CME

Irritable bowel syndrome: Clinical practice update

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Abstract

Irritable bowel syndrome (IBS) is a common and burdensome disorder characterized by chronic recurrent abdominal pain and altered bowel habits. IBS remains misunderstood, leading to delayed diagnosis, impaired quality of life, and substantial healthcare costs. Advancing clinicians' understanding of this complex biopsychosocial process, using a positive diagnostic strategy rather than a diagnosis of exclusion, and incorporating a multimodal treatment approach expedite time to diagnosis, facilitate symptom relief, and reduce financial expenditure.

Keywords: irritable bowel syndrome, brain-gut axis, Rome IV criteria, positive diagnostic strategy, low FODMAP diet, IBS

Learning objectives

- Describe the pathophysiology of IBS and its role in patient-centered management.
- Explain how the Rome IV symptoms-based diagnostic criteria and selective testing are used to support a positive diagnostic strategy.
- Describe a multimodal treatment approach

Irritable bowel syndrome (IBS) affects about 35 million patients in the United States, women more than men, and is the seventh most common diagnosis by primary care providers.[1] The average time to IBS diagnosis is 4 years, with the delay in part because patients and clinicians tend to limit or bypass conversations about bowel symptomatology and its effects.[1] IBS can be debilitating and impair patients' quality of life; affecting physical, emotional, and social functioning and vitality.[2] Gastrointestinal (GI)-specific anxiety, defined as hypervigilance and worry about experiencing GI sensations, and depressive symptomatology can play central roles in mental health.[2] Patients with IBS report that symptoms lead to reduced travel, avoidance of sex, and decreased time with friends and family.[1] Absenteeism and reduced work productivity are common, with an average of 2 missed days of school or work and 9 days of lost productivity per month.[1,3] Annual direct medical costs in excess of $1 billion, related to healthcare use and diagnostic testing, create significant financial challenges for patients and the medical community.[3] Understanding the pathophysiology, using a positive diagnostic strategy, and incorporating a multimodal treatment approach are strategies to help achieve a timely diagnosis, improve patient quality of life, and reduce healthcare costs.

PATHOPHYSIOLOGY

IBS is characterized by two cardinal features: chronic recurrent abdominal pain and altered bowel habits in the absence of an organic cause.[4] The condition has no single, definitive cause. IBS is a multifactorial and complex disorder of brain-gut interaction involving biologic, psychologic, and social factors.[2-7] Multiple physiologic mechanisms including visceral hypersensitivity, intestinal permeability, immune activation, and dysmotility are known.[3-7] Visceral hypersensitivity secondary to luminal distension and activation of nociceptive pathways contribute to pain.[3,7] Impaired gut barrier function and increased immune activation contribute to abnormal motor and visceral responses.[4] Abnormal responses to serotonin and other neurotransmitters regulating intestinal transit lead to constipation, diarrhea, or mixed bowel habits.[4] Previous infectious gastroenteritis, early life stressors such as sexual or physical abuse or trauma,

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DOI:10.1097/01.JAA.0000000000000035

Key points

- Factors involved in the cause of IBS include brain-gut dysfunction, visceral hypersensitivity, intestinal permeability, immune activation, dysmotility, altered gut microbiome, food sensitivities, and psychosocial stressors.
- A thorough history and physical examination coupled with the Rome IV criteria and selective laboratory evaluation support a positive diagnostic strategy, which is favored over a diagnosis of exclusion to support a timely diagnosis and delivery of therapies.
- The cornerstones of IBS management are dietary and behavioral modifications, pharmacologic therapies, psychotherapies, and a therapeutic clinician-patient relationship.

cognitive/behavioral/emotional responses, altered gut microbiome, and food sensitivities may predispose patients to developing IBS and may perpetuate symptom frequency and severity.[2,4,7] Although food sensitivities are common, true IgE-mediated food allergies are rare.[4,7] A comprehensive understanding of the brain-gut axis and exploration of the biopsychosocial process can enhance the evaluation and management of IBS.

DIAGNOSTIC EVALUATION

A paradigm shift from a diagnosis of exclusion toward a positive diagnostic strategy, as recommended by the American College of Gastroenterology (ACG), has paved the way for clinicians to confidently diagnose IBS.[3,4,7] The perception and management of IBS as a diagnosis of exclusion, with pursuit of consultation and invasive endoscopic testing to exclude organic disease, can delay diagnosis and receipt of therapy, is of low diagnostic yield, and increases healthcare costs.[4,8] Further, despite clinicians' best intentions, a diagnosis of exclusion does not reassure patients.[5,7,8] A thorough history and physical examination coupled with the Rome IV criteria and selective laboratory evaluation support a positive diagnostic strategy.[7]

HISTORY AND PHYSICAL EXAMINATION

Asking patients about symptomatology, aggravating and alleviating factors, and alarm features, as well as reviewing the patient's past medical history and medications, can aid in the clinical suspicion of IBS and development of a differential diagnosis, and can offer insights into a targeted treatment plan.

Patients with IBS typically report periodic exacerbations of lower abdominal pain described as cramping or spasms of variable intensity.[4,9] Pain is accompanied by constipation, diarrhea, or both. Assessing potential triggers, such as previous gastroenteritis and stress, may raise clinical suspicion for IBS. A food diary/symptomatology log can help identify whether specific foods induce or exacerbate symptoms and may aid in developing a dietary/behavioral modification plan. Asking patients about extraintestinal symptoms such as eye pain, joint pain, rash, and oral ulcers, which may be associated with GI disorders such as inflammatory bowel disease (IBD) and celiac disease can help differentiate these disorders from IBS.[7] Assessing for alarm features, including onset after age 50 years; unintentional weight loss of 10% or more of body weight in 3 months; presence of melena; hematochezia; heme-positive stool; unexplained iron-deficiency anemia; or personal or family history of colorectal cancer (CRC), IBD, or celiac disease raise suspicion for organic disorders; refer patients to gastroenterology for further evaluation.[3,4,7] Recognizing the presence of comorbid conditions such as somatoform disorders, migraine headaches, fibromyalgia, chronic pain, and interstitial cystitis may raise clinical suspicion for IBS and support the use of targeted therapies.[3,4] Reviewing prescription and over-the-counter (OTC) medications and supplements may reveal agents contributing to altered bowel habits, with an opportunity to reconcile and discontinue these drugs, if possible, to reduce adverse reactions.[4]

The physical examination in patients with suspected IBS is relatively nonspecific.[6] The abdominal examination may reveal mild nonfocal tenderness on palpation but otherwise is unremarkable; the anorectal examination may yield additional findings. The anorectal examination is an often-underused physical examination tool that clinicians may feel is of limited value, too invasive, and requires a chaperone; however, the examination can help evaluate the mechanics of defecation and assess for anorectal pathology.[3,7,10] The digital rectal examination (DRE) lets clinicians inspect for perianal disease such as hemorrhoids, fissures, fistulas; assess perineal sensation and anocutaneous reflex; palpate for tenderness and masses; and assess sphincter tone, squeeze pressure, and stimulated defecation.[4,7,10] An abnormal DRE may necessitate visualization with a flexible sigmoidoscopy or colonoscopy, anorectal physiology testing including anorectal manometry, and/or defecography to evaluate for pathologies such as pelvic floor disorders.[3,4,7,10]

ROME IV CRITERIA

The Rome IV criteria are symptoms-based criteria that outline the frequency and chronicity of symptoms.[11] The criteria are: recurrent abdominal pain on average at least 1 day/week in the past 3 months with at least two of the following: pain is related to defecation, pain is associated with a change in stool frequency, or pain is associated with a change in stool form.[3,7] Pain may be relieved or exacerbated by defecation.[12] Criteria must be fulfilled for the past 3 months with symptom onset at least 6 months before diagnosis.[3,7] The Bristol Stool Form Scale (BSFS) is a validated instrument and helpful visual aid that assists in identifying an IBS subtype based on seven stool pat-

terns.[4,7] A quantification of stool habits helps classify the appropriate IBS subtype and guide therapy.[4,7] This article focuses on the subtypes of constipation and diarrhea.

- **IBS-C (constipation predominant)** is defined as BSFS types 1 and 2 (hard, lumpy, and sausage-shaped) more than 25% of the time with types 6 and 7 (mushy, ragged, watery) occurring less than 25% of the time.[3,4,7]
- **IBS-D (diarrhea predominant)** is defined as BSFS types 6 and 7 more than 25% of the time with types 1 and 2 occurring less than 25% of the time.[3,4,7]
- **IBS-M (mixed type)** is a heterogenous subtype with varying symptoms of constipation and diarrhea.[3,4,7]

The patient's primary stool consistency is based on days that the patient reports abnormal bowel movements in the absence of therapies that could affect bowel patterns.[7] The stool scale alone is not diagnostic of IBS; the pain criteria also must be met. Bloating often is present but is not required to make the diagnosis of IBS.[7]

SELECTIVE LABORATORY EVALUATION

No specific biomarkers can diagnose IBS.[7,11] A selective laboratory evaluation is appropriate for patients with suspected IBS.[4]

- All patients should have age-appropriate CRC screening and complete blood cell (CBC) count.[4,7] A CBC count is helpful in the evaluation of anemia that may be associated with CRC, IBD, or celiac disease rather than IBS.[3,4]
- Additional laboratory tests and stool studies may be ordered pending clinical suspicion of IBS subtype.[3] Celiac serologies with a tissue transglutaminase IgA level in conjunction with a total IgA level (if concerned about potential IgA deficiency) can help differentiate celiac disease from IBS.[3,4,7,13]
- C-reactive protein (CRP) and fecal calprotectin levels can be helpful in differentiating IBD from IBS.[4] An elevated CRP and positive fecal calprotectin, which are associated with inflammation, may be seen in patients with IBD.[3,4,7]
- Thyroid function testing with a thyroid-stimulating hormone (TSH) level may or may not be ordered pending clinical indication. Stool analysis for bacterial or parasitic causes such as *Campylobacter jejuni, Salmonella, Cryptosporidium,* and *Giardia lamblia* may be obtained pending clinical indication and risk exposures.[7] Stool testing for infectious diarrhea may be considered in patients with suspected foodborne outbreak, community exposure, and high-risk pet contact including dogs and cats.[7,14] *Giardia lamblia* is most associated with postinfectious IBS.[7] Consider *Giardia* antigen testing in patients with high pretest probability and definite risk exposure (for example, travel to endemic areas, daycare outbreaks, unsanitary water, and camping).[7] Bile acid malabsorption may be seen in a subset of patients with IBS-D, perhaps influenced by gut microbiome and intestinal transit.[3,4,15] Excess bile acids increase colonic motility and fluid secretion, exerting a laxative effect. Diagnostic tests for bile acid malabsorption are not widely available, are cumbersome, and are associated with moderate sensitivity and specificity.[15] Fecal bile acid testing is challenging and not routinely ordered. Clinically, in appropriate circumstances, such as in patients with cholecystectomy, an empiric trial with a bile acid sequestrant may be considered.[7,12] Food allergy and food sensitivity panel testing is not recommended in all patients because of concern for potential false positives.[7]

Additional workup, as clinically indicated, is appropriate for patients who present with an atypical history, have alarm features, or have severe or refractory IBS symptoms. In these circumstances, a gastroenterology referral is recommended with consideration of additional laboratory/stool studies, imaging, and endoscopic and/or physiologic testing.

MANAGEMENT

The goal of IBS management is to relieve symptoms and improve quality of life. This can be achieved with dietary and behavioral modifications, pharmacologic therapy, and psychotherapies.[3,4,6,7] Noninvasive strategies such as dietary and behavioral modifications and OTC therapies are considered first-line. Escalation of management with prescription and off-label agents and/or psychotherapies may be considered as needed, based on the patient's severity of symptoms.[3,4]

> Probiotics help modulate GI flora and may improve symptoms of bloating and gas.

Dietary and behavioral modifications Foods high in fermentable oligo-di-monosaccharides and polyols (FODMAPS) may contribute to symptoms of gas, bloating, pain, and altered bowel habits.[16,17] FODMAPS are poorly absorbed, osmotically active carbohydrates that increase intestinal water secretion and bacterial fermentation in the small bowel and colon, producing short-chain fatty acids and gases that can lead to luminal distension and accelerated transit.[3,4,7,16,17] Common FODMAP foods include honey, apples, watermelon, milk, wheat, onion, garlic, and sugar alcohols.[17] A low FODMAP diet, a dietary approach aimed at eliminating foods that contribute to symptomatology, may prove to be successful in these patients.[16,17] The low FODMAP diet involves a three-phase approach, starting by the patient eliminating high FODMAP foods from the diet for 2 to 6 weeks, followed by reintroduction of individual FODMAP foods in increasing amounts over 3 days, then personalization.[7,16,17] Patients typically respond within 2

to 6 weeks if they are sensitive to FODMAPs.[7,16] If the patient has no response to restriction of FODMAP foods, consider another treatment.[16] Applying the low FODMAP diet requires patience, time-intensive counseling, patient motivation, planning, and preparation.[7,16] Patients with disordered eating, anorexia nervosa, bulimia nervosa, binge eating disorder, or avoidant/restrictive food intake disorder are not suitable for elimination diets; cautious use of the low FODMAP diet should be exercised.[16,17] Discrepancies in resources identifying FODMAPs can affect adherence and FODMAP portion size and dose can affect tolerability.[16] A registered dietitian nutritionist can assist in providing personalized nutrition and diet therapy.[7]

The role of the gut microbiome in IBS has spurred interest in the utility of probiotics.[7] Probiotics help modulate GI flora and may improve symptoms of bloating and gas.[4] Unfortunately, because of variance in specific strains, preparations, and doses, research and recommendations are limited.[4]

Several lifestyle and behavioral modifications may help improve IBS symptoms. Mindful eating and a focus on mitigating behaviors that can contribute to aerophagia, (for example, chewing food slowly and thoroughly, avoiding gum, and limiting straw use) may prove beneficial in some patients.[18,19] Physical activity, such as walking 20 to 30 minutes a day, can help improve overall health and promote gut motility in patients with IBS-C.[4] Sleep hygiene and stress reduction techniques can be helpful.[20] Toileting behavior with a focus on defecating after meals and minimizing prolonged sitting and straining may improve symptomatology.[21]

Pharmacologic therapies Patients whose IBS symptoms are unresponsive or not controlled with dietary/behavioral modifications alone and those with impaired quality of life may benefit from adjunctive pharmacologic therapies. Evidence-based, expert consensus guidelines exist regarding the pharmacologic management of patients with IBS.[22,23]

TABLE 1. Pharmacologic therapies for IBS[3,4,22,23]

Drugs for abdominal pain and discomfort
- Antispasmodics: dicyclomine, hyoscyamine, peppermint oil
- Neuromodulators: tricyclic antidepressants (not FDA-approved for treating IBS)

IBS-C
- Fiber: psyllium
- Osmotic laxatives: polyethylene glycol
- Secretagogues: lubiprostone, linaclotide, plecanatide
- Ion channel blocker: tenapanor

IBS-D
- Antidiarrheal: loperamide
- Gut flora modulator: rifaximin
- Bile acid sequestrant: cholestyramine (not FDA-approved for treating IBS)
- Opioid receptor modulator: eluxadoline
- 5-HT3 receptor antagonist: alosetron

The armamentarium of prescription agents approved for IBS continues to grow with the addition of tenapanor for the treatment of IBS-C. **Table 1** outlines pharmacologic therapies characterized by mechanism of action. Therapies are selected based on predominant symptomatology, IBS-subtype, and risk benefit profile.[4]

Treatments for abdominal pain/discomfort Pharmacologic therapies for abdominal pain and discomfort include antispasmodics and neuromodulators.[3] Antispasmodics, such as dicyclomine or hyoscyamine reduce smooth muscle contraction and may reduce pain as well as stool frequency.[7,22] Potential adverse reactions to antispasmodics include anticholinergic effects such as dizziness, dry mouth, blurred vision, and constipation.[3,4,22] Peppermint oil with l-menthol as its active component is a calcium channel antagonist that relaxes intestinal smooth muscle and modulates visceral sensation.[3,4] An OTC enteric-coated formulation of peppermint oil is designed to promote sustained distal release in the small intestine while minimizing reflux symptoms.[4] Neuromodulators such as tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors may be helpful in patients with features of mood disorders, somatization, and pain.[3,4] Neuromodulators exert antidepressant action, visceral analgesia, and smooth muscle relaxation affecting pain perception and motility.[4,22] TCAs may reduce bowel frequency in patients with IBS-D.[7] Potential adverse reactions to neuromodulators include dose-dependent anticholinergic effects, risk of sexual dysfunction, and drowsiness.[4] Neuromodulators are off-label therapies for the management of IBS.

Treatments for IBS-C First-line pharmacologic therapies for IBS-C include OTC agents such as fiber and laxatives.[3] Psyllium fiber is widely available and low-cost. Fiber helps bulk stool to improve frequency and consistency. It should be introduced at a nominal dose and slowly titrated toward 25 to 35 g/day with adequate water daily.[4,7,16] Common adverse reactions to fiber include bloating, gas, and abdominal cramping. Osmotic laxatives such as polyethylene glycol help promote intestinal water secretion and improve stool frequency and consistency.[4] Osmotic laxatives are less effective in improving pain or bloating.[4] Adverse reactions to osmotic laxatives include diarrhea and flatulence. Stimulant laxatives have not been widely studied in randomized controlled trials.[4]

Second-line pharmacologic therapies to treat IBS-C include secretagogues such as lubiprostone, linaclotide, and plecanatide, which stimulate intestinal fluid secretion via chloride-channel activation or production of cyclic guanosine monophosphate.[3,4,22] Secretagogues improve stool frequency and reduce visceral hypersensitivity.[22] The most common adverse reaction to secretagogues is diarrhea.[22]

Tenapanor is a relatively new prescription agent for treating IBS-C. This ion channel blocker inhibits the GI

sodium/hydrogen exchanger isoform 3, reducing sodium absorption and increasing intestinal water secretion.[22] It improves stool frequency and reduces abdominal pain given antinociceptive effects.[22] The most common adverse reaction to tenapanor is diarrhea.[22]

Treatments for IBS-D Pharmacologic therapies for diarrhea-predominant bowel habits include antidiarrheals, gut flora modulators, bile acid sequestrants, opioid receptor modulators, and 5-HT3 receptor antagonists. Loperamide is an antidiarrheal that inhibits peristalsis, prolongs gut transit, and exerts antisecretory activity reducing fecal volume.[4,23] It can help improve stool urgency, frequency, and consistency but has less effect on pain. Loperamide is well tolerated and non-habit-forming because it does not cross the blood-brain barrier.[4]

Rifaximin is a gut-selective antibiotic that can modulate flora to improve abdominal pain and fecal urgency.[23] The most common adverse reactions to rifaximin are nausea, upper respiratory infection, nasopharyngitis, and urinary tract infection.[23]

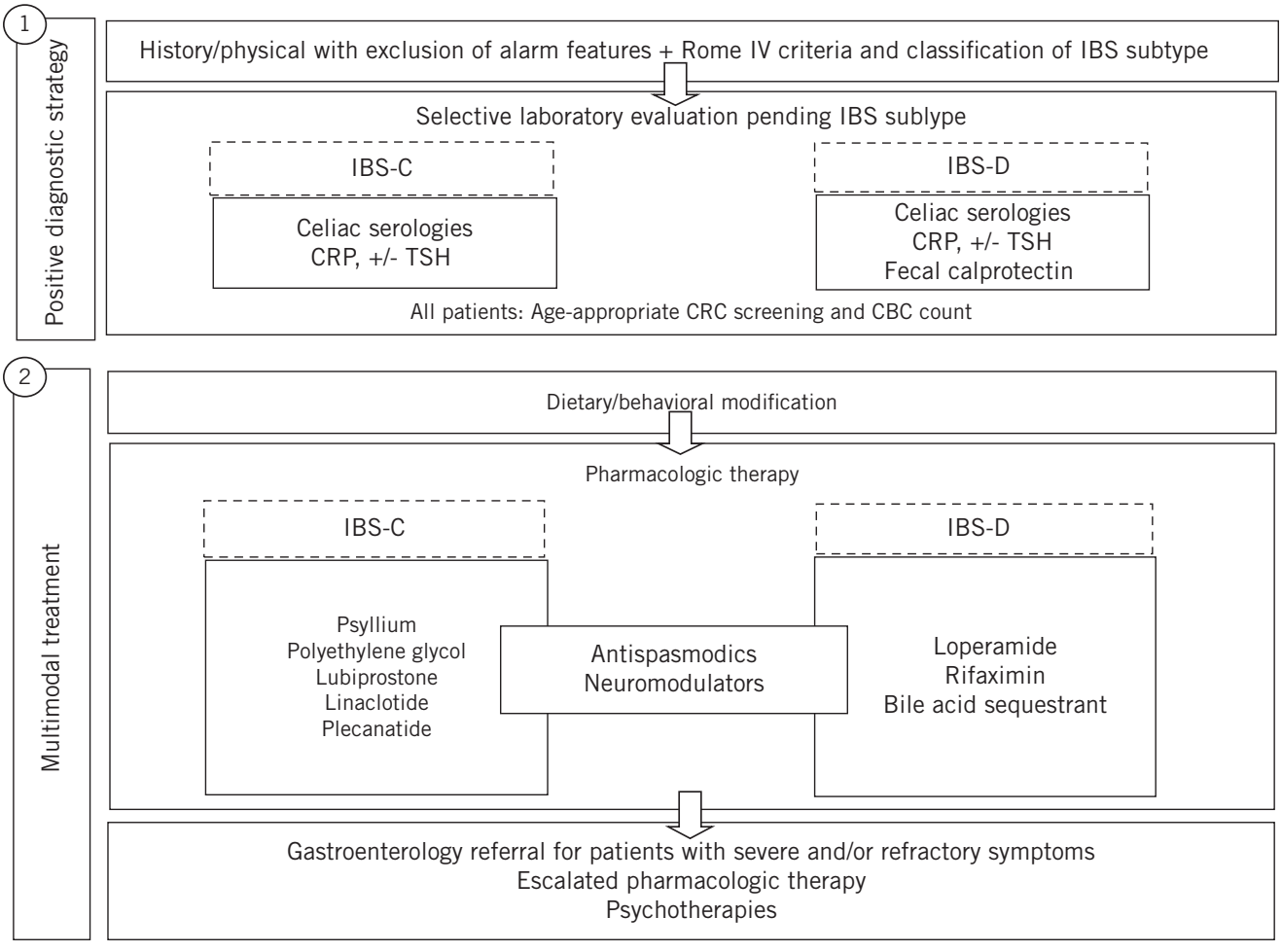
Bile acid sequestrants such as cholestyramine and colestipol can help improve fecal urgency and diarrhea in patients with bile acid malabsorption.[3,15] The ACG advises the use of these therapies at the discretion of the clinician.[13]

Eluxadoline is a mixed opioid receptor modulator that acts on opioid receptors in the GI tract to improve pain and stool consistency while reducing the incidence of constipation.[23] Eluxadoline may be appropriate for patients whose IBS symptoms have not responded to conventional therapies. Eligibility and contraindications must be reviewed. The most common adverse reaction to eluxadoline is constipation.[23]

Alosetron is a 5-HT3 receptor antagonist that is centrally and peripherally mediated.[23] It slows colonic transit, improves stool consistency, relieves fecal urgency, and reduces visceral pain.[3,23] Alosetron is indicated for women with severe IBS-D whose symptoms have not responded to conventional therapies.[3,4,23] Alosetron is restricted for use under an FDA-administered risk-management program, because of serious GI adverse reactions such as ischemic colitis and complicated constipation.[3,4,7,23]

Psychotherapies Growth in understanding the brain-gut axis and neurosciences has paved the way for psychotherapies in the management of IBS.[7,9,20] Multiple

FIGURE 1. Diagnostic and treatment approach to IBS[3,4,6,7,9,16,17,20,22,23]



psychologic therapies including mindfulness, relaxation techniques such as diaphragmatic breathing, cognitive behavioral therapy, and gut-directed hypnotherapy may be of benefit.[3,7,9,20] These therapies help target visceral hypersensitivity and facilitate coping skills and self-regulation techniques.[20] Psychotherapies are not widely available, require time-intensive counseling and patient motivation, and response is largely therapist- and patient-dependent.

THERAPEUTIC CLINICIAN-PATIENT RELATIONSHIP

A therapeutic clinician-patient relationship can improve rapport, adherence to therapy, and symptom relief.[12] Bowel habits are a sensitive topic; open communication is key. Clinicians must be proactive, patient, and transparent when asking patients about bowel habits.[1] Active listening is necessary to understand the full effect of symptoms on patient quality of life.[4] Validating symptoms, educating patients about the brain-gut axis, and reassuring them of the benign nature of IBS is paramount.[3,20] Despite periods of exacerbations and quiescence, IBS is not associated with long-term complications or malignancy.[1] Encouraging continuity of care; offering interdisciplinary support with gastroenterology, nutrition, and behavioral health; and incorporating shared decision-making create a solid foundation for effective management. **Figure 1** outlines a diagnostic and treatment approach in primary care.

CONCLUSION

IBS is attributed to disorders of the brain-gut axis.[12] This common and burdensome disorder remains misunderstood leading to delayed diagnosis, impaired quality of life, and substantial healthcare costs. Advances in clinicians' understanding of this complex biopsychosocial process, coupled with a paradigm shift from a diagnosis of exclusion to a positive diagnostic strategy, and incorporation of dietary/behavioral modifications, pharmacologic therapies, and psychotherapies aim to improve this gap.[7,12] A therapeutic clinician-patient relationship focused on open communication and shared decision-making is the cornerstone of managing patients with IBS. **JAAPA**

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