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Recognizing and Managing Irritable Bowel Syndrome in Quiescent Inflammatory Bowel Disease

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Patients with inflammatory bowel disease (IBD) commonly experience new or persistent gastrointestinal symptoms despite quiescent disease. These symptoms may be attributed to a wide range of etiologies, including IBD-associated complications, concomitant gastrointestinal or extra-intestinal pathologies, and medications side effects. Disorders of gut-brain interaction (DGBIs) – formerly termed functional gastrointestinal disorders (FGIDs) – can be seen in up to two thirds of patients with IBD, the most common being irritable bowel syndrome (IBS). DGBIs in IBD are often under-recognized and are associated with worse quality of life, impaired mental health, and greater healthcare utilization. In this article, we provide a systemic approach to assessing GI symptoms in quiescent IBD, and focus on the overlap and interplay between IBD and DGBIs, in particular IBS, and review management options for IBS in patients with IBD.

INTRODUCTION

Inflammatory bowel disease (IBD) encompasses a spectrum of chronic inflammatory diseases of the gastrointestinal tract, classically categorized as Crohn disease (CD) and ulcerative colitis (UC). The pathophysiology of IBD includes genetic predisposition, aberrant immunity, dysbiosis of the gut microbiota, and a disrupted intestinal epithelial barrier. Symptoms of luminal IBD reflect intestinal inflammation and include abdominal pain, diarrhea, occasional constipation, and bloody stool. In addition to extraintestinal manifestations such as arthritis, uveitis, and skin rashes, patients with IBD often report fatigue, poor sleep and particularly in CD, decreased quality of life. Treatment of IBD focuses on controlling clinical symptoms, achieving endoscopic healing, and preventing disease-related disability. Unfortunately, despite effective therapies that induce and maintain remission of the intestinal inflammation, many patients with IBD continue to experience gastrointestinal (GI) symptoms. The differential diagnosis for patients

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with ongoing symptoms while in remission is extensive (Table 1), but a significant proportion of these symptoms can be attributed to disorders of gut-brain interaction (DGBIs, formerly functional gastrointestinal disorders) including irritable bowel syndrome (IBS).

Approach to GI Symptoms in Quiescent IBD

The first step in assessing new or ongoing GI symptoms in patients with IBD is to exclude active disease. Personalized evaluation of disease activity begins by measuring inflammatory markers (C-reactive protein, fecal calprotectin), imaging [computed tomography (CT)/magnetic resonance (MR) enterography], and/or endoscopy. In addition, the presence of enteric infections, particularly *Clostridioides difficile*, should be assessed. If symptoms are due to ongoing inflammation, IBD therapy needs to be adjusted accordingly. Note that non-inflammatory structural IBD complications can lead to persistent GI symptoms, such as strictures or post-operative adhesions in CD causing abdominal pain, constipation, and bloating; ileal resection causing bile acid diarrhea; or a tubular lumen in long-standing UC causing diarrhea and fecal urgency.

The differential diagnosis of new GI symptoms in quiescent IBD is wide (Tables 1 and 2). Fortunately, a detailed history, physical examination, and targeted investigation, can help lead to a diagnosis.

Differential Diagnosis of Ongoing GI Symptoms in Quiescent IBD

Infectious Etiologies	Inflammatory Immune-mediated Intestinal Etiologies	Malabsorptive Etiologies	Dysmotility and visceral hypersensitivity due to structural/ nerve damage from prior IBD activity	Anatomic changes due to IBD	Extra-intestinal Etiologies	Disorders of gut-brain interaction
C difficile infection Viral gastroenteritis Giardiasis CMV *Campylobacter* *E. coli* *Salmonella* *Shigella* Amebiasis *Yersinia* Intestinal tuberculosis Histoplasma Coccidioides Aeromonas	Celiac disease Microscopic colitis Autoimmune enteropathy CVID enteropathy Immunotherapy induced colitis	Lactose intolerance Disaccharidase deficiency Bile acid diarrhea Small intestinal bacterial overgrowth Exocrine pancreatic insufficiency Drug-induced enteropathy	Esophageal dysmotility GERD Gastroparesis Small bowel or colonic dysmotility Decreased rectal compliance Pelvic floor dyssynergia Anorectal pain Pelvic pain and Vulvodynia	Gastrointestinal stricture Loss of ileocecal valve Tubular colonic and/or rectal lumen Post-operative or post-inflammatory adhesions Post-surgical changes	Thyroid disease Endometriosis Adenomyosis Interstitial cystitis Abdominal and pelvic tumors Carcinoid syndrome Lead poisoning Anxiety Depression Trauma Vulvodynia Vaginismus Chronic pelvic pain	IBS Centrally mediated abdominal pain syndrome Functional dyspepsia Disorders of nausea and vomiting Functional diarrhea or constipation Anorectal pain disorders Central Sensitization Syndrome

Table 1. Differential Diagnosis by Category

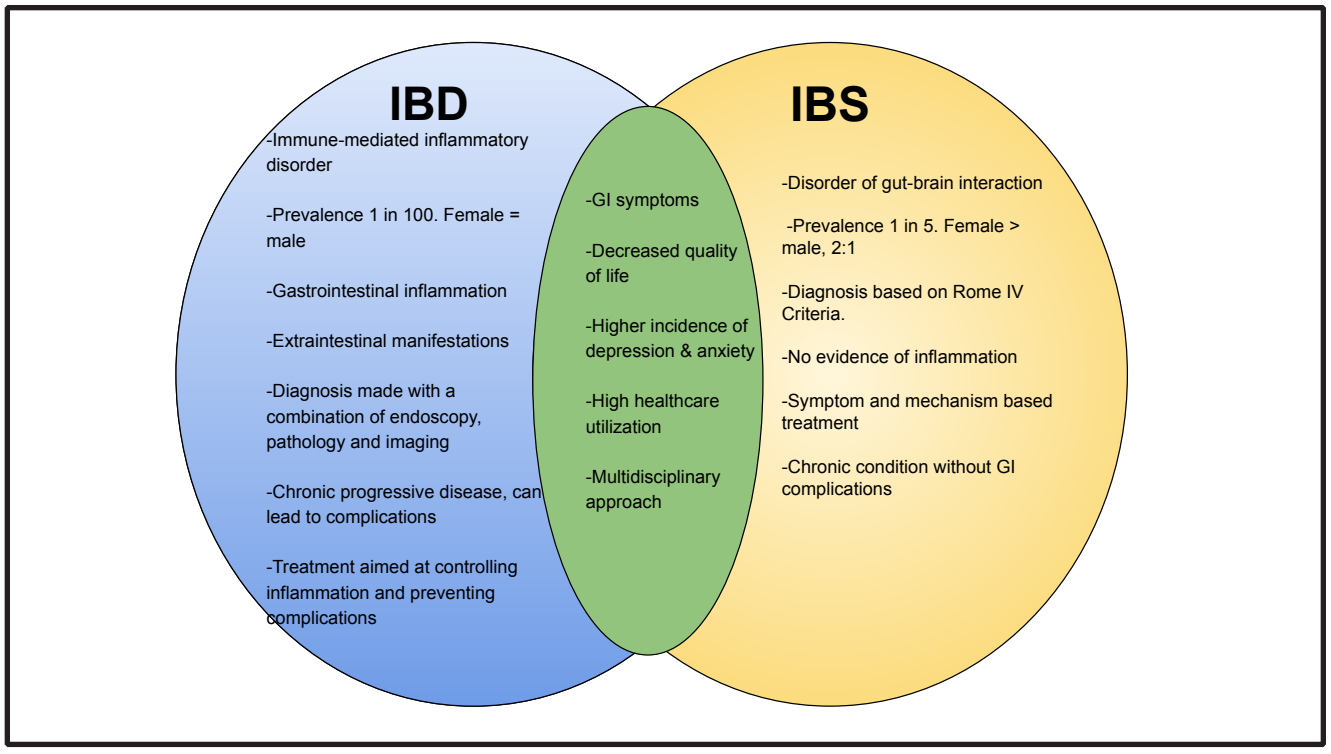

Figure 1. Comparing and Contrasting IBD and IBS

DGBIs in Patients with IBD

DGBIs comprise a group of disorders characterized by gastrointestinal symptoms related to any combination of the following: "motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and altered central nervous system (CNS) processing."[1] These include 33 adult and 20 pediatric disorders defined by symptoms as delineated by the Rome IV criteria. Risk factors for DGBIs include female sex, adverse childhood events, psychological trauma and other psychosocial stressors, enteric infection, disordered eating, and antibiotic use. Approximately two-thirds of IBD patients meet criteria for at least one DGBI, which is associated with significantly decreased quality of life, anxiety, depression, and increased healthcare utilization.[2]

The high prevalence of DGBIs in IBD may exist due to overlapping pathophysiologic features including visceral hypersensitivity, central sensitization, gut dysbiosis, small intestinal bacterial overgrowth (SIBO), abberant immune responses, and gut dysmotility. In addition, the bidirectional impact that exists between mental health and both DGBIs in IBD plays an important role in the co-existence of these two conditions (Figure 1, 2). IBS is a DGBI characterized by abdominal pain and altered bowel habits, either diarrhea or constipation predominant or mixed (Table 3). The prevalence of IBS in quiescent IBD is estimated at 39%.[3] Risk factors include younger age, female sex, antidepressant use, opioid use, anxiety, depression, somatization, IBD flares, CD (more than UC), and reported lower quality of life.[4]

Overlap of DGBIs, IBS and IBD Pathogenesis and Interplay between IBS and IBD

Visceral Hypersensitivity: A principal component of DGBIs is visceral hypersensitivity, characterized by a reduced threshold for pain even to physiologic stimuli.[5] Visceral hypersensitivity is driven by peripheral sensitization and contributors include enteric infection (postinfectious IBS), intestinal inflammation (mediated by mast cells, substance P, vasoactive intestinal peptide, and inflammatory cytokines), and trauma and psychosocial stress (mediated in part by corticotropin releasing hormone), enterochromaffin serotonin receptors, and other cell receptors/ion channels.[6] Enteric infection causes localized inflammation leading to degradation of the intestinal epithelial barrier,

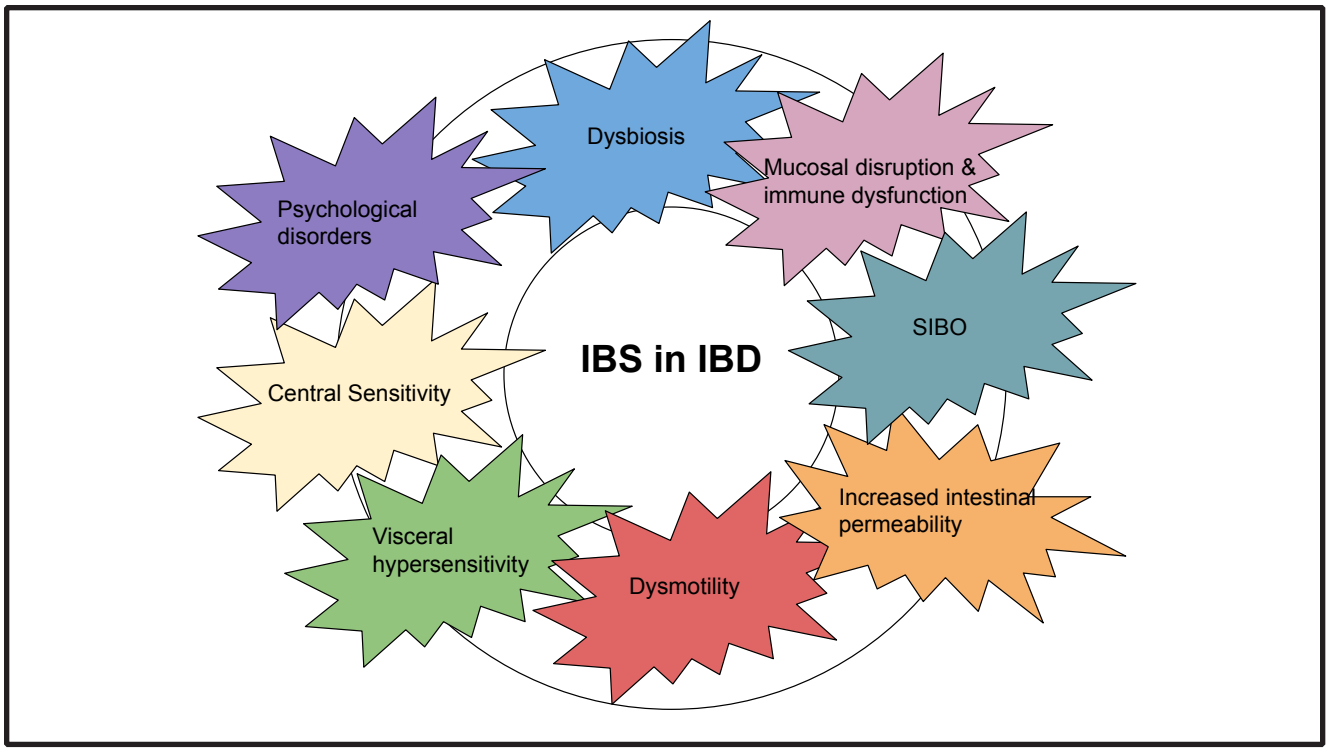

Figure 2. Shared Pathophysiologic Mechanisms in IBD and IBS

inducing loss of tolerance to dietary antigens. Subsequent exposure to these food antigens causes localized immune activation manifesting symptomatically as pain and altered bowel habits, as seen in IBS.[7] Chronic low grade inflammation has been documented in IBS, and mast cells may be an important mediator. IBD patients in remission who have IBS also have elevated density of mucosal mast cells, 5-HT and nerve growth factor compared to healthy controls and even to patients with IBS alone.[8] Transient receptor potential vanilloid type 1 (TRPV1) expression is also increased in quiescent IBD with GI symptoms. Peripheral sensitization can in part explain why patients with IBD commonly have rectal hypersensitivity (especially during disease flares), dyspepsia, esophageal pain, and pelvic and vulvovaginal pain.[9]

Central Sensitization: A related but distinct phenomenon is central sensitization, where abnormal connectivity within the brain and pain modulation system leads to widespread pain, hyperalgesia, allodynia, and hypersensitivity to noise and odors. Both patients with IBS and IBD have been shown to exhibit abnormal functional connectivity of neural networks in the brain pertaining to pain perception and emotional regulation. While central sensitization has long been heralded as a key mechanism in IBS, one study identified that central sensitization is actually a stronger contributor to GI symptoms in IBD than in IBS.[10]

Psychological Disorders: The combination of central and peripheral sensitization, as well as traumatic experiences, are thought to contribute to IBS and the multiple overlapping comorbidities, such as psychiatric illness (anxiety, depression, and somatization), but also chronic fatigue syndrome, chronic pelvic pain, and sleep disorders. While these same physical disorders are seen in patients with IBD due to their disease, psychiatric disorders are also twice as common in IBD compared with the general population. There is also evidence of a gut-to-brain bidirectional effect in IBD, where anxiety and depression increase the risk of IBD flare, severity of disease, and health care utilization, whereas a diagnosis of IBD increase the risk of developing psychiatric comorbidities in the future.[11] Anxiety and depression can affect more than half of IBD patients during times of disease flare, and

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Mimickers of Irritable Bowel Syndrome

Common Mimickers	Rare Mimickers
Celiac disease	Chronic mesenteric ischemia
Small intestinal bacterial overgrowth	Biliary disease
Microscopic colitis	Food allergies
Lactose intolerance	Acute intermittent porphyria
Pancreatic insufficiency	Carcinoid syndrome
Disaccharidase deficiencies	Lead toxicity
Enteric infections	Familial Mediterranean fever
Bile acid malabsorption	Ehlers-Danlos syndrome
Endometriosis	Mast cell activation syndrome
Thyroid disorders	Visceral angioedema

Table 2. Common and Rarer Etiologies Mimicking IBS

in a study of adults with a diagnosis of either IBD or IBS, significant post-traumatic stress was seen in 32% of those with IBD and 26% of those with IBS, highlighting the emotional impact of IBD.[12]

Gut Dysbiosis and Increased Intestinal Permeability: Dysbiosis feature prominently in both IBD and IBS, characterized broadly by a decrease in microbiome diversity and an imbalance between pro- and anti-inflammatory organisms. Though not clear if dysbiosis is a cause or effect of the underlying disease process, several studies point to dysbiosis being a key component in IBD pathogenesis. Decreased diversity of the microbiome combined with enrichment of pathogenic families and genera, such as Enterobacteriaceae and *Bacteroides*, and depletion of beneficial genera, including *Lactobacilli*, contribute to abnormal immune responses inducing increased intestinal permeability and local and systemic inflammation.[13] In turn, increased intestinal permeability may contribute to pain and diarrhea even when IBD is in remission.[14] Enteric infections are a known environmental trigger for new-onset IBD and IBD flares,[15] and up to 15% of patients develop IBS after an episode of infectious diarrhea, further highlighting the role of gut dysbiosis in both conditions. In addition, increased intestinal permeability related to dysbiosis is also seen in IBS-D and post-infectious IBS, which may contribute to visceral hypersensitivity.[6]

Small Intestinal Bacterial Overgrowth (SIBO): SIBO has a strong association with IBD (odds ratio 9.5). It has also been associated with IBS, but the extent and significance of the association is debated.[16] SIBO can cause abdominal pain, altered bowel habits, and bloating, which can all be confused with IBD or IBS symptoms. CD portends a higher likelihood of SIBO than UC, especially in patients with bowel strictures, ileocecal resection, and prior bowel surgeries. Other risk factors for SIBO in IBD include female sex, hypoalbuminemia, and longer intestinal transit times. Testing and treating for SIBO is associated with improved symptoms and outcomes in patients with IBD.[17]

Dysmotility: Dysmotility has been documented in IBS, but also in IBD from the esophagus to the anorectum, likely due to the effects of inflammatory cytokines on the enteric nervous system and structural change of gastrointestinal musculature. Dysmotility can contribute to reflux, chest pain, dyspepsia, gallstones, abdominal pain, constipation, diarrhea, rectal pain, and fecal incontinence.[18]

Diagnosis of IBS in Patients with IBD

However in otherwise healthy patients, IBS should be a positive diagnosis based on the Rome IV criteria and not a diagnosis of exclusion. The overlap of symptomatology between IBS and IBD requires that IBD patients undergo a judicious and limited work-up to exclude active IBD and mimickers of IBS (Table 2). In patients who meet the Rome IV criteria, a diagnosis of IBS should be made (Table 3).

IBS Diagnosis

IRRITABLE BOWEL SYNDROME
Diagnostic Criteria*
Recurrent abdominal pain on average at least 1 day/week in the last 3 months, associated with two or more of the following criteria:
Related to defecation
Associated with a change in frequency of stool
Associated with a change in form (appearance) of stool
* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Table 3. Rome IV Criteria for IBS

Other DGBIs in IBD

While IBS is the most common DGBI in IBD, patients with IBD may experience other or multiple DGBIs. In one study, 66% of patients with IBD met criteria for one or more DGBIs, and 34% had more than one disorder. After IBS, the most common types of DGBIs include functional dyspepsia, belching disorders, disorders of nausea and vomiting, functional diarrhea or constipation, fecal incontinence, and proctalgia fugax.[2] These are important diagnoses to consider in patients with ongoing symptoms despite quiescent IBD.

Treatment of IBS in Patients with IBD

Reassurance is paramount for management of DGBIs in IBD.[19] Patients with IBD often fear that their symptoms are reflective of ongoing IBD activity or IBD complications, including colorectal cancer. It is important to validate their symptoms, but explain that they do not reflect ongoing inflammation from IBD. Education vis-à-vis the gut-brain axis and the mechanisms of IBS symptoms can be helpful. When IBS treatment is needed for symptoms significantly affecting quality of life, therapy choice should target the patient's most pressing symptom(s) and be adjusted to the severity and combination of symptoms.

In addition to simple dietary changes, such as avoiding food triggers and ensuring adequate fluid and fiber intake, reasonable first line nonpharmacologic options for IBS include peppermint oil and probiotics. Peppermint oil (taken in an enteric coated pill formulation) has various mechanisms of action which may contribute to improving global symptoms of IBS including modulation of histaminergic and cholinergic receptors in the gut, k-opioid agonist activity, serotonergic antagonism, anti-inflammatory effects, and transient receptor potential melastatin 8 agonism. In fact, peppermint oil may be superior in efficacy to soluble fiber, antispasmodics, and neuromodulators, with a number needed to treat (NNT) of 4, and is recommended for the treatment of IBS by several GI societies.[20,21] Given its efficacy, favorable safety and tolerability profile, and low cost, it is a reasonable cost-effective first-line option for IBS in patients with IBD.

Probiotics are defined as live microorganisms which when administered in adequate amounts confer a health benefit on the host. While probiotics are commonly used by patients and prescribed by physicians for an array of gastrointestinal diseases, probiotics are not effective in treating active IBD (except for pouchitis and mild UC), but can help with IBS symptoms in patients with IBD.[22] According to a 2018 meta-analysis, probiotics are effective in treating IBS symptoms, including abdominal pain, bloating, and flatulence. Combination probiotics may be the most effective with an NNT of 7, with specific (combination of) strains being particularly effective, such as *Lactiplantibacillus plantarum299v* (DSM 9843) with a NNT of 3.[23] One must recognize however that probiotics can exacerbate GI symptoms in a subset of patients, and some preliminary studies show an association between probiotics use and "brain fog" in IBD patients.[24]

IBS Treatment Options

Abdominal Pain	Diarrhea	Constipation	Bloating
	• Bulking fiber supplements	• Fiber supplements	
• Peppermint oil (NNT 4)			• Peppermint oil
• Probiotics (NNT 7)	• Probiotics	• Probiotics	• Probiotics
• Low-FODMAP diet (NNT 5)	• Low-FODMAP diet		• Low-FODMAP diet
• Antihistamines	• Antihistamines		
• Pancreatic enzymes	• Pancreatic enzymes		• Pancreatic enzymes
		• Osmotic laxatives	
		• Magnesium salts	
		• Senna, bisacodyl	
• Antispasmodics (NNT 3-5)			• Antispasmodics
• Rifaximin (NNT 10-11)	• Rifaximin	• Rifaximin + neomycin	• Rifaximin (+/- neomycin)
	• Bile acid binders		
• TCAs (NNT 4)	• TCAs		• Amitriptyline (TCA)
• SSRIs (NNT 5)			• Escitalopram, citalopram (SSRI)
• SNRIs			
• Atypical antidepressants (bupropion, mirtazapine)			• Buspirone (partial 5HT1a agonist)
• Antipsychotics			
• Pregabalin, gabapentin			
• Secretagogues: lubiprostone, linaclotide, plecanatide	• Alosetron (NNT 7)	• Linaclotide (NNT 3.7-8.9)	*If associated with constipation, secretagogues and 5HT modulators improve bloating*
• Mimed mu opioid receptor agonists/ antagonists: eluxadoline	• Eluxadoline (NNT 13)	• Plecanatide	
		• Lubiprostone (NNT 12.5)	
• Serotonin modulators: alosetron, tegaserod		• Tegaserod (NNT 14-17)	
		• Prucalopride	
• Cognitive behavioral therapy (NNT 4-6)	• Cognitive behavioral therapy (NNT 4-6)	• Cognitive behavioral therapy (NNT 4-6)	• Cognitive behavioral therapy (NNT 4-6)
• Gut-directed hypnosis	• Gut-directed hypnosis	• Gut-directed hypnosis	• Gut-directed hypnosis

Table 4. Symptom-Based Treatment Options for IBS

Dietary modification is one of the mainstays of IBS management. The most well studied dietary intervention in IBS is the low-FODMAP diet (LFD). In patients with IBS, fermentable oligo-, di-, monosaccharides and polyols (FODMAPs), which are poorly digested short-chain carbohydrates, contribute to IBS symptoms via induction of dysbiosis, fermentation, and osmotic potential within the lumen. The LFD consists of three parts: elimination of FODMAPs, gradual reintroduction of FODMAPs (to identify trigger foods), and personalization (to maximize liberalization of the diet as tolerated).[25] Studies have consistently demonstrated efficacy of the LFD in alleviating symptoms of IBS in patients with quiescent IBD.[26] Due to the restrictive nature of the LFD and related concerns about effects on the gut microbiota, potential to promote disordered eating patterns leading to increased risk of malnutrition and social isolation in an at-risk population, there is interest in exploring more liberal diets in the treatment of IBS. The Mediterranean Diet (MD), characterized by a diet rich in fruits, vegetables, legumes, nuts, seeds, whole grains, oily fish, olive oil, and red wine and low on red meat and processed foods, has shown benefit in IBS and was recently shown to be well tolerated and to improve overall GI symptoms in patients with CD.[27] With any dietary therapy and intervention, it is recommended to involve a specialized dietician to educate the patient about the diet, choose foods that are tolerated by the patient with IBD, design meals that align with the patient culture, taste and lifestyle and ensure adequate and balanced nutrient intake.

There are various pharmacologic options for the management of IBS as outlined in Table 4. Therapy should be chosen to address the predominant symptom(s).[28,29,30] In patients with abdominal pain, bloating, and diarrhea, a trial of antibiotics for SIBO should be considered after testing or in the presence of predisposing anatomic factors; pancreatic enzymes can also be effective in the management of these symptoms, as exocrine pancreatic insufficiency can co-exist with IBD. Fiber supplements can be used both as bulking agent in patients with diarrhea or to treat constipation (unless symptoms are due to a CD stricture, in which case the amount and type of fiber should be carefully assessed). The judicious use of neuromodulators can treat IBS symptoms as well as associated non-GI disorders: bupropion is a good option for a patient with CD and abdominal pain, depression, or anxiety, who is attempting smoking cessation, while tricyclic antidepressants can treat abdominal pain, diarrhea, and sleep disturbances.

Several psychological interventions from simple measures including routine exercise, sleep hygiene, stress reduction, and social support, to professional techniques such as mindfulness techniques, cognitive behavioral therapy, and gut-directed hypnotherapy can benefit IBS symptoms in patients with IBD. Early referral to a psychotherapist and psychiatrist should be made in patients with concomitant anxiety, depression, somatization, or trauma.

CONCLUSION

New onset or persistent GI symptoms are common in quiescent IBD. Etiologies include immune-mediated/inflammatory, infectious, malabsorptive, anatomic, dysmotility, and extra-intestinal causes. After appropriate exclusion of active IBD and IBD-related complications, a limited workup guided by a comprehensive history often leads to the diagnosis. DGBIs, particularly IBS, are common in patients with IBD and should be appropriately recognized and treated. IBS should be treated based on the predominant symptom(s) and underlying predisposing factors, and with a multidisciplinary team. It is important however to recognize that patients with quiescent IBD often have persistent GI symptoms secondary to several concomitant and overlapping etiologies and require a multifaceted approach to control their symptoms and improve their quality of life. ■

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