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THERAPY OF THE POSTINFECTIOUS IRRITABLE BOWEL SYNDROME: AN UPDATE

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Abstract

After acute infectious gastroenteritis, up to thirty percent of patients present prolonged gastrointestinal symptoms and a part of those affected patients can have the diagnostic criteria for postinfectious irritable bowel syndrome.

Treatment is symptom directed rather than curative and includes agents prescribed for the treatment of irritable bowel syndrome in general. Prophylaxis or early treatment of acute bacterial diarrhea may reduce the risk of postinfectious irritable bowel syndrome development by reducing the occurrence, duration, and severity of the chronic inflammation and mucosal alterations (all these believed to play an important role in disease persistence). Probiotic treatment is effective in restoring the intestinal microbiota in patients with irritable bowel syndrome and in animal models there are improvements of postinfectious irritable bowel syndrome. Fecal microbiota transplantation seems to be one of the most effective methods of treating the postinfectious irritable bowel syndrome (with recurrent episodes) caused by Clostridium difficile.

Keywords: gastroenteritis, microbiota, postinfectious irritable bowel syndrome

The irritable bowel syndrome (IBS) is an association of chronic and recurrent symptoms such as constipation, diarrhea, bloating and/or abdominal pain, having no abnormalities (biochemical or structural) detectable by conventional laboratory methods. The irritable bowel syndrome affects 9-13% of the normal population at any particular period in time [1].

Irritable bowel syndrome is defined as recurrent abdominal pain on average at least 1 day a week in the last 3 months associated with two or more of the following: related to defecation, associated with a change in a stool frequency and/or form (consistency). The onset of symptoms must be at least 6 months before, according to Rome IV criteria [2].

The earliest description of postinfectious irritable bowel syndrome (PI-IBS) dates from 1962; Chaudhary and Truelove reported that one third of their patients with a history of gastroenteritis went on to develop irritable bowel syndrome type symptoms [3]. Since then, other authors have suggested that patients with an episode of infectious diarrhea have a high incidence of developing irritable bowel syndrome in the following months, with estimates ranging from 4% to 32%. However, these studies have used varying methodologies, have studied different populations, and a control group was mostly absent [4,5,6]. There are numerous reports, indicating that up to a third of people suffering from bacterial enteritis report persisting ongoing symptoms compatible with irritable bowel syndrome between six months and one year afterwards. Furthermore, though some will recover spontaneously, even at six years, nearly two thirds remain symptomatic [7].

The current conceptual framework regarding the pathogenic mechanisms for postinfectious irritable bowel syndrome suggests that postinfectious irritable bowel syndrome is associated with alteration of motility, increased intestinal permeability, an increased numbers

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of enterochromaffin cells and persistent intestinal inflammation. This was characterized by an increased number of T-lymphocytes and also mast cells and an increased expression of proinflammatory cytokines. This suggests an exposure to pathogenic organisms that disrupts the intestinal barrier function and alters the neuromuscular function and triggers chronic inflammation, which sustains irritable bowel syndrome symptoms [8].

Definition

The postinfectious irritable bowel syndrome is characterized by the sudden onset of symptoms mentioned in the diagnostic criteria for irritable bowel syndrome (with Rome IV criteria being the most recently defined) [2]. They appear following an episode of acute infectious gastroenteritis characterized by two or more of the following symptoms and findings: diarrhea, vomiting, fever and a positive stool culture result [9].

Microbiota

The human gastrointestinal (GI) microbiota is a rich and dynamic community inhabited by approximately 1014 bacteria, most of which uncultivated yet in the laboratory (Zoetendal et al, 2006). Multiple theories linking irritable bowel syndrome etiology with the intestinal microbiota have been proposed, which, together with the discovered irritable bowel syndrome- associated GI microbiota alterations, imply that bacteria could play a part in irritable bowel syndrome etiology [10].

The overall microbial community from fecal samples of irritable bowel syndrome subjects has been analyzed applying denaturing gradient gel electrophoresis (DGGE), microarray (HITCip and PhyloChip), and sequencing (conventional Sanger sequencing and 2nd generation 454 pyrosequencing). These methods are capable of detecting the unculturable species in the microbiota, although they have restrictions due to primer and probe dependency and technical biases. The possibility to gain a non-restricted overview with sequencing, to design targeted primers and probes for applications based on PCR or hybridization is the main advantage. The differences in the intestinal microbiota between irritable bowel syndrome patients and healthy controls (HCs) have mostly been studied using fecal material, known as the most accessible source of the GI microbiota [11]. Carroll et al. [12] developed a study regarding the alteration in composition and diversity of the intestinal microbiota in patients with diarrhea-predominant irritable bowel syndrome. Therefore, fecal DNA was isolated from 23 D-irritable bowel syndrome patients and 23 healthy controls (HC). Variable regions V1-V3 and V6 of the 16S rRNA gene were amplified from all samples. PCR products were sequenced using 454 high throughput sequencing. Using quantitative insights into microbial ecology pipeline the composition, richness and diversity of microbial communities were determined and compared between D-irritable bowel syndrome and HC. The results were the fact that the contribution of bacterial groups to the composition of the intestinal microbiota differed between D-irritable bowel syndrome and HC. D-irritable bowel syndrome patients had significantly higher levels of Enterobacteriaceae ($P=0.003$) and lower levels of Faecalibacterium genera ($P=0.04$) compared to HC. Beta-diversity values demonstrated significantly lower levels of UniFrac distances in HC compared to D-irritable bowel syndrome patients. The richness of 16S rRNA sequences was significantly decreased in D-irritable bowel syndrome patients ($P<0.04$). Their 16S rRNA sequence data demonstrated that a community-level intestinal microbiota in D-irritable bowel syndrome is associated with significant increase, which is detrimental and decreases beneficial bacterial groups, and a reduction in microbial richness [12]. Tana et al. [13] suggest that altered intestinal microbiota contributes to the symptoms of irritable bowel syndrome through increased levels of organic acids. In fecal samples, irritable bowel syndrome patients had significantly higher numbers of Veillonella and Lactobacillus than healthy controls.

Significantly higher levels of acetic acid and propionic acid were also showed. Furthermore, in irritable bowel syndrome patients with high acetic acid or propionic acid levels the symptoms were more severe, they presented negative emotions and an impaired quality of life. The results are in accordance with the concept that the gut microbiota interacts with higher brain centers that influence the sensory, motor and immune system of the gut. The bacterial overgrowth in the small intestinal observed in a subset of irritable bowel syndrome patients shows quantitative changes in the small bowel microbiota. Data are lacking on qualitative changes in the gut microbiota in irritable bowel syndrome patients. Several different members of gut bacteria can have a different influence on gut function. The concepts identified here may lead to the development of novel therapeutic strategies for irritable bowel syndrome using manipulation of the intestinal microbiota [13].

Dysbiosis of the intestinal microbiota in irritable bowel syndrome has been detected on several levels: the overall community appears to be less diverse with more variation between individuals and overtime. These phenomena may reduce the resilience of the microbiota to external stressors, and both trigger and sustain functional aberrations in the gut. In addition to overall dysbiosis, specific bacterial groups are either elevated (Lactobacillus, Veillonella, Ruminococcus, Enterobacteriaceae, aerobes group, S. aureus) or reduced (Bifidobactrium, B.catenulatum, Bacteroides) in irritable bowel syndrome, with the exception of bifidobacteria [10].

Treatment

Currently, there is no widely accepted management strategy for postinfectious irritable bowel syndrome.

Treatment is frequently symptom directed rather than curative and includes agents prescribed for the treatment of irritable bowel syndrome- D [14]. High fiber diets increase bowel frequency and reduce the consistency of stool. It follows therefore that reducing fiber intake might be beneficial in D-irritable bowel syndrome.

Drug Therapy

Opiates: codeine or loperamide inhibit rapid transit whatever the cause and also inhibit secretions. Although loperamide is effective in improving stool consistency it is less effective in controlling pain in irritable bowel syndrome [15]. Antispasmodics, such as the anticholinergic agent hyoscyamine, reduce intestinal the activity of smooth muscle [14].

Tricyclic antidepressants: these have multiple actions with anti-histaminic, anti-muscarinic as well as serotonin reuptake inhibition. Tricyclics have been shown in large clinical trials to reduce pain, nausea and diarrhea in irritable bowel syndrome [16].

5HT3-antagonists: Alosetron slows colonic transit and improves stool consistency and frequency in D-irritable bowel syndrome [17]. It has never been tried specifically in post-infective irritable bowel syndrome. Side effects include constipation which can be severe, and rarely ischemic colitis which caused a temporary suspension of the drug. In an outbreak of waterborne giardiasis where 1300 subjects were diagnosed, with G. lamblia 139 patients continued to have abdominal symptoms of whom two of three had negative stool microscopy and culture. They were considered to have a postinfectious functional gastrointestinal disorder. Dizdar et al. investigated visceral hypersensitivity in patients with persisting abdominal symptoms after G. lamblia infection; they also assessed the effect of 5HT(3)-antagonist ondansetron. Patients with G. lamblia – induced gastrointestinal symptoms developed both functional dyspepsia and irritable bowel syndrome. They exhibited gastric hypersensitivity with lower drinking capacity and delayed gastric emptying. Ondansetron (5-HT(3) antagonist), did not improve gastric emptying, drinking capacity, or symptoms except nausea [18].

5HT4 agonists: Tegaserod is the only one agent marketed in this class, and it stimulates colonic transit in both healthy volunteers and patients with constipated irritable bowel syndrome. It is successful in improving global symptoms, it softens the stool consistency, increases the frequency of bowel movement, and reduces the symptoms of bloating (NNT = 10–12). Prucalopride, another $5HT_4$. Agonist is very effective in treating constipation [19].

Cholestyramine is useful in diarrhea due to bile salt malabsorption [20] which may develop following acute gastroenteritis. Several studies have documented that postinfectious irritable bowel syndrome can respond to cholestyramine [21] which is nevertheless rather poorly tolerated owing to its unpleasant taste in its current formulation.

Antibiotics: the diagnostic criteria for irritable bowel syndrome include symptoms (bloating, abdominal pain and altered bowel habits) are similar to those experienced by subjects with small intestinal bacterial overgrowth (SIBO). Studies have demonstrated an association between SIBO and irritable bowel syndrome using breath testing techniques. When Galatola et al. [22] performed $_{14}$C-xylose breath tests on subjects with a number of gastrointestinal disorders, the prevalence of abnormal breath tests demonstrating SIBO was 56% and 29% in diarrhea and constipation predominant irritable bowel syndrome, respectively. This was used to suggest a poor sensitivity and specificity for breath testing. However, Nayak et al. [23] demonstrated that irritable bowel syndrome subjects treated with metronidazole were significantly better than placebo-treated patients. This suggested that bacteria could play a part in the symptomatology of the irritable bowel syndrome. Pimentel et al. [24] showed that eradication of SIBO improves the gastrointestinal symptoms of irritable bowel syndrome. The antibiotics used in the treatment of SIBO in the 47 subjects were neomycin, ciprofloxacin, flagyl and doxycycline, 7-10 days. Although efficacy data for antibiotic prophylaxis in the prevention of acute bacterial diarrhea are limited, antibiotics have demonstrated efficacy for treating bacterial diarrheal illnesses and reducing the duration of illness by 1–2 days compared with placebo or no intervention. Even though fluoroquinolones have become standard therapy for the treatment of travelers' diarrhea, in double-blind, placebo-controlled, randomized, and comparative studies rifaximin 600–1,800 mg/day for 3–5 days has also been shown to be effective treatment. The efficacy of antibiotics for the treatment of postinfectious irritable bowel syndrome has not been specifically evaluated, but research suggests that antibiotics may be effective in treating a subset of patients with irritable bowel syndrome [25].

Prophylaxis aimed at preventing or early treatment of acute bacterial diarrhea may reduce the risk of postinfectious irritable bowel syndrome development by reducing the occurrence, duration, and severity of the chronic inflammation and mucosal alterations believed to play a role in disease persistence. Several agents, including bismuth subsalicylate and antibiotics (e.g., fluoroquinolones and rifaximin), have been evaluated for the prevention of travelers' diarrhea. Bismuth subsalicylate is not as effective as antibiotics in preventing diarrheal illness, and concerns about bacterial resistance may limit the use of fluoroquinolones prophylactic [26]. Probiotics can restore the intestinal microbiota in patients with irritable bowel syndrome and result in an improvement of postinfectious irritable bowel syndrome in animal models [27].

Table I. Drug therapy in PI-IBS.

DRUG	EFFECTS	DISADVANTAGES
Opiates (codeine, loperamide)	- inhibit rapid transit and secretion - improving stool consistency	- less effective in controlling pain in irritable bowel syndrome
Anticholinergic agent (antispasmodics)	- reduce intestinal the activity of smooth muscle	
Tricyclic antidepressants	- anti-histaminic, anti-muscarinic, serotonin reuptake inhibition - reduce pain, nausea and diarrhea in IBS	
5HT3-antagonists (Alosetron)	- slows colonic transit - improves stool consistency and frequency in D-irritable bowel syndrome	- never been tried specifically in post-infective irritable bowel syndrome - severe constipation, rarely ischemic colitis
5HT4 agonists (Tegaserod, Prucalopride)	- stimulates colonic transit patients with constipated irritable bowel syndrome - softens the stool consistency - increases the frequency of bowel movement - reduces the symptoms of bloating	
Cholestyramine	- useful in diarrhoea due to bile salt malabsorption - very effective in PI—IBS	- poorly tolerated owing to its unpleasant taste in its current formulation
Antibiotics (Doxycycline, Ciprofloxacin, Flagyl, Neomycin, Rifaximin)	- small intestinal bacterial overgrowth (SIBO) - effective on both diarrhea and constipation IBS - improves the gastrointestinal symptoms	
Probiotics	- restore the intestinal microbiota - improvement of postinfectious irritable bowel syndrome in animal models	

Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) – can be probably more beneficial, as donated feces, in a sense, are the ultimate human probiotic. In a case series of 55 patients with irritable bowel syndrome and IBD treated with FMT, cure was reported in 20 (36%), decreased symptoms in nine (16%) and no response in 26 (47%) patients. In another series, 45 patients with chronic constipation were treated with colonoscopic FMT and subsequent fecal enema infusions, 89% of whom (40 of 45 patients) reported relief in abdominal pain, bloating and defecation, immediately after the procedure [27]. Normal defecation, without using laxatives, persisted in 18 of 30 patients (60%) contacted 9–19 months later [27]. Treatment of recurrent Clostridium difficile infection (CDI) with antibiotics leads to recurrences in up to 50% of patients. Mattila E et al. investigated the efficacy of fecal transplantation in treatment of recurrent CDI. They reviewed records from 70 patients with recurrent CDI who had undergone fecal transplantation. Fecal transplantation by infusing fresh donor feces into cecum was performed at colonoscopy. The patients had whole-bowel lavage with polyethylene glycol solution before transplantation. Persistent or recurrent symptoms and signs were defined as clinical failure and a need for new therapy. Symptoms resolved in all patients who did not have strain 027 CDI during the first 12 weeks after fecal transplantation. Of 36 patients with 027 CDI, 32 (89%) had a favorable response; all 4 nonresponders had a pre-existing comorbidity or serious condition, caused by a long lasting diarrheal disease and subsequently died of colitis. During the first year after transplantation, 2 patietnts were treated successfully with another fecal transplantation and 2 with antibiotics for CDI; 4 patients with an initial favorable response after receiving antibiotics for unrelated causes had a relapse. Within 1 year after transplantation 10 patients died of unrelated illnesses. No immediate complications of fecal transplantation were observed. Fecal transplantation through colonoscopy seems to be an effective treatment for recurrent CDI and also for recurrent CDI caused by the virulent Clostridium difficile 027 strain [28].

Diet

Patients diagnosed with irritable bowel syndrome (IBS) have observed the association between specific foods with worsening of symptoms. Because of limited data and guideline consensus and also because of the nuances of symptoms associated with IBS subtypes, clinical guidance for doctors and nurse practitioners can be challenging. By addressing the relevance of diet for symptom alleviation, doctors and nurse practitioners are able to better support patients and collaborate with dieticians to improve symptom management [29].

There is no convincing evidence that gluten causes the new and debated diagnosis of non-coeliac gluten sensitivity (NCGS), as well as there is no evidence that IBS patients suffer from food allergy or food intolerance. The component in wheat that triggers symptoms in NCGS

seems to be the carbohydrates. Patients with NCGS appear to be IBS patients who are self-diagnosed and self-treated with a gluten-free diet. The consumption of the poorly absorbed fermentable oligo-, di-, monosaccharide and polyols (FODMAPs) and insoluble fiber might be a trigger in IBS symptoms. FODMAPs and insoluble fiber increase the osmotic pressure in the large-intestine lumen and provide a substrate for bacterial fermentation, on reaching the distal small intestine and colon. This leads to gas production, abdominal distension and abdominal pain or discomfort. Poor FODMAPs and insoluble fibers diet reduces the symptom and improve the quality of life in IBS patients. Low intake in FODMAPs can change favorably the intestinal microbiota and restores the abnormalities in the gastrointestinal endocrine cells. Five gastrointestinal endocrine cell types that produce hormones regulating appetite and food intake are abnormal in IBS patients. Based on these hormonal abnormalities, it is expected that IBS patients might have increased food intake and body weight gain. The link between obesity and IBS is not fully studied. Individual dietary guidance for intake of poor FODMAPs and insoluble fibers diet in combination with probiotics intake and regular exercise is to be recommended for IBS patients [30].

A diet with reduced content FOSMAPs has been reported to be effective in the treatment of patients with irritable bowel syndrome (IBS). Böhn et al. compared the effects of a diet low in FODMAPs with traditional dietary advice in a randomized controlled trial of patients who met Rome III criteria for IBS and reached to the conclusion that a diet low in FODMAPs reduces IBS symptoms as well as traditional IBS dietary advice. Combining elements from these 2 strategies might further reduce symptoms of IBS [31].

Approximately 70% of IBS patients point at certain foods as triggers for their symptoms. To help identify potential trigger foods, practitioners often rely on patient food and gastrointestinal (GI) symptom journaling. Zia et al. evaluated the feasibility and usability of a novel food and symptom journal app, specifically designed for patients with IBS. The results were that the app appeared to be a feasible and usable tool for IBS patients. The findings were that most IBS patients have food triggers and that these vary by individual. Future studies can explore whether individualized dietary changes guided by an app can result in IBS symptom improvement [32].

Conclusion

Rome IV recognize further the postinfectious IBS as a specific entity, according to the multidimensional clinical Chronic mucosal inflammation triggered by enteric infection may underlie persistent bowel symptoms in patients who develop postinfectious irritable bowel syndrome.

Antimicrobials, such as rifaximin, have shown potential benefit in the prevention and treatment of acute bacterial illness in international travelers, as well as in the treatment of established irritable bowel syndrome.

Combining a diet low in FODMAPs with traditional IBS dietary advice, might further reduce symptoms of IBS.

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