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Special iGLOBE 2019

The international Gastro Liver Oesophagus and Bowel Event

What's new on Irritable Bowel Syndrome

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The International Digestive Experts Articles Journal is a peer-reviewed journal on prevention, diagnosis and management of gastrointestinal disorders. The journal is primarily intended for the update of gastroenterologists, hepatologists, and all medical doctors focusing their practice on digestive pathologies.

The International Digestive Experts Articles Journal encourage the submission of spontaneous manuscripts, when in line with the aims and scope of the journal. Specific topics articles can be covered by invitation of the Board.

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When appropriate, the manuscript must be structured in sections as background and aims, methods, results, conclusion or using appropriate headings where needed.

The full generic name of pharmaceutical active ingredients must be used.

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Editorial

Inflammatory bowel syndrome: Definition, Burden and Clinical Features

by the editorial staff of The IDEA Journal

Functional bowel disorders are highly prevalent disorders found worldwide. Research in the basic and clinical sciences during the past decade has produced new information on the pathophysiology of these disorders. Improving our understanding of functional bowel disorder is critical, as they impose a negative economic impact to the global health care system in addition to reducing quality of life.

Among functional gastrointestinal disorders, irritable bowel syndrome (IBS) is the most prevalent and is more commonly diagnosed in women and younger individuals (age <50). IBS imposes a significant burden to the health care system and to individuals. Studies have demonstrated consistently that IBS impairs work-related activities and reduces quality of life.

The symptom-based diagnosis of IBS has not been established in everyday clinical practice, and the diagnosis of this disorder remains one of exclusion. It has been demonstrated that the densities of duodenal chromogranin A, rectal peptide YY and somatostatin cells are good biomarkers for the diagnosis of sporadic IBS, and low-grade mucosal inflammation is a promising biomarker for the diagnosis of postinfectious IBS. Genetic markers are not useful as biomarkers for IBS since the potential risk genes have yet to be validated, and the intestinal microbiota cannot be used because of the lack of an association between a specific bacterial species and IBS. A combination of symptom-based assessment, exclusion of overlapping gastrointestinal diseases and positive biomarkers appears to be the best way to diagnose IBS.

Several receptors related to GI motility and abdominal pain have been recently investigated: 5-Hydroxytryptamine (5-HT) is an important neurotransmitter that activates the colonic mucosal 5-HT4 receptor without causing severe cardiovascular adverse effects. The clinical potential of ramosetron for diarrhea-predominant IBS has been suggested because of a lower risk of ischemic colitis than conventional 5-HT3 receptor antagonists. Toll-like receptors (TLRs), especially TLR2 and TLR4, show a significant effect on the post-infection symptoms and lipopolysaccharide-mediated regulation of GI motility.

What's New in Pathophysiology

by the editorial staff of The IDEA Journal

ABSTRACT

Functional bowel disorders (FBD) are highly prevalent disorders found worldwide. These disorders have the potential to affect all members of society, regardless of age, sex, race, creed, color, or socioeconomic status. Improving our understanding of functional bowel disorder is critical, as they impose a negative economic impact to the global health care system in addition to reducing quality of life. Research in the basic and clinical sciences during the past decade has produced new information on the pathophysiology of FBDs.

INTRODUCTION

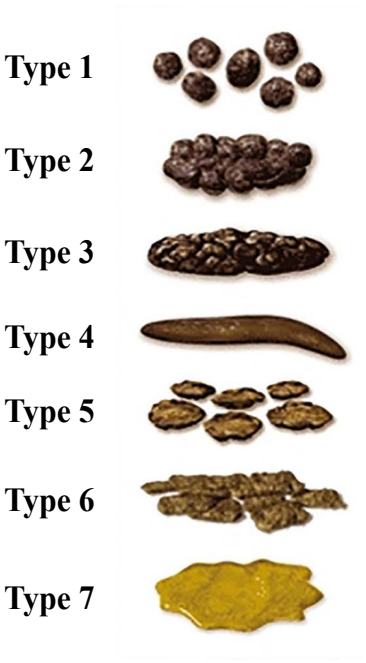
Irritable bowel syndrome (IBS) is a functional bowel disorder (FBD) in which recurrent abdominal pain is associated with defecation or a change in bowel habits. Abdominal pain must be present; the absence of abdominal pain precludes the diagnosis of IBS. Pain can be present anywhere throughout the abdomen, although it is more common in the lower abdomen. A history of disordered bowel habits (e.g., constipation or diarrhea or both) should be identified, along with their temporal association with episodes of abdominal pain. Unpredictable bowel pattern (>3 different stool form types/week) reinforces the diagnosis of IBS in the diarrhea subtype (IBS-D). An increasing number of consecutive days without a bowel movement is associated with the diagnosis of predominant constipation (IBS-C). Abdominal bloating is present in a majority of IBS patients; abdominal distension may be reported as well, although neither is required to make the diagnosis of IBS (Figure 1) (1).

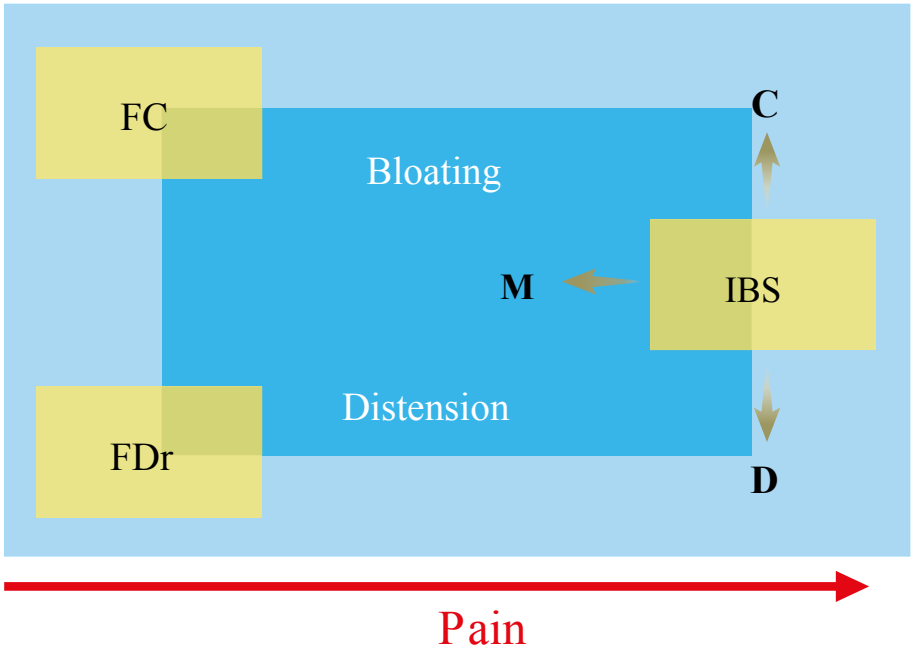
The Bristol Stool Form Scale should be used to record stool consistency. IBS with predominant constipation: more than one fourth (25%) of bowel movements with Bristol stool form types 1 or 2. IBS with predominant diarrhea (IBS-D): more than one fourth (25%) of bowel movements with Bristol stool form types 6 or 7.

IBS is a multifactorial disease. Hence, the underlying pathogenesis is considered complex and the precise molecular pathophysiology is not completely understood. Several functional alterations have been described, such as altered visceral sensitivity, functional brain alterations, bowel motility and secretory dysfunctions, and somatic and psychiatric comorbidities.

Furthermore, gastrointestinal abnormalities - such as immune activation, gut dysbiosis (microbial imbalance), impaired mucosal functions, nerve sensitization, post-infectious plasticity, altered expression and release of mucosal and immune mediators, and altered gene expression profiles - have been associated with IBS. However, a coherent link between particular pathologies and IBS symptoms is yet to be established.

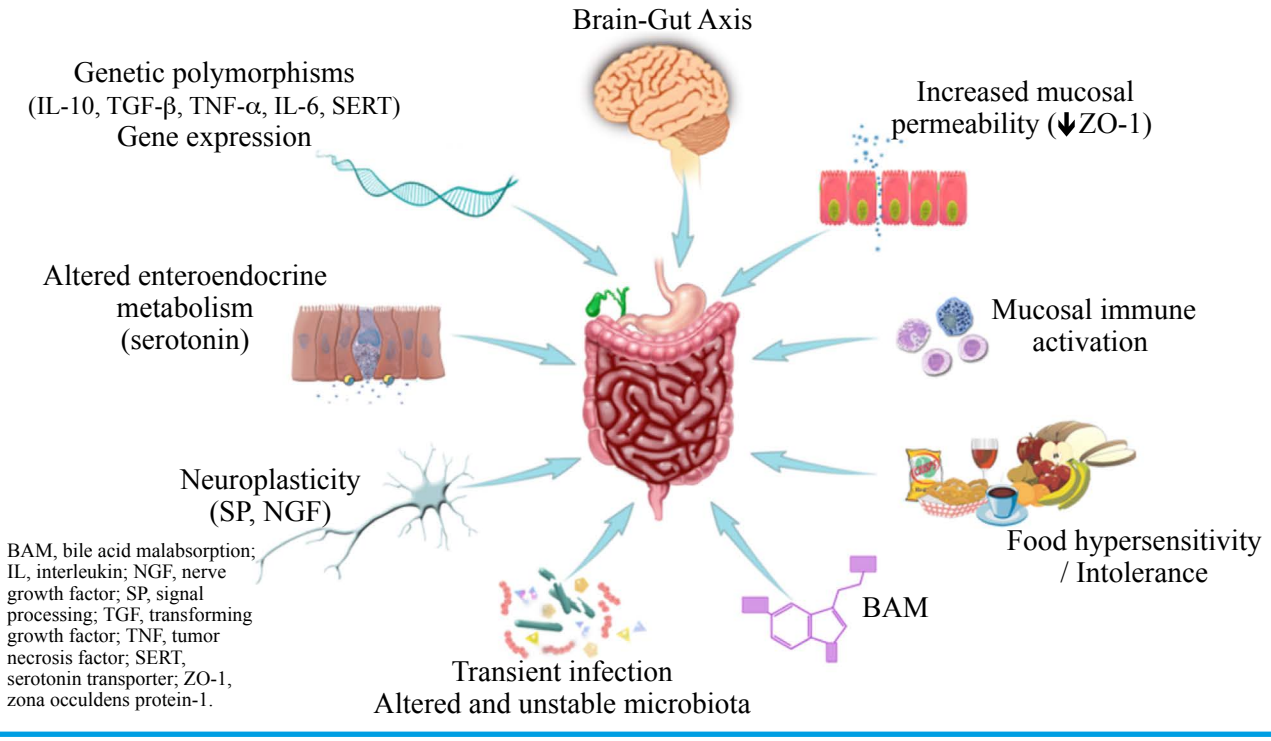
Growing evidence suggests that in IBS the epithelial barrier, gut microbiota, food antigens and bile acids elicit abnormal responses in the key regulators of sensorimotor functions, including the hypothalamus-pituitary-adrenal (HPA) axis, the immune system, the brain-gut axis and the enteric nervous system (ENS) (Figure 2). Accordingly, these factors might have a role as potential biomarkers of disease. In addition to these putative biomarkers, psychological factors ('psychomarkers') such as depression and anxiety, which are known to respond to abdominal symptoms (bottom-up), and psychosocial factors ('stress') that influence physiological (intestinal)





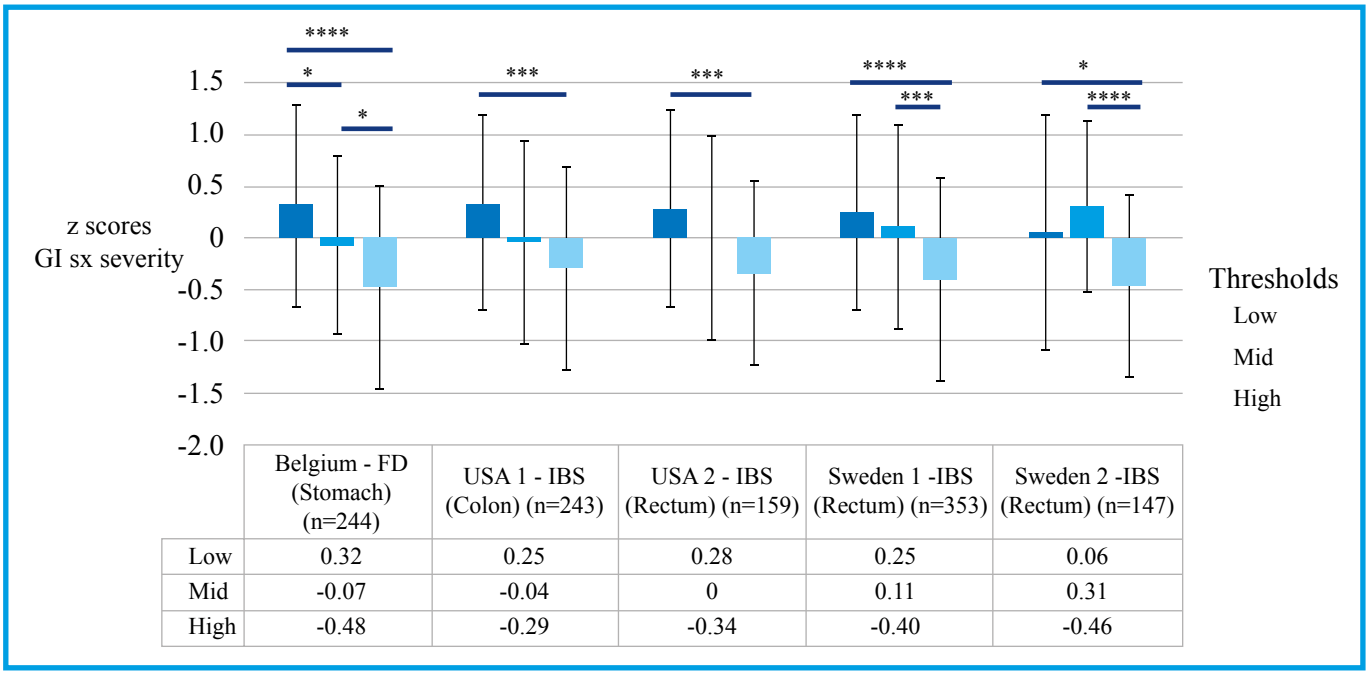
FC: Function constipation
FDr: Functional diarrhea
IBS-C: lrritable bowel syndrome with predominant constipation
IBS-D: lrritable bowel syndrome with predominant diarrhea
IBS-M: lrritable bowel syndrome with mixed bowel habits (D and C)

Figure 1. IBS and subtypes (mod. from Lacy BE. Gastroenterology 2016)



BAM, bile acid malabsorption; IL, interleukin; NGF, nerve growth factor; SP, signal processing; TGF, transforming growth factor; TNF, tumor necrosis factor; SERT, serotonin transporter; ZO-1, zona occuldens protein-1.

Figure 2. IBS abnormal responses in the key regulators of sensorimotor functions (mod. from Barbara et al. Gastroenterology 2016)



	Belgium - FD (Stomach) (n=244)	USA 1 - IBS (Colon) (n=243)	USA 2 - IBS (Rectum) (n=159)	Sweden 1 -IBS (Rectum) (n=353)	Sweden 2 -IBS (Rectum) (n=147)
Low	0.32	0.25	0.28	0.25	0.06
Mid	-0.07	-0.04	0	0.11	0.31
High	-0.48	-0.29	-0.34	-0.40	-0.46

Figure 3. GI symptoms severity in IBS (mod. from Simrén et al. Gut 2018)

functions, such as motility and visceral sensitivity (top-down), have been acknowledged.

Visceral hypersensitivity

Divergent results have been reported regarding the association between visceral hypersensitivity and GI symptoms in patients with functional GI disorders (FGIDs). Moreover, it has been proposed that the association between hypersensitivity and GI symptoms is secondary to psychological factors and tendency to report symptoms. Five cohort studies were conducted in patients with FGIDs (IBS or functional dyspepsia; n=1144), who had undergone visceral sensitivity testing using balloon distensions (gastric fundus, descending colon or rectum), completed questionnaires to assess GI symptom severity, non-GI somatic symptoms, anxiety and depression. Subjects were divided into sensitivity tertials based on pain/discomfort thresholds. GI symptom severity was compared between sensitivity tertials in each cohort and corrected for somatization, and anxiety and depression. A gradual increase in GI symptom severity with increasing GI sensitivity was demonstrated in IBS and functional dyspepsia. This association was independent of tendency to report symptoms or anxiety/depression comorbidity (Figure 3) (2).

Colonic Transit Time

Törnblom H et al. investigated the total and segmental colonic transit time (CTT) and their relationship to symptoms and subgroups in a large sample of IBS patients.

The total and segmental colonic transit time (CTT) was assessed using radiopaque markers in 359 patients with IBS. Results were compared with existing normal values for healthy men and women without GI symptoms. Stool frequency and consistency (Bristol Stool Form (BSF) scale), and the perceived severity of three GI symptoms (bloating, flatulence, and abdominal pain) were noted in a daily diary during the measurement week.

CTT was normal in 287 patients (80%), whereas 53 (15%) had accelerated and 19 (5%) had delayed CTT. Transit abnormalities in relation to gender-specific reference values were more common in males (30.0%) than in females (17.2%). No correlations of clinical significance were found between transit data and the three GI symptoms.

This study reveals that total and segmental colonic transit alterations are of importance for the abnormal bowel habit seen in men and women with IBS, but of no or minor importance for other IBS symptoms (Figure 4) (3).

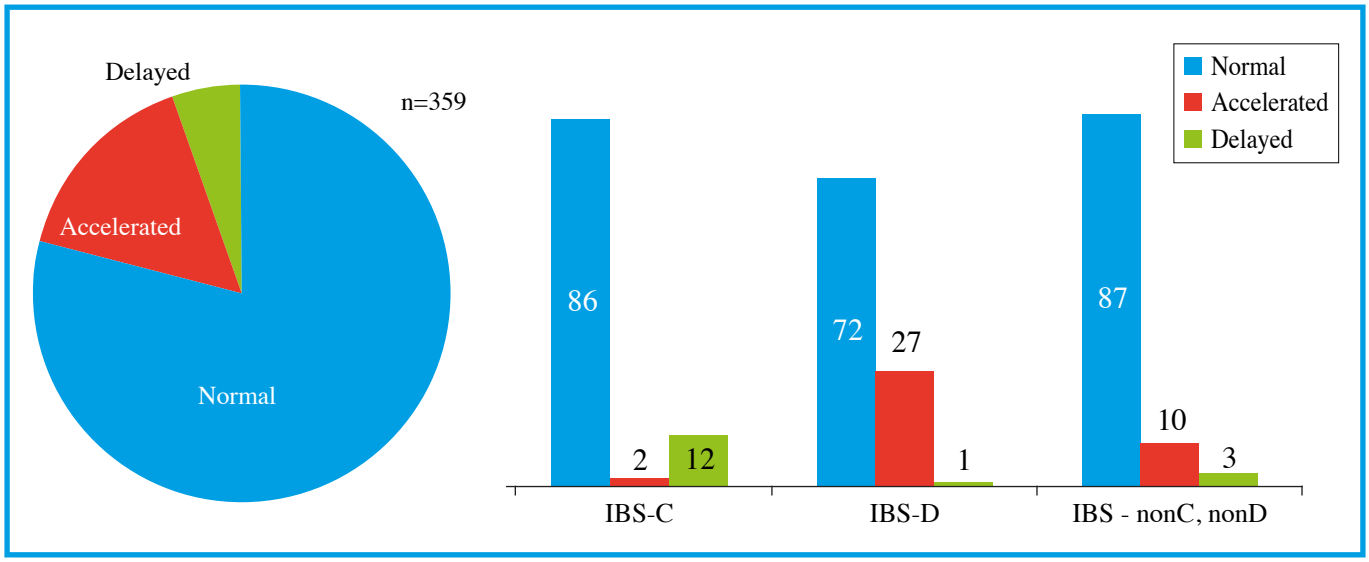


Figure 4. Colonic transit time in IBS (mod. from Törnblom et al. AJG 2012)

PSYCHOSOCIAL FACTORS

Up to 75% of patients with IBS symptoms usually have coexisting anxiety or depression. One study (4) found that patients exposed to stressful events in their life tended to have more IBS symptoms, whereas those who had support showed fewer. Another study (5) that compared anxiety and depression levels in IBS patients and healthy individuals found that the activity of the dorsolateral prefrontal cortex in IBS patients was dysregulated in behavioral selection duties. This indicates that patients with IBS can experience alterations in brain function, even without suffering

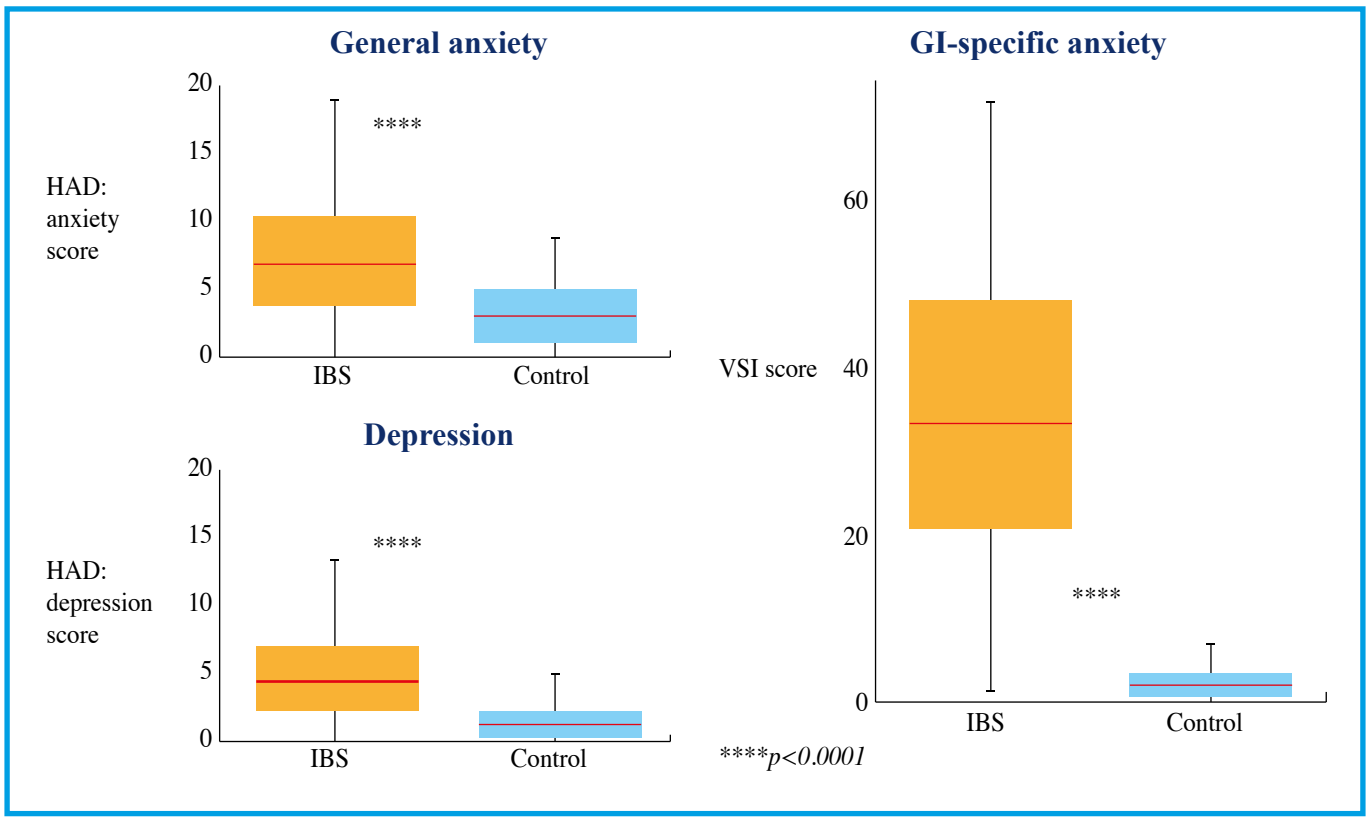


Figure 5. Coexisting psychosocial factors in IBS (mod. from Jerndal et al Neurogastroenterol Motil 2010)

depression or anxiety, that make them more vulnerable to stressful stimuli.

Newer epidemiological studies (6) have found out that, in almost half of the patients, intestinal symptoms appear first and mood disorders after, probably because the gut disturbances send signals to affect the brain. Likewise, in another study (7), psychiatric patients reported that they developed their psychiatric symptoms after they were diagnosed with IBS.

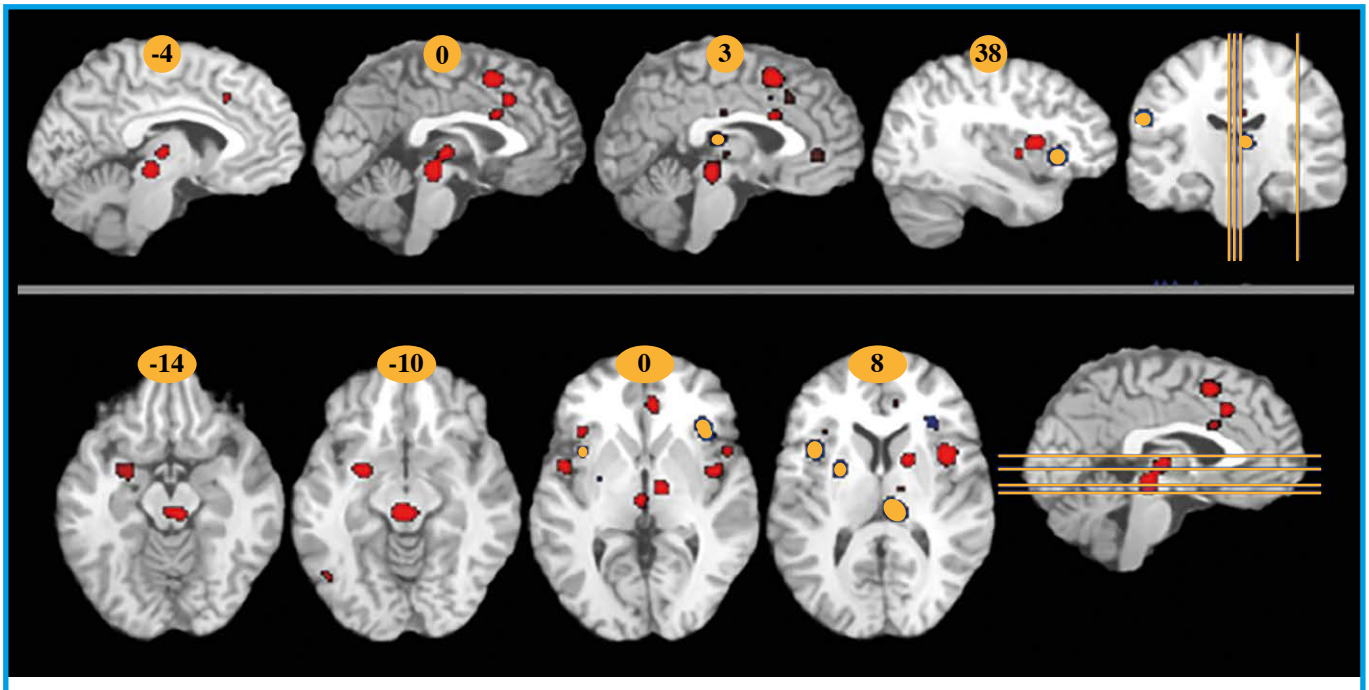
GI-specific anxiety (GSA) influences symptom severity and quality of life (QOL) in patients with IBS. The Visceral Sensitivity Index (VSI) is a recently developed, reliable and valid measure of GSA. Sixty healthy subjects and 306 IBS patients were studied and completed VSI and the GI Symptom Rating Scale (GSRS) and questionnaires to determine psychological symptoms severity (Hospital Anxiety and Depression Scale), QOL, and presence of functional GI disorders. Compared with healthy subjects, patients with IBS had more severe GSA. In the IBS group, more severe GSA was seen in patients with more severe GI symptoms ($P < 0.0001$), general anxiety and depression ($P < 0.0001$), and with lower socioeconomic status. Gastrointestinal-specific anxiety seems to be an important factor for GI symptom severity and QOL in patients with IBS (Figure 5) (8).

GUT-BRAIN

The responsiveness of the central nervous system is altered in patients with IBS. There was consistent activation in regions associated with visceral afferent processing (i.e. thalamus, insula, anterior midcingulate) among IBS patients and controls, but considerable differences in the extent and specific location of foci. IBS patients differed from controls in that there were more consistent activations in regions associated with emotional arousal (pregenual anterior cingulate cortex, amygdala) and activation of a midbrain cluster, a region playing a role in endogenous pain modulation (Figure 6) (9).

Cumulative Effects

QOL in patients with IBS is greatly disturbed. The degree of disturbance of general QOL in patients with



Selected axial and sagittal slices representing brain areas demonstrating differences in greater activation during rectal distension in irritable bowel syndrome (red) and greater activation in controls (orange) across all studies

Figure 6. Gut brain alterations in patients with IBS (mod. from Tillisch et al. Gastroenterology 2011)

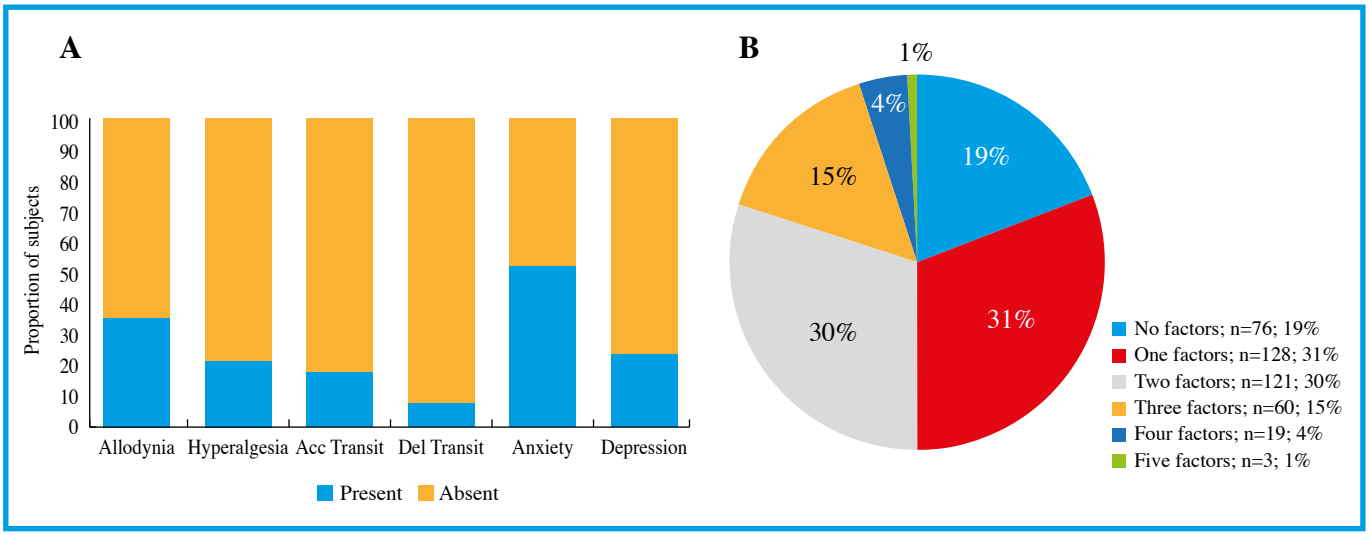


Figure 7. Pathophysiologic alteration associated with IBS (mod. from Simrén et al Gastroenterology 2019)

IBS has shown to be worse in several subcategories such as physical role, bodily pain, general health perceptions and social functioning. In severe IBS, both gastrointestinal symptoms and psychiatric comorbidity independently contribute to disturbed QOL. However, also extraintestinal symptoms - such as tiring easily, low in energy, the feeling that there is something seriously wrong with their body, feeling tense, feeling nervous, feeling hopeless, difficulty in sleeping and low sexual interest - decrease patients' QOL. The psychological and psychosocial dimensions of food ingestion might also have a role. An inability to participate in daily life events (ie lunch with friends, family, etc) for fear of pain, urgency, diarrhoea or distension, occurring during or immediately after a meal, can be devastating and can result in social isolation.

A retrospective analysis of data from 3 cohorts of patients investigated whether pathophysiologic alterations associated with IBS have cumulative or independent effects on patient-reported outcomes (PROs). Allodynia was observed in 36% of patients, hyperalgesia in 22%, accelerated colonic transit in 18%, delayed transit in 7%, anxiety in 52%, and depression in 24%: each of these factors was associated with severity of at least one symptom of IBS. At least three pathophysiologic factors were present in 20% of patients, 2 in 30%, 1 in 31%, and none in 18% (Figure 7). With increasing number of pathophysiologic abnormalities, there was a gradual increase in IBS and somatic symptom severity, as well as a gradual reduction in QOL (10).

ALTERED MICROBIOTA

It is assumed that IBS patients have altered microbiota in their intestines (11). An increasing number of reports have provided good evidence of altered gut

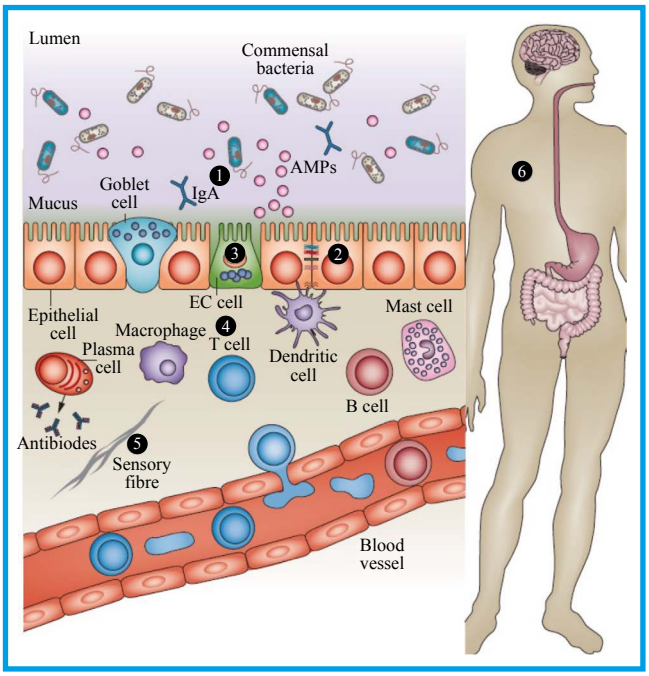


Figure 8. Altered microbiota in IBS patients (mod. from Öhman L. Nat Rev Gastroenterol Hepatol. 2015)

microbiota composition, aberrant expression pattern and function of EC cells, abnormal gut permeability and increased immune activity in at least subgroups of patients with IBS (Figure 8).

Understanding the relative importance of each of these factors and their interactions is needed to better comprehend the complex pathophysiology of IBS. It might be proposed that altered composition of the gut microbiota community impairs epithelial permeability, possibly by degrading epithelial tight junction proteins. Moreover, the gut microbiota might also influence the activity of enteroendocrine cells, resulting in an altered hormonal milieu in the gut and affecting immune cells, causing increased immune activity. Increased activity of immune cells, caused by triggers other than gut microbiota, could potentially harm epithelial integrity and the endocrine activity of the gut, thereby facilitating microbiota adherence to the gut mucosa.

Furthermore, cytokines and other mediators secreted by immune cells, as well as mediators secreted by the gut microbiota and enteroendocrine cells, could have effects beyond the gut, giving rise to extraintestinal symptoms and events (12).

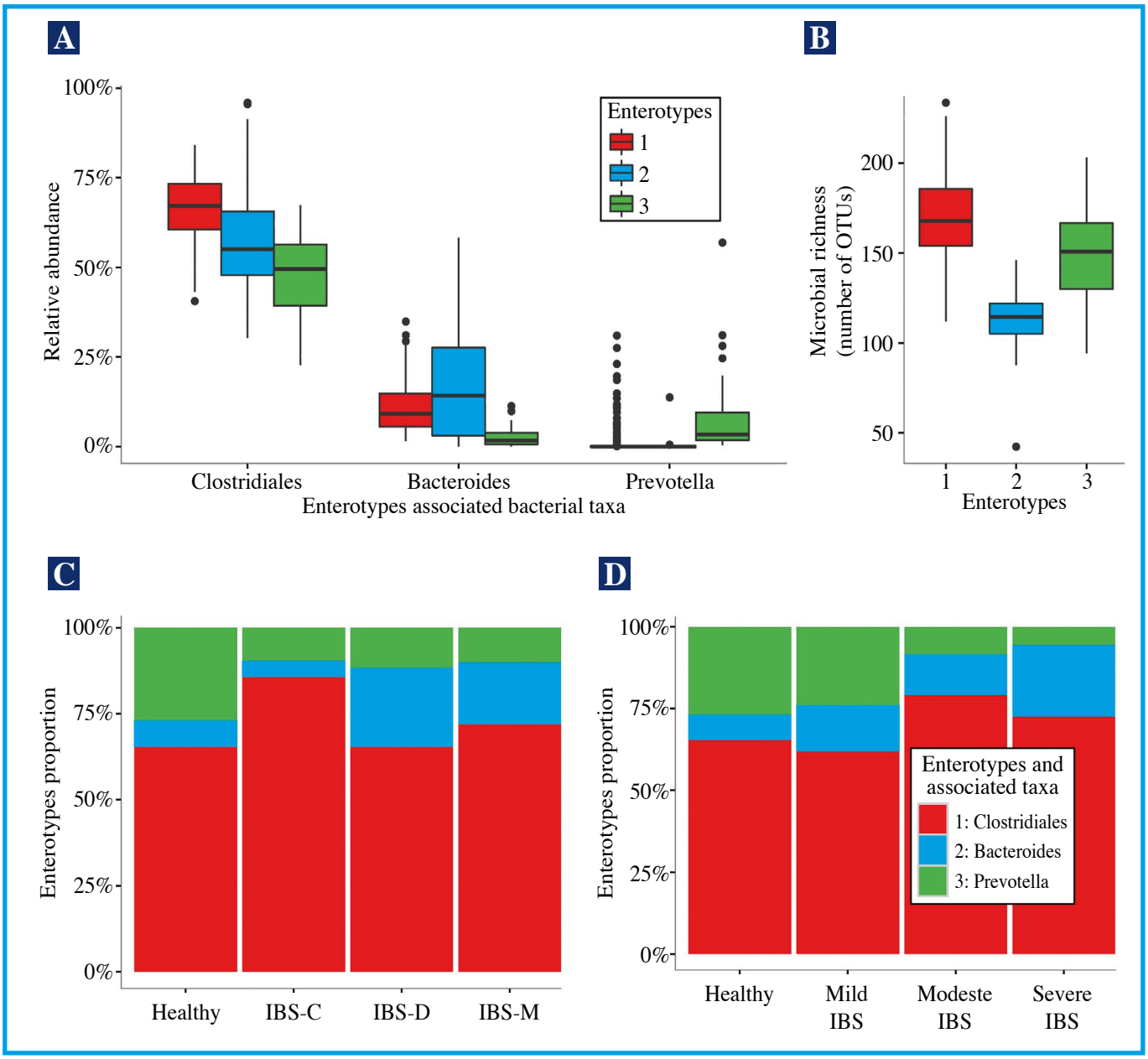


Figure 9. Enterotypes alteration in IBS patients (mod. from Tap J et al. Gastroenterology 2017)

Observations from a study (13) in 110 IBS patients show that patients with IBS have different intestinal microbiota, with lower microbial variety and lower numbers of Methanobacteriales and Prevotella species. Lactobacillus and Bacteroides species, known beneficial bacteria, are also depleted, while the numbers of pathogenic bacteria, such as Streptococcus spp., are increased (14-15). In a study (16) of IBS patients with abdominal pain, the investigators observed that patients with pain had 5 times smaller amounts of Bifidobacteria in their intestines (Figure 9).

BILE ACID MALABSORPTION IN IBS WITH DIARRHEA

Studies support the proposal that a subset of patients with features compatible with diarrhoea-predominant IBS (IBS-D) have bile acid malabsorption (BAM). Studies recruiting adults with IBS-D, defined by the Manning, Kruis, Rome I, II or III criteria and which used 23-seleno-25-homotaurocholic acid (SeHCAT) testing for the assessment of BAM showed that patients meeting accepted criteria for IBS-D have bile acid malabsorption. This distinction has implications for the interpretation of previous studies, as well as contemporaneous clinical practice and future guidelines development (Figure 10) (17).

FOOD INTOLERANCE

One of the most common factors causing symptoms in IBS patients is food intolerance (18), with some studies reporting it in up to 89% of their patients. Patients with IBS understand that specific types of food trigger their symptoms. Usually, these include legumes, vegetables, lactose-containing foods, fatty foods, stone fruits, and artificial sweeteners. In general, a category of foods that contains fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) worsen IBS symptoms because of their osmotic and fermentation effects (19). Small bowel distension was observed in

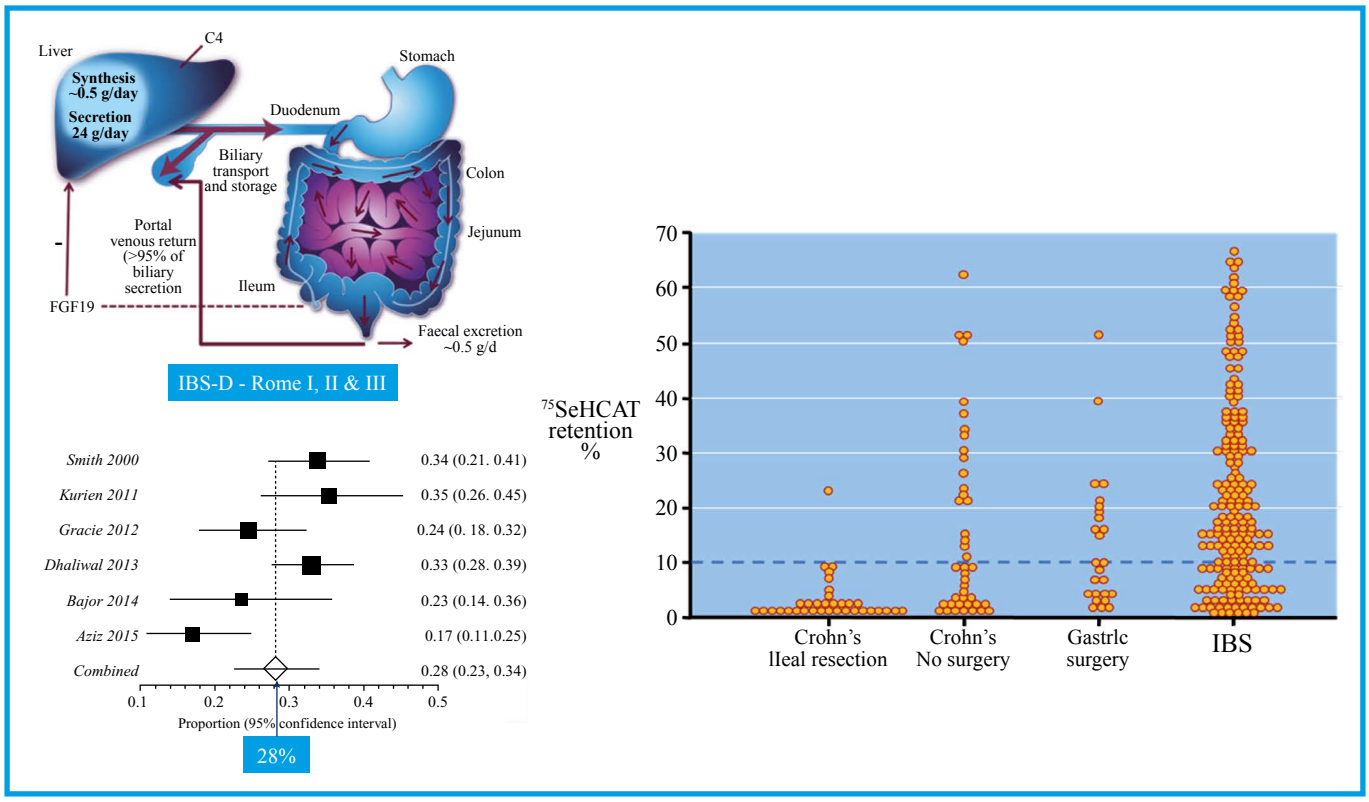


Figure 10. Bile acid malabsorption in IBS with diarrhea (mod. from Slattery et al. APT 2015; Smith et al. J R Coll Physicians Lond 2000)

magnetic resonance imaging studies after fructose was administered to patients with IBS (20), as a result of osmotic effects. Interestingly, a meta-analysis found improvement in symptoms and 70% improvement in quality of life in patients after a low-FODMAP diet (21). However, the problem with a low-FODMAP diet is that it very restrictive. Hence, monitoring by an experienced dietician is necessary to prevent any nutritional deficiencies and weight loss (22).

Other investigators reported an improvement in symptoms after gluten was eliminated from their patients' diet and relapse when it was reintroduced. Patients were not diagnosed with or suspect for celiac disease (23). Another study reported that patients with IBS on a gluten diet had higher small bowel permeability, and the mRNA expression of tight junction proteins was considerably lower (24) than in non-gluten takers. Therefore, gluten might affect the pathogenesis of IBS by changing the epithelial barrier function, having a role in a pathway that we are not yet aware of.

Poorly absorbed fermentable carbohydrates can cause symptoms in some patients, visceral sensitivity is the key to why some individuals experience symptoms and some do not, at least in the case of lactose malabsorption.

The physical form of food is another key variable whose importance is yet to be defined. Many of the dietary components implicated in IBS symptoms are actually consumed as solids and hence delivered into the duodenum more slowly after trituration by antral contractions. The rapid entry of osmotically active poorly absorbed substrates - mainly in liquid form - such as lactose in a patient with lactose or mannitol malabsorption result in a rapid influx of water into the small intestine, which probably stimulates transit and rapid delivery into the colon. This leads to the instantaneous generation of gas, mainly hydrogen, given that the microbiota are unable to fully metabolize the sudden excess of substrate. Furthermore, distension of the ascending colon generates propulsive colonic motility, which a sensitized individual may experience as cramps; a slower delivery in a solid matrix may be better tolerated (Figure 11) (25).

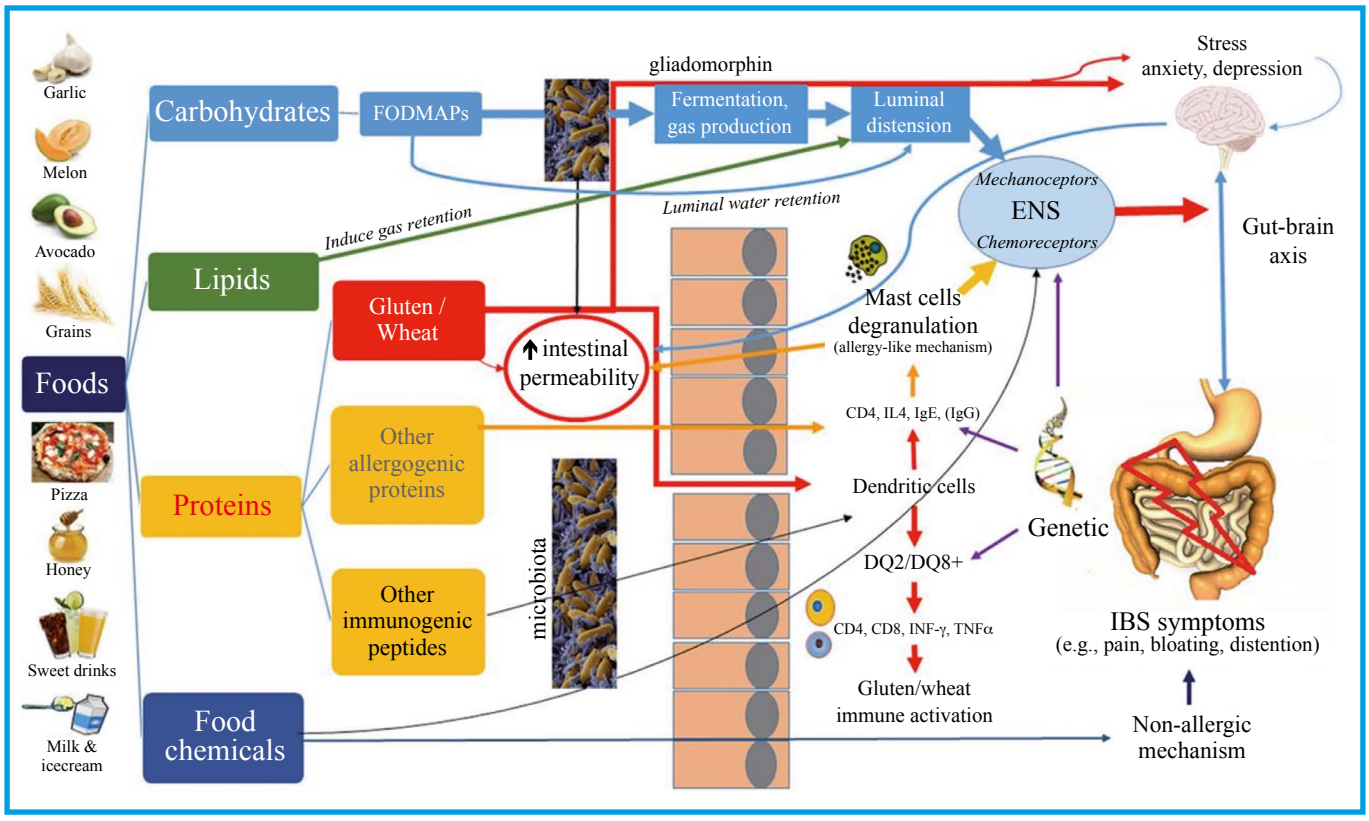


Figure 11. Dietary factors and symptoms in IBS (mod. from De Giorgio et al. Gut 2016)

CONCLUSION

Activation of the immune system of the intestinal mucosa associated with dysbiosis, diet, stress and endogenous factors results in increased permeability of the intestinal barrier and the induction of motor-sensory functions of the gastrointestinal tract. A clinical evaluation of pathophysiology of IBS is essential to understand symptoms and choose the appropriate therapeutic option for improved health, quality of life and reduced healthcare costs.

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What's New in Post Infection IBS

by the editorial staff of The IDEA Journal

ABSTRACT

The existence of post-infection irritable bowel syndrome (PI-IBS) has been substantiated by epidemiology studies conducted in diverse geographic and clinical settings. The ROME Foundation has produced a working team report to summarize the available evidence on the prevalence and pathophysiology of PI-IBS and provide guidance for diagnosis and treatment, based on findings reported in the literature and clinical experience.

PREVALENCE AND RISK OF PI-IBS.

The prevalence (1,2) of PI-IBS among those suffering from infectious enteritis has been estimated between 4% and 54% (Figure 1) (1). A recent systematic review of 45 studies, comprising approximately 21,000 individuals with enteritis who were followed up for 3 months to 10 years, found a pooled prevalence of IBS at 12 months, after infectious enteritis, of 10.1%. PI-IBS has more frequently been described as a consequence of bacterial rather than viral infection, which is in contrast to the higher prevalence of viral etiology compared with bacterial etiology of infectious diarrhea (2,3). This could be explained by the fact that mucosal damage and inflammation caused by bacterial gastroenteritis is often greater than that caused by viral agents. Recently, PI-IBS has also been described after Clostridium difficile infection in up to 25% of cases (4). Additionally, Vibrio cholerae has recently been associated with PI-IBS development in 16.5% of cases as well (5).

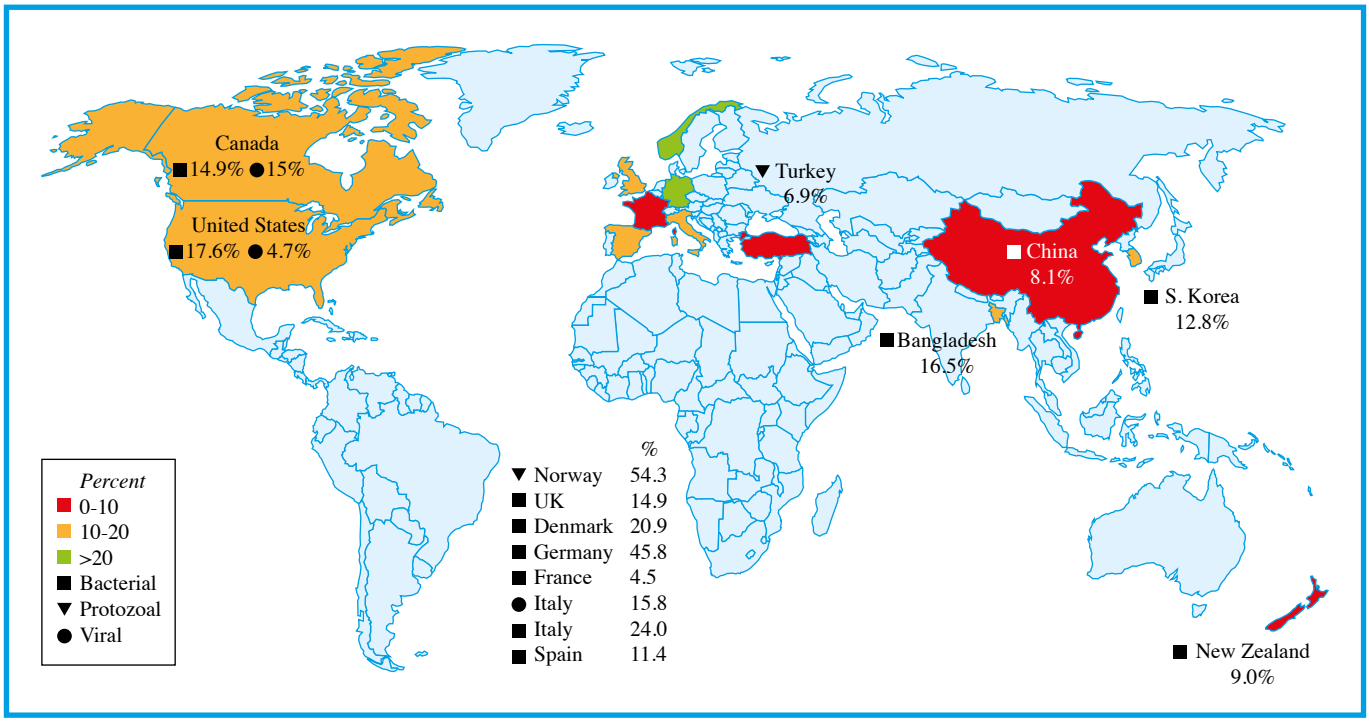

Figure 1. Worldwide prevalence of PI-IBS (mod. from Barbara G et al. Gastro 2019)

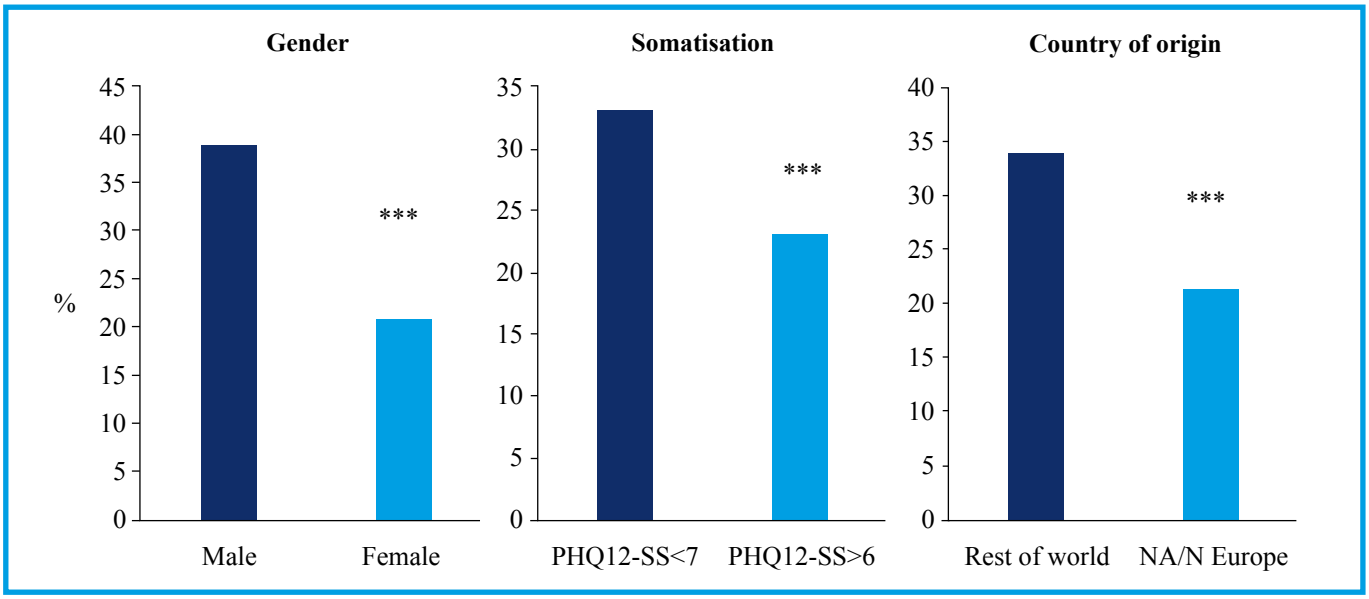

Figure 2. Effect of gender, somatisation and Country of origin on percentage recovery at one year follow up (mod. from Card T. Gastroenterol J. 2018)

Internet surveys show that PI-IBS accounts for around 13% of all IBS. Seventy per cent of PI-IBS patients described sudden onset, 35% onset while travelling, 49.6% vomiting, 49.9% fever and 20.3% bloody diarrhea. Compared to other IBS individuals, PI-IBS was significantly associated with living in Northern Europe and North America, having a hysterectomy, not having an appendicectomy, and having more frequent stools. At one-year recovery rate in the PI-IBS and non-PI-IBS group was 19.7% and 22.2% respectively. Recovery rates were lower for females (20.7%) vs males (38.8%), those with somatization (23.0%) vs those without (33.2%) and those living in North America or Northern Europe (21.1%) vs living elsewhere (33.9%) (Figure 2) (6).

Risk of IBS is significantly increased in women and individuals with antibiotic exposure, anxiety, depression, somatization, neuroticism, clinical indicators of enteritis severity and Clostridium difficile infection (CDI). A cohort study shows that new-onset IBS is common after CDI. Longer CDI duration, current anxiety and higher BMI are associated with the diagnosis of C. difficile PI-IBS. This chronic sequela should be considered during active management and follow-up of patients with CDI. A large study including 508,278 patients with a first diagnosis of gastrointestinal infection matched to a control cohort of 1,016,556 individuals showed that all types of infection were associated with an increased risk of IBS and chronic fatigue syndrome (7).

PATHOPHYSIOLOGY

PI-IBS is a complex and likely multifactorial disorder. Studies on the pathophysiology have been performed in small groups of patients and at different time points post-infection, which may contribute to incomplete information. The pathophysiology of PI-IBS is dominated by the interaction between the central and peripheral factors, the latter including the microbiota, epithelial, enteroendocrine, immunologic, and neuromotor mechanisms (Figure 3) (8).

Campylobacter jejuni infection is a leading cause of PI-IBS. This pathogen increases distal small bowel and colon permeability that may enhance neuromuscular exposure to bacterial and other luminal antigens, which, in turn, may lead to altered visceral sensitivity and enteric dysmotility through chronic inflammatory mechanisms (9).

A subset of patients with PI-IBS have elevated faecal proteolytic activity (PA). Serine proteases in faecal supernatants disrupt barrier through PAR-2-mediated signaling, myosin light chain phosphorylation and

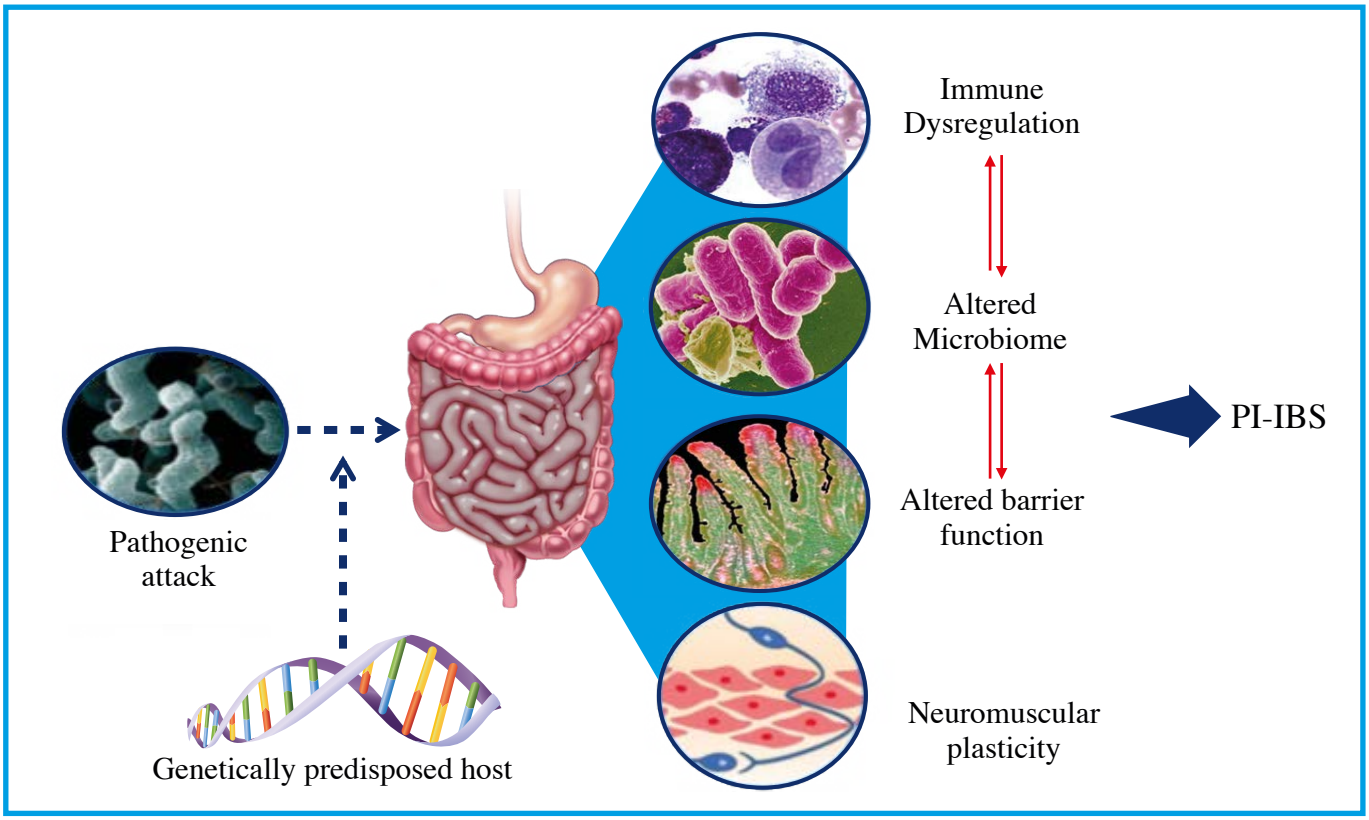

Figure 3. The pathophysiology of PI-IBS (mod. from Thornley JP et al. J Infect Dis 2001)

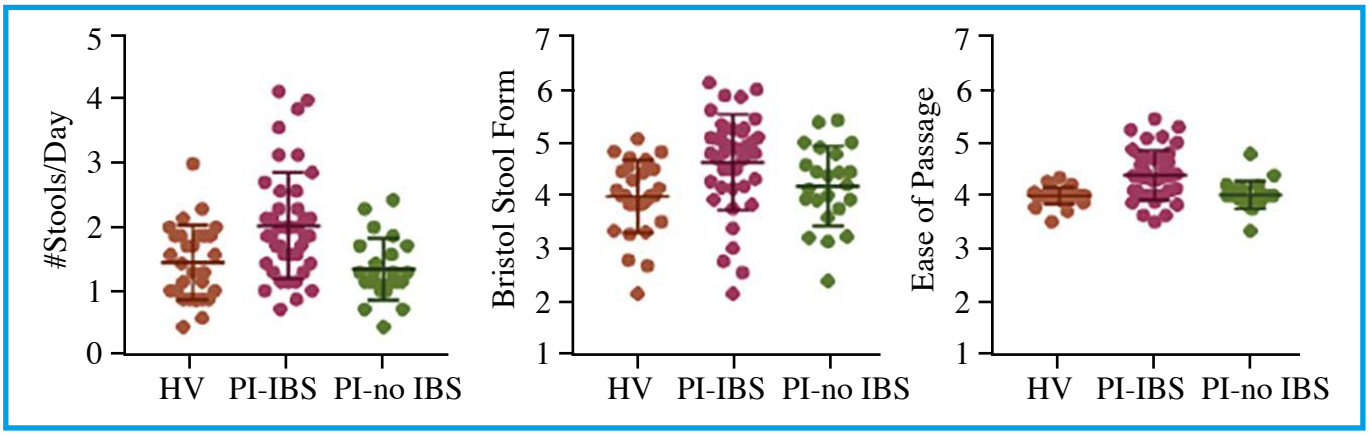

Figure 4. IBS symptoms improvement with barrier loss reversal (mod. from Peters S, Grover M. DDW 2019)

loss of occludin. Patients with high faecal PA have greater diarrhea, worse symptoms severity, increased permeability (in vivo and ex vivo) and wider tight junctions on ultrastructure. Identifying and supplementing microbiota with protease inhibitory properties might prevent or reverse barrier dysfunction in PI-IBS (10). Reversal of barrier loss has been associated with symptoms improvement in pre-clinical and clinical settings (Figure 4).

Also, mucosal immune activation has been postulated to play an important role in the pathogenesis of IBS. A cohort study, on 171 IBS patients, showed that 33% of patient reveals evidence of immune activation in the colon descendent, but not in the rectum. In these patients there is an increased gene expression of IL1B (3-fold change), prostaglandin synthase PTGS2 (2.1-fold change), and the G-protein-coupled receptor MRGPRX2 (10.7-fold change) (Figure 5). However, gene expression is unrelated to clinical symptoms (11). Infectious diarrheal episodes are connected with

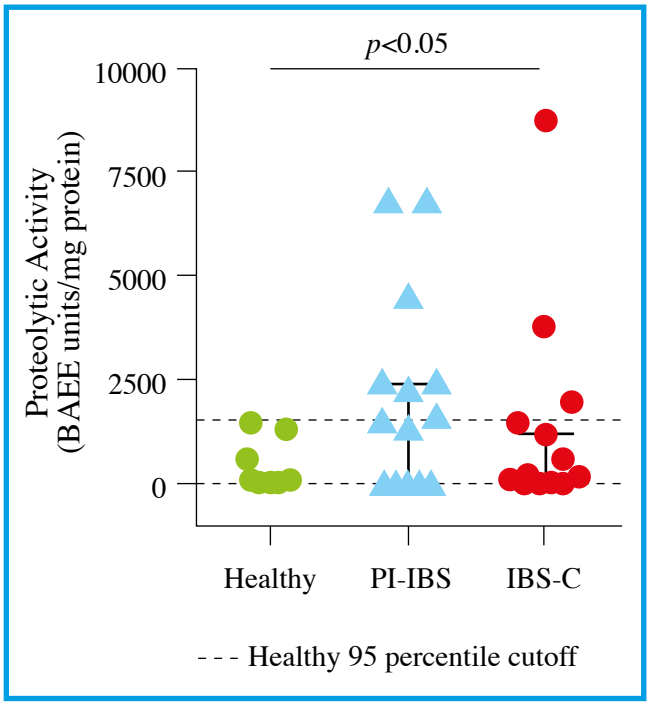

Figure 5. Proteolytic activity in IBS patients vs healthy controls (mod. from Edogawa S. Gut, 2018)

significant loss of symbiotic bacteria in gastrointestinal lumen. The consequence is transformation of microbial signature due to lack of inhibiting products such as fatty acids. Several members of Bacteroidetes phylum increased, Collinsella decreased (Figure 6) (12). Those developing PI-IBS may have a primary inability to restore the microbial ecosystem or a secondary inability to restore gut microbiota because of host factors.

It is currently unknown if there are unique pathophysiological mechanisms for PI-IBS. Animal models have been instrumental for understanding the mechanisms underlying gut and behavioral dysfunction after acute infection. These include the experimental models of post-infection evoked by T spiralis, N brasiliensis, C parvum, G duodenalis, C jejuni, and C rodentium. Various pathogen types have unique or overlapping mechanisms associated with irritable bowel syndrome. The proximity to the center (Figure 7) reflects the strength of association.

TREATMENT AND CONSENSUS STATEMENTS

The Rome Foundation adopted a Delphi process to rate quality of evidence on patient's education regarding the condition and guidance on therapy, including the few specific treatments tested in controlled clinical trials in PI-IBS patients. The following statements were accepted:

- **Statement 1.** The first step in the treatment is to educate patients about the link between intestinal infections and subsequent development of IBS. There is now substantial evidence indicating that acute infectious gastroenteritis may lead to the development of IBS in a subgroup of subjects. The link between infectious

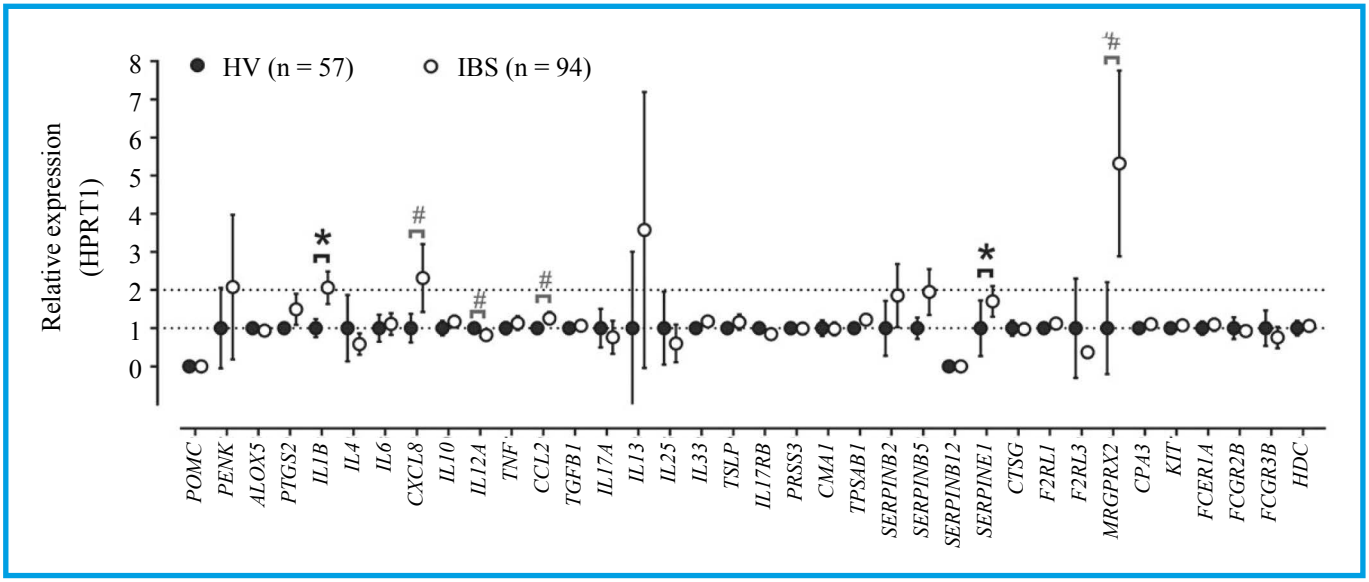

Figure 6. Loss of symbiotic bacteria in gatrointestinal lumen of IBS patients vs healthy volunteers (mod. from Aguilera-Lizarraga. Neurogastroenterol Motil. 2019)

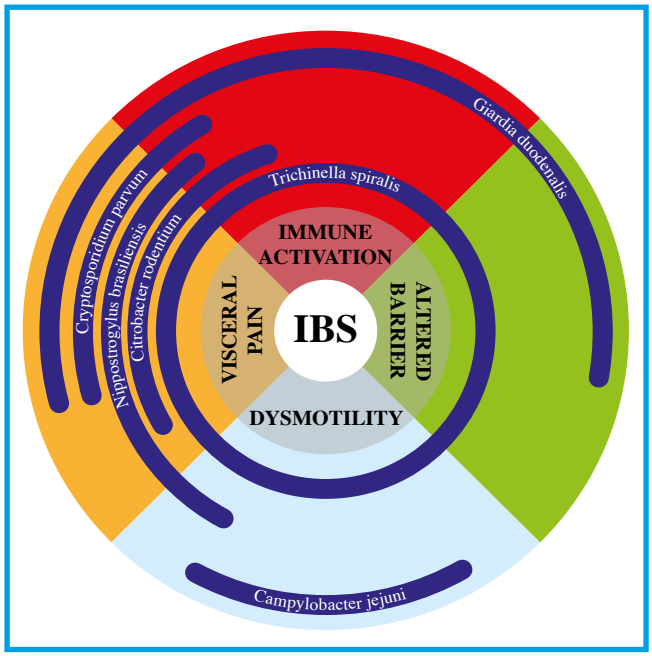

Figure 7. Summary of animal models for postinfection IBS (mod. from Barbara G et al. Gastro 2019)

gastroenteritis and subsequent development of IBS should be searched in all IBS subtypes but especially among patients developing IBS-D and IBS-M symptoms acutely.

- **Statement 2.** Reassurance should be provided, especially with suspected viral associated PI-IBS, that symptoms are likely to improve or resolve in several patients over time. Several studies showed that the risk of IBS decreased over time and became nonsignificant beyond 3 years (13,14).
- **Statement 3.** There are no specific treatment options for PI-IBS, and treatment should be guided by treatment of IBS in general (depending upon the subtype: IBS-D, IBS-M, or rarely IBS-C).

There is limited evidence from the current literature indicating specific treatment strategies for PI-IBS. Because most patients with PI-IBS have the mixed- or diarrhea-predominant subtype, they are treated accordingly. Nonpharmacologic measures such as elimination of foods high in FODMAPs have also been found useful in patients with IBS-D (15). Antispasmodics as a class have been shown to provide symptomatic, short-term relief in IBS. Manipulation of gut microbiota using antibiotics, probiotics, and possibly fecal microbial transplantation is an emerging method for treating IBS-D and likely PI-IBS.

In consideration of these statements, an expert opinion

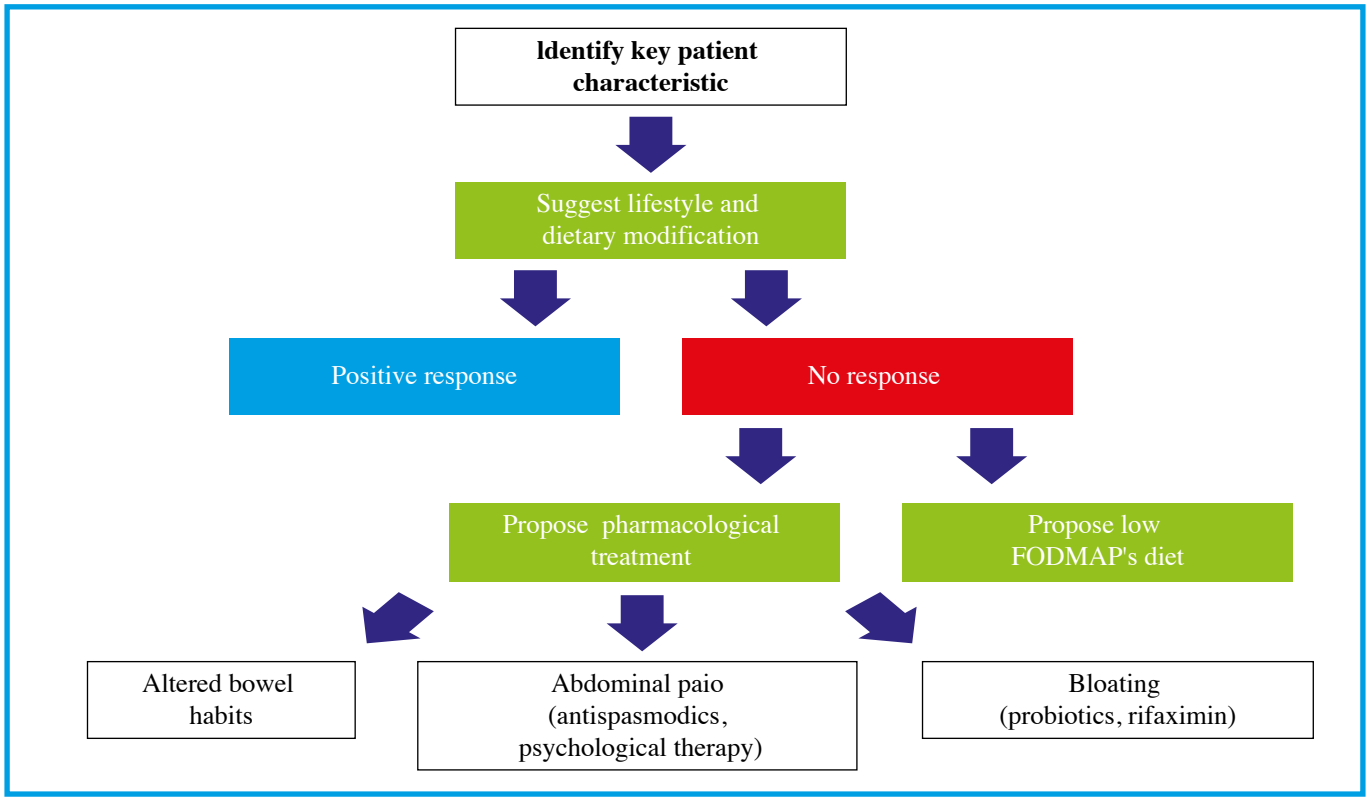

Figure 8. Experts' proposed algorithm to manage PI-IBS (mod. from Barbara G et al. Gastro 2019)

algorithm has been proposed and is reported in Figure 8 to guide the management of patients with PI-IBS.

One study found that visceral hypersensitivity can also be improved with administration of myosin light chain kinase inhibitor (MLCK) or Tight Junction blocker in PI-IBS mice. Eight weeks after inoculation with T. spiralis, PI-IBS mice developed decreased pain and volume thresholds during colorectal distention, increased urine lactulose/mannitol ratio, elevated colonic Th1/Th2 cytokine ratio, and decreased zonula occludens-1 expression compared to the control mice. Administration of MLCK inhibitor and TJ blocker both reversed the increased intestinal permeability, visceral hypersensitivity, and Th1-dominant immune profile in PI-IBS mice (16,17).

	Glutamine	Placebo
IBS-SS		
Baseline	301.39	301.63
Treatment	181.39	296.06
Stool frequency		
Baseline	5.41	5.31
Treatment	2.91	5.26
Intestinal permeability		
Baseline	0.11	0.11
Treatment	0.05	0.1

Figure 9. Mod. from Zhou Q. Gut 2019

A recent study (18) showed that in patients with IBS-D with intestinal hyperpermeability following an enteric infection, oral dietary glutamine supplements dramatically and safely reduced all major IBS-related endpoints (daily bowel movement frequency, intestinal permeability) (Figure 9). Large randomized clinical trials (RCTs) should now be done to validate these findings, assess quality of life benefits and explore pharmacological mechanisms.

CONCLUSION AND FUTURE CONSIDERATION

Although PI-IBS has received increasing attention, these studies are challenging. The condition is best studied prospectively, and only large outbreaks make possible to recruit substantive numbers of patients. Future mechanistic studies should focus on pathogen-specific subgroups that could lead to identification of specific pathophysiological mechanisms. Development of biomarkers that can be used in acute stages for the prevention of PI-IBS development and for the diagnosis and specific targeting of the PI-IBS subgroup would help preventing the development of PI-IBS and personalizing its treatment.

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Current and Novel Therapies

by the editorial staff of The IDEA Journal

ABSTRACT

Irritable bowel syndrome (IBS) is the most prevalent among functional gastrointestinal disorders (FGIDs). IBS is more common in women and is most commonly diagnosed in younger individuals (age <50). IBS is characterized by recurrent abdominal pain and altered bowel habits; bloating and distention frequently coexist.

IBS imposes a significant burden to the health care system and to individuals. Studies have demonstrated consistently that IBS impairs work-related activities (e.g. lost work time, reduced productivity while at work) and also reduces quality of life. Given the clinical heterogeneity that is a hallmark of the disorder and the absence of a single effective therapy for all sufferers, available therapies tend to focus on predominant symptomatology at presentation.

A variety of novel therapeutic strategies are being explored and new compounds have appeared since the last iteration of the American College of Gastroenterology Monograph on IBS. The goal of this document, therefore, is to provide an updated, evidence-based document on the therapy of this common and, at times, debilitating disorder.

INTRODUCTION

Irritable bowel syndrome (IBS) is a common condition that affects the digestive system. The disease is characterized by abdominal pain, diarrhea, constipation or a combination of both diarrhea and constipation, mucus discharge along with stools and changes in the form (appearance) of stools.

The main cause of disease is not entirely apparent as various factors play key roles in its etiology. It is a disorder that is not confirmed by a specific test, instead, diagnosis is based on specific symptoms termed the Rome criteria. Symptoms can be debilitating in many individuals, but may be mild or moderate in other patients. In addition, IBS is often associated with other somatic comorbidities (for example, pain syndromes, overactive bladder and migraine), psychiatric conditions (including depression and anxiety) and visceral sensitivity.

The population prevalence of IBS is high (11%) and the condition has considerable consequences for quality of life (QOL) that are comparable to other chronic diseases, such as diabetes mellitus and hepatitis. IBS is diagnosed based on symptoms, and a distinction is made between the following subtypes: IBS with pain or discomfort and predominant constipation (IBS-C), IBS with diarrhoea (IBS-D), mixed IBS (IBS-M) and unsubtyped IBS (IBS-U) (Figure 1).

Although a substantial proportion of patients will experience spontaneous remission over time, there is currently no treatment that cures IBS; relief of symptoms is the most that can be achieved.

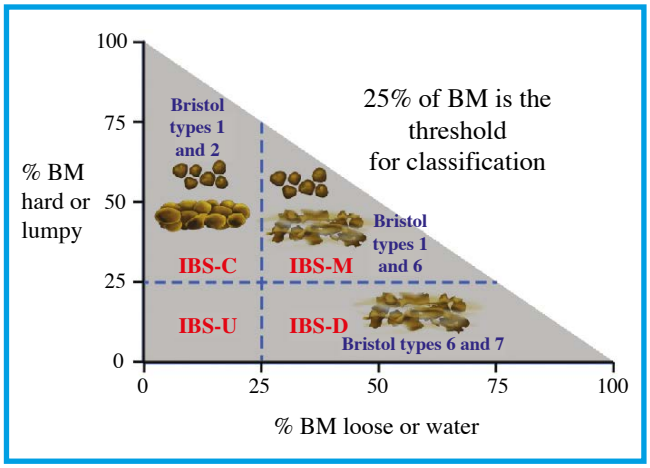

Figure 1. IBS and subtypes (mod. Lacy BE, Gastroenterology 2016)

TREATMENTS

While a variety of different therapy options are available to target the symptoms of IBS, many have not been evaluated in high-quality, randomised controlled trials. Several articles have provided detailed evaluation of different treatment approaches for the management of IBS. However, guidance in terms of how to prioritise the use of different agents is lacking.

MEDICATIONS

The medications currently available for IBS-C are:

- Fiber
- PEG
- Antispasmodics
- Pharmacological therapies
- Diet and dietary manipulation
- Antidepressants and Psychological Therapies
- Prebiotics, probiotics, symbiotics and antibiotics
- Secretagogues.

Fibre

Poorly fermentable, soluble fiber remains an evidence-based treatment for IBS (1,2,3). Insoluble fibre may exacerbate pain and bloating in IBS, and has no evidence for efficacy. The low cost and lack of significant side effects makes soluble fibres a reasonable first-line therapy for IBS patients and, in combination with the moderate quality of evidence, is the basis of a strong recommendation. The ability to improve stool viscosity and frequency logically argues for the use of fibre in patients with IBS-C, although the evidence base to support this contention is far from conclusive.

PEG

PEG is an osmotic laxative that is not absorbed in the intestinal lumen and is widely available. In a randomized clinical trial (4), recruiting 139 patients with IBS-C, there was an increase in spontaneous bowel movements compared with placebo at 4 weeks, but there was not significant effect on abdominal pain or discomfort (Table 1).

Spontaneus bowel movement		
	Peg	Placebo
1.28	4.4	3.11
Severity of abominal pain/discomfort		
	Peg	Placebo
1.57	1.23	1.23

Table 1. Effect of PEG vs placebo in IBS patients (mod. from Chapman RW. Am J Gastroenterol. 2013)

Antispasmodics

Although anti-spasmodics have been a mainstay of IBS management for decades, based on the assumption that dysmotility or "spasm" may be fundamental to the pathogenesis of IBS symptoms and pain; however, the evidence base supporting their use remains modest. Antispasmodics, as a category, do appear to exert short-term benefits in IBS (5,6).

Pharmacological therapies

A systematic review and network meta-analysis (7) identified 18 randomised controlled trials of pharmacological therapies in IBS-D an IBS-M, on 9844 patients. Although all drugs were superior to placebo, according to the FDA-recommended composite endpoint for trials in IBS, alosetron 1 mg twice daily ranked first in terms of efficacy in the network meta-analysis. It was also the top ranked treatment when either global relief of symptoms or improvement in stool consistency were used to define treatment response, but ramosetron 2.5 µg once daily was ranked first in terms of improving abdominal pain. With regard to safety, rifaximin 550 mg three times daily was least likely to cause adverse events and was the only drug that did not significantly increase the risk of constipation.

Eluxadoline 100 mg twice daily was significantly better than placebo across all endpoints, but its overall performance was modest. This information will hopefully assist clinicians in choosing a second-line treatment for IBS-D, and to a lesser extent IBS-M, based on the patient's most troublesome symptom, considering both efficacy and safety.

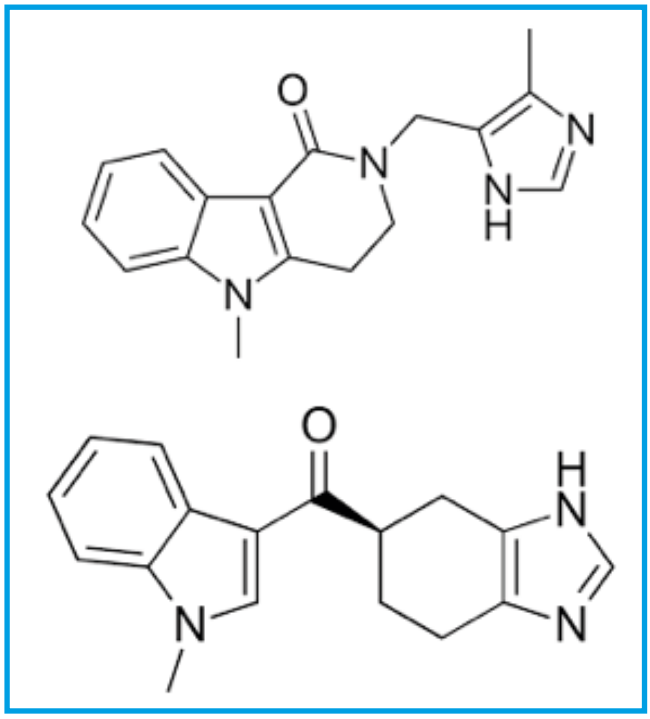

Figure 2. Structure of alosetron and ramosetron

Alosetron and ramosetron (Figure 2) remain unavailable in many countries. Given the chronic and frequently debilitating nature of IBS, this lack of availability may need to be reconsidered, in order to widen access to potentially effective second-line treatments for those patients with IBS-D or IBS-M when conventional first-line therapies fail.

The TRITON (TReatment of Irritable bowel syndrome using Titrated ONdansetron Trial) trial is a funded multi-site, parallel group, randomised, double-blinded, study investigating the effectiveness and mechanism of action of ondansetron.

It will recruit 400 patients with IBS-D from 13 UK sites who will be randomised on a 1:1 basis to receive either ondansetron (dose titrated up to 24 mg daily) or Placebo for 12 weeks. Participants meeting Rome IV criteria for IBS-D will be recruited from outpatient and primary care clinics and by social media. Throughout the trial, participants will record their worst abdominal pain, worst urgency, stool frequency, and stool consistency on a daily basis.

The primary endpoint is the proportion of "responders" in each group, using Food and Drug Administration (FDA) recommendations. Secondary endpoints include pain intensity, stool consistency, frequency, and urgency. Mood and quality of life will also be assessed. Mechanistic assessments will include whole gut transit, faecal tryptase and faecal bile acid concentrations at baseline and between weeks 8 and 11. A subgroup of participants will also undergo assessment of sensitivity (n=80) using the barostat, and/or high-resolution colonic manometry (n=40) to assess motor patterns in the left colon and the impact of ondansetron. The chemical structure of ondansetron is depicted in Figure 3. Figure 4 shows the indirect comparison among second line pharmacological therapies for the treatment of IBS.

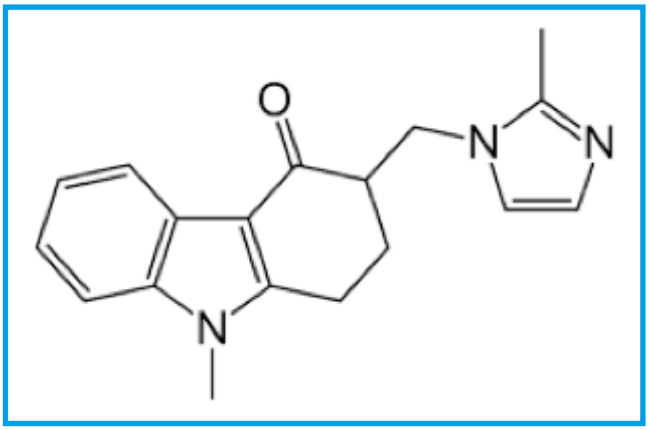

Figure 4. Structure of ondasetron

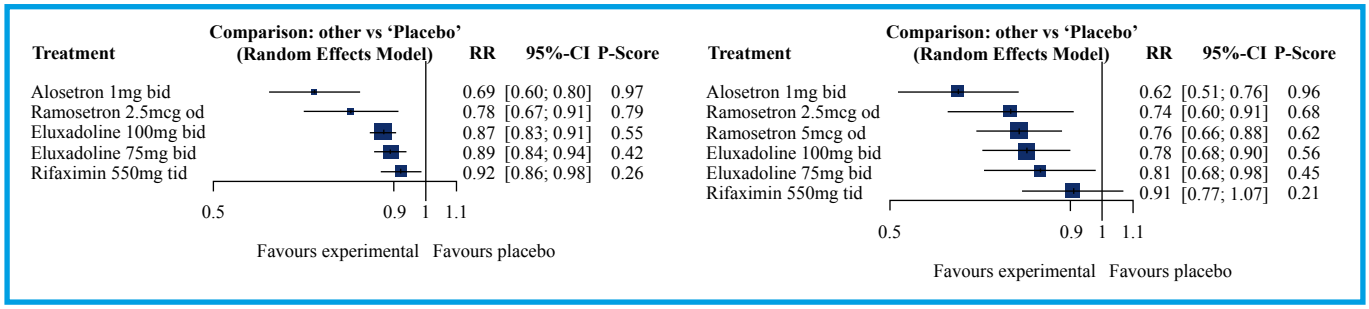

Figure 3. Forest plot of the indirect evidence for failure to achieve an abdominal pain response (right) and stool consistency respons (left) (mod. from Black CJ. Gut 2019)

DIET AND DIETARY MANIPULATION

The majority of IBS patients associate symptoms onset or worsening with eating a meal. Although true food allergy is uncommon in IBS patients, perceived food intolerances or sensitivities are quite common. Up to 90% of IBS patients exclude certain foods in the hope of avoiding or improving their GI symptoms. Although various diets have been suggested to benefit IBS patients, the largest body of evidence relates to two specific diets: a diet low in fermentable oligo-saccharides, di-saccharides, and mono-saccharides, and polyols (FODMAPs) and a gluten-free diet (8).

A systematic review and meta-analysis of randomized controlled trials (RCTs) (9) examined the efficacy of exclusion diets in IBS. There were two RCTs of a gluten-free diets GFD, involving 111 participants. A GFD was associated with reduced global symptoms compared with a control diet, although this was not statistically significant. There were seven RCTs comparing a low FODMAP diet with various control interventions in 397 participants. A low FODMAP diet was associated with reduced global symptoms compared with control interventions (Figure 5). The three RCTs that compared low FODMAP diet with rigorous control diets had the least heterogeneity between studies, but also the least magnitude of effect. The overall quality of the data was "very low" according to Grading of Recommendations, Assessment, Development and Evaluations (Grade) criteria.

ANTIDEPRESSANTS AND PSYCHOLOGICAL THERAPIES

The high prevalence of overlapping psychological disorders in IBS patients, including anxiety, depression, and somatization, has encouraged many providers to use centrally acting therapies, including neuromodulators and psychological therapies (10,11,12).

The two classes of central neuromodulators

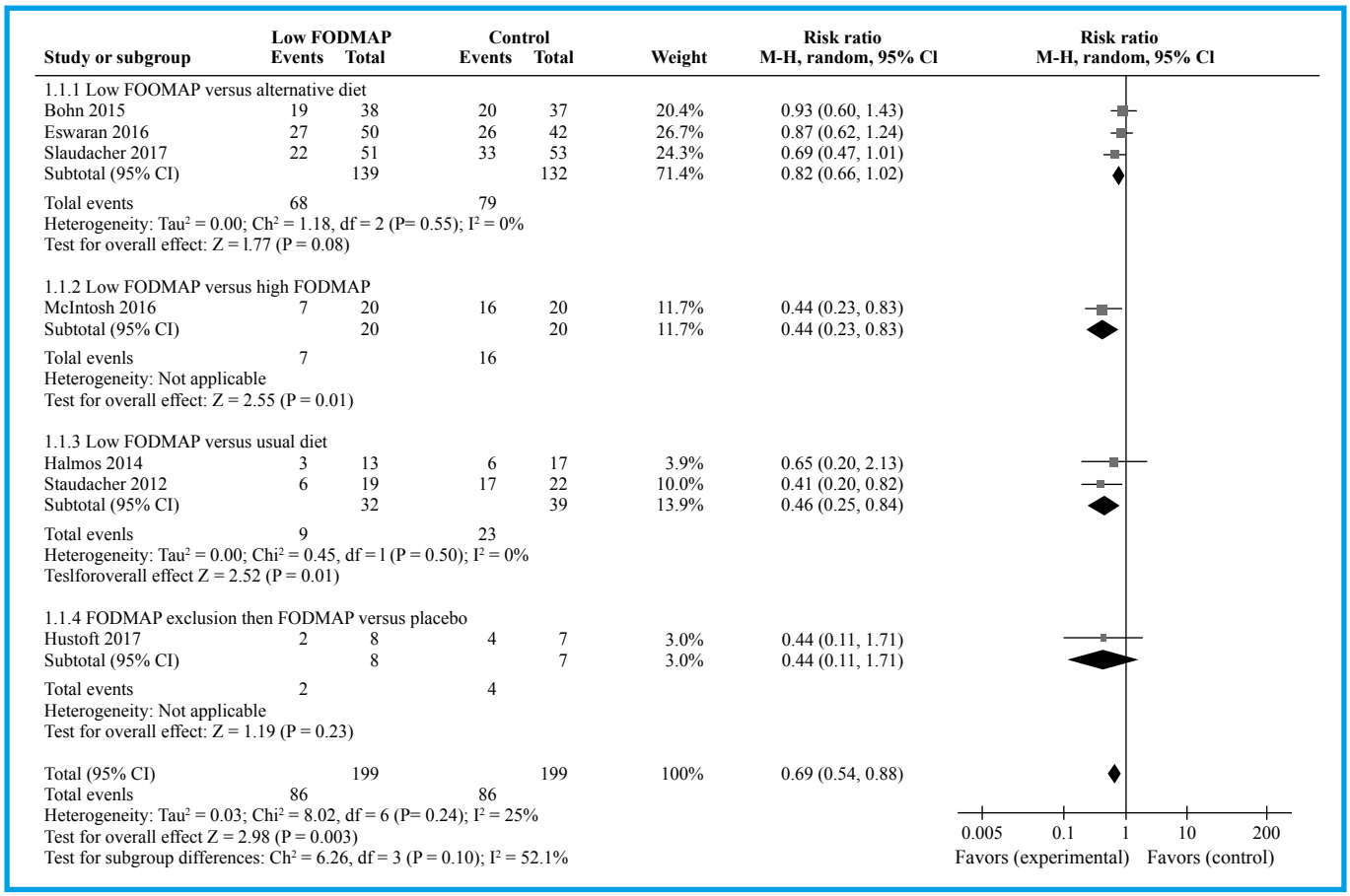

Figure 5. The role of low FODMAP diet in IBS (mod. from Dionne J. Am J Gastroenterol 2018)

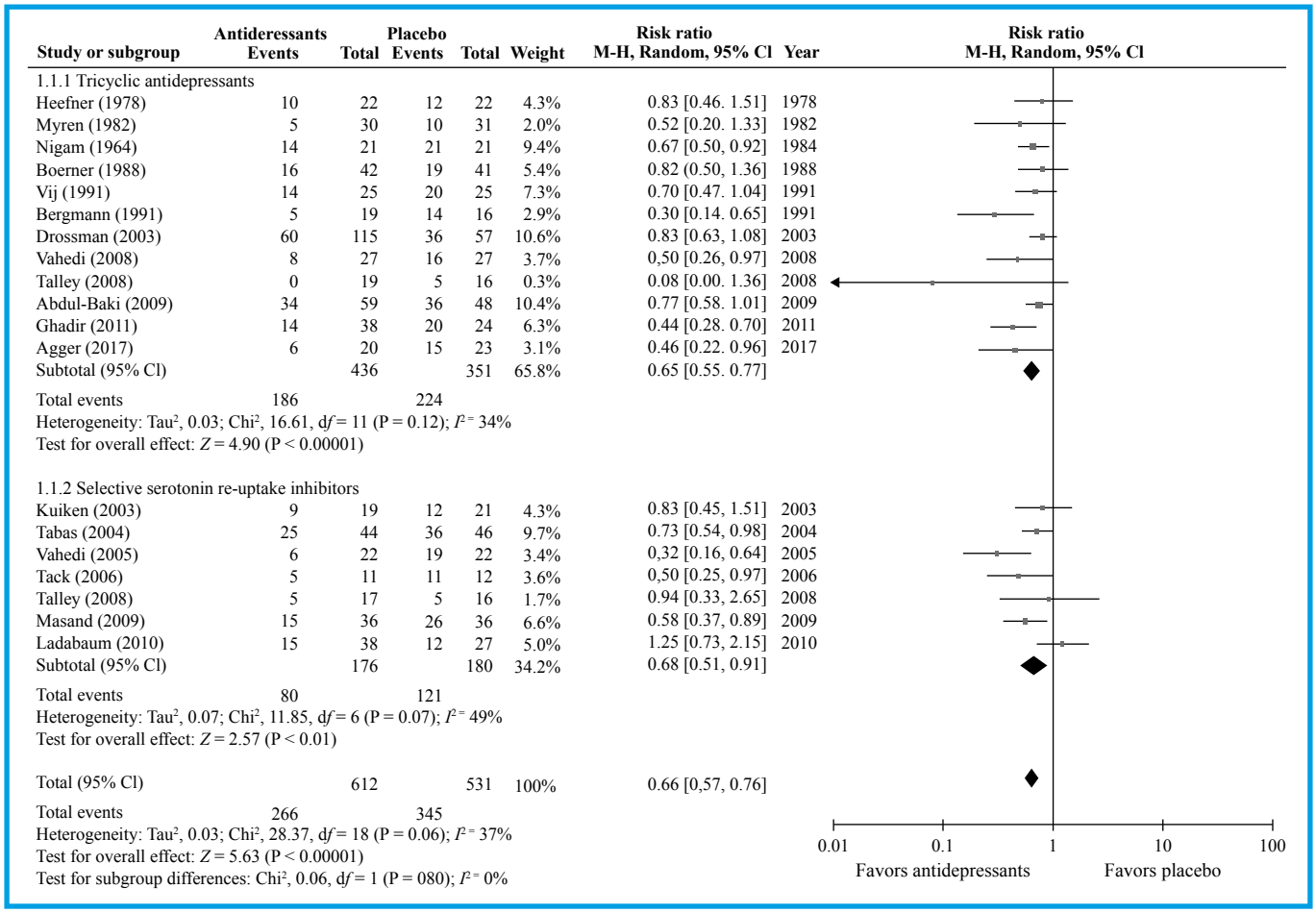

Figure 6. The role of antidepressants in IBS (mod. from Ford AC. Am J Gastroenterol 2019)

most commonly used to treat FGIDs are tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). In addition to their effects on central pain and psychological distress, TCAs and SSRIs may also impact on bowel function, with TCAs improving diarrhea by slowing GI transit, and SSRIs ameliorating constipation by accelerating GI transit. In total, there were 18 RCTs comparing antidepressants with placebo in the treatment of IBS , which evaluated 1127 patients. Overall, 266 (43.5%) of 612 patients assigned to antidepressant therapy reported unimproved IBS symptoms following therapy, compared with 340 (66.0%) of 515 allocated to placebo (Figure 6) (13).

The psychological therapies include stress management, dynamic psychotherapy, mindfulness meditation training, multicomponent psychological therapy and cognitive behavioral therapy (CBT) (e.g. psychoeducation, relaxation, cognitive restructuring, problem-solving skills) administered by a trained therapist that are aimed at modifying specific forms of negative thinking.

Gut-focused hypnotherapy is a highly adaptable and effective treatment for refractory functional gastrointestinal disorders (FGIDs) which can be customized to the patient's symptoms. Not only it has consistently shown to be superior to standard medical care, but hypnosis has also the added advantages of improving extra-intestinal symptoms of FGIDs, improving psychological, cognitive function, and quality of life, and reducing healthcare utilization.

Gastroenterologists should, therefore, seriously consider referral for hypnotherapy (HT) in patients with refractory FGIDs (Figure 7).

Patients who do not respond well to first-line conventional therapies or antidepressants may consider acupuncture as an alternative. Results from pairwise meta-analysis showed that both needle acupuncture

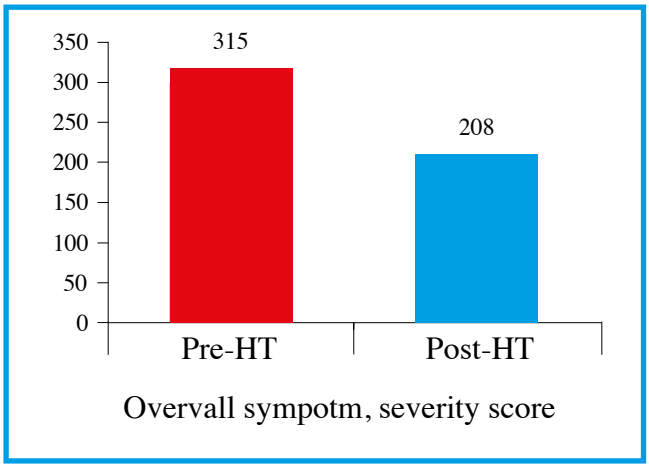

Figure 7. Mod. from Vasant PH, Neurogastroenterol Mot 2019

and electroacupuncture were superior in improving global IBS symptoms when compared with pinaverium bromide. A network meta-analys NMA results showed needle acupuncture plus Geshanxiaoyao formula had the highest probability of being the best option for improving global IBS symptoms among 14 included treatment options, but a slight inconsistency exists. Future trials should investigate the potential of: 1. acupuncture as an add-on to antidepressants and 2. the combined effect of Chinese herbs and acupuncture, which is the norm of routine Chinese medicine practice (14).

PREBIOTICS AND ANTIBIOTICS

Despite the fact that patients and clinicians may use or recommend prebiotics or symbiotics, there are few data supporting their use. Although overall there is a benefit of probiotics, the evidence is low quality and hence, they receive a weak recommendation.

Amongst combination probiotics, seven-strain combination of three Bifidobacterium, three Lactobacillus and one Streptococcus were associated with significant improvements in global symptoms, and there was a trend towards an improvement in global symptom scores or abdominal pain scores with VSL#3. Among individual probiotics, Lactobacillus plantarum DSM 9843, Escherichia coli DSM17252, and Streptococcus faecium also had beneficial effects on global symptoms.

Variations in study design, IBS subtype recruited, type and dose of probiotic, as well as the small size of some of the study populations, and lack of comparative studies, preclude a recommendation on use of a particular species or strain for the treatment of IBS, or the subtype most likely to respond. Although rifaximin treatment appears to be beneficial in IBS, its efficacy is modest in non-constipated IBS (15).

Both probiotics and antibiotics appeared to be safe in IBS, but the longer terms effects of repeated treatment

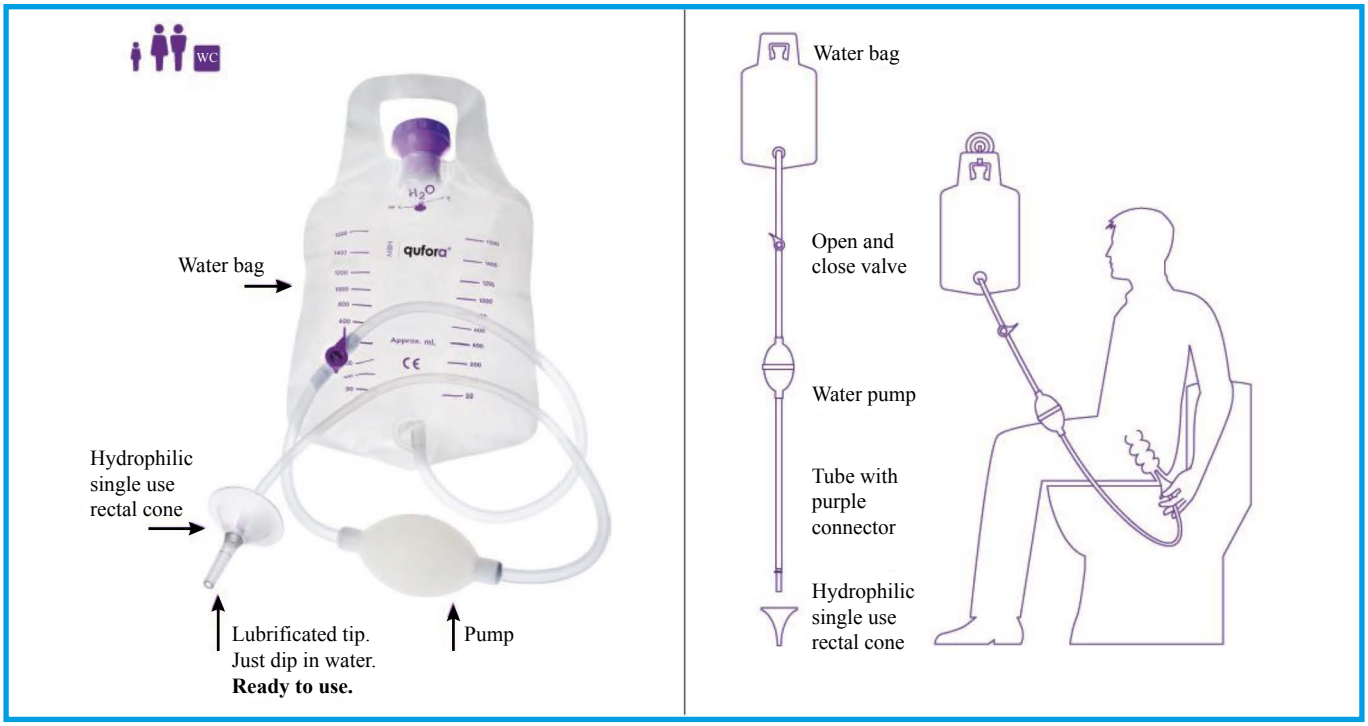

Figure 8. Example of rectal irrigation system

with the latter on the microbiome, and the safety of this approach, remains unclear.

SECRETAGOGUES

In a network analysis of randomized controlled trials of secretagogues (linaclotide, lubiprostone, plecanatide, and tenapanor) for IBS-C (15), it has been shown all drugs to be superior to placebo. Efficacy is similar among individual drugs and dosages for most endpoints. However, data were extracted at the 12-week time point, so the long-term relative efficacy of these drugs is unknown.

OTHER TREATMENTS

Rectal irrigation

Rectal or colonic irrigation has been shown to be successful in treating neurogenic, congenital, and idiopathic bowel dysfunction, constipation, and fecal incontinence, as well as improving QoL. Patients with fecal incontinence after low anterior resection may also benefit from colonic irrigation. Medical treatments are often temporary and disappointing. The role of colonic irrigation for IBS, however, is not yet well established. Different systems are available for rectal irrigation (Figure 8).

CONCLUSION

Many treatment options are currently available for IBS in clinical practice. They act targeting different mechanisms. The knowledge of their supposed mechanisms of action can help guiding the combination of these in complex patients.

Studies evaluating the actual mechanism of action of these medications in vivo in humans have the potential of confirming, confuting or even revealing unexpected effect in vivo in humans.

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