Managing the Diagnostic and Therapeutic Challenges of Irritable Bowel Syndrome

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Abstract: The management of patients with irritable bowel syndrome (IBS) remains a common clinical challenge for health care providers. IBS is a prevalent disorder that encompasses a constellation of symptoms that may be caused by a variety of underlying conditions; as a result, there is no one-size-fits-all approach, and clinicians must tailor their approach to the individual. This article outlines the challenges associated with the management of IBS and offers practical solutions to help providers care for patients with IBS.

Keywords
Irritable bowel syndrome, diagnosis, management, therapies, constipation, diarrhea

Disorders of gut-brain interaction (DGBIs), formerly known as functional gastrointestinal disorders, affect greater than 40% of individuals worldwide and frequently overlap (Figure).[1] Irritable bowel syndrome (IBS) affects 4% to 10% of individuals, depending on the Rome version of diagnostic criteria used.[2] IBS is one of the most common reasons for referral to a gastroenterology clinic, necessitating that clinicians are well-versed in its diagnosis and management. The diagnosis itself may be difficult to make, as outlined in this article, and individuals may have varying degrees of response to recommended therapies. Importantly, symptoms are chronic in nature for most patients and can be debilitating, leading to major negative impacts on quality of life, thus underscoring the importance of effective care for patients with IBS.

The Diagnostic Dilemma of Irritable Bowel Syndrome

IBS remains a diagnostic dilemma for several reasons. To start, symptoms of recurrent abdominal pain and changes in bowel habits are nonspecific and can be alarming to patients. Such symptoms can be signs of a serious, life-threatening condition, such as malignancy, and thus cannot be overlooked. Further complicating the diagnostic challenge is that similar symptoms can occur with known organic diagnoses, such as inflammatory bowel disease or celiac disease, and can also overlap with extraintestinal conditions such as fibromyalgia and psychological comorbidities.[3,4] Table 1 provides a list of diagnoses to consider, beyond IBS, in the evaluation of chronic abdominal pain with diarrhea or constipation. Currently, a positive diagnosis of IBS is made using the Rome IV symptom-based criteria

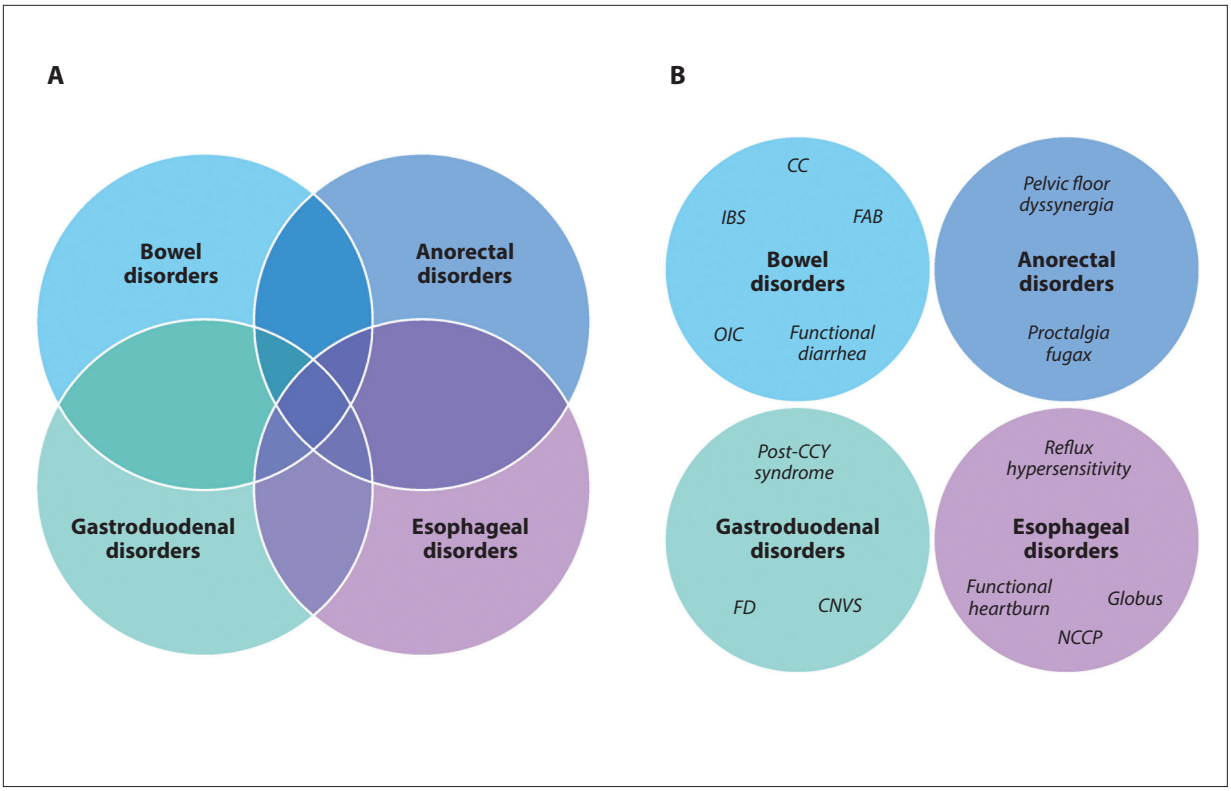

Figure. Common DGBIs. **A:** Overlap of the major categories of DGBIs. **B:** The most common DGBIs within each group.

CC, chronic constipation; CCY, cholecystectomy; CNVS, chronic nausea vomiting syndrome; DGBIs, disorders of gut-brain interaction; FAB, functional abdominal bloating; FD, functional dyspepsia; IBS, irritable bowel syndrome; NCCP, noncardiac chest pain; OIC, opioid-induced constipation.

and excluding other organic conditions, especially when alarm symptoms are present.[5] Notably, IBS remains a clinical diagnosis, as there are no well-established biomarkers.

Not All Patients Respond to Therapy (or Only Partially Respond)

The principles of management include lifestyle changes, behavioral interventions, and medications. Dietary changes such as a low–fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diet are often recommended as first-line therapies.[5] Although a low-FODMAP diet has become a common recommendation for patients with IBS, data have shown that the diet is primarily helpful in treating symptoms in patients with diarrhea-predominant IBS (IBS-D), whereas studies assessing the low-FODMAP diet for treatment of constipation-predominant IBS (IBS-C) are lacking.[6] Similarly, although a number of medications are now available to treat IBS, these agents may only improve some symptoms of IBS, such as bowel habits, while incompletely addressing other symptoms such as abdominal pain.

Challenges in Management

The evaluation of a patient with suspected IBS can be challenging for many health care providers (HCPs). Uncertainty may occur at a number of stages, including symptom evaluation, diagnosis, explanation of the disease state, and treatment. These challenges, reviewed in the following sections, explain why most HCPs still practice with the mindset that IBS is a diagnosis of exclusion. For example, one survey of UK primary care providers found that 70% believe that IBS is a diagnosis of exclusion, and another multinational survey study of primary care providers in the United States and 9 different European countries reported that 80% practice using IBS as a diagnosis of exclusion.[7,8] This approach has several negative consequences. One, making IBS a diagnosis of exclusion inevitably leads to unnecessary testing. This consumes national health care resources that could be better utilized for other patients and also increases risks for patients (ie, unnecessary/additional imaging studies using radiation or invasive tests such as colonoscopy). Two, unnecessary and/or repetitive testing

Table 1. Differential Diagnosis for Chronic Abdominal Pain With Bowel Habit Changes[3,30]

Chronic diarrhea[a]	Chronic constipation[a]
Celiac disease	Colorectal cancer
Chronic infection (eg, *Giardia*)	Diverticulitis
Chronic pancreatitis	Hypothyroidism
IBS with diarrhea	IBS with constipation
Inflammatory bowel disease	Intestinal methanogen overgrowth
Intermittent obstruction	Mechanical bowel obstruction
Malignancy	Medication-induced
Mesenteric ischemia	Neurologic diseases (eg, Parkinson disease)
Microscopic colitis	Rectal evacuation disorders (eg, dyssynergic defecation)
Porphyria	
Postsurgery (eg, Roux-en-Y gastric bypass)	
Radiation-induced colitis	
Severe endometriosis with bowel wall infiltration	
Small intestinal bacterial overgrowth	

IBS, irritable bowel syndrome.
[a]Some conditions listed may present with both constipation and diarrhea; however, for simplicity, they have been grouped with the more common presentation.

increases health care costs for the individual, which is a financial burden for many patients. Several studies have investigated the burden of excess testing. One study found that HCPs who practiced a diagnosis of exclusion ordered twice as many tests as those who used a positive diagnostic strategy.[9] A large US claims database analysis of more than 200,000 patients with IBS found that those who were older than 50 years, female, and had multiple comorbidities were more likely to undergo excess testing.[10] An employer-based health claims study found that nearly 80% of health care costs for patients with IBS-D were associated with a diagnosis of exclusion approach.[11] Three, focusing on IBS as a diagnosis of exclusion delays the diagnosis, which inexorably postpones the initiation of appropriate therapy. Lastly, excessive and prolonged testing may signal to the patient that the HCP is unsure of the diagnosis and thus undermine a positive working relationship between the patient and HCP. In support of this, a study of nearly 500 patients with IBS undergoing a peace-of-mind colonoscopy found that a normal study did not reassure them nor did it improve quality of life or psychological symptoms.[12] These findings led the American College of Gastroenterology to recommend that a positive diagnostic strategy be used, rather than a diagnosis of exclusion, for patients with IBS symptoms; this was given a strong recommendation based on high quality of evidence.[5]

Difficult Symptoms

HCPs can struggle with the diagnosis of IBS using a symptom-based approach for myriad reasons. One, as mentioned, symptoms are nonspecific. The keystone to the diagnosis of IBS is the presence of chronic abdominal pain[13] in conjunction with temporally-related altered bowel habits. However, the differential diagnosis of chronic (≥6 months in duration using Rome IV criteria) abdominal pain is quite lengthy, as are the differential diagnoses for both constipation and diarrhea (Table 1). Two, symptoms may fluctuate over time, or in response to therapy, and this can make the HCP believe that the disorder is harder to diagnose than it truly is. Three, IBS has 4 subtypes based on stool pattern—IBS-C, IBS-D, IBS with a mixed bowel pattern, and unsubtyped IBS—further adding to diagnostic complexity[14]; although there is overlap, management must be individualized based on subtype. Four, a variety of conditions can mimic or coexist with IBS. For example, lactose or fructose intolerance may be confused with IBS-D, while pelvic floor dyssynergia may be mistaken for IBS-C. Five, DGBIs frequently overlap. This means that some patients report a dizzying array of symptoms to the HCP, thus increasing their concern that an organic disorder is the root cause of the reported symptoms. However, HCPs should be reassured when patients report multiple symptoms that

are consistent with a DGBI (eg, a patient presenting with globus, reflux, early satiety, epigastric pain, postprandial nausea, bloating, lower abdominal pain, and altered bowel habits). The presence of multiple nonspecific gastrointestinal symptoms increases the pretest probability that the underlying disorder is IBS, often paired with another DGBI. For example, up to 40% of patients with IBS have overlapping functional dyspepsia (FD).[15] Six, IBS can overlap with organic disorders. This is likely a key factor for why primary care providers reach the diagnosis of IBS using a diagnosis of exclusion approach, rather than a positive diagnostic strategy. For example, patients with IBS are 6-fold more likely to have celiac disease than the general population.[15] Thus, the concern about missing a serious underlying organic disorder is valid. However, in the absence of alarm features, the diagnosis of a serious organic disorder, such as colorectal cancer, is made in only 1% of patients with IBS symptoms, and there is no increased mortality in patients with IBS.[16,17] This reinforces the concept that a careful review of symptoms, including the presence/absence of alarm features, combined with a targeted physical examination, the use of the Rome criteria, and limited diagnostic testing is an efficient and effective approach to making an accurate diagnosis of IBS.

Difficult to Explain

It seems intuitive that disorders with complex and incompletely understood pathophysiology may be difficult to explain in lay language to patients. Although DGBIs remain incompletely understood as a whole, specific pathophysiologic abnormalities have been identified for many DGBIs. For example, for FD, one of the most common DGBIs, which affects approximately 10% of the global population, impaired gastric accommodation, delayed gastric emptying, rapid gastric emptying, and abnormalities in intestinal permeability, among other causes, have been shown to contribute to symptoms.[4] Putative mechanisms in IBS similarly include changes in tight junction intestinal permeability and gut microbiota, leading to immune activation and cytokine release, which in turn drive central (ie, brain, mood) and peripheral (ie, gut) symptoms.[14] Precipitants of this cascade include insults to the gastrointestinal tract such as infection, inflammation, diet, and medications.

Such recognized pathophysiologic abnormalities can be mentioned to patients to help validate their symptoms and foster understanding, particularly as it is commonly viewed that no organic abnormalities contribute to DGBI symptoms. Beyond this, what unifies all DGBIs is the understanding that symptoms are largely the result of alterations in the gut-brain, or brain-gut, axis—hence the name disorders of *gut-brain* interaction.[18] The gut-brain axis may be perceived as an intangible and nebulous entity to some HCPs; however, it would behoove providers to learn a way in which to effectively discuss and convey this phenomenon in clear and simple terms to patients. Being able to provide a brief explanation as to how the alteration in gut-brain interaction may have occurred (eg, as a result of infection, surgery, or abuse/trauma) may provide further understanding and concordance from the patient.

Moreover, HCPs face a number of systems barriers that inherently make DGBIs more difficult to explain than traditional disease states. For one, there is evidence that gastroenterologists do not receive adequate training with respect to DGBIs. A recent survey of gastroenterology fellowship program directors found that only 22% of fellowship programs met the minimum standards for motility training according to The Gastroenterology Core Curriculum.[19] In another recent survey study of gastroenterology trainees in the United Kingdom, 39.5% of senior trainees reported being rarely comfortable making a DGBI diagnosis, and 50% of senior trainees were not comfortable initiating treatment with a neuromodulator.[20] Additionally, in a survey of gastroenterologists in the United States, the use of neuromodulators was significantly higher among providers in academic practice (odds ratio [OR], 2.6) or a DGBI-focused practice (OR, 4.8), further indicating the influence of experience in managing DGBIs.[21] A review by the Rome Foundation Working Team highlighted several important factors that can negatively influence the patient-provider relationship, including health care system constraints (ie, the decline in face-to-face interaction with patients in lieu of the electronic health record, shorter appointment times, and increased administrative tasks), all of which can further impede the ability of the HCP to adequately explain a DGBI diagnosis and connect with the patient.[22]

Difficult to Treat

Although the low-FODMAP diet can be considered as a first-line approach, particularly for IBS-D, it is important to recognize that not all patients with IBS respond to this diet. Current guidelines recommend that patients be transitioned to an alternative treatment if symptoms do not improve after a low-FODMAP diet 2- to 6-week trial.[5] Moreover, it is essential that patients who do respond to the low-FODMAP diet properly transition to the reintroduction phase of the diet to avoid restrictive eating habits and malnutrition. Importantly, a recent clinical trial suggested that the Mediterranean diet is noninferior and, in fact, may be superior to the traditional low-FODMAP diet in managing symptoms

Table 2. NNT and NNH for Common IBS Therapies[5,31-33]

Treatment	Indication	NNT[a]	NNH
Secretagogues			
Linaclotide	IBS-C	6 (5-8)	35
Plecanatide	IBS-C	10 (8-14)	59
ClC-2 agonists			
Lubiprostone	IBS-C	12.5 (8-25)	53
NHE3 inhibitors			
Tenapanor	IBS-C	8 (8-13)	16
Serotonin-4 receptor agonists			
Tegaserod	IBS-C	8-15	58
Gut-selective antibiotics			
Rifaximin	IBS-D	8-11	8791
Mixed opioid agonists/antagonists			
Eluxadoline (75 mg)	IBS-D	10-15	25
Eluxadoline (100 mg)	IBS-D	9-13	23
5-HT_3 antagonists			
Alosetron	IBS-D	6-8	14
Neuromodulators			
TCA	All subtypes	4.5-8	24
SNRI	All subtypes	NA	NA
Mirtazapine	IBS-D/IBS-M	NA	NA
Psychological therapies			
All therapies	All subtypes	4	>1000
Cognitive behavioral therapy	All subtypes	4	None
Hypnotherapy	All subtypes	5	238
Other			
Probiotics	All subtypes vs not stated	7	NA, very high
Smooth muscle antispasmodics	All subtypes vs not stated	5	22

[a]NB: Values from NNT have been extracted from varying sources, which is why some are reported as ranges.

5-HT_3, 5-hydroxytryptamine type 3; ClC-2, chloride channel 2; IBS, irritable bowel syndrome; IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; IBS-M, IBS with a mixed bowel pattern; NA, not available; NaSSA, noradrenergic and specific serotonergic antidepressant; NHE3, sodium/hydrogen exchanger isoform 3; NNH, number needed to harm; NNT, number needed to treat; SNRI, serotonin-norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant.

in patients with IBS.[23] This highlights the evolving role of diet in addressing symptoms of IBS and likely other DGBIs. Given the complexity and evolving evidence for the role of nutrition in DGBIs, collaboration with dietitians can be helpful; however, limited availability of registered dietitians is a common barrier, and patients often make these dietary changes independently.

Treatment options, particularly pharmacotherapeutic options, vary widely among different DGBIs. For example, there are 5 US Food and Drug Administration–approved

treatments for IBS-C[24]; however, for many DGBIs like FD, there are none. Thus, a lack of approved treatments for many (but not all) DGBIs serves as a common obstacle for providers, even if a confident diagnosis is made and the patient is engaged in the care plan. As an example, every recommended treatment for FD, including commonly used neuromodulators, is technically off-label, and this principle can understandably dissuade HCPs in the treatment process. Fortunately, there are high-quality studies (randomized controlled trials and meta-analyses) as well as expert consensus statements and clinical guidelines that can be referenced to guide management for many (but not all) DGBIs. That said, no DGBI treatments are universally effective owing in large part to their diverse and complex pathophysiology, as well as individualized factors (eg, psychosocial) that influence symptom manifestation. Therefore, it is imperative that HCPs be knowledgeable about different treatment options and flexible in their approach to treatment.

Another barrier to treatment of DGBIs is the fact that the therapeutic gain for many treatments is modest at best, although it is inherently difficult to demonstrate a large therapeutic gain in clinical trials involving DGBIs, as the placebo response rate in patients with DGBIs is historically high. For example, in a landmark randomized controlled trial by Talley and colleagues demonstrating the efficacy of amitriptyline to treat FD, 53% of patients experienced adequate symptom relief with amitriptyline compared with 40% of those given placebo.[25] Similarly, in the identical randomized controlled trials (TARGET 1 and TARGET 2), which demonstrated the efficacy of rifaximin to treat IBS without constipation, 40.8% and 40.6%, respectively, of patients treated with rifaximin achieved adequate symptom relief compared with 32.2% and 31.7%, respectively, of patients treated with placebo.[26] Table 2 lists the number needed to treat compared with the number needed to harm for common IBS therapies for reference.

Should a patient respond to treatment, another challenge may present if the response to treatment is partial or incomplete. In these situations, augmentation therapy, such as the addition of a second neuromodulator, or perhaps the incorporation of psychological-based therapies, such as cognitive behavioral therapy and hypnotherapy, should be considered.[27] Ideally, referral to a gastrointestinal psychologist should be considered for all patients with persistent DGBI symptoms.[28] In reality, a number of challenges hinder patient access to gastrointestinal psychologists, including a limited number of specialized providers, lack of insurance coverage, and limited appointment availability. These may be circumvented by expanding virtual or digital options and increasing the number of trained providers.

Finally, just as a lack of biomarkers poses a challenge to the diagnosis of DGBIs, the lack of biomarkers also limits the ability to reliably monitor response to treatment. Thus, in clinical practice, response to treatment is largely determined by a patient's subjective report of symptoms, which as referenced previously, can be influenced by other factors, thereby further complicating treatment.

Practical Solutions

There are simple steps to take to avoid the difficulties of IBS management. First, it is important to understand the fears and concerns of the patient and to ensure that these are adequately addressed. For example, persistent concerns that symptoms represent undiagnosed cancer may lead to a battery of unnecessary tests (which frequently does not reassure the patient, as previously noted). Two, educating the patient about IBS symptoms and disorders of the gut-brain axis may help alleviate concerns and explain why symptoms persist despite all test results being normal. Three, reassuring the patient that the natural history of IBS is benign may also resolve concerns about persistent symptoms. Letting patients know that IBS does not increase the risk of cancer nor shorten lifespan may be reassuring for some. Four, the HCP should ensure that clear language is used when discussing the diagnosis and treatment of IBS. Using imprecise or vague language may further confuse the patient as to the correct diagnosis. For example, clear language would be for the HCP to confidently tell their patient they have IBS, a disorder of the gut-brain axis, that is characterized by abdominal pain and altered bowel habits. Vague statements telling the patient it is possible they may have IBS are important to avoid. Five, patients should be reminded that although there are now many therapeutic options for the treatment of IBS symptoms, none cure IBS. Similar to other chronic disease states such as hypothyroidism, migraine headaches, and interstitial cystitis, the goal is to reduce and manage symptoms, thereby improving quality of life. Setting that expectation early on is critical and helps minimize disappointment about persistent symptoms despite reasonable therapeutic interventions. Lastly, it is important to be comfortable with a broad-minded approach to help achieve better symptom control. For many patients with IBS, a coordinated team effort involving a dietitian, a behavioral therapist, and a gastroenterologist is the key to success.[29] Integrative medicine—formally referred to as complementary and alternative medicine—is a growing field that provides a wide range of options to enhance conventional care. When conventional medicine reaches its limits, which can happen, integrative medicine restores hope by focusing on healing the whole

person. These steps can transform patient interactions from difficult to straightforward.

Conclusion

Safe, efficient, and meaningful patient care can be challenging in the current medicolegal climate where providers are constantly told to see more patients over shorter periods of time while adhering to increased documentation demands. Some, but not all, patients with IBS present with additional challenges, including symptoms that wax and wane, which can make a diagnosis elusive; multiple overlapping symptoms (eg, globus, noncardiac chest pain, and dyspeptic symptoms); symptoms that persist despite reasonable therapeutic interventions; and symptoms that continue despite normal diagnostic findings. The lack of an IBS-specific biomarker to confirm the diagnosis and provider misunderstanding of the disease state and hesitancy to confidently make the diagnosis only add to the challenges associated with caring for patients with IBS. Overcoming these challenges, however, does not have to be difficult and can be accomplished by following the series of steps outlined in this article. Providers who follow these steps will successfully improve patient care and reduce the chances of conflict.

Disclosures

The authors have no relevant conflicts of interest to disclose.

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