REVIEW

A Narrative Review of Irritable Bowel Syndrome with Diarrhea: A Primer for Primary Care Providers

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ABSTRACT

Irritable bowel syndrome with diarrhea (IBS-D) is a chronic disorder of gut–brain interaction, characterized by recurrent abdominal pain in association with more frequent, loose stools. The pathophysiology of irritable bowel syndrome (IBS) includes disordered gut motility, alterations in gut microbiota, neural-hormonal system abnormalities, immune reactivity, and visceral hypersensitivity. Timely diagnosis of IBS-D can be achieved easily using clinical criteria. Formal IBS diagnosis is important for optimizing treatment and patient outcomes and facilitating patient access to appropriate educational resources. Yet, given the symptom overlap with other gastrointestinal conditions, diagnosis of IBS-D often is perceived to be challenging. Treatment of IBS includes both nonpharmacologic and pharmacologic options. Rifaximin, alosetron, and eluxadoline are effective treatments indicated for IBS-D, but have limited availability internationally. Dietary approaches may also be indicated for certain patients with IBS-D. Psychological interventions may be effective in treating abdominal pain alone and global symptoms in IBS. We describe use of these diverse therapies and provide an overview to facilitate the primary care provider's approach to distinguishing IBS-D from other conditions with symptom overlap.

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Key Summary Points

Irritable bowel syndrome (IBS) is a commonly encountered disorder of gut–brain interactions characterized by recurrent abdominal pain and altered defecation

Symptoms of IBS with diarrhea (IBS-D) overlap with other conditions frequently encountered by primary care providers

Diagnosis of IBS-D relies primarily on symptom-based criteria, with the addition of minimal fecal and serologic testing to increase confidence in diagnosis

IBS-D management strategies involve nonpharmacologic and pharmacologic therapies

INTRODUCTION

Gastrointestinal (GI) symptoms have been associated with approximately 40.7 million US ambulatory visits (2014), with abdominal pain (21.8 million) and diarrhea (3.4 million) the symptoms most commonly reported [1]. Total expenses associated with abdominal pain were $10.2 billion in 2015, driven primarily by inpatient hospitalizations (77.9%) and diagnostic testing [1]. According to Rome IV diagnostic criteria, irritable bowel syndrome (IBS) is characterized by recurrent abdominal pain and changes in stool form and/or frequency [2, 3]. It is classified further by bowel habits (based on Rome IV criteria): IBS with constipation (IBS-C; 28.5%), with diarrhea (IBS-D; 35.0%), or with mixed bowel habits (IBS-M; 31.0%) [2]. The US prevalence of IBS has been estimated to range from 4.8% to 5.3%, versus 0.7% for celiac disease and 0.5% for inflammatory bowel disease (IBD) [4–7]. Optimal diagnostic and therapeutic strategies for IBS management consider the predominant symptoms (i.e., pain, discomfort, bloating) and the predominant bowel habit

(i.e., diarrhea, constipation, or mixed) [8]. Accordingly, approaches for each IBS subtype may vary considerably. This review focuses on diagnosis and treatment of patients with diarrhea-predominant IBS, with an emphasis on US gastroenterology guidelines. However, when appropriate, attempts were made to highlight contrasting recommendations for European society guidelines. This review is based on previously conducted studies and does not contain any new data from human or animal studies conducted by any of the authors.

PATHOPHYSIOLOGY

IBS-D is a chronic disorder of gut–brain interaction (previously regarded as functional bowel disorders) for which a distinct isolated structural pathology is not identified [3]. It is a heterogeneous condition with a multifactorial, evolving pathophysiology that includes alterations in visceral sensitivity, gut microbial changes, increased intestinal epithelial permeability, disrupted motility, and immune and neural-hormonal system involvement [3, 9–15]. GI-related infections can predispose to development of postinfectious IBS [16], a distinct condition in which IBS diagnostic criteria are met. Postinfectious IBS occurs after resolution of a GI-related infection (e.g., *Campylobacter jejuni*, *Salmonella*) without a prior history of IBS symptoms [8, 17–19].

Clinical pearl: *IBS-D is a heterogenous condition with multifactorial etiologies.*

Diagnosis of IBS

The evaluation of a patient with suspected IBS includes a detailed medical history and physical examination [2]. Rome IV criteria facilitate a confident IBS diagnosis based on the presence and/or history of abdominal symptoms (i.e., pain, discomfort, bloating), commonly occurring in the lower abdomen, and altered bowel habits in the absence of alarm symptoms [2]. The American College of Gastroenterology (ACG) guideline for IBS management strongly recommends a positive IBS diagnostic strategy, rather than a diagnosis of exclusion, to improve

patient care and decrease health care costs [20]. The Bristol Stool Scale helps identify the most frequent stool consistency experienced by patients and aids in choosing subsequent treatment for the predominant bowel pattern [20]. Limited laboratory testing, such as measurement of C-reactive protein (CRP) and fecal calprotectin or fecal lactoferrin levels, is recommended to exclude IBD [20]. The rapidly obtained CRP may be more useful than fecal analyses, which are more challenging to collect. Finally, psychological markers (e.g., patient health questionnaire-15 score, anxiety and depression components of the Hospital Anxiety and Depression Scale) may have some utility for diagnosing IBS [21].

A prospective trial of patients with symptoms suggestive of IBS found that GI referral for colonoscopy is only warranted for patients with alarm symptoms and, as appropriate, for colon cancer screening (age 45 years or more to 75 years; Fig. 1) [8, 20, 22]. The diagnostic yield of colonoscopy for organic disease (i.e., colon cancer, IBD, microscopic colitis) was greater in patients with IBS-D than in patients with IBS-C and IBS-M [23]. In all cases, the pathologic findings were associated with red flag features, including unintended weight loss, recent antibiotic use, and hematochezia (Fig. 1) [8, 20, 22]. Referral to a gastroenterologist may occur at the patient's request, usually when the patient fails treatment, when symptoms are severe, or when a diagnosis cannot easily be established [24].

COMORBID DISORDERS: TESTING TO EXCLUDE IBS

Comorbid conditions are common in patients with IBS and can include anxiety and depression, chronic fatigue, fibromyalgia, and sleep disorders [25, 26]. Awareness of comorbidities may help guide management decisions and may lead to a multidisciplinary approach to best address all physical and psychological comorbidities [26]. Establishing a diagnosis of IBS-D is important for patient reassurance and to minimize undue cost to the patient or health care system [26]. Given the symptom overlap between IBS-D and other disorders often encountered in primary care practices, consideration of other conditions can guide clinicians (Table 1) [20, 27–39].

Other Diagnoses That May Mimic IBS-D

Celiac Disease
Celiac disease presents with diarrhea, abdominal pain, and bloating [20, 30]. Celiac disease is found in 1.1% of patients with IBS in the US [40]. Serologic testing for celiac disease with
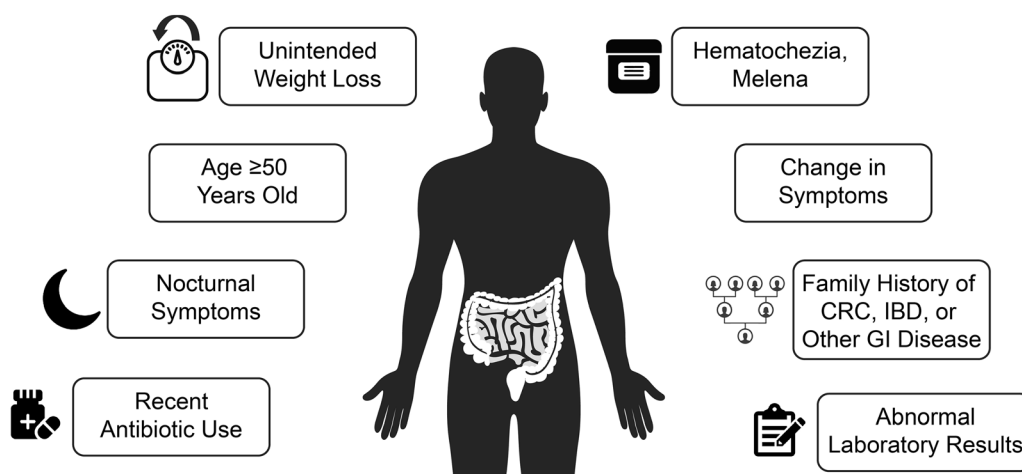
Fig. 1 Alarm features warranting colonoscopy [8, 20]. *CRC* colorectal cancer, *GI* gastrointestinal, *IBD* inflammatory bowel disease

Table 1 Differential diagnosis of IBS-D

Condition	Clinical features	How to diagnose
Bile-acid malabsorption [27]	Causes include ileal dysfunction, presence of comorbid GI disorders (e.g., celiac disease, chronic pancreatitis), bile-acid malabsorption, and idiopathic bile acid diarrhea Abdominal symptoms less prominent	Empiric treatment with bile-acid sequestrants (not recommended by ACG) Quantification of fecal bile acids Serum C4 SeHCAT (nuclear medicine technique)
Carbohydrate intolerance [28, 29]	Lactose/fructose/sucrose intolerance (congenital or hereditary) Common in pts with IBS or with SID (congenital or hereditary)	Elimination of dairy from diet to determine if IBS symptoms decrease Enzyme immunoassay for carbohydrate malabsorption Genetic testing for congenital SID rarely performed (usually in pediatric patients) Breath testing not recommended unless prior results were unclear and pts request testing
Celiac disease [30, 31]	Immune-mediated (malabsorption and/or immune activation); symptoms are associated with dietary gluten consumption and overlap with IBS	Serologic testing TTG antibodies Total IgA levels (when IgA deficiency is suspected) Deamidated gliadin IgG testing for pts with low or deficient IgA Duodenal biopsies when serologic testing is negative and celiac disease is strongly suspected
Food allergy [20, 32–34]	Immune-mediated; temporal relationship with food exposure	Routine testing is not recommended for pts with IBS Do not perform IgE or IgG testing Angioedema—symptoms of swelling and shortness of breath—refer to allergist
IBD [20, 35–37]	Crohn's disease Can occur throughout the GI tract Extraintestinal symptoms (fatigue, arthralgias, skin manifestations, weight loss, eye involvement) are common Severe diarrhea, often with bleeding Intermittent "skip" ulcers Ulcerative colitis Rectum involvement, contiguous colitis Rectal bleeding, abdominal pain, and tenesmus are not common	CRP $\leq$ 0.5 mg/dL makes a diagnosis of IBD less probable Fecal calprotectin level < 40 µg/g makes a diagnosis of IBD less probable (pts have a $\leq$ 1% chance of having IBD) Increased chance of IBD with the rise in fecal calprotectin levels (at 1000 µg/g, maximum predictive value 78.7%) Fecal lactoferrin levels between 4.0 µg/g and 7.25 µg/g are recommended to optimize sensitivity of IBD testing Colonoscopy for patients $\geq$ 45 years of age, and to rule out microscopic colitis

Table 1 continued

Condition	Clinical features	How to diagnose
Pelvic floor disorders [38]	Dyssynergia characterized by increased anal contraction	Digital rectal exam (paradoxical contraction, weak sphincter with incontinence)
	Symptoms of incomplete evacuation, straining, prolonged toileting	Anorectal manometry testing
		Balloon expulsion test (confirmatory for impaired evacuation)
	Predominantly constipated, overflow diarrhea	
	Distinguish diarrhea from fecal incontinence	Defecography
SIBO [39]	Excessive bacteria levels in the small intestine	Glucose or lactulose hydrogen breath testing used for diagnosing
	Associated gas-bloat symptoms	
		Small bowel aspirations (invasive and done by endoscopy)—gold standard
		Empiric trial of antibiotics

ACG American College of Gastroenterology, *CRP* C-reactive protein, *GI* gastrointestinal, *IBD* inflammatory bowel disease, *IBS* irritable bowel syndrome, *IBS-D* irritable bowel syndrome with diarrhea, *pt* patient, *SeHCAT* selenium homocholic acid taurine, *SIBO* small intestinal bacterial overgrowth, *SID* sucrase-isomaltase deficiency, *TTG* tissue transglutaminase

both serum IgA and tissue transglutaminase (TTG) should be conducted in patients with IBS-D symptoms, as a small percentage of patients with celiac disease are IgA deficient and could have a false negative TTG test result [31]. If IgA deficiency is found, follow-up testing should be performed with deaminated gliadin IgG antibodies; in some cases, an upper endoscopy and duodenal biopsies may be warranted [31] (Table 1).

IBD

Symptoms of IBS-D and IBD overlap, making it difficult to distinguish between the two conditions [41]. Blood CRP levels and fecal testing (i.e., calprotectin, lactoferrin) can be considered to exclude an IBD diagnosis (Table 1) [20, 35, 36].

Clinical pearl: Celiac disease and IBD should be considered in the differential diagnosis for IBS-D, and celiac antibody testing and inflammatory marker testing (CRP, fecal calprotectin/lactoferrin) are recommended to rule out the former.

Food Allergy Should Not Be Considered in IBS-D

Food contents can lead to GI symptoms (e.g., abdominal pain, bloating), which may, in part, be related to a local immune response to food antigens (i.e., gluten, milk, soy, wheat) [34]. Food allergies are estimated to affect 2.5% of the US population [42] and are a rapid (i.e., within several minutes), systemic, immune-mediated reaction to food (Table 1) [32–34]. Referral to a board-certified allergist is recommended for patients with obvious allergic reactions (i.e., angioedema, rash) [32]. The ACG guideline for IBS management does not recommend testing for food allergies in patients with IBS unless there is reproducible symptomatology suggesting a possible food allergy, given that current tests for food allergies have not been validated or standardized [20].

Carbohydrate Intolerances

Intolerances to carbohydrates, such as lactose and sucrose, can cause diarrhea [28, 29] and can be ruled out by food elimination trials or, if not confirmatory, by breath testing. Lactose intolerance is a common condition that may be misdiagnosed as IBS, given the similarity in symptoms (e.g., diarrhea, flatulence; Table 1) [28]. After consuming a lactose-free diet for 1 month, patients with IBS and lactose intolerance experienced a decrease from baseline in

both IBS and lactose malabsorption symptom severity scale scores [28]. Sucrase-isomaltase (SI) deficiency also can cause symptoms of abdominal pain, bloating, and diarrhea [29], and *SI* gene variants have been associated with IBS in some patients [43, 44]. However, the prevalence of SI deficiency in IBS has not been determined [29].

Pelvic Floor Disorders

Dyssynergia is a defecatory disorder characterized by increased anal sphincter pressure (i.e., anal contraction; Table 1) for which biofeedback—using visual or auditory cues to improve muscle control—is efficacious [38, 45]. It is important to ascertain whether the patient has intermittent constipation or solid stools, in which case, diarrhea may reflect an "overflow" phenomenon. Diarrheal symptoms also may overlap with weak sphincter tone and fecal incontinence, as well as a structural abnormality (e.g., rectocele) [46]. The ACG guideline for IBS management suggests that anorectal physiology testing be performed in patients with IBS and symptoms of pelvic floor disorder, despite limited data supporting this testing [20].

Bile-Acid Malabsorption

Diarrhea is the primary symptom of bile-acid malabsorption [47], occurring when bile acids are not reabsorbed in the small intestine, such as with conditions causing bile-acid malabsorption (e.g., cholecystectomy, terminal ileal resection, radiation) or primary bile-acid diarrhea [27]. Bile-acid testing (i.e., fasting serum C4, fasting serum FGF19) is limited in the USA [20]; empiric treatment with bile-acid sequestrants can provide diagnostic insight but is not currently recommended by the ACG given the relative paucity of data currently supporting this approach (Table 1). However, in contrast, British Society of Gastroenterology (BSG) guidelines recommend that patients with symptoms of IBS-D with atypical features (e.g., prior cholecystectomy) undergo bile-acid testing to exclude bile-acid diarrhea [24].

Small Intestinal Bacterial Overgrowth

Prevalence of small intestinal bacterial overgrowth (SIBO) has been estimated at 38% in patients with IBS [48]. SIBO has several symptoms that overlap with IBS-D and the other IBS subtypes. In patients suspected to have SIBO (e.g., with prior abdominal surgery or systemic illnesses predisposed to development of SIBO), SIBO may be diagnosed via breath testing utilizing carbohydrate substrates (e.g., glucose, lactulose) [49]. Breath samples are collected from patients following an overnight fast and ingestion of a carbohydrate substrate to detect hydrogen and methane levels over a specific time period [49]. However, given the lack of standardization across breath tests (e.g., substrate dosing, test duration) and high false-positive rates, interpretation of findings is not straightforward and breath testing is not recommended for IBS-D [49].

PATIENT–PROVIDER RELATIONSHIP

Both the BSG and ACG guidelines emphasize the important role of a strong provider–patient relationship in effective management of IBS, highlighting its positive effects on patient treatment adherence, quality of life, and symptoms [20, 24]. Foundational elements of this relationship include clear communication, practical support, and compassion [24].

DIETARY INTERVENTIONS

Best practice guidance from the American Gastroenterological Association (AGA) is to give dietary advice to patients with IBS who have reported onset or worsening of GI symptoms (e.g., abdominal pain, altered bowel habits, bloating) after a meal [50]. The BSG recommends that providers offer dietary advice to all patients with IBS [24]. Further, survey data from patients with IBS in the Netherlands have indicated a preference for dietary interventions as first-line therapy compared with pharmacologic treatments [51].

Elimination Diets

Up to two-thirds of patients believe that diet plays a role in their IBS symptoms [52], and approximately one-third to two-thirds of patients have reported managing IBS symptoms with dietary modification [53]. Fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs) were significantly associated with bloating in patients with IBS-D [54], and elimination of FODMAPs has led to improvement in global IBS symptoms [55]. Elimination diets involve withholding various foods for a short amount of time (i.e., days to weeks), rather than permanently. The ACG guideline for IBS management recommends a limited trial of a low FODMAP diet to evaluate improvement in global IBS symptoms, and this is the only diet endorsed by the ACG guideline committee (Table 2) [20, 24, 56]. The BSG recommends the low FODMAP diet as second-line therapy, with supervision from a trained dietician [24].

Although gluten-containing foods have been associated with diarrhea, abdominal cramping, and bloating, a gluten-free diet is not routinely recommended in the absence of celiac disease, and food containing glutens (e.g., wheat-based foodstuffs) often contain fructans, a FODMAP constituent [24, 57].

High Fiber Therapy in IBS

Survey data have indicated that 69.6% of primary care providers and gastroenterologists (n = 302) have recommended fiber supplementation to patients with IBS-D, although only 41.3% of patients reported being somewhat or very satisfied with this treatment [58]. The ACG guideline for IBS management strongly recommends soluble (e.g., barley, beans, oat bran, psyllium) rather than insoluble (e.g., wheat bran, whole grains, some vegetables) fiber for the treatment of global IBS symptoms, though the former class of agents may increase the incidence of bloating (Table 2) [20].

Probiotics, Prebiotics, and Synbiotics

A meta-analysis of 21 randomized, controlled studies of IBS (n = 1931 patients) has reported that combination probiotics significantly reduced IBS symptoms versus placebo (RR 0.8; 95% CI 0.7–0.9) [59]. The 2021 BSG guidelines recommend a trial of probiotics for up to 12 weeks, with discontinuation if no symptom improvement is observed [24]. Data for prebiotics (substrates selectively used by microorganisms [e.g., oligosaccharides] [60]) and synbiotics (combination of prebiotics and probiotics [61]) in IBS are limited, with a meta-analysis of prebiotics (n = 3 studies) and synbiotics (n = 2 studies) finding no benefit of either for reducing IBS symptoms [59]. Whether more-targeted probiotic therapy will be beneficial in treating all IBS subtypes remains to be seen. The 2021 ACG guideline for IBS management recommends against the use of probiotics for global IBS symptoms (Table 2) on the basis of inconsistencies in the types and strains of probiotics evaluated, heterogeneity among studies, and lack of studies examining US Food and Drug Administration (FDA) efficacy outcomes for IBS [20, 24].

Herbal/Supplement Therapies

Peppermint oil is an over-the-counter herbal therapy that has proven antispasmodic properties [62, 63]. A 2019 meta-analysis reported that enteric-coated peppermint oil improved global IBS symptoms (n = 7 studies; RR 2.4; 95% CI 1.9–3.0) and abdominal pain as compared with placebo (n = 6 studies; RR 1.8; 95% CI 1.4–2.2) [63]. The ACG guideline for IBS management suggests the use of peppermint oil for relief of global IBS symptoms on the basis of a low quality of evidence [20]. A randomized, double-blind, placebo-controlled trial of patients with postinfectious IBS-D with increased GI permeability showed that orally administered glutamine powder 5 g three times daily (n = 54) had 14-fold greater efficacy for improving the Irritable Bowel Syndrome Symptom Severity Scale scores from baseline versus placebo (n = 52) after 8 weeks of treatment (79.6% vs

Table 2 Summary of practice do's and don'ts [20, 24]

Infectious diarrhea suspected		
Postinfectious IBS	✓	Perform fecal immunoassay or PCR-based testing in pts at risk for giardiasis
	–	Visited area at risk or exposured to *Giardia*
	–	Swallowing water from recreational area
	x	Do not perform complete viral, parasitic, or bacterial panel in all pts with chronic diarrhea
	x	Do not perform routine stool testing in pts with IBS
Clostridioides difficile infection	✓	Confirm if pts were recently hospitalized or institutionalized, or had long-term care facility stay
	✓	Confirm if pts had recent antibiotic use
	✓	Test pts with symptoms indicating CDI (≥ 3 unformed stools in 24 h)
	x	Do not perform testing in pts with formed stools
Management of IBS		
Nonpharmacologic interventions		
Exercise	✓	Advise pts to participate in regular exercise activities
Dietary interventions	✓	Offer all pts dietary advice
	✓	Consider limited trial of dietician-guided low FODMAP diet
	✓	Recommend soluble fiber (e.g., barley, beans, oat bran, psyllium) for global IBS symptoms in IBS-D
	✓	Discuss fructan content in gluten-containing foods (may be source of perceived gluten-free benefits)
	x	Do not routinely recommend gluten-free diet to pts
	x	Do not use in pts at risk of developing eating disorders
Psychological/behavioral therapies	✓	Recognize that psychological approaches have good evidence for use and may be as effective as standard therapy
	✓	Consider use in combination with pharmacotherapies
	x	Do not imply that IBS-D symptoms are psychological in origin
Probiotics/prebiotics	✓	Adhere to better-studied preparations containing *Lactobacillus plantarum*, *Bifidobacterium*, *Streptococcus faecium*, or *Escherichia coli* DSM 17252
	✓	Recognize the potential for durable benefit with prebiotic strategies (e.g., oligosaccharides)
	✓	Discuss costs with patients—usually not covered by prescription coverage plans
	x	Do not presume that all probiotic preparations are created equally

Table 2 continued

Peppermint oil	✓	Discuss potential for improvement in overall IBS symptoms
	✓	Recognize dyspepsia and heartburn symptoms as potential side effects
	✓	Consider triple-coated peppermint as a better-studied option
	x	Do not assume equal efficacy with all commercially available peppermint preparations
Pharmacologic interventions		
Antidiarrheal agents (diphenoxylate/atropine, loperamide)	✓	Use for intermittent, as-needed control of diarrhea symptoms
	✓	Advise pts that these agents may induce constipation
	x	Do not use diphenoxylate/atropine or loperamide as maintenance therapy
Bile-acid sequestrants	✓	Consider as alternate antidiarrheal agent
	x	Do not use for first-line treatment of IBS-D
	x	Do not take at the same time as other medications (may bind and inactivate other drugs [56])
Rifaximin	✓	Prescribe for the treatment of global IBS-D symptoms
	✓	Consider retreatment up to 2 times with symptom recurrence
Alosetron	✓	Consider as treatment for women with severe IBS-D symptoms who have failed conventional therapy
Eluxadoline	✓	Prescribe in appropriate pt population for treatment of global IBS-D symptoms
	x	Do not use in pts who are postcholecystectomy, or those who have histories of pancreatobiliary disease (pancreatitis, sphincter of Oddi dysfunction) or excess alcohol consumption (contraindicated)
Antispasmodics (e.g., dicyclomine)	✓	Discuss anticholinergic adverse effects, which are common
	x	Do not expect impact on global IBS symptoms; primarily effective on diarrhea
Neuromodulators— antidepressants (e.g., TCAs)	✓	Start at low dose and titrate slowly
	✓	Discuss anticholinergic adverse effects, which are common
	✓	Consider SNRIs when adverse effects are limiting
	x	Do not expect rapid response; IBS-D symptoms respond gradually over weeks of use

CDI Clostridioides difficile infection, *FODMAP* fermentable oligo-, di-, and monosaccharides and polyols, *IBS* irritable bowel syndrome, *IBS-D* irritable bowel syndrome with diarrhea, *PCR* polymerase chain reaction, *pt* patient, *SNRI* serotonin-norepinephrine reuptake inhibitor, *TCA* tricyclic antidepressant

5.8%, respectively; $P < 0.0001$) [64]. Further, patients receiving glutamine experienced significant improvements in daily bowel movement frequency and stool form and normalization of intestinal permeability versus placebo ($P < 0.0001$ for all comparisons) [64].

ANTIDIARRHEAL AGENTS

Over-the-counter loperamide is not recommended as first-line treatment for patients with IBS-D, as it is ineffective for improving global

IBS symptoms and abdominal pain [20, 65], but it can be considered for intermittent use to control diarrheal symptoms as needed. Diphenoxylate/atropine, a prescription antidiarrheal agent, has been shown to significantly decrease stool frequency and weight in patients with chronic diarrhea and fecal incontinence versus placebo after 3 days ($P < 0.02$ and $P < 0.001$, respectively) [66, 67].

FDA-APPROVED THERAPIES FOR IBS-D

Rifaximin

Rifaximin is a nonsystemic antibiotic indicated for the treatment of adults with IBS-D and is administered as short-course therapy (one 550-mg tablet three times daily for 2 weeks) [68]. Patients may receive up to two additional rifaximin courses for symptom recurrence [68]. In two randomized, double-blind, clinical studies of patients with nonconstipation IBS ($n = 1260$), a significantly larger percentage of patients treated with rifaximin 550 mg three times daily for 2 weeks had adequate relief of global IBS symptoms versus placebo for at least two of the first 4 weeks post-treatment (40.7% vs 31.7%, respectively [pooled]; $P < 0.001$) [69].

In a repeat treatment trial, 44.1% of 2579 patients were open-label responders to rifaximin (patients with at least a 30% decrease from baseline in abdominal pain, plus at least a 50% reduction in frequency of loose stools for at least two of the first 4 weeks post-treatment) [70]. Initial responders with symptom recurrence entered a randomized, double-blind, placebo-controlled repeat treatment phase, wherein a significantly higher percentage of responders were observed with rifaximin ($n = 328$) versus placebo ($n = 308$) for 2 weeks (38.1% vs 31.5%, respectively; $P = 0.03$) [70]. Across all studies, rifaximin exhibited a favorable safety profile, with adverse events (AEs) comparable to those reported with placebo, including incidence of *C. Clostridioides difficile* colitis [69, 70]. The ACG guideline for IBS management recommends rifaximin for the treatment of global IBS-D symptoms [20];

however, rifaximin is not a guideline recommendation for treatment of IBS-D in some countries [24].

Alosetron

The selective serotonin (5-HT$_3$) receptor antagonist alosetron is approved at a dose of 0.5 to 1.0 mg twice daily for the treatment of women with severe IBS-D with chronic (at least 6 months) IBS symptoms and a lack of adequate response to conventional therapy, under a modified risk evaluation and mitigation strategy program [71–73]. A systematic review reported that alosetron improved global IBS symptoms versus control treatment (three studies; RR 1.6; 95% CI 1.4–1.8), including improved abdominal pain/discomfort (eight studies; RR 1.24; 95% CI 1.2–1.3) [74]. However, AEs of ischemic colitis and complications of constipation, though rare, have occurred with alosetron [75]. Alosetron is an effective treatment for the relief of global IBS-D symptoms in women with moderate to severe IBS-D symptoms for whom conventional treatment has failed; however, access to this medication may be limited in the USA and other countries, related to the indication and risk evaluation and mitigation strategy program [71–73].

Eluxadoline

Eluxadoline is a peripherally acting mixed mu- and kappa-opioid receptor agonist/delta-opioid receptor antagonist indicated for the treatment of adults with IBS-D [76, 77]. Recommended eluxadoline dosing is 75–100 mg bid, taken with food [76]. In two randomized, double-blind, placebo-controlled trials of patients with IBS-D, eluxadoline 100 mg bid ($n = 809$) for up to 6 months resulted in a significantly greater percentage of patients achieving a decrease from baseline of at least 30% in the daily average worst abdominal pain for at least 50% of days and, on the same days, a stool consistency score less than 5 (score range, 1 [hard stool] to 7 [watery diarrhea]) versus placebo ($n = 808$; 31.0% vs 19.5%, respectively [pooled]; $P < 0.001$) [77]. The most common AEs in two

Table 3 Summary of efficacy and safety of therapies used for the management of IBS-D

Therapy	NNT	NNH
Pharmacologic therapies		
Antidepressants	4.5	8.5[a]
TCAs [20, 78]	4.5 and 8	9[a] and 18[b]
Alosetron [20, 78]	7.5	10[a] and 19[b]
Antispasmodics [79]		
Dicyclomine	4	NA
Hyoscine	3	NA
Eluxadoline [20]	75 mg: 10–14	75 mg: 25[b]
	100 mg: 9–10	100 mg: 23[b]
Rifaximin [20, 78]	9	8971[b]
	11	
Nonprescription therapies		
Cognitive behavioral therapy [20]	4	NA
Low FODMAP diet [79]	5	NA
Peppermint oil [20]	3 (overall IBS symptoms)	NA
	4 (abdominal pain)	
Probiotics [59, 80]	7	35[a]

NNT and NNH are provided for therapies with data available

AE adverse event, *FODMAP* fermentable oligo-, di-, and monosaccharides and polyols, *IBS-D* irritable bowel syndrome with diarrhea, *NA* not available, *NNH* number needed to harm, *NNT* number needed to treat, *TCA* tricyclic antidepressant

[a]NNH based on experiencing an AE

[b]NNH based on discontinuation due to an AE

clinical trials of eluxadoline 100 mg versus placebo were constipation (8.6% vs 2.5%, respectively), nausea (7.5% vs 5.1%), and abdominal pain (7.2% vs 4.1%) [77]. Eluxadoline is contraindicated in patients with IBS-D with prior sphincter of Oddi dysfunction or cholecystectomy, alcohol dependence, pancreatitis, or severe hepatic impairment [24, 76]. Use of eluxadoline is limited because of its lack of availability and approval in many countries [24]. The ACG guideline for IBS management and BSG guidelines both recommend mixed opioid agonists/antagonists for treatment of global IBS-D symptoms [20, 24].

While the therapies currently approved by the FDA for treatment of patients with IBS-D have comparable number needed to treat values (Table 3) [20, 59, 78–80], rifaximin has been shown to have the highest (superior) number needed to harm value (8971; i.e., 8971 patients need to be treated to observe one adverse event) [20, 78]. Though these medications differ by intended patient population, mechanism of action, and duration of treatment (short-term vs continuous) [68, 71, 76, 77], they play an important role in overall management of IBS-D for providers with access to these therapies.

NON-FDA-APPROVED THERAPIES FOR IBS-D

Neuromodulators

Levels of depression have been shown to be significantly greater in patients with IBS compared with healthy individuals [81–83]. Neuromodulators, including the more commonly termed antidepressants, may reduce symptoms of IBS, as indicated by a meta-analysis ($n = 12$ studies) reporting that 42.7% of 436 patients with IBS experienced no improvement in IBS symptoms with tricyclic antidepressants (TCAs) versus 63.8% of 351 patients receiving placebo [84]. Of note, the anticholinergic side effects of TCAs may be beneficial for some patients with IBS-D, as GI transit is slowed [85]. The Rome Foundation Working Group recommended use of peripherally acting agents (e.g., gabapentin) when pain is mild to moderate and intermittent in nature but recommended adding or substituting centrally acting agents (e.g., tricyclic antidepressants) when pain is severe or persistent [85]. Starting doses of TCAs typically range from 10 to 25 mg. TCAs should be titrated slowly over several weeks, and it may take several months to achieve maximal effects on IBS-D symptoms. The ACG guideline for IBS management strongly recommends TCAs for treatment of global IBS symptoms [20].

Antispasmodics

Antispasmodics are a broad therapeutic class of agents with multiple mechanisms of action, including smooth-muscle relaxants, calcium antagonists, and combination therapies [20]. Dicyclomine, hyoscine, and hyoscyamine are the three antispasmodics currently available in the USA [20]. Clinical trials of these agents are of low quality, dated, and limited by the small size of the patient populations; further, studies differed in design, inclusion criteria, and outcomes [20]. While the ACG guideline for IBS management recommends against the use of antispasmodics for treating global IBS symptoms in any IBS subtype, including IBS-D [20], the BSG guidelines, in contrast, suggest that some antispasmodics may be beneficial [24]. These conflicting recommendations, in part, reflect differences in availability of specific antispasmodic agents in international markets [20, 24].

Bile-Acid Sequestrants

Bile-acid sequestrants may have efficacy in patients with IBS-D who have bile-acid malabsorption [86–88]. A randomized controlled trial of patients with chronic, watery diarrhea or IBS-D and bile-acid malabsorption ($n = 26$) showed that clinical remission (i.e., mean of at most three stools per day in the week before the study visit, with fewer than one watery stool per day) was achieved by a greater percentage of patients receiving cholestyramine 4 g bid versus hydroxypropyl cellulose after 8 weeks, although the difference was not significant (53.8% vs 38.5%, respectively; $P = 0.4$) [88]. Bile-acid sequestrants currently are not recommended by the ACG for treatment of IBS-D but may be considered as a second-line approach for the management of diarrhea. By virtue of their mechanism of action, bile-acid sequestrants are expected to have less impact on abdominal pain symptoms.

OTHER THERAPIES

Exercise

Data from a randomized controlled trial of patients with IBS showed that an increase in physical activity improved both GI symptoms and the physical domains of the IBS Quality of Life questionnaire after 12 weeks [89]. The 2021 BSG guidelines state that regular exercise should be considered part of first-line therapy for patients with IBS [24].

Psychologic Therapies in IBS

Gut-directed psychotherapies (e.g., cognitive behavior therapy [CBT], hypnotherapy) effectively target the cognitive and affective factors that modulate IBS symptoms and can improve

abdominal pain and altered bowel habits in patients with IBS [20]. Further, a systematic review and meta-analysis found CBT and hypnotherapy improved abdominal pain and overall response in patients with IBS compared with placebo, although differences between the interventions were not significant [90]. The ACG guideline for IBS management conditionally recommends GI-directed psychotherapies for the treatment of global IBS symptoms on the basis of very low-quality evidence [20].

Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT) involves the transfer of donor fecal matter by enema, endoscopy, or an oral pill [91]. A meta-analysis of seven randomized controlled studies reported that FMT did not significantly decrease global symptoms of IBS compared with placebo after 12 weeks (RR 0.8; 95% CI 0.4–1.3) [92]. For the three studies with 1-year follow-up data, FMT did not significantly improve global IBS symptoms compared with placebo (RR 0.9; 95% CI 0.7–1.1) [92]. Given that studies of FMT for treatment of IBS are limited, the ACG guideline for IBS management recommends against the use of FMT for treatment of global IBS symptoms [20]. Further, FMT is not an FDA-approved treatment for IBS-D.

CONCLUSIONS

Diagnosing IBS may be challenging, given that symptoms of IBS overlap with many other conditions that present in the primary-care setting. However, in the presence of symptoms, a "positive diagnostic strategy" establishing a diagnosis of IBS does not require extensive and costly laboratory testing [2]. Patients who are refractory to initial treatment approaches or those manifesting alarm symptoms should be referred to a gastroenterologist for further evaluation. A clear patient–provider relationship with reassurances regarding the nature of the condition and meaning of the diagnosis is needed, as this can improve outcomes and minimize unnecessary testing. Additionally, various nonpharmacologic and pharmacologic

interventions are available and have shown varying degrees of success in patients with IBS-D. Providers will need to consider the profiles of the three FDA-approved agents for treatment of IBS-D. Some interventions (e.g., dietary modification, CBT) are best employed with the involvement of trained and experienced providers (i.e., dieticians, health psychologists).

Patients should be encouraged to communicate with their providers if they have an insufficient response to therapy or notice an increased impact on daily life, as these patients may require a gastroenterology referral. Furthermore, providers should refer patients with IBS with multiple comorbid conditions to a gastroenterologist, as these patients may experience more severe symptoms and tend to be more challenging to manage. Timely diagnosis of IBS-D and proper management, coupled with patient feedback on their symptom experiences and treatment responses, may optimize outcomes and reinforce the patient–provider relationship in individuals with this chronic condition.

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Compliance with Ethics Guidelines. This review is based on previously conducted studies and does not contain any new data from human or animal studies conducted by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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