Post-infectious Irritable Bowel Syndrome: an opportunity for prebiotics as an adjunct therapy of oral rehydration salts/solutions

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Abstract

The purpose of this review is to assess the potential benefits of prebiotics as an adjunct therapy of oral rehydration salts/solutions (ORS) in the management of acute gastroenteritis and in the prognosis of post-infectious irritable bowel syndrome (PI-IBS) in children and adults. The review focuses on the clinical issues of IBS as a functional gastrointestinal disorder of multifactorial etiology and its impact on both quality of life and economic cost. Also, it addresses the quantitative contribution of PI-IBS to IBS in order to define the full potential of prebiotics as an adjunct therapy of ORS: An infectious diarrheic episode increases six times the likelihood of developing PI-IBS compared to the general population of unexposed. In the United States, norovirus acute gastroenteritis alone is the cause of disease in 19-21 million people a year; therefore, the impact of ORS with prebiotics may be substantial not only in reducing dehydration, but also in reducing the risk of IBS.

ABBREVIATIONS

IBS: Irritable Bowel Syndrome; PI-IBS: Post-Infectious IBS; CDC: Centers Disease Control and Prevention; GI: Gastrointestinal; AGE: Acute gastroenteritis; ORS: Oral rehydration salts/solutions; GOS: Galacto- Oligosaccharide; FODMAP: Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols; SIBO: Small Intestinal Bacterial Overgrowth

INTRODUCTION

Irritable bowel syndrome (IBS) is a persistent and relapsing functional gastrointestinal disorder. The Rome III criteria in children and adults are required in diagnosing IBS. The criteria include recent abdominal pain or discomfort present in three or more days/months with two or more of the following changes related to bowel movements: symptoms improving with defecation; excretion frequency change with onset of symptoms; or changes in stool form (hardness) with onset of symptoms [1]. The clinical presentation of constipation, diarrhea, or a combination, constitutes the different subtypes: IBS with constipation (IBS-C), with diarrhea (IBS-D), and mixed (IBS-M). The distribution of patients is about equal among the subtypes [2]. This syndrome poses a significant social problem and clinical challenge, because it is one of the most frequent alimentary tract illnesses reported by patients, young and old, and also the most common reason for referrals [1,3]. The clinical challenge rises from the fact that its diagnosis is based on symptomatology in the absence of organic disease. This review will emphasize the clinical importance of Post-Infectious IBS (PI-IBS) in contributing to IBS prevalence and highlight the alterations of the intestinal microbiota observed in IBS. Based on the microbiota changes, the implementation of prebiotics as an adjunct therapy of ORS may be a preventive measure of IBS in susceptible individuals.

Prevalence of IBS and its impact on quality of life

IBS affects 15% of the western population with a worldwide prevalence of 10-20% [1,2,4]. However, its prevalence varies by country from as low as 4% in some countries to as high as 25% in others [2]. The annual incidence of IBS recently reported by El-Salhy [2] is between 196 and 260 patients per 100 000 persons, based on data from Locke [5] and García Rodríguez [6]. This figure may be an underestimate, considering that these studies used early Rome criteria in the diagnosis of the IBS patients.

which tends to underestimate the prevalence of IBS when compared to Rome III criteria [7]. Nonetheless, this incidence rate underlines the fact that IBS causes a higher burden of disease than colon cancer (i.e., 46 cases per 100,000 persons, CDC) [8] and inflammatory bowel disease (Crohn’s disease USA incidence, 3.1 to 14.6 cases per 100,000 person-years) [9]. IBS occurs more often in women and is more commonly diagnosed in patients younger than 50 years of age [2,7,8], although in some populations, the incidence has been associated with advanced age [5]. These data suggest that IBS affects populations independent of age. The observed variability in the prevalence among countries reflects the clinical challenge that IBS represents due to variability of symptom severity (from tolerable to severe) and the variable time pattern of symptoms [2].

In children, IBS is the most common cause of recurrent abdominal pain worldwide [10]. Its prevalence rate is 10%-15% in children and adolescents [10]. In a recent case study, it was 22.6% in children from Turkey [11]. IBS poses a significant social problem in children and adults, as it reduces the patient’s quality of life to the same degree of impairment as major chronic diseases [2,10]. In addition there is a significant economic impact. Doshi et al.[12] showed that the annual all-cause health care costs to IBS-C were US$11,182, and an incremental cost of $8,086 associated with frequent use of medical services. These IBS-C costs are higher than the cost burden of migraines or asthma [12]. Buono et al.[13] demonstrated in a post-hoc analysis that non-treated patients with IBS-C had 35.1% overall work productivity loss and 40% daily activity impairment than those treated.

Factors associated with the pathology of IBS

The pathogenesis of IBS is multifactorial. El-Salhy [2] concluded that several factors and their interactions play a key role in the disease: “heritability and genetics, environment and social learning, dietary or intestinal microbiota, low-grade inflammation and disturbances in the neuroendocrine system of the gut.” In addition, Morcos et al. [14]. Concluded that the symptomatology of IBS involves the gut-brain axis. To facilitate a therapeutic approach, these factors and their mechanisms of action can be sorted into three distinct spheres: bio-behavioral factors including genetic predisposition and inherited-behavioral sensitivities and responses; environment-cultural factors, those exogenous triggers and their related-learned responses; and finally, the milieu through which they interact, food/diet and the intestinal microbiota. Of these, food/diet and the microbiota are prominent determinants of the symptoms, their severity and the success of the treatment [2-4,14].

Many IBS patients describe exacerbation of symptoms immediately following food ingestion. The triggering of symptoms and their exacerbation may be not only a response to digestion (stimulation of gut motility and secretion), but also to the food itself vis-à-vis its ingredients and their digestive residues, as may be the case for fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) [2,10,14]. These food ingredients are fructans, galactans and sugar alcohols such as sorbitol, maltitol, manitol, xylitol and isomaltose [15,16]. Lactose and fructose are usually well absorbed, but some individuals lack the respective disaccharidases and have impaired digestion and absorption [14,17,18]. Accordingly, these sugars and their alcohols when poorly absorbed in the small intestine, they can be fermented by the colonic microbiota, and due to their osmotic effects in the distal small intestine and colon, they may potentiate IBS symptoms of bloating and diarrhea. Studies on the impact of FODMAP-free diets in patients with IBS suggest that this approach may be of value in some patients [14,19-21] and thus, dietary restriction of FODMAP-containing foods is accepted in the management of IBS symptoms [3]. However, these sugars and complex carbohydrates are ingredients in many available foods [14-16] and this limits the efficacy of FODMAP-restricted diets [14,22]. Furthermore, the role of FODMAPs on IBS symptoms is dependent on bacterial colonization of the small intestine or on alterations of the intestinal microbiota [4,14].

Small intestinal bacterial overgrowth (SIBO) and intestinal microbiota alteration in IBS

The most frequent complaints by IBS patients are those of abdominal distension causing abdominal pain or discomfort and bloating, associated with altered stool form (such as diarrhea, constipation) and defecation. This gut symptomatology reflects poor absorption of food ingredients and their subsequent fermentation by intestinal bacteria as in the case of FODMAP containing foods. The early or enhanced fermentation can be explained by two possible mechanisms, SIBO or altered intestinal microbiota.

SIBO is associated with an increased number and/or type of bacteria (> 10⁵ colony forming units/mL) on cultures of upper gut aspirates [23]. SIBO has been associated with IBS symptomatology in various studies; however, this association depends on the diagnostic method. Ghoshal and Srivastava [23] reviewed 17 clinical studies that measured expired H₂ or CH₄ post-oral intake of lactulose or glucose, and determined that SIBO frequency among patients with IBS varied from 4% to 78% whereas in the controls was from 1% and 40%. In contrast, clinical studies using luminal secretions and mucosal samples from the proximal small intestine showed little difference between IBS patients and their respective controls [25]. Overall, reviews by Bye et al. [24], Varner [25], and Simren et al. [26] indicate that the importance of SIBO in the symptomatology of IBS is probably limited to only a minority of patients irrespective of the definition employed or method of diagnosis.

Most studies on the gut microbiota in IBS have analyzed fecal samples using culture-based methods, and have demonstrated disturbances in a range of bacterial populations in both adults and children [4,10,24,26]. Molecular biology techniques like 16S rRNA-based micro arraying have accelerated profiling of microbiota, and have demonstrated both quantitative and qualitative changes of mucosal and fecal gut microbiota in IBS [26].

The microbiota of the human GI tract can be divided into three robust clusters called enterotypes formed by groups of species that jointly contribute to their respective preferred community composition [4,27]. Arumugam et al. [27] identified three robust enterotypes. These enterotypes are not as sharply delineated as human blood groups, but each can be identifiable by the variation in the levels of one of three genera: Bacteroides (enterotype...
1), *Prevotella* (enterotype 2) and *Ruminococcus* (enterotype 3). This characterization is important because a recent study demonstrated that fecal microbiota of IBS patients could be grouped in a cluster which was completely different from that of healthy controls [28]. Rajilić-Stojanović et al. [28] using global and deep molecular analysis of fecal samples from 62 IBS patients and 46 healthy individuals demonstrated that IBS patients had on average 2-fold less of various groups belonging to the *Bacteroidetes* and a 1.5 fold increase in numbers of *Ruminococcus* than healthy subjects (p-values < 0.01). These findings suggested that the microbiota of the IBS patients belonged to enterotype 3 mainly [28]. The IBS patients also showed a 1.5-fold decreased level of *Bifidobacteria* with an increased abundance of members of the *Firmicutes* in the feces with a 2-fold increased ratio of the *Firmicutes* to *Bacteroidetes* (P < 0.001), confirming previous studies that used fecal culture-based analyses [4]. Thus, the above studies and epidemiological, clinical and experimental studies documenting the existence of post-infectious IBS suggest that alterations of the enteric microbiota may play a key role in the pathogenesis of IBS [4,29-33].

**Acute gastroenteritis as a cause of IBS**

Acute gastroenteritis (AGE) is commonly reported by IBS patients as the first trigger of their symptomatology [3,14]. Post-infectious IBS (PI-IBS) is a functional gastrointestinal disorder defined as the acute onset of new IBS symptoms in a patient who has not previously met the Rome criteria for IBS, immediately after AGE that is characterized by 2 or more of the following: fever, vomiting, diarrhea, or a positive bacterial stool culture [33,34]. The clinical features of PI-IBS are similar to those of IBS-D; however, it is defined by the appearance of new IBS symptoms following an episode of AGE [29]. There are at least four meta-analyses that find strong evidence that an episode of AGE is one of the most commonly identifiable risk factors for the development of IBS [31,35-37], and a comprehensive review using based grading medical evidence of PI-IBS studies [29]. It is important to note that the majority of the selected studies in each of the meta-analyses were analyzed in 3 or 4 of the meta-analyses, indicating that different methods in the study selection criteria and statistical analyses agree with the likely contribution of AGE to the IBS burden.

These studies, all together, indicate that AGE increases six times the likelihood of developing PI-IBS compared to the general population of unexposed [29], an odds ratio of 6.03 (95% CI 3.58-10.13) [37]. Based on the high risk of PI-IBS, it has been suggested that almost all IBS is caused by acute gastroenteritis [38]. Two factors need to be considered in the interpretation of the odds ratios. First, studies examining this association are retrospective, most used older Rome criteria, and are based on recall information, all of which may biased the estimated odds ratio of IBS. Second, the majority of patients with AGE do not develop PI-IBS [39]. Therefore, to understand the overall contribution of AGE to the total IBS prevalence, Shah et al. [40] used available published studies to develop an empiric steady-state model based on factors of population dynamics, infectious disease incidence, PI-IBS risk, and characteristics of IBS illness duration. The model with the most conservative assumptions based on meta-analysis data that only those genetically susceptible (i.e., inflammatory hypersensitivity) would develop PI-IBS predicted a steady-state of 9% of IBS cases after an initial episode of AGE. This is notable given the worldwide prevalence of 10-20% of IBS [2,4]. These highly theoretical models suggest that PI-IBS could account for the majority of IBS in the community over time.

Indeed, evidence from the outbreaks of infectious AGE supports the above predictions. In a prospective follow up of a *Salmonella* AGE outbreak in Spain, the infection across the adult population was associated with a 1-year incidence of new IBS of 12% [41]. Recently, Zanini et al. [42], reported on the incidence of PI-IBS from a massive water-borne outbreak of norovirus in an Italian city. The virus was isolated in water samples collected at the time of the outbreak and from stool samples of patients. Within one month of the epidemic period, all subjects who experienced AGE provided a baseline self-administered questionnaire on symptoms and their severity. A control cohort was selected six months later for their consecutive attendance to the same local physicians for any reason other than IBS. The odds ratio of PI-IBS (according to Rome III criteria) was 11.40 (95% CI: 3.44-37.82) 12 months after the outbreak in the AGE group [42].

These findings have led, in the case of AGE caused by bacterial, protozoan and helmith infections, to a primary hypothesis explaining PI-IBS as intestinal wall inflammation triggered by infection leading to subtle but permanent changes in the structure and function of the digestive system [43,44]. However, the risk factors associated with PI-IBS after viral AGE differ from those factors associated with bacterial and protozoan infections. As shown by Zanini et al. [42], there was no association between PI-IBS and gender, age, longer duration of diarrhea, increased stool frequency, abdominal cramping, bloody stools, reported weight loss, fever, or pre-existing psychological disorders. Thus, it is possible that mechanisms contributing to the development of PI-IBS may vary with the etiology of the AGE and its effect on the intestinal microbiota [43].

**Diarrheal mechanisms affecting intestinal mucosa and causing dysbiosis**

The normal balance of enterotypes 1, 2 and 3 (especially the saccharolytic genera/species, e.g. bifidobacteria) in the gut microbiome [27,45,46] has led to the concept of ‘normobiosis’/’eubiosis’ to characterize a normal gut microbiota. In contrast, ‘dysbiosis’ is characterized by a gut microbiota with one or more pre-existing psychological disorders. Thus, it is possible that mechanisms contributing to the development of PI-IBS may vary with the etiology of the AGE and its effect on the intestinal microbiota [43].

The underlying mechanisms of infectious diarrhea include alterations in ion transport and tight junctions as well as the pathogen-virulence factors, which may affect the bowel either directly or indirectly through inflammation and neurotransmitters [47]. In general, viral infections including norovirus cause villus blunting. This decreases the number of cells and reduces the overall absorptive surface, inducing osmotic diarrhea [47]. In tandem, the host’s inflammatory response to the pathogen’s virulence and the effect of diarrhea on the intestinal mucosa contribute to dysbiosis. Lupp et al. [48]...
used mouse models of gut inflammation, including pathogen bacteria to mimic human diarrheal pathogens and chemical inducers of intestinal inflammation or genetically inflammation-deficiency mice to assess the effect of inflammation alone. They showed that the presence of an invading pathogen and the host-inflammatory response are necessary to enhance its colonization and to maximize the decrease in the total numbers of natural intestinal bacteria. The hydrodynamic forces induced by osmotic diarrhea can also contribute to dysbiosis. Gorkiewicz et al. [49] induced osmotic diarrhea in four healthy adults by oral administration of polyethylene glycol 4000, and evaluated the bacterial composition in mucosa specimens from the colon and from stool samples. Osmotic diarrhea decreased phylotype richness and showed a strong tendency to equalize the otherwise individualized microbiotas on the mucosa. Moreover, the diarrhea led to significant shifts in the phyla Bacteroidetes and Firmicutes, where Bacteroidetes decrease in the mucosa. There was also a relative increase in the abundance of Proteobacteria in the mucosa with several opportunistic pathogens including pseudomonads like Pseudomonas and Acinetobacter. The results from this study are notable for two important reasons. First, they provide a plausible mechanism for the effects of the outbreak of norovirus infection on PI-IBS reported by Zanini et al. [42]. Second, the shift in phyla observed in this model of osmotic diarrhea agrees with Rajilic-Stojanovic et al. [28], who showed in PI-IBS patients a two-fold decrease in the number of Bacteroidetes and a significant correlation between the presence of the microbial groups like Firmicutes and Proteobacteria with IBS symptom scores. These results are also compatible with clinical studies showing that fecal samples of PI-IBS patients have a characteristic and specific Index of microbial dysbiosis [30].

Finally, these results are in line with the current working hypothesis on the pathogenesis of IBS, in which an abnormal microbiota (dysbiosis) activate mucosal innate immune responses that increase epithelial permeability, activate nociceptive sensory pathways and deregulate the enteric nervous system [26,43]. Moreover, they provide a mechanism for the cause of dybiosis in IBS, via host-induced inflammation or osmotic diarrhea.

**Prevalence of Infectious Diarrhea Disease and ORS**

Norovirus has been the leading cause of gastroenteritis in the United States (US) since 2006, when rotavirus vaccine was recommended for US infants [50]. It now causes 19–21 million total illnesses per year [51]. In the United Kingdom, rates of outpatient norovirus range from 21 to 54 outpatient visits/10,000 people, while US estimates range from 57 to 64 outpatient visits/10,000 people [51]. Considering that there are many different types of norovirus, people may be re-infected many times during a lifetime. Although it is possible to develop immunity to specific types, this immunity may last only four years [52]. Indeed, a US resident can experience at least 5 episodes of Norovirus gastroenteritis in his or her lifetime.

Other risk factors for infectious diarrhea besides person-to-person contagion include travelers’ diarrhea and foodborne outbreaks. The most frequent illness among people traveling from industrialized regions to developing countries is travelers’ diarrhea (TD). Recently, Lalani et al. [53] showed in a prospective cohort study that 24% of participants (270/1,120) met the criteria for TD among the Department of Defense beneficiaries who traveled outside the United States for ≤6.5 months. In the US, the most common reported pathogens are bacterial, causing up to 80% of TD cases [54]. The Europe Travel and Tropical Medicine Network (EuroTravNet) reported in 2008 that in 6,957 ill returned travelers, AGE was the most frequent concern [55]. Regarding food borne outbreaks, the CDC reported 13,405 outbreaks during 1998–2008, which resulted in 273,120 reported cases of illness [56]. Of 7,998 outbreaks with a known etiology, 45% were caused by viruses and 45% were caused by bacteria. Overall, norovirus was the most common cause of outbreaks and illnesses, causing 43% of the outbreaks with a confirmed or suspected single etiology [56]. Noteworthy, TD and food borne-associated pathogens are equally present among in IBS and PI-IBS patients [26,44]. Taking into account these AGE rates and their likely contribution to PI-IBS, an intervention to reduce the risk of PI-IBS during the treatment of infectious diarrhea is highly desirable.

For all cases of diarrhea, attention to fluid and electrolyte replacement is fundamental. Oral rehydration salt/solution (ORS) has been the cornerstone of therapy for dehydration secondary to acute infectious diarrhea for more than 40 years [57]. ORS is effective in replacing fluid and electrolyte losses, but it has no effect on stool volume, stool frequency or duration of diarrhea [58,59]. The World Health Organization (WHO) supported the development of an improved ORS that could reduce the morbidity of diarrhea while maintaining the concentration of salts, a “Super ORS” [57,59]. Thus, the original formulation of ORS has been challenged with the advent of hypotonic formulations, formulations based on rice, or formulas containing amylase-resistant starches [57,58]. However, a review of studies using price-ORS determined no benefit on clinical outcomes in children with non-cholera diarrhea [60]. Another proposal is the adjunct use of probiotics or prebiotics (fructo-oligo-saccharides, inulin, etc.) on the premise of improving microbial balance in the gut [4,45,59,61].

**Galacto-oligosaccharide (GOS) as adjunct therapy of ORS**

The focus of nutrition in IBS is on the diet, and like with FODMAP the recommendation is to avoid food intolerance and food allergies through dietary modifications [3,10,62]. However, caution needs to be observed with exclusion diets as they may place patients at risk of nutritional deficiencies [62]. Recently, a case report, in which high doses of vitamin D3 intake (daily 2000–4000 IU) for three years reduced IBS symptoms, has suggested its potential as treatment of IBS [63]. The report provided supporting evidence from internet-based social media sites, patient blogs and forums. This type of recall data and the lack of an experimental design require that these findings be interpreted cautiously. Especially after the authors noted that from the information collected, there is a lack of detail on the severity of IBS among sufferers, dosage of vitamin D3, its source, or other treatments used [63].

Another strategy is modulating the enteric microbiota and reducing the comorbid aspects of IBS with the use of probiotics and prebiotics. Probiotics are proposed to enhance eubiosis...
in IBS as well as during diarrheal disease [59,61]. A recent ESPGHAN working group position paper has indicated that clinical studies on the use of probiotics have demonstrated that only two strains may successfully reduce diarrheal morbidity, *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii* [64]. Considering that each individual has a unique gut microbiota, it should not be assumed that because one organism is beneficial, related organisms will behave similarly [45] and thus, it limits their application to specific populations. Regarding probiotic use in IBS, a Rome Foundation Report concluded that the strongest evidence is for *Bifidobacterium infantis*, but overall, there are many incompletely answered questions surrounding this therapeutic approach including which patients would benefit and which probiotic(s) offer potential benefits [26].

On the other hand, there are several prebiotics that benefit the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon. Among these, fructooligosaccharides (FOS) containing 2 to 70 fructose units are the most studied [45,61]. Clinical trials assessing prebiotics during diarrheal disease are few and not many have been successful. However, Passariello et al [65], in a randomized-controlled trial of 119 young Italian children with acute diarrhea, demonstrated that 73% of those receiving a new hypotonic ORS containing zinc plus a mix of prebiotics (FOS/xilooligosaccharide of 0.35 g/L and 0.35g/L) resolved their diarrhea within 72 hours compared to 50% in those assigned to a standard hypotonic ORS (p=0.01). Also, the number of stools was significantly reduced in the prebiotic group compared to controls at 24, 48 and 72 hours. Although the positive clinical effects exerted by the ORS could be related to a synergistic action between the prebiotics and zinc, it is important to note that this study was conducted in children from a developed country, who on average were in the 50th percentile of the weight-for-age growth curve. This suggests that the resolution of diarrhea was probably due to the prebiotic mix. In adults with TD, Cummings et al [66] using FOS alone were not able to show a significant decrease in episodes of diarrhea, however, the recording of episodes of diarrhea was low and disproportionate among the FOS and control groups.

The efficacy of prebiotics on IBS has been assessed in several clinical studies. Guandalini et al [67] reviewed clinical studies using oligofructose at 2 g three times daily, FOS at 20 g/day, or short-chain FOS at 5g/day, and they determined there was no significant reduction of the symptoms and that in some cases FOS increased the symptomatology of IBS. The failure of FOS in reducing the symptomatology of IBS is probably related to its mechanism of action and the dysbiosis in IBS patients as noted on the failure of FOS in travelers’ diarrhea [66]. FOS primarily affects the large intestinal microflora and may well improve colonization resistance; however, the dysbiosis of IBS and TD includes pathogens that affect the small intestine such as enteropathogenic *E. coli*, *Campylobacter*, or *Giardia* [44]. Also, the Rome Foundation report indicated that many dietary prebiotics including oligofructose and FOS in inulin-containing juices are considered FODMAP and as such these are substrates for bacterial fermentation [26].

The prophylactic use of another prebiotic, galactooligosaccharide (GOS) which is manufactured from lactose by transglycosylation reactions has been successful in reducing TD. Drakoularakou et al showed that the daily consumption of 2.64 g of GOS significantly reduced the incidence, duration and symptoms of diarrhea in a randomized placebo-controlled study among 119 healthy adults travelling for minimum of 2 weeks to countries with risk for TD, [68]. The incidence of diarrhea was 23.5% in the GOS group vs. 38.5% (p<0.05) in the control group receiving maltodextrin, and the duration was reduced by 51% while improving quality of life.

Moreover, Simré et al [26] in a Rome Foundation Report indicated that only GOS at a low dose has demonstrated an increased predominance of *bifidobacteria* with concomitant significant improvements in bloating, flatulence, and global relief of IBS symptoms. Silk et al [69] in a 12-week parallel crossover controlled clinical trial evaluated GOS in 44 patients with Rome II positive IBS, given GOS at 3.5 g/d or 7 g/d, or a placebo. The trial showed a significant predominance of fecal *bifidobacteria* with GOS at 3.5 g/d and 7 g/d doses, while the placebo was without effect. Additionally, GOS at 3.5 g/d changed stool consistency, improved flatulence and bloating, mended composite score of symptoms and subjective global assessment (SGA) (p-values < 0.05). The 7 g/d dose only improved SGA and anxiety scores (p-values < 0.05).

Experimental studies documenting the specific bifidogenic effect of GOS as well as its non-prebiotic effects on the intestinal mucosa provide a mechanistic explanation for these clinical results. Maathuis et al [70] using a dynamic, validated model of the human proximal large intestine containing an adult-type microbiota and unlabeled control or (13) C-labeled GOS showed that the *Bifidobacteria* family was the primary member within the complex microbiota that fermented GOS. GOS fermentation led to an increase in luminal acetate (+49%) and lactate (+23%) compared with the control. Moreover, the incorporation of the 13-C label from GOS into the 16S-rRNA of the biomass of *Bifidobacterium* and *Lactobacillus* families occurred within 2-4 hours of adding the labeled GOS. Using *in vitro* cultures of infant fecal samples, others have similarly shown that GOS substantially increases the growth of total bifidobacteria. Much of this growth was attributed to the growth of *B. longum*, which corresponded to an increase in acetic acid concentrations and a trend to lower *E. coli* levels and pH [71]. In tandem with its prebiotic effects, animal models examining intestinal alterations in mucosal structure and cell function showed that mice receiving GOS had significantly higher sucrase activity, which was a specific effect on mucosal epithelial cells [72]. Also, Bathi et al [73] using human adenocarcinoma-derived LS174T cells that exhibit an intestinal goblet cell-like phenotype exposed to GOS for 72 hours showed enhancement of the mucosal barrier function through direct stimulation of intestinal goblet cells.

To summarize, GOS has been shown to have a therapeutic effect in reducing the symptomatology of IBS and as prophylaxis for TD [26,67,68]. The effect of GOS is probably due to its prebiotic and to non-prebiotics actions. Thus, based on the importance of AGE in contributing to PI-IBS burden, the implementation of prebiotics such as GOS as an adjunct therapy of ORS is a reasonable preventive measure of IBS.
CONCLUSION

Most people have multiple episodes of diarrhea during their lifetime. Individuals with AGE have a likelihood of developing PI-IBS six times higher than those unexposed in the general population. Therefore, reducing the risk of PI-IBS by taking an early measure during the diarrheal episode is of paramount importance. The use of prebiotics, especially GOS, as an adjunct therapy of ORS during the treatment of diarrhea can reduce both the risk of dehydration and the dysbiosis that is associated with IBS. Future trials to confirm the effect on dysbiosis in naturally occurring diarrheal disease are needed.

Finally, it is important to understand that the primary action of prebiotics is to stimulate the growth of beneficial bacteria that are already present in the gut.

Moreover, the use of prebiotics offers technical advantages in formulating ORS. Prebiotics are non-viable and thus, stability is not an issue as it is with probiotics.

For probiotics to deliver a healthy benefit, they need to remain viable in a product at a level of potency to meet the recommended number of organisms for the intended use. None of these are constraints with prebiotics as adjunct therapy of ORS.

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Conflict of Interest

Dr. Rosales is an employee of Abbott Laboratories, Abbott Nutrition.

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