Practical Evaluation and Management of Irritable Bowel Syndrome with Diarrhea: A Case Study Approach

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CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

- Identify patients who are appropriately diagnosed based on history and symptoms
- Describe the roles of the Rome-IV criteria, colonoscopy, and other tests in the diagnosis of irritable bowel syndrome (IBS)
- Differentiate subtypes of IBS
- Characterize the benefits and limitations of currently available prescription medications for IBS
- Individualize treatment for IBS based on current evidence-based guidelines

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of IBS-D.

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CASE STUDY

A 32-year-old science teacher is referred for further management of abdominal symptoms. His symptoms started after a trip to Mexico 1 year ago where he and his wife both developed severe food poisoning. Since then he has had daily loose, watery, non-bloody, urgent bowel movements. He says he feels somewhat bloated and distended. He reports daily pain in his lower abdomen that worsens

just before a bowel movement and improves after having urgent diarrhea.

His weight has remained stable. He does not report fevers, chills, rashes, oral ulcers, myalgia, or arthralgia. He does not take any medications or use complementary or alternative therapies. Past medical and surgical history are unremarkable. He does not have a family history of irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), celiac disease, or colorectal cancer.

He went to an urgent care clinic 3 months after his symptoms began. A complete blood count (CBC), complete metabolic panel, celiac serology cascade, and stool studies were all within normal limits. His wife's symptoms resolved completely. A 2-week trial of a lactose-free diet did not help. Loperamide taken as needed has not helped his abdominal pain, bloating, or diarrhea.

The patient has done some research and brings several questions to the visit, which are listed below. The discussion in response to his questions serves as the basis for this article.

WHAT IS MY DIAGNOSIS?

IBS is a common functional bowel disorder characterized by recurrent abdominal pain associated with altered bowel habits (diarrhea, constipation, or both).[1] Abdominal bloating and distension also often are present, but neither is required to make an IBS diagnosis.[1] IBS is classified according to the type of bowel habit alteration (based on stool form only on days with at least 1 abnormal bowel movement): diarrhea-predominant IBS (IBS-D), constipation-predominant IBS (IBS-C), or mixed-type IBS (IBS-M). IBS-M has alternating periods of diarrhea and constipation.[1] IBS-D is the most common subtype, affecting approximately 40% of IBS patients, and is the focus of this discussion.[2]

Diagnosing IBS can be challenging because the symptoms can mimic other disorders (eg, lactose or fructose intolerance, small intestine bacterial overgrowth, celiac disease, IBD, microscopic colitis, or functional diarrhea) and could fluctuate over time. Moreover, there is no precise biomarker for IBS.[3,4] The Rome IV criteria (**TABLE 1**) are intended to facilitate making a positive diagnosis of IBS, rather than making an IBS diagnosis only after a battery of tests has been performed (ie, a diagnosis of exclusion).[1,5] A key difference from Rome III is that the ROME IV criteria classifies IBS subtypes by the proportion of days with symptomatic bowel movements rather than measuring all days.

The diagnosis of IBS is based on a thoughtful history and a limited physical examination to assess the presence of the distinguishing symptom of IBS, which is abdominal pain in association with: 1) defecation, 2) change in stool frequency, and/or 3) change in stool form or appearance. Limited diagnostic tests to confirm the diagnosis and exclude other disorders, eg, IBD, are recommended.[1,5] This approach is supported by several practice guidelines.[6,7]

TABLE 1 Rome IV Irritable Bowel Syndrome Diagnostic Criteria[a1,5]

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 the frequency of stool
• Associated with a change in the form (appearance) of stool

[a]These criteria should be fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis

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TABLE 2 Alarm signs/symptoms that warrant further investigation[3,8]

• Age >50 years without prior colon cancer screening
• Presence of overt gastrointestinal bleeding
• Nocturnal passage of stool
• Unintentional weight loss
• Family history of inflammatory bowel disease or colorectal cancer
• Recent changes in bowel habits
• Presence of a palpable abdominal mass or lymphadenopathy

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IS THERE ANYTHING WORRISOME IN MY HISTORY? DO I NEED ANY FURTHER TESTS?

Alarm symptoms or warning signs ("red flags") discovered on history and physical examination that warrant further evaluation are listed in **TABLE 2**.[3,8]

In patients without alarm symptoms, extensive diagnostic testing to rule out other disorders is unlikely to yield a new diagnosis in those with IBS symptoms who meet Rome IV criteria.[4,8,9] New to Rome IV criteria is the use of limited testing to consider in patients without alarm symptoms, which includes CBC to ensure the patient is not anemic, C-reactive protein (CRP) or fecal calprotectin to lower suspicion for IBD and prevent indiscriminate use of colonoscopy, and celiac serologic testing because IBS-D can mimic this disorder.[9]

CASE STUDY (CONTINUED)

A detailed history ruled out warning signs for other organic diseases. Further information to quantify the duration and frequency of symptoms, the proportion of days with symptomatic stools,

the association of abdominal pain with bowel habits, and a benign physical examination confirmed he met Rome IV criteria for IBS-D. A CBC was normal without evidence of anemia; CRP and celiac serum tests were both negative, effectively excluding IBD and celiac disease. Examination of the eyes, mouth, skin, extremities, and perianal area did not show evidence of IBD.

WHY DID MY SYMPTOMS DEVELOP?

The pathophysiology of IBS is complex, multifactorial, and not completely understood. It involves genetic predisposition, visceral hypersensitivity, abnormalities in GI motility, secretory function and permeability, immune activation, and autonomic nervous system dysregulation.[10,11]

IBS traditionally has been thought of as a brain–gut disorder because of the high frequency of coexisting conditions such as anxiety and depression.[9] It has been postulated that among individuals with a genetic predisposition or exposure to environmental factors, an abnormal stress response combined with psychological distress and an infectious or inflammatory response could alter intestinal permeability and trigger a cascade of events (eg, infiltration of inflammatory cells, localized edema, and release of cytokines or chemokines) that results in development of IBS symptoms.[9]

There is a growing body of evidence implicating the gastrointestinal microbiota—the complex ecosystem of microorganisms inhabiting the intestine—and alterations in its composition and function (dysbiosis) as important components in the pathogenesis of IBS.[12,13] The intestinal microbiota in patients with IBS is altered compared with healthy controls in terms of both a general decrease in diversity, and more specifically, decreases in *Bifidobacterium* and *Lactobacillus* species, and an increase in *Gammaproteobacterium* species.[12,14] Among risk factors for IBS, infectious gastroenteritis (IGE) is the strongest, with 3% to 36% of individuals who have experienced IGE developing IBS-D (referred to as post-infectious IBS) with symptoms lasting months to years.[15,16] IGE is the likely cause of IBS in this patient, especially because of the temporal relationship of symptom onset after an episode of food poisoning. Emerging evidence also suggests that changes in the gut microbiome and the release of inflammatory mediators could modulate the gut–brain axis.[17,18] In up to one-half of patients with IBS, gastrointestinal symptoms appear before development of mood disorders.[19]

WILL MY SYMPTOMS GO AWAY?

Treatment of IBS-D is directed at decreasing abdominal pain, bloating, and diarrhea. Treatment should be individualized in a stepwise manner according to disease symptoms and severity because symptom severity can impact realistic expectations for treatment outcomes. (**FIGURES 1** and **2**).[1,20]

FIGURE 1 Treatment guided by severity of IBS-D

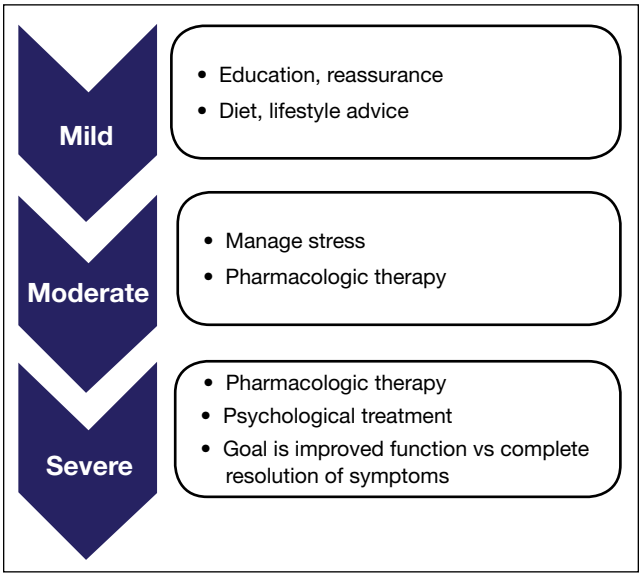

FIGURE 2 Therapies for IBS-D by symptom

Abdominal pain/ discomfort	Bloating/ distension	Diarrhea
• Alosetron • Rifaximin • Antidepressants (TCA, SSRI)[a] • Smooth muscle antispasmodics (dicyclomine, hyoscyamine[a]) • Low FODMAP diet[a]	• Rifaximin • Probiotics[a] • Diet[a]	• Alosetron • Eluxadoline • Rifaximin • Cholestyramine[a] • Diphenoxylate-atropine[a] • Loperamide[a]

[a]Not approved for IBS-D by the US Food and Drug Administration

Abbreviations: FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS-D, diarrhea-predominant irritable bowel syndrome; SSRI, serotonin selective reuptake inhibitor; TCA, tricyclic antidepressant

Mild symptoms of IBS-D that the patient considers a nuisance, but that don't significantly impact daily life, often are effectively managed with diet and lifestyle modifications (see below) and loperamide as needed. Moderate symptoms that affect patients' home, social, and professional life likely will require scheduled pharmacologic treatment with ≥1 medication options. In patients with more severe disease, symptoms could resolve after months or years, but achieving improved symptom management and daily functioning might be a more attainable goal.[21] For patients with severe symptoms, consider referral to a gastroenterologist for specialty care or combination therapy. An additional option is referral for psy-

chological or behavioral intervention (eg, cognitive-behavioral therapy, hypnosis, or relaxation methods).[1,22,23]

Evidence-based treatment guidelines for IBS are available from the American Gastroenterological Association (AGA) (http://www.gastrojournal.org/article/S0016-5085(14)01089-0/pdf) and the American College of Gastroenterology (ACG) (http://gi.org/wp-content/uploads/2014/08/IBS_CIC_Monograph_AJG_Aug_2014.pdf).[7,24] This review article includes updated information on options for managing patients with IBS-D that were released after publication of the guidelines in 2014, including eluxadoline and rifaximin for IBS-D.

ARE THERE ANY DIETARY INTERVENTIONS THAT MIGHT HELP? DOES EXERCISE HELP?

Lifestyle and dietary modifications are reasonable first-line approaches that could provide adequate relief for many patients with mild IBS symptoms.[23] These include exercise, stress reduction (eg, meditation, counseling), and attention to impaired sleep.[1,20,25,26] Healthy eating habits include limiting intake of potential dietary triggers, such as alcohol, caffeine, spicy foods, fat, and gas-producing foods.[23]

The role of fiber in IBS remains subject to debate because of contradictory data, but recent studies suggest that soluble fiber with a low rate of fermentation (eg, psyllium) might have some benefit in addressing diarrhea and constipation in IBS patients.[7,23]

For patients in whom symptoms persist despite following general diet and lifestyle advice, a growing body of evidence supports the efficacy of the low FODMAP diet (approximately 70% response rate) to reduce gastrointestinal symptoms such as abdominal pain, bloating, diarrhea, abdominal distention, and flatulence.[27-31] The FODMAP diet restricts short-chain carbohydrates known collectively as fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) found in such foods as wheat, broccoli, legumes, dairy, apples, and stone fruits.[28] A low FODMAP diet should be guided by a dietitian because of its complexity and potential risks for inadequate nutritional intake. Observational studies suggest durable efficacy even with reintroduction of FODMAPs, as recommended.[29]

Although limited data suggest a gluten-free diet could be helpful in reducing global symptoms, abdominal pain, and bloating, at least 1 randomized trial demonstrated no additive effect of a gluten-free diet over a low-FODMAP diet alone.[9]

WILL PROBIOTICS HELP?

Probiotics, composed of live microorganisms that are beneficial to human health when ingested, have been studied extensively to treat IBS.[11] Their role in treating IBS is supported by generally beneficial effects and a benign adverse event profile in >80 trials consisting of >10,000 patients, including several meta-analyses.[32-35] Interpretation of results is difficult because of heterogeneity of populations (ie, IBS subtype) and the myriad of probiotics (variety of single and multi-strain products and dosages) studied. The most convincing data are derived from multi-strain probiotics containing both *Lactobacillus* and *Bifidobacteria* with a concentration of 200 million to 10 billion colony-forming units/d.[14,34] ACG guidelines indicate that probiotics improve global symptoms, bloating, and flatulence, but make a weak recommendation for their use based on the low quality of evidence.[7]

WILL AN ANTIBIOTIC HELP?

Neomycin, the first nonabsorbable antibiotic investigated for IBS, produced a 50% improvement in global IBS symptoms compared with placebo, but also showed rapid bacterial resistance.[36] Rifaximin, an oral, nonsystemic antibiotic with a low bacterial-resistance profile and a favorable side-effect profile, was approved in May 2015 for treating adults with nonconstipation IBS, including IBS-D.[37,38]

A combined analysis of 2 separate phase 3 trials showed that a 14-day course of rifaximin, 550 mg three times daily, resulted in significant improvement compared with placebo in patients with IBS without constipation.[38] Improvements included a significant increase in the percentage of patients who had adequate relief of global IBS-D symptoms (40.7% vs 31.7% at 4 weeks; $P < .001$), improved IBS-related bloating (40.2% vs 30.3% at 4 weeks; $P < .001$), and relief in the composite endpoint of abdominal pain/discomfort and loose or watery stools.[38] Rifaximin exhibited favorable durability of effect, with a significantly greater percentage of rifaximin-treated patients than placebo-treated patients reporting adequate relief of global IBS symptoms at 10 weeks posttreatment (42% vs 32% in TARGET 1; 40% vs 32% in TARGET 2, respectively).[38] The incidence of adverse effects (headache, upper respiratory infection, nausea, and diarrhea) was comparable with placebo.[38] More recently, another randomized, placebo-controlled trial demonstrated that repeat treatment with rifaximin, 550 mg 3 times daily for up to 3 cycles of 2 weeks, in patients with IBS-D was safe, well tolerated, and significantly more effective than placebo (38.1% vs 31.5%, respectively; $P = .03$) in improving IBS symptoms and IBS-related quality of life.[39,40]

WHAT IF NONE OF THIS WORKS? ARE THERE ANY OTHER OPTIONS?

Beyond agents that target the gut microbiota, other pharmacologic interventions available for management of IBS-D vary from those specifically targeting diarrhea (eg, loperamide) to those addressing multiple symptoms.

Eluxadoline

Eluxadoline is a novel mixed mu- and kappa-opioid receptor agonist and delta-opioid receptor antagonist that reduces contractility and secretion in the GI tract, and has low oral bioavailability.[41] In two phase 3 trials, eluxadoline, 75 mg and 100 mg twice daily, significantly improved the composite endpoint of decrease in abdominal pain and improvement in stool consistency from weeks 1 through 12 compared with placebo (31.0%, 27.7%, 21.9%, respectively) and from weeks 1 through 26 (31.0%, 26.7%, 19.5%, respectively).[41,42] There was no significant difference compared with placebo with respect to improvement in abdominal pain.[42] Eluxadoline is contraindicated in patients with cholecystectomy, history of biliary obstruction, alcohol abuse, or pancreatitis.[43]

Alosetron

Alosetron is a 5-hydroxytryptamine-3 receptor antagonist approved only in women with severe, chronic IBS-D with inadequate response to conventional therapy.[44] It has demonstrated improvement in stool consistency and frequency (relative risk [RR], 1.59; 95% CI, 1.04-2.41), abdominal pain (RR, 1.24; 95% CI, 1.16-1.33), and overall IBS symptoms (RR, 1.58; 95% CI, 1.42-1.75).[45] Severe constipation and ischemic colitis have occurred with cumulative incidence rates of 0.25 cases and 1.03 cases per 1000 patient/years, respectively.[46]

Loperamide

Loperamide is a mu-opioid receptor agonist that improves diarrhea by decreasing peristalsis, prolonging GI transit time, and reducing fluid secretion in the intestinal lumen.[4] Loperamide is not approved for diarrhea related to IBS, and the few controlled trials examining its efficacy for this indication report improvements in individual symptoms of stool frequency, consistency, and urgency, but usually no improvement in bloating or in abdominal pain.[47-50] Loperamide, 2 mg/d to 8 mg/d, could be useful in some patients with IBS-D.[4,7]

Tricyclic antidepressants

Antidepressants have become a widespread treatment option for IBS because of their effects on pain perception, mood, and motility, as well as on the brain–gut axis.[9,51] A meta-analysis of 17 studies showed a lower risk of remaining symptomatic with antidepressants vs placebo (RR, 0.67; 95% CI, 0.58-0.77), with similar treatment effects for both tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors.[52] The most frequent side effects with TCAs were drowsiness and dry mouth.[20] TCAs should be initiated at low dosages (10 to 25 mg) at bedtime and gradually increased based on symptom response and tolerability.[51]

Bile acid sequestrants

These agents bind bile acids in the intestine to prevent free bile acid from stimulating electrolyte and water secretion in the colon. Because a subset (approximately 28%) of patients with IBS-D have bile acid malabsorption, an empiric trial of a bile acid sequestrant could be considered for diarrheal symptoms based on evidence of efficacy in recent pilot studies (eg, cholestyramine, 9 g two to three times daily, colestipol, 2 g once or twice daily, or colesevelam, 625 mg once or twice daily).[1,21,53,54] A bile acid sequestrant could be considered after other therapies targeting diarrhea have not been successful.[23]

SUMMARY

An individualized approach to managing patients with IBS-D begins with reassurance, explanation, and a positive diagnosis that includes limited testing to rule out disorders that may mimic IBS-D (eg, IBD or celiac disease). Treatment options should be considered in the context of symptoms, possible etiologic factors, and benefits vs risks. Treatment typically begins with dietary modifications, increased exercise, and stress reduction. A probiotic could be considered, particularly for bloating, and a TCA for pain. Diarrhea might be ameliorated with loperamide or a bile acid sequestrant. For persistent and/or more severe symptoms, rifaximin, eluxadoline, or alosetron could be considered, with the specific choice guided by patient-specific factors. ●

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