

New insights into irritable bowel syndrome: from pathophysiology to treatment

Alexandros Hadjivasilis^a, Constantinos Tsioutis^a, Adamantios Michalinos^a, Dimitrios Ntourakis^a,
Dimitrios K. Christodoulou^b, Aris P. Agouridis^a

European University Cyprus, Nicosia, Cyprus; University Hospital of Ioannina, School of Health Sciences, University of Ioannina, Greece

Abstract

Irritable bowel syndrome (IBS) is the most common reason to visit a gastroenterologist. IBS was believed to be a functional disease, but many possible pathophysiological mechanisms can now explain the symptoms. IBS patients are classified into subtypes according to their predominant bowel habit, based on the Rome IV criteria. These include diarrhea-predominant and constipation-predominant IBS, as well as the mixed type, a combination of the two. Usually, IBS treatment is based on the predominant symptoms, with many options for each subtype. A new promising treatment option, fecal microbiota transplantation, seems to have beneficial effects on IBS. However, treating the pathophysiological causative agent responsible for the symptoms is an emerging approach. Therefore, before the appropriate therapeutic option is chosen for treating IBS, a clinical evaluation of its pathophysiology should be performed.

Keywords Irritable bowel syndrome, pathophysiology, Rome IV criteria, treatment, fecal microbiota transplantation

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Introduction

Irritable bowel syndrome (IBS) is the most common reason to visit a gastroenterologist and the second most common reason, after common flu, to be absent from work [1]. It is estimated that around 15% [2] of the general population is affected, with some studies even reporting up to 45% [3]. Usually, women are more commonly affected than men, in a ratio of 2:1, and the peak of the disease often starts in early adulthood [4]. In general, patients are evenly distributed among 3 subtypes (diarrhea-predominant [IBS-D], constipation-predominant [IBS-C], or mixed [IBS-M]) but studies from specific geographical areas such as Europe found fewer patients with IBS-D than in the other 2

categories [5]. Women more commonly suffer from IBS-C and men from IBS-D [6]. It is believed that more than 20 billion dollars per year are spent on IBS treatment in the USA alone [7].

Pathophysiology

Food intolerance

One of the most common factors causing symptoms in IBS patients is food intolerance [8], with some studies reporting it in up to 89% of their patients [9]. Patients with IBS understand that specific types of food trigger their symptoms [10]. Usually, these include legumes, vegetables, lactose-containing foods, fatty foods, stone fruits, and artificial sweeteners [9]. In general, a category of foods that contain fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) are known triggers that worsen IBS symptoms because of their osmotic and fermentation effects [11]. Small bowel distension was observed in magnetic resonance imaging studies after fructose was administered to patients with IBS [12], as a result of osmotic effects [11]. Interestingly, a meta-analysis found improvement in symptoms and 70% improvement in quality of life in patients after a low-FODMAP diet [13]. However, the problem with a low-FODMAP diet is that is very restrictive. Hence, monitoring by an experienced dietician is necessary to prevent any nutritional deficiencies and weight loss [14].

^aSchool of Medicine, European University Cyprus, Nicosia, Cyprus (Alexandros Hadjivasilis, Constantinos Tsioutis, Adamantios Michalinos, Dimitrios Ntourakis, Aris P. Agouridis); ^bDepartment of Gastroenterology, University Hospital of Ioannina, School of Health Sciences, University of Ioannina, Greece (Dimitrios K. Christodoulou)

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Correspondence to: Aris P. Agouridis, MD, PhD, Diogenis Str 6 Nicosia CY, 2404 Cyprus, email: a.agouridis@euc.ac.cy

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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 [15]. 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 [16] 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.

Enteric infection

Patients sometimes complain about IBS symptoms after an infection. This is generally known as post-infectious IBS [8] and usually occurs after an acute bacterial, viral or protozoal gastroenteritis, when around 20% of patients will develop symptoms of IBS [17]. Risk factors include prolonged infection, prolonged fever, younger age, depression, and anxiety [1].

It is not yet clear whether or not IBS and post-infectious IBS share similar pathophysiology, since different characteristics of the 2 conditions have been observed by different investigators. Patients with IBS usually have a chronic relapsing disease, but in post-infectious IBS symptoms may resolve naturally in half of the patients within 6-8 years after the infection [18]. Furthermore, whereas several studies have found similarities in the microbiome between the two [10], other studies have reported completely different compositions [19].

The groups of pathogens that lead to IBS symptoms are still unknown, but colonic spirochetosis was linked previously with colonic eosinophilia, lymphoid follicles, and IBS-D [10,20]. Notably, in a study of almost 20,000 people [21] drinking water from a contaminated source, with pathogens such as *Giardia lamblia*, norovirus and *Campylobacter jejuni*, the investigators showed that the risk for IBS symptoms was greater in those with known anxiety, depression and younger age, enhancing the theories of a connection between brain and gut. Similar results were shown in a study of soldiers doing their military service [22].

Inflammation - immunology

Many patients who report IBS symptoms have inflammatory diseases [8]. Celiac disease [23], inflammatory bowel disease (IBD) [24], and severe acute gastroenteritis [25] are just some examples. Therefore, inflammation could be a predisposing factor for IBS symptoms, but the pathophysiology behind this still remains unclear. A probable explanation is that, after the inflammatory response, intestinal permeability is altered and infiltration with inflammatory cells occurs, which predisposes to localized edema and thence to the release of cytokines [26] that could probably, in combination with altered peristalsis and neuromuscular dysfunction [27], result in IBS symptoms.

Increased activation of the innate and adaptive immune systems was observed in the enteric mucosa of some IBS

patients [28]. The immune system has the ability to distinguish harmless microorganisms from potentially pathogenic ones using recognition receptors, the toll-like receptors on neurons of the enteric nervous system (ENS), enteroendocrine and immune cells. Toll-like receptors contribute to an improvement in barrier function and to epithelial lumen repair, and are highly expressed in IBS patients [9].

Visceral hypersensitivity has also been associated with mucosal inflammation in a rat study [29] and with increased colonic and small bowel permeability in IBS-D patients [30]. Moreover, there are studies [31] that show high numbers of mast cells and increased concentrations of proinflammatory cytokines in IBS patients, in close proximity to the enteric nerve fibers, while other studies [32] have confirmed the mucosal inflammation from histology samples.

One study reported that patients with IBS have a 15-50% increase in their intestinal permeability [33]. This could be because patients with IBS seem to have increased amounts of interleukin-10, interleukin-6, tumor necrosis factor- α , and other cytokines, and their concentration is associated with the frequency and severity of pain [34], but also with anxiety [35]. Additionally, alterations in tight junction proteins [36] and mast cell degranulation have been described in IBS patients, with tryptase release being a likely cause for the first [10]. Mucosal alterations were observed in a study [37] with IBS patients, after exposure to food antigens to which the individuals were intolerant. Those alterations included an increase in intraepithelial lymphocytes, widening of intervillous spaces, and epithelial gap formation [37].

Gut-brain axis

IBS is a good example of gut-brain axis dysregulation [26]. The gut-brain axis comprises the central nervous system (CNS), the hypothalamic pituitary axis (HPA), the autonomic nervous system and the ENS [9]. Triggers come from the gut via the vagus, the spinal and the enteric nerves [38]. The vagus nerve is the most important way of communication between the brain and the gut [38]. The HPA axis is also a very important component of this communication, because it regulates stress through production of corticosteroids, as well as aiding in digestion and the immune system [9]. CNS signals to the gut are transmitted by neuroendocrine neurotransmitters (serotonin, corticotropin-releasing hormone, cholecystokinin, and somatostatin), produced in the gut by immune and enterochromaffin cells (EC) to alter microbiota behavior [39]. This is possible because bacteria also have some neurotransmitter receptors and are influenced by those signals [38].

Serotonin

The ENS has been previously described as the second brain and contains 5 times the neurons of the spinal cord. Ninety percent of 5-hydroxy-tryptamine (5-HT) and 50% of dopamine production is in the gastrointestinal tract, mainly by EC [9]. The 5-HT production is stimulated even more by spore-forming bacteria

and changing immune responses, secretions and gastrointestinal motility [9]. This 5-HT stimulation is also influenced by microbiota, after exposure to short chain fatty acids (SCFA) [40] that come either from food and a FODMAP diet, or from SCFA-producing bacteria [9]. These SCFAs increase gut transit time via sympathetic nervous system and ENS stimulation [41] and could be possibly a causative factor for IBS symptoms.

The role of serotonin in the pathogenesis of IBS is also confirmed by studies [42] that examined different 5-HT receptor drugs with positive effects on IBS symptoms. It has been observed that patients with post-infectious IBS have chronic increases in EC [43]; they also have increased serotonin after food intake, whereas IBS-C patients have reduced serotonin release [44]. Likewise, another study [45] found that in IBS-D patients the ratio of 5-hydroxyindoleacetic acid to 5-HT was reduced and concluded that those with IBS-D have lower serotonin reuptake while those with IBS-C have lower serotonin release.

Serotonin metabolism can be influenced by genetic factors, many of which have been described in IBS patients [46]. In addition, in patients with IBS-C the long-long (LL) allele genotype appears to be a risk factor, at least for patients from East Asia [46]. In another study, the investigator found that IBS patients had much higher mucosal serotonin levels, associated with the number of mast cells and the severity of abdominal pain [47].

Stress - depression

Up to 75% of patients with IBS symptoms usually have coexisting anxiety or depression [10]. One study found that patients exposed to stressful events in their life tended to have more IBS symptoms, whereas those who had support showed fewer [1]. A large number of women with IBS describe prior abuse of one kind or another at some point in their life. A possible pathophysiological explanation for this could be the connection of the brain with the gut through the gut-brain axis, as explained above. One study of notable interest [48] reported that after rectal balloon distension in IBS patients, their brain regions associated with pain modulation and emotional arousal were highly engaged and activated. Furthermore, IBS patients have weaker inhibitory feedback mechanisms for emotional arousal and higher activity after visceral stimuli [48].

One interesting study [49] 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 depression or anxiety, that make them more vulnerable to stressful stimuli.

Norepinephrine production by stressful stimuli appears to enhance the growth of many intestinal pathogens, including *Campylobacter jejuni* [50], *Escherichia coli* (*E. coli*) and *E. coli* 0157:H7, with activation of the HPA axis [9]. It appears that this stress stimulation also affects the non-pathogenic bacteria, such as *Lactobacilli* and *Bifidobacteria*, promoting even more invasion from other potential pathogens [51].

Interestingly, IBS patients with children visit the pediatrician more often than non-IBS parents [1]. Newer epidemiological studies [52] 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, psychiatric patients who also had IBS reported that they developed their psychiatric symptoms after they were diagnosed with IBS [53]. These extra-intestinal symptoms of IBS could again be explained in terms of the intestinal inflammation and cytokine mechanism altering the gut-brain axis [10,34], as described above. This is very interesting because it suggests the possibility of a newer approach to the treatment of mood disorders and psychiatric diseases in general [10].

γ -Aminobutyric acid (GABA)

GABA is an important inhibitory neurotransmitter that prevents abnormal firing of neurons in the CNS. Dysregulation of GABA leads to diseases such as epilepsy and anxiety disorders [9]. There are also thought to be GABA-b receptors involved in the gastrointestinal tract, affecting visceral sensation, pain and intestinal motility [9]. It is believed that the gut microbiota has the potential to produce GABA, with *Bifidobacterium dentium* and *Lactobacillus brevis* being the best producers, and that some foods produced by bacterial fermentation also contain GABA. This knowledge, though, has not yet been applied in clinical practice [54].

Genetics

IBS is more common in monozygotic twins than in dizygotic, suggesting a possible genetic background for the disease [55]. This is plausible, since a specific mutation was found to be common in 2% of IBS patients in one study and the majority of those had IBS-C [56]. *5CN5A* is a sodium channel gene mutation correlated with congenital prolonged QT interval and abdominal pain [57]. It was reported that an IBS-C patient had normalization of his stool habits after using mexiletine, an antiarrhythmic drug [56], suggesting possible new therapeutic approaches in such individuals. Congenital sucrose isomaltase deficiency has also been observed in many families with IBS, possibly affecting the disease in a yet unknown manner [58].

Bile acid metabolism

Idiopathic bile acid diarrhea is estimated to affect up to 20% of IBS-D patients [59], while IBS-C patients have altered bile acid metabolism [60]. Bile acids are produced in the liver and are mostly in a conjugated state with other proteins [61]. De-conjugation occurs in the intestine and is caused by the bacteria there. Consequently, there is an increase in chloride secretion and a decrease in sodium absorption. Therefore, if the intestine is exposed to large amounts of bile acids, diarrhea may result. Conversely, if there is an insufficient amount of bile acids

in the feces, constipation may occur [9]. The most important step in the negative feedback mechanism is the inhibition of bile acid formation by fibroblast growth factor 19 [60]. Fecal bile acids were observed to have higher levels in IBS-D and lower levels in IBS-C patients; their concentration was associated with stool number and shape [62]. In addition, IBS-D patients have higher levels of 7 α -hydroxy-4-cholesten-3-one (C4), a bile acid synthesis marker [63], increased fecal bile acid, with greater colonic transit and intestinal and colonic permeability [64]. Moreover, intestinal dysbiosis was observed in patients with higher amounts of fecal bile acids, particularly an increase of *E. coli* and reduction in *Bifidobacteria* [65]. The association between bile acid metabolism and IBS can also be confirmed by the improvement of IBS symptoms seen in patients who took the bile acid sequestrant colestipol [59].

Microbiota

As many as a few trillion microbes live in our bowel and make up more than 1000 different species, outnumbering the number of the cells in our body by 10 times [66]. The 4 most important bacterial phyla in microbiota are Firmicutes (including *Lactobacillus*), Actinobacteria (including *Bifidobacteria*), Bacteroidetes (including *B. fragilis*) and Proteobacteria (including *E. coli*, *Yersinia*, *Shigella*, *Salmonella* and many more), but it also contains viruses, fungi and protozoa [67]. Some types of bacteria, such as *Lactobacilli*, *Bifidobacteria* and *E. coli*, have the ability to interfere with the immune system, causing anti-inflammatory responses [68]. Furthermore, microbiota is believed to protect bowel barrier function and ensure homeostasis of the gut-brain axis [69], commonly described as pathophysiological pathways for IBS.

It is assumed that IBS patients have altered microbiota in their intestines [70]. Observations from a study 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 [71]. *Lactobacillus* and *Bacteroides* species, known beneficial bacteria, are also depleted, while the numbers of pathogenic bacteria, such as *Streptococcus spp.*, are increased [72]. In a study of IBS patients with abdominal pain, the investigators observed that patients with pain had 5 times smaller amounts of *Bifidobacteria* in their intestines [73].

One of the most common symptoms in IBS is abdominal distension [74], and gas-producing bacteria may be responsible for this. It occurs because gas distends the bowel, not allowing the diaphragm to completely relax, which in turn pushes the abdomen outwards, leading to profound abdominal distension [75].

Presentation

Patients with IBS are classified into subtypes according to their predominant bowel habit (Table 1). These include IBS-D, IBS-C and mixed IBS (IBS-M), a combination of the previous two. Usually, IBS-D and IBS-C have similar prevalence [76]. Common signs and symptoms of IBS are abdominal pain,

bloating, straining during defecation, sensation of incomplete evacuation, mucus with stools, urgency [77], postprandial symptoms [78], depression, and anxiety [79].

Differential diagnosis

Given the lack of any diagnostic marker or examination, IBS can be presented or misdiagnosed as another disease with similar signs or symptoms [81]. The differential diagnosis includes many diseases, not only of the gastrointestinal tract, but also from extraintestinal causes. Diseases that commonly present with diarrhea and should be excluded first are microscopic colitis [82], IBD [83], celiac disease [84], infections [85], hyperthyroidism [86], carbohydrate malabsorption [87], and bile acid diarrhea [88]. On the other hand, disorders that present with constipation and should be excluded are colorectal cancer or anal malignancy that obstructs the lumen [89], dyssynergic defecation [90], and hypothyroidism [86]. Other reasons for abdominal pain should also be excluded in patients with IBS. Endometriosis, diverticulitis, pelvic inflammatory disease, and ovarian cancer are just some examples of diseases that could possibly present with similar abdominal pain [86].

Workup

History and physical examination are both very important in the evaluation of patients with IBS [91]. Usually, if no alarming signs or symptoms are present, nor other risk factors for organic disease, the diagnosis of IBS can be made with confidence, especially for IBS-C [86]. Alarming signs and symptoms should be excluded and if present further investigated (Table 2). These include blood in stools, more than 10% unintentional weight

Table 1 Subtypes of irritable bowel syndrome according to Rome IV criteria

Subtype	Characteristics
Diarrhea-predominant	>25% loose stools, <25% hard stools
Constipation-predominant	>25% hard stools, <25% loose stools
Mixed-type	>25% loose stools, >25% hard stools

Table 2 Alarming features

Alarming features
Blood in stools
More than 10% unintentional weight loss
Disease that wakes the patient up during the night
Fever
New onset of signs and symptoms after the 50 th year of age
Family history of colorectal cancer, inflammatory bowel disease, or celiac disease

loss, disease that wakes the patient up during the night, fever, new onset of signs and symptoms after the 50th year of age, and a family history of colorectal cancer, IBD or celiac disease [82]. During physical examination, perianal area inspection for fissures or fistulas should be performed [77] as well as a digital rectal exam to check for any anal pathology [90].

A full blood count and a C-reactive protein tests are usually enough to reassure the patient that no organic disease exists, provided that no other risk factors or alarming signs and symptoms are present [77]. Otherwise, anything suspicious should be investigated. Investigations include serological tests for celiac disease in IBS-D patients [92], thyroid hormone evaluation, fecal calprotectin for IBD, and stool analysis for infectious microorganisms in IBS-D patients [85].

Invasive procedures, such as colonoscopy and upper gastrointestinal endoscopy, should only be performed if there is a specific indication for them, like blood in stools, increased inflammatory markers, or according to the colorectal cancer screening guidelines in each country [93]. IBS-D patients should be evaluated for microscopic colitis with biopsies during colonoscopy, especially if they are women aged more than 50 years [82]. They should also be tested for bile acid-induced diarrhea using a 75-homocholeic acid taurine test or serum C4 levels, but if those are not available a simple bile acid binding agent will help to diagnose patients with such a disease [88]. Likewise, carbohydrate malabsorption should also be excluded by lactose breath test or by excluding suspected foods or drinks that trigger symptoms [94]. Last but not least, celiac disease with duodenal biopsies should be excluded if the patient's history or serological testing point in this direction [84].

Diagnosis: Rome IV criteria

The first attempt to produce IBS diagnostic criteria was back in 1978: the so-called Manning criteria [95], which include common symptoms for IBS that do not exist so often in other organic diseases (Table 3). A few years later, the Rome foundation developed the Rome I criteria, the first version of the Rome IV criteria (Table 4) currently used to diagnose patients with IBS [80]—at least for research purposes, since they are complex and difficult to remember in everyday practice [96]. Rome IV criteria replaced their previous version, Rome III criteria (Table 5), in 2016 because of their uncertainties and because they had not been adequately validated [97]. The sensitivity of Rome III criteria was 73% and their specificity 93%, whereas Rome IV criteria have 62% sensitivity and 97% specificity [96]. Accordingly, several studies found a positive likelihood ratio of 21 for the Rome IV criteria, but only 10 for Rome III, where the higher the ratio, the more likely the finding is associated with a true disease [96]. The main difference between the 2 is that abdominal discomfort, a vague term, was removed from the Rome IV criteria and now only patients with abdominal pain can be diagnosed with IBS [98]. Moreover, with the Rome III criteria pain was relieved after defecation, but now, with the Rome IV criteria, this has been altered to refer to pain “changes” after defecation, because there are also patients who

experience more pain after defecation [91]. In addition, in the Rome IV criteria abdominal pain has to be present at least 1 day per week for 3 months, whereas in Rome III this was at least 3 days per month [96]. Equally important is that the subtypes of the disease (IBS-D, IBS-C, IBS-M, and IBS-U), using the Rome IV criteria, are categorized based on the number of abnormal bowel movements, rather than on all bowel movements as with the Rome III criteria [96]. Lastly, IBS is now considered a gut-brain axis disorder and not a functional disease, removing the stigmatization from IBS patients [91].

Besides IBS, the Rome IV criteria include many functional disorders. Some examples are functional diarrhea, functional constipation, functional dyspepsia, functional bloating, functional abdominal pain, and unspecified functional bowel disorder [98]. In addition, the presence of other functional disorders, including fibromyalgia, chronic fatigue, and other gastrointestinal or extraintestinal functional disorders, makes IBS most likely as a diagnosis [99].

Treatment

The treatment for IBS is usually based on the predominant symptoms. However, treating the pathophysiological

Table 3 Manning criteria

Manning criteria (at least 3 of the following)
Abdominal pain gets better after defecation
Pain associated with looser stools
Pain associated with more frequent stools
Feeling of incomplete evacuation
Mucus in stools
Abdominal distention

Table 4 Rome IV criteria

Rome IV criteria
Recurrent abdominal pain, at least 1 day per week for the last 3 months associated with 2 or more of the following:
Defecation
Change in stool frequency
Change in stool appearance (form)

Table 5 Rome III criteria

Rome III criteria
Recurrent abdominal pain or discomfort at least 3 days per month for the past 3 months associated with 2 or more of the following:
Improvement with defecation
Onset associated with change in frequency of stool
Onset associated with a change in stool appearance (form)

causative agent responsible for the symptoms is an emerging approach [91]. An acceptable initial therapy, especially for patients with mild disease, is lifestyle modification and education. This starts with removing gas-producing foods and by following a low-FODMAP diet (Table 6). If this is helpful, then reintroduction of foods, one at a time, is encouraged. Otherwise, these specific foods should be avoided in the long term [100]. A low-FODMAP diet has been shown to help patients in relieving abdominal pain, bloating, and stool consistency [101]. Lactose avoidance is also an option in some patients, both those with and without lactose intolerance, since it is possible that an ingredient in milk other than lactose triggers symptoms [101]. Likewise, it was reported that a gluten diet also causes IBS symptoms in non-celiac disease patients, but this may be because of fructans, also found in wheat, and not gluten. Nevertheless, in the latest guidelines for IBS from the American College of Gastroenterology (ACG), a gluten-

free diet is not recommended, because the studies suggesting it have not shown statistically significant results [102].

Treatment for IBS-C should be targeted to alleviate constipation (Table 7). Increased fiber consumption is recommended, and soluble fibers such as psyllium are preferred to insoluble fibers such as bran as a first step [103]. An initial first pharmacological treatment could include osmotic laxatives, such as polyethylene glycol, but it may not help with pain [104]. Thus, in their latest guidelines the ACG no longer recommends it, since the evidence to support its use is not statistically significant [102]. Therefore, linaclotide or lubiprostone can be used instead, since they improve colonic transit time and abdominal pain [105]. Moreover, plecanatide, used for chronic idiopathic constipation, is a recent promising option for IBS-C that has been shown to improve IBS symptoms in general [102]. Last but not least, lactulose, also an osmotic laxative, should be avoided because it produces a lot of gas and results in bloating [80].

Table 6 Examples of diet with high and low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs)

Type of food	High FODMAP	Low FODMAP
Vegetables	Onion, garlic, leek, asparagus, artichoke, cauliflower, mushrooms, green peas	Carrots, eggplants, bell peppers, lettuce, cucumber, tomato, potato, zucchini
Fruits	Watermelon, apples, cherries, mango	Grapes, kiwi, oranges, strawberries, pineapple
Dairy	Cow's milk, evaporated milk, soy milk, cottage cheese, ice cream	Almond milk, coconut milk, hard cheese, butter, lactose free
Protein	Legumes, processed meat, marinated meats	Eggs, tofu, non-marinated meats, fish, chicken
Cereals	Wheat, rye, barley, spelt	Oats, quinoa, corn, sourdough bread
Sugars	High fructose, honey	Maple syrup, table sugar
Nuts and seeds	Cashews, pistachios	Peanuts, pumpkin seeds, walnuts

Table 7 Drugs for irritable bowel syndrome

Drugs	Mode of action	Side effects
Drugs for IBS-C		
Linaclotide	Guanylate cyclase-C receptor agonist [1]	Diarrhea, headache [26]
Lubiprostone	Type 2 chloride channel activator [1]	Nausea, diarrhea [26]
Plecanatide [102]	Guanylate cyclase-C receptor agonist	Diarrhea
Drugs for IBS-D		
Cholestyramine [1]	Bile acid sequestrant	Constipation
Eluxadoline [91]	μ and κ opioid receptor agonist and δ -receptor antagonist	Constipation, pancreatitis
Alosetron	Selective 5-HT ₃ receptor antagonist [77]	Constipation, ischemic colitis [86]
Rifaximin	Modulation of gut microbiota [91]	Headache, nausea, diarrhea [26]
Drugs for abdominal pain		
Dicyclomine or hyoscyamine	Reduce smooth muscle contractions [1]	Constipation, dry mouth, dry eyes [26]
Peppermint oil	Relaxes smooth muscles [91]	Heartburn, dyspepsia [26]
More pharmacological options		
Tricyclic antidepressants	Inhibition of active neuronal uptake of the biogenic amines (5-HT and norepinephrine) [77]	Arrhythmias, sexual dysfunction, sedation, orthostatic hypotension [26]
SSRIs	Serotonin reuptake inhibitors	Dry mouth, drowsiness [77]

IBS-C, constipation-predominant irritable bowel syndrome; IBS-D, diarrhea-predominant irritable bowel syndrome; 5-HT, 5-hydroxy-tryptamine; SSRIs, selective serotonin reuptake inhibitors

Likewise, treatment for IBS-D should be targeted to alleviate diarrhea (Table 7). Loperamide can help with diarrhea by inhibiting peristalsis and increasing colonic transit time, but again it may not help with abdominal pain [106]. It is not recommended by the latest ACG guidelines because its efficacy in IBS-D patients was not statistically significant [102]. Therefore, cholestyramine, a bile acid sequestrant, could be tried as first-line treatment if bile acid diarrhea is suspected [107], or eluxadoline, a μ and κ opioid receptor agonist and a δ -receptor antagonist in the ENS that has been proven to improve global symptoms in IBS-D [102]. However, eluxadoline increases the risk of pancreatitis, so it should be used with caution in patients with increased risk factors for that disease [102]. Alosetron, a 5-HT type 3 antagonist, appears to improve abdominal pain, but should be used with caution only in women with severe IBS-D symptoms [108] because of serious side-effects, including ischemic colitis [109]. Last but not least, rifaximin, a poorly absorbed drug used for traveler's diarrhea, has been shown to improve symptoms in general and to help patients with IBS-D. However, its effect seems to diminish over time, so treatment should be repeated if effective [110].

Additionally, regardless of the predominant type, every patient with IBS suffers from abdominal pain, according to the Rome IV criteria [98]. Antispasmodics on an as-needed basis are the treatment of choice to relieve pain; they work by reducing smooth muscle contractions and possibly by altering visceral hypersensitivity (Table 7). However, they should be used with caution in IBS-C because of their anticholinergic effects [111]. Examples of such drugs are dicyclomine and hyoscyamine, but peppermint oil can also be included among the available treatment options (Table 7). Peppermint oil, which has antispasmodic effects, has been shown to provide symptomatic relief in abdominal pain but was associated with heartburn [112].

Tricyclic antidepressants are the category of antidepressants that have been tested the most for IBS, and many studies found that they relieve abdominal pain and diarrhea symptoms, and improve slow colonic transit times (Table 7). However, their use is limited by their numerous side effects, which include drowsiness, dry mouth, fatigue, and constipation [77]. On the other hand, serotonin reuptake inhibitors have a safer profile and improve symptoms in general compared with placebo [112]. Interestingly, cognitive behavioral therapies, hypnotherapy and psychotherapy appear to be helpful in reducing global symptoms [113], most probably because of the gut-brain connection. Likewise, regular mild exercise appears to reduce bloating and gas production [114].

In addition, 5-aminosalicylates have been used in randomized controlled trials in patients with IBS because of the theory about low-grade intestinal inflammation; however, they are not yet recommended, despite the promising results that these studies found [102].

Last but not least, probiotics seem to be helpful in reducing symptoms, but it is not yet clear which strains of bacteria are the most effective [115]. It is believed that they improve symptoms like abdominal pain and bloating by altering the intestinal microbiota, which may play an important role in the pathogenesis of IBS [116]. As a matter of fact, *Bifidobacterium*

infantis 35624 has been found beneficial in improving global symptoms and in normalizing bowel movements in all IBS subtypes. Likewise, *Bifidobacterium lactis* DN-173010 and VSL#3 probiotics have been proven effective in treating flatulence, distention and bloating [86]. On the other hand, prebiotics and synbiotics are not recommended [102].

Fecal microbiota transplantation (FMT)

An altered microbiota is believed to be a main pathophysiological factor behind IBS. Patients with IBS have been found to have different microbiota composition from healthy patients [117], but it is not yet clear which bacteria species are the ones responsible for the symptoms [118]. FMT is a relatively new and promising procedure for the treatment of IBS. It has been well studied in patients with *C. difficile* infection and is already considered as an effective option [119]. Over the last few years, FMT has been considered as a potential therapeutic option in other diseases apart from *C. difficile* infection. These include inflammatory bowel diseases, metabolic syndrome [120], colonization of the gastrointestinal tract by pathogenic and multi-resistant microorganisms, type 2 diabetes mellitus, obesity [121], chronic stress [122], the autistic spectrum of disorders, and depression [123].

Before the procedure, donors should be interviewed regarding their medical history and lifestyle. Specific attention should be paid to infectious diseases, because there is a high possibility that any such will also pass to the recipient, but also to metabolic and neurological diseases [124]. The relation of the donor with the recipient should also be determined, since IBS pathogenesis also has a genetic component and a first-degree relative might have a similar microbiota. However, one study found that this might not be significant, reporting similar outcomes from first-degree relatives and unrelated donors [125].

For the procedure, at least 30 g of stool should be used [126] and the effect is the same whether fresh or frozen stools are used [127]. The stools are then introduced into the patient's intestines in the form of a suspension, using a colonoscope, enema, nasoenteric tube or gastroscope. All these methods have similar outcomes [125].

FMT appears to be effective based on already published studies [128,129]. Those studies reported that the response to the treatment was successful and patients had significant improvement in abdominal pain, bloating and flatulence. Symptom relief was from 70-85% in the first 3 months and from 45-60% in 6 months, suggesting that the procedure might need to be repeated again in the future.

Concluding remarks

IBS is a very common disease. However, its pathophysiology is still not fully understood. Usually, treatment for IBS is based on the predominant symptoms, with many options for each

subtype. FMT is a promising new option for patients with IBS and seems to have a beneficial effect. However, treating the pathophysiological causative agent responsible for the symptoms is an emerging approach. Hence, before choosing the appropriate therapeutic option for treating IBS, clinical judgement on its pathophysiology should be made.

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