels as a marker of recovery from the infection[82].

As for gastroenteritis triggered by viral agents, the alterations in the microbiota seem to be less consistent. The immune response to the viral injury is usually less harmful, resulting in a decreased diversity and the expansion of *Proteobacteria* species in some patients with viral gastroenteritis[83]. A study including patients with all-cause traveler's diarrhea investigated their gut microbial composition using fecal samples. In diarrheal patients, there was a decreased *Bacteroidota/Bacilliota* ratio and changes in β-diversity, compared to healthy travelers who displayed an unexpected increased abundance of *Bacilliota* phylum (*Streptococcus* and *Lactococcus* genera). Stool samples of patients with confirmed norovirus infection had an increased diversity of species characterizing their microbiota during the active infection, including *Clostridium XIVb, Bilophilia, Alistipes, Barnesiella,* and *Roseburia* species[84]. When assessing the gut microbiome correlation in symptomatic and asymptomatic patients infected with norovirus, Patin *et al*[85] found no significant difference between the alpha and beta diversity of the two groups studied.

The symptomatic subjects presented relatively more species of *Bacilliota* phylum, especially in the order *Clostridia*, while *Bacteroidota* phylum displayed fewer species than the asymptomatic subjects, particularly in the *Bacteroidia* order. In asymptomatic patients, three members of the genus *Parasutterella* and one in the *Nitrosomonadaceae* family were found in higher levels. The increased levels of *Bacteroidota* in the asymptomatic individuals suggest that its presence could improve the host's effort of resisting enteric viral infection or neutralizing its pathogenicity and symptoms[85]. Another study on Chinese patients with diarrhea of viral etiology reported a decreased diversity in the gut microbiota at stool sample examination, when compared to healthy individuals. *Bacilliota* phylum with species of *Enterococcus, Peptostreptococcaceae, Incertae Sedi, Shigella, Weissella,* and *Clostridium* dominated the microbiota during the acute episode, while beneficial bacteria such as *Bacteroides vulgatus, Bifidobacterium,* and *Lactobacillus* species were found in decreased amounts[83]. Nelson *et al*[86] also tried to characterize the stool microbiota in norovirus-infected human patients. Their research found similarities between infected patients' and uninfected healthy individuals' microbiota. However, in a small number of infected patients there was found a significantly altered microbiome characterized by a reduced relative number of *Bacteriodota* and a corresponding increase in *Pseudomonadota.* Interestingly, the increased level of *Pseudomondota* phylum was due to a single operational taxonomic unit of *E. coli*[86]. This finding raises the concern that the alteration in gut microbiota during an acute viral gastroenteritis exposes the affected patients to some possible long term gastrointestinal complications.

SARS-CoV-2 infected patients seem to present an altered gut microbiota, characterized by the depletion of anti-inflammatory butyrate-producing bacteria and the enrichment of taxa with proinflammatory properties[87,88]. The Alpha and beta diversity index values appear to be significantly lower than in healthy individuals, all through the active infection and the recovery period[87,89]. Furthermore, an important reduction in the major bacterial phylum composition and diversity was also observed[90]. *Ruminococcusm gnavus* and *Bacteroides vulgatus* were found in increase amounts in post-acute COVID-19

patients' microbiomes, while *Faecalibacterium prausnitzii*, known for its anti-inflammatory proprieties, was characterized as decreased, when compared to healthy individuals[70].

Streptococcus, *Enterococcus*, and *Corynebacterium* species, well known as opportunistic pathogens, seem to be found in higher amounts in COVID-19 patients' stools than in healthy individuals[87]. *Fusicatenibacter*, *Romboutsia*, *Intestinibacter*, *Actinomyces*, and *Erysipelatoclostridium* species could actually be used as biomarkers in order to identify COVID-19 positive patients[91]. There is proof that the development of PI-IBS may be predicted by the composition of the salivary microbiome during acute SARS-CoV-2 infection[40,92]. Butyrate-producing bacteria showed an inverse correlation with IBS symptom onset 6 mo post-acute viral infection[93]. The gut microbiota composition was reported to be correlated with proinflammatory cytokine levels, as proof of its contribution to the immune response. The *Faecalibacterium* genus, belonging to the *Clostridia* class, was found to be decreased in COVID-19 patients during the acute episode and was inversely correlated with the IL-8 and IL-12 serum levels. The same study reported an enrichment of the *Actinomycetota* phylum and the *Propionibacteriaceae* family, which was positively correlated with the gp130/sIL-6Rb level[90]. The *Streptococcus* species was also associated with an increased expression of proinflammatory cytokines such as IL-18, TNF-α, and IFN-γ[87]. In contrast, IFN-gamma and IL-28A/IFN-12 levels were found to be negatively correlated to the class *Clostridia*, reduced in abundance in COVID-19 patients[90]. Changes in the microbiome composition were also identified in COVID-19 patients without antibiotic exposure. Depletion of beneficial commensal species and enrichment of opportunistic pathogenic bacteria, such as *Clostridium hathewayi*, *Actinomyces viscosus*, and *Bacteroides nordii*, were found in COVID-19 patients' stool samples. According to Zuo *et al*[94], the disease severity and the baseline abundance of certain genera and strains might be in close relationship, as the gut microbiota might actively influence the immune system response. Moreover, it appears that 50% of COVID-19 patients had an active intestinal infection, even in cases with no gastrointestinal complaints[94]. The deleterious effect of SARS-CoV-2 infection on beneficial gut microbiota seems to persist even after disease resolution, sustaining the possibility of the

gut microbiome alteration's role in PI-IBS pathogenesis[95]. The intestinal infection persisted despite respiratory viral clearance[19,94]. There were cases described, where dysbiosis was persistent 30 d after the acute viral episode, suggesting the long-term influence of COVID-19 on gut microbiota[96]. Opportunistic pathogens such as *Collinsella aerofaciens*, *Collinsella tanakaei*, *Streptococcus infantis,* and *Morganella morganii* have been found in large amounts in stool samples with high SARS-CoV-2 infectivity. In stool samples with low-to-no viral infectivity, there were higher amounts of *Parabacteroides merdae*, *Bacteroides stercoris,* and *Lachnospiraceae bacterium 1_1_57FAA*, some of these within important role in augmenting host immunity[19,94]. Current evidence suggests that a high microbial exposure to Gram-negative bacteria could offer protective effects against COVID-19, possibly due to the increased interferon type I levels[43]. These findings sustain the idea that the gut homeostasis may suffer some alterations during the acute COVID-19 episode, independent from the presence of gastrointestinal symptoms, alterations that can persist beyond disease resolution[73]. There is evidence that COVID-19-induced impairment of the gut–lung axis might create predisposing factors for IBS development[43,97].

Moreover, there is evidence that microbiota composition prior to infection may also influence the possibility of developing an acute infection as well as PI-IBS[33]. Dicksved *et al*[98] reported that an increased abundance of *Bacteroidota* in pre-employment stool samples of abattoir workers increased the risk of developing a *C. jejuni* infection during the period of employment[98]. A *Clostridiales*-predominant microbiota type has a protective role, as an individual with such intestinal microbiota is more likely to return to a state of eubiosis after the remission of the infectious episode and pathogen clearance. A *Bacteroidota* predominant community, in contrast, may increase the risk of long-term dysbiosis after the acute episode's resolution[21].

Although the gut microbiota profile of IBS patients has been evaluated in several studies, there is not the same consistency of data regarding PI-IBS patients' gut microbiome alteration. In their study of the real-time PCR assay of rectal epithelium RNA expression, Jalanka-Tuovinen *et al*[51] concluded that the intestinal microbiota of PI-IBS

patients were significantly different from healthy individuals but similar to patients with IBS-like symptoms (PI bowel disease, PI-IBS and IBS-D). They identified an "index of microbial dysbiosis" (IMD) that characterized the intestinal microbiota of PI-IBS. The IMD included 27 genus-like microbial groups including a twelvefold increased level of *Bacteroidota* phylum, including as *Bacteroides* and *Prevotella* species. The *Bacilliota* phylum was less abundant, with decreased levels of various uncultured *Clostridiales* and *Clostridium* clusters. Moreover, dysbiosis was associated with gastrointestinal symptoms' severity and not with psychological symptoms. Dysbiosis was also associated with biopsy findings, such as increased levels of eotaxins, mast cells, and goblet cells and decreased EC cells[51]. Similar results were obtained by Sundin *et al*[99], when analyzing the mucosal and fecal microbiota of patients with PI-IBS. The fecal microbiota composition of PI-IBS patients was significantly different from the fecal microbiota of IBS patients and healthy individuals. Patients with PI-IBS had a reduced mucosal and fecal microbial diversity, with reduced levels of *Bacillota*, including *Clostridium* clusters IV and XIVa, and increased *Bacteroidota*, including *Bacteroides* species. The reduced diversity of the fecal microbiota was associated with increased activated lymphocytes in the lamina propria. At the level of major butyrate producer bacteria abundance, there was no difference identified between the PI-IBS patients and healthy individuals. Unlike Jalanka-Tuovinen *et al*[51], the reduced diversity of the microbiota was associated with the presence of psychological symptoms[99]. In PI-IBS patients, the *Bacteroidota* phylum seems to have a relatively greater abundance of microbes than in healthy individuals, while *Bacillota* phylum display a relative reduction in representative members in the gut microbiota[78]. The main findings are summarized in Table 1.

MICROBIOME-DIRECTED THERAPY

Acute gastroenteritis, as mentioned above, can alter the gut microbiota, initiating the underlying mechanisms of PI-IBS. Modulation of the microbiota can be performed using probiotics, symbiotics, prebiotics, and antibiotics or by performing a fecal microbial transplantation, with the purpose of downregulating inflammation, improving barrier

function, and reducing visceral sensitivity[100]. To date, there is no specific practice guideline or treatment strategies for PI-IBS. Different drug classes can be used for treating PI-IBS similar to patients with IBS in general[37].

Probiotics are known to be "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host"[101]. *Lactobacillus casei* DG (LC-DG) and its postbiotic were shown to attenuate the inflammatory mucosal response in an *ex vivo* organ culture model of PI-IBS-D[102]. Similarly, Hong *et al*[103] reported that probiotic administration (*Lactobacillus acidophilus* LA5, *Bifidobacterium animalis* subsp. *lactis* BB12, and *Saccharomyces cerevisiae* var. *boulardii*) decreased proinflammatory cytokine levels in both the control and PI-IBS induced mice[103].

Saccharomyces boulardii, given 750 mg/day for a period of 6 wk, was reported to improve the quality of life and the cytokine profile in PI-IBS patients[104]. *Bifidobacterium infantis*, M-63 1 × 109 cfu/sachet/day given daily for 3 mo, restored the normal composition of the gut microbiota and improved mental health in individuals with post-flood acquired IBS[105].

Given the current evidence that serotonin levels are increased in PI-IBS patients, serotonin-based therapy is a treatment option that deserves further study[106]. Cao *et al*[107] proved that an *Lactobacillus rhamnosus* supernatant had a positive effect on serotonin transporter (SERT) expression in colon tissues of rats with PI-IBS. By modulating the microbial composition, the serotonergic imbalance can be restored, followed by the improvement in IBS symptoms[107]. Another similar study on an animal model evaluated the efficacy of a *Bacillus subtilis* (*B. subtilis*), *Enterococcus faecium*, and *Enterococcus faecalis* (*E. faecalis*) supernatant, administrated in PI-IBS rats. The researchers reported that the supernatants could upregulate the expression level of SERT in intestinal cells, mentioning the fact that the combined supernatants of *B. subtilis* and *E. faecalis* had a superior effect to the administration of a single supernatant[108]. Studies regarding prebiotic and symbiotic use in PI-IBS patients are not available.

Fecal microbiota transplantation (FMT) is used in order to restore microbial dysbiosis by transferring a healthy microbiome to an individual with an alteration of

microbial composition[109]. FMT has shown benefits in IBS patients. However, there is a lack of data on FMT use in PI-IBS. A recent randomized clinical trial assessed FMT's safety as well as its clinical and microbiological efficacy in patients with PI-IBS. The results demonstrated FMT's effectiveness compared to traditional pharmacotherapy, its safety, and tolerability[110].

However, FMT could be used in reestablishing the microbiota homeostasis following acute gastroenteritis, with the purpose of decreasing the risk of PI-IBS development. It is known that FMT is recommended for recurrent or refractory *C. difficile* enterocolitis, as a proved effective therapy[111]. There is evidence that FMT treatment can improve gut microbiota alteration in recovered COVID-19 patients, particularly in those who presented severe gastrointestinal symptomatology during the acute phase[112].

Jin *et al*[113] assessed the action of rifaximin on the VHS, barrier function, gut inflammation, and microbiota in a PI-IBS mouse model. Rifaximin administration improved the VHS, recovered the intestinal barrier function, and inhibited low-grade inflammation in the colon and ileum, without changing the composition and diversity of the gut microbiota[113]. However, Harris *et al*[114] and Tuteja *et al*[115] reported no benefit of rifaximin therapy on PI-IBS patients.

The results of mesalazine's efficacy in treating PI-IBS patients are contradictory. Lam *et al*[116] reported a significant improvement in symptoms such as abdominal pain, urgency, and stool consistency, when mesalazine was given to a small group of PI-IBS patients[116]. Bafutto *et al*[117] found that mesalazine administration in PI-IBS patients decreased the stool frequency and improved its form and consistency, after 30 d of treatment[117]. In contrast, another double-blind controlled trial including a small number of patients with diarrhea predominant PI-IBS reported no positive effect on clinical symptoms or quality of life[118]. However, mesalazine use during the acute infectious gastroenteritis may have a protective effect on PI-IBS development, as reported by a study on patients affected by hemorrhagic enterocolitis with *Shiga*-like toxin-producing *E. coli*[119]. Dunlop *et al*[120] found a significant reduction in the T- lymphocyte counts in

the rectal tissue of PI-IBS patients treated with prednisone, although there was no positive effect on the EC cell count or symptom improvement[120].

Bile acid malabsorption may occur after an episode of acute gastroenteritis. It is confirmed that cholestyramine administration can alleviate symptoms in PI-IBS patients, especially with diarrhea symptoms[121]. The information regarding the therapeutic options in PI-IBS are summarized in Table 2.

CONCLUSION

Acute gastroenteritis can significantly increase the risk of developing IBS, a chronic gastrointestinal pathology with high health-care utilization. Current studies in humans as well as animal models describe specific host–pathogen interactions that may lead to the onset of post-infection IBS symptoms. There is no curative treatment option for PI-IBS, and patients rely only on symptomatic therapy. There are numerous studies on IBS treatment options. However, there is a lack of data regarding PI-IBS therapeutic management, and there is a great need for evidence-based recommendations in post-acute gastroenteritis IBS.

These advancements in understanding will be helpful in elaborating specific biomarkers used to identify patients with a high risk of developing IBS symptoms following an acute infectious gastroenteritis, as well as designing targeted pharmacotherapy. Microbial restoration, augmentation of barrier function, and targeting VHS remain the most promising areas for therapeutic interventions and represent a future research perspective.

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