REVIEW ARTICLE

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Irritable Bowel Syndrome

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The irritable bowel syndrome (IBS) is a chronic and sometimes disabling functional bowel disorder.[1,2] Traditionally, this functional diagnostic label has been applied when no obvious structural or biochemical abnormalities are found, but emerging evidence suggests that distinct pathophysiological disturbances may account for the symptoms and that IBS is unlikely to be one disease or merely a psychiatric (somatosensory) disorder.[2] The Rome IV criteria,[1] derived from a consensus process by a multinational group of experts in functional gastrointestinal disorders, constitute the current standard for diagnosing IBS. According to these criteria, IBS is diagnosed on the basis of recurrent abdominal pain related to defecation or in association with a change in stool frequency or form (Table 1). Bloating is a common accompanying symptom. Symptoms must be chronic, occurring at least once per week, on average, in the previous 3 months, with a duration of at least 6 months.

IBS negatively affects quality of life and work productivity. It has been estimated that patients would give up 10 to 15 years of life expectancy for an instant cure of the disease.[3] The prevalence of IBS in the United States is between 7% and 16%, and the condition is most common in women and young people.[4] Direct costs associated with IBS in the United States have been estimated, conservatively, at more than $1 billion.[5] Thus, diagnosing IBS accurately, minimizing invasive investigations, and recommending effective treatment have an important role in efforts to reduce the societal and economic effects of the disease.

Classification

On the basis of the Rome IV criteria, IBS is classified into four subtypes (IBS with diarrhea, IBS with constipation, IBS with mixed symptoms of constipation and diarrhea, or unsubtyped IBS) according to patients' reports of the proportion of time they have hard or lumpy stools versus loose or watery stools.[1] The rationale for these subtypes is to improve the homogeneity of patients recruited for clinical trials, guide effective diagnosis and therapy, and increase knowledge of potential pathophysiological mechanisms.

Diagnosis

National guidelines for IBS management state that in a patient who has symptoms meeting the Rome IV criteria, with no alarm features (Table 1), the physician should make a positive diagnosis of IBS without resorting to a battery of tests.[6] However, a survey suggests that community or primary care providers are more likely to request confirmatory tests and less likely to adopt a positive diagnostic strategy than are experts in the field.[7] Nevertheless, the yield of investigations performed to rule out organic disease in patients presenting with symptoms suggestive of IBS is low.

Ordering a panel of blood tests routinely is unsupported by the evidence, although clinicians often request a complete blood count and C-reactive protein measurement to help rule out inflammatory bowel disease. Guidelines for the management of celiac disease recommend screening persons with IBS-type symptoms by means of serologic testing.[8] This recommendation is supported by a recent meta-analysis showing that the prevalence of biopsy-confirmed celiac disease was significantly increased among patients with any IBS subtype, as compared with controls who did not have IBS.[9] Whether any further testing is required depends on the IBS subtype. A diagnostic algorithm is outlined in Figure 1.

In patients with IBS-like symptoms dominated by chronic constipation, obstructive defecation (pelvic-floor dyssynergia) should be considered, since the condition responds to biofeedback.[11] Symptoms such as the need for self-digitation are a poor guide to the diagnosis of obstructive defecation, but a rectal examination that reveals paradoxical anal contraction on straining can be helpful, and anorectal manometry can confirm the diagnosis. Performing a pelvic and rectal examination, followed by ultrasonography (transabdominal and transvaginal) if a mass is detected, should be considered in postmenopausal women with constipation of recent onset, localized lower abdominal pain, and abdominal bloating or distention, since ovarian cancer, although rare, may be the underlying cause of the symptoms.[12]

In patients who have IBS with diarrhea or with both diarrhea and constipation, distinguishing between organic and functional lower gastrointestinal disease on the basis of symptoms may be more difficult. In patients with these subtypes of IBS, measurement of the fecal calprotectin level is useful because it can discriminate between IBS and inflammatory bowel disease with good accuracy (i.e., high sensitivity and specificity).[13] Fecal calprotectin testing is also an alternative to indiscriminate use of colonoscopy, which has a low yield. In a cross-sectional study involving 466 patients with the diarrheal or mixed subtype of IBS who underwent colonoscopy, no cases of colorectal cancer were detected, and inflammatory bowel disease was observed in less than 2% of the patients.[14] A meta-analysis showed that more than 1 in 4 persons with the diarrheal subtype of IBS has evidence of bile acid diarrhea on 23-seleno-25-homotaurocholic acid (^{75}SeHCAT) testing,[15] which involves administration of ^{75}Se-homocholyltaurine, a bile acid radiolabeled with the gamma-emitting isotope selenium-75, with whole-body retention measured by means of gamma-camera scanning at 7 days. However, this test is not available in the United States. Biochemical testing of blood (e.g., testing for serum 7α-hydroxy-4-cholesten-3-one [C4, a bile acid precursor]) is becoming available. A therapeutic trial of a bile acid sequestrant may be an alternative diagnostic approach.

IBS is thus not a diagnosis of exclusion. Support for a positive diagnostic approach is provided by data showing the stability of a diagnosis of IBS during longitudinal follow-up of patients, in whom the development of subsequent organic lower gastrointestinal disease is rare.[16] Further evidence for this approach comes from a Danish randomized, controlled trial involving 302 patients with suspected IBS.[10] A positive diagnostic approach based on symptoms was compared with an approach in which organic disease was ruled out by performing an extensive panel of blood tests, stool analysis, and flexible sigmoidoscopy with biopsies. The two approaches did not differ with respect to quality of life, IBS symptoms, or patient satisfaction, and costs were lower with the positive diagnostic strategy.

Table 1. Rome IV Criteria for the Irritable Bowel Syndrome.*

Patient has recurrent abdominal pain (≥1 day per week, on average, in the previous 3 mo), with an onset ≥6 mo before diagnosis
Abdominal pain is associated with at least two of the following three symptoms:
Pain related to defecation
Change in frequency of stool
Change in form (appearance) of stool
Patient has none of the following warning signs:
Age ≥50 yr, no previous colon cancer screening, and presence of symptoms
Recent change in bowel habit
Evidence of overt GI bleeding (i.e., melena or hematochezia)
Nocturnal pain or passage of stools
Unintentional weight loss
Family history of colorectal cancer or inflammatory bowel disease
Palpable abdominal mass or lymphadenopathy
Evidence of iron-deficiency anemia on blood testing
Positive test for fecal occult blood

* The information is from Mearin et al.[1] GI denotes gastrointestinal.

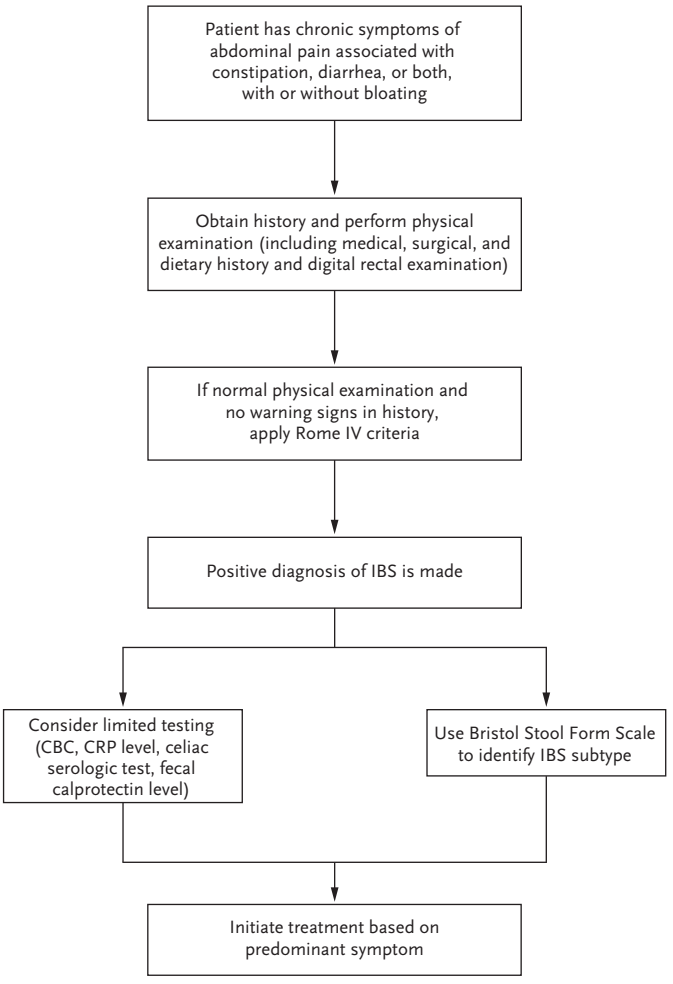


Figure 1. Diagnostic Algorithm for the Irritable Bowel Syndrome (IBS).

IBS can be accurately diagnosed with the use of a stepwise approach.[10] Patients with suspected IBS have symptoms of abdominal pain[1]; the absence of abdominal pain precludes the diagnosis. Disordered bowel habits also need to be present. Abdominal bloating is not required but is frequently present and supports the diagnosis. A detailed history should be obtained to rule out warning signs and to consider disorders that can mimic IBS (e.g., carbohydrate malabsorption, celiac disease, ovarian cancer, and microscopic colitis). Physical examination in patients with IBS generally reveals no abnormalities other than abdominal tenderness, which is more common in the lower abdomen than in the upper abdomen; tenderness is not increased by tensing abdominal wall muscles. The presence of ascites, hepatosplenomegaly, enlarged lymph nodes, or a mass should prompt the clinician to seek an alternative diagnosis. A digital rectal examination should be performed, especially in patients with constipation; overlapping pelvic-floor dyssynergia can be identified with a careful digital examination. In the absence of warning signs, the Rome IV criteria should be applied to make a positive diagnosis. The clinician may order appropriate limited diagnostic testing to rule out other, less common, causes of similar symptoms. The Bristol Stool Form Scale can be used to accurately classify the patient as having IBS with constipation, IBS with diarrhea, or IBS with mixed symptoms of constipation and diarrhea. Treatment should be initiated as soon as the diagnosis is made and should focus on the predominant symptoms.

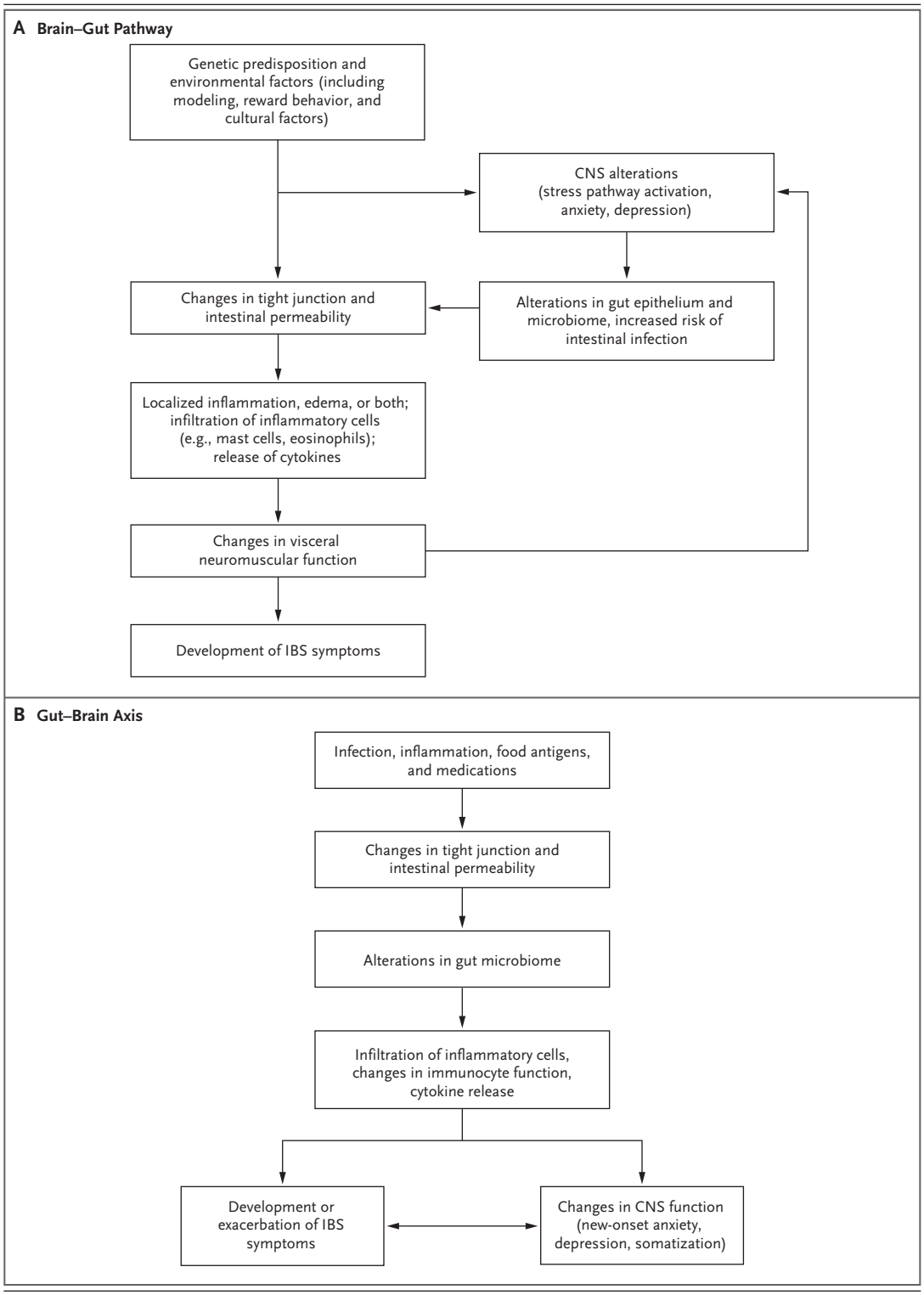
Figure 2 (facing page). Pathogenesis of IBS.

IBS has traditionally been thought of as a brain–gut disorder (Panel A). In susceptible persons (e.g., those with a genetic predisposition or exposure to environmental factors), an abnormal stress response, in combination with psychological distress (e.g., anxiety, depression, or somatization), and an infectious or inflammatory response may alter intestinal permeability and initiate a cascade of events (e.g., infiltration of inflammatory cells, localized edema, and release of cytokines or chemokines) that results in the development of IBS symptoms. Recent data show that immunocytes may play an important role in some patients.[20] Coexisting depression, somatization, and catastrophization may also mediate changes in gut permeability, the immune system, and the microbiome, leading to the development of IBS symptoms. The presence of IBS symptoms may exacerbate symptoms of anxiety, depression, or somatization, further intensifying the gastrointestinal symptoms. Emerging data show that in up to half of patients with IBS, gastrointestinal symptoms develop first, with subsequent development of mood disorders (Panel B).[21] Changes in the gut microbiome and the release of inflammatory mediators may be responsible for the central nervous system (CNS) disorders that arise after the development of IBS symptoms.[22] The ensuing psychological distress may further exacerbate IBS symptoms.

In the absence of established structural lesions to account for IBS symptoms, an accurate, noninvasive diagnostic test remains elusive. Research has focused on developing novel biomarkers (physiological mechanisms, genes, proteins, or metabolites) to aid in the diagnosis. In a meta-analysis examining all currently described approaches to diagnosing IBS,[17] biomarkers performed no better than symptom-based criteria. A recent study examined the accuracy of two serum biomarkers (antibodies to a bacterial toxin produced by *Campylobacter jejuni* and vinculin),[18] which distinguished IBS from inflammatory bowel disease with good specificity (92% for *C. jejuni* and 84% for vinculin) but low sensitivity (44% for *C. jejuni* and 33% for vinculin). These results require confirmation. Certain biomarkers, such as measures of colonic transit or fecal bile acids, may also enable the detection of mechanistic subtypes of IBS, allowing for more individualized, targeted therapy.[19]

PATHOPHYSIOLOGY

Although subtyping of IBS currently guides management, each subtype probably comprises more than one disease entity, which may account for



heterogeneous responses to treatment.[2] Traditionally, IBS has been conceptualized as a brain–gut disorder because of its high association with coexisting psychiatric and psychological conditions, especially anxiety and depression (Fig. 2A).[1] This is not explained by health care–seeking behavior and is probably intrinsically linked to gut symptoms.[2] Although an exaggerated stress

response with increased circulating levels of corticotropin-releasing factor has been observed in patients with IBS[23] and associations with severe trauma such as childhood abuse have been noted, blocking corticotropin-releasing factor has not been successful therapeutically.[24] In about half of cases, IBS originates in the gut, not the brain, with IBS symptoms starting first and psychological distress developing later (Fig. 2B).[21] The fact that probiotics can alter signal processing in the brain also supports a gut-to-brain pathway.[25]

After acute bacterial, protozoal, or viral gastroenteritis, IBS-type symptoms persist in 10 to 20% of infected patients.[20] Persons with a type 2 helper T-cell phenotype may be at increased risk.[26] The pathophysiology of postinfectious IBS appears to be different from that of IBS due to noninfectious causes. For example, patients with postinfectious IBS are more likely to have subtle intestinal inflammation; some have increased infiltration of colonic and small intestinal mast cells.[20] It is unclear whether specific persistent infections can lead to IBS, although colonic spirochetosis has been linked to previously unrecognized, subtle colonic eosinophilia and IBS with diarrhea.[27]

The intestinal microbiome might be altered in IBS,[28] although a characteristic signature and causation have not been established. A prospective study involving 110 patients with IBS showed that the severity of IBS was associated with a distinct fecal microbiota signature, characterized by reduced microbial diversity, and a reduced prevalence of Methanobacteriales and prevotella.[29] The mucosa-associated microbiome is not the same as the stool microbiome, and cross-contamination during endoscopic biopsy may be a factor that accounts for the heterogeneous findings among individual studies.[30] Gas production by bacteria may induce intestinal reflex responses through bowel distention that leads to inadequate relaxation of the diaphragm, pushing out the abdomen and causing visible abdominal distention.[31] Dietary change rapidly alters the microbiome,[32] although whether this explains the benefit of dietary therapies in some patients with IBS is unclear.

Alterations in sensory function (e.g., intestinal hypersensitivity) and motor function (e.g., rapid intestinal transit in IBS with diarrhea or slow intestinal transit in IBS with constipation) have been documented,[33] although none are pathognomonic. Intestinal permeability may be altered in some patients with IBS, especially those with diarrhea (Fig. 3).[34] This may partly explain why immune activation has been observed in IBS, potentially altering local release of serotonin and modulating sensory and motor function.[35] It is unknown whether immune activation is more pronounced in women than in men and whether it wanes with advancing age, but theoretically, it may account for the observed epidemiology of IBS. Biologic markers of jejunal immune activation, perhaps occurring as a consequence of altered gastrointestinal barrier function, appear to correlate with the severity of diarrhea and also depression.[36] Furthermore, circulating levels of tumor necrosis factor α may be increased in patients with IBS, and increased levels correlate significantly with anxiety.[22] These observations suggest that intestinal inflammation drives psychological distress directly in some cases.

IBS clusters in families, and genetic and early-life influences are both important.[37,38] A specific mutation has been identified in a sodium channel gene (*SCN5A*), probably explaining 2% of cases. Mexiletine reversed many of the sodium channel defects in vitro and normalized bowel habits in vivo in a patient who had IBS with constipation.[39] Congenital sucrase–isomaltase deficiency may represent another explanation for familial clustering of the IBS phenotype.[40] Other investigators have observed altered small-bowel mucosal expression of genes involved in ion transport, barrier and immune function, and mast-cell function.[41]

Symptoms of IBS are similar whether they arise primarily from the gut, after infectious gastroenteritis, or from the brain, after severe life trauma. This observation may eventually alter treatment paradigms, defining the initial target for IBS therapy.

TREATMENT

The heterogeneity of IBS, even within individual subtypes, makes it difficult to design an algorithm to fit all patients. Evidence for various therapies is summarized in Table 2.[6] Older drugs and dietary interventions have been tested in small studies, with end points that would not currently be considered acceptable by the Food

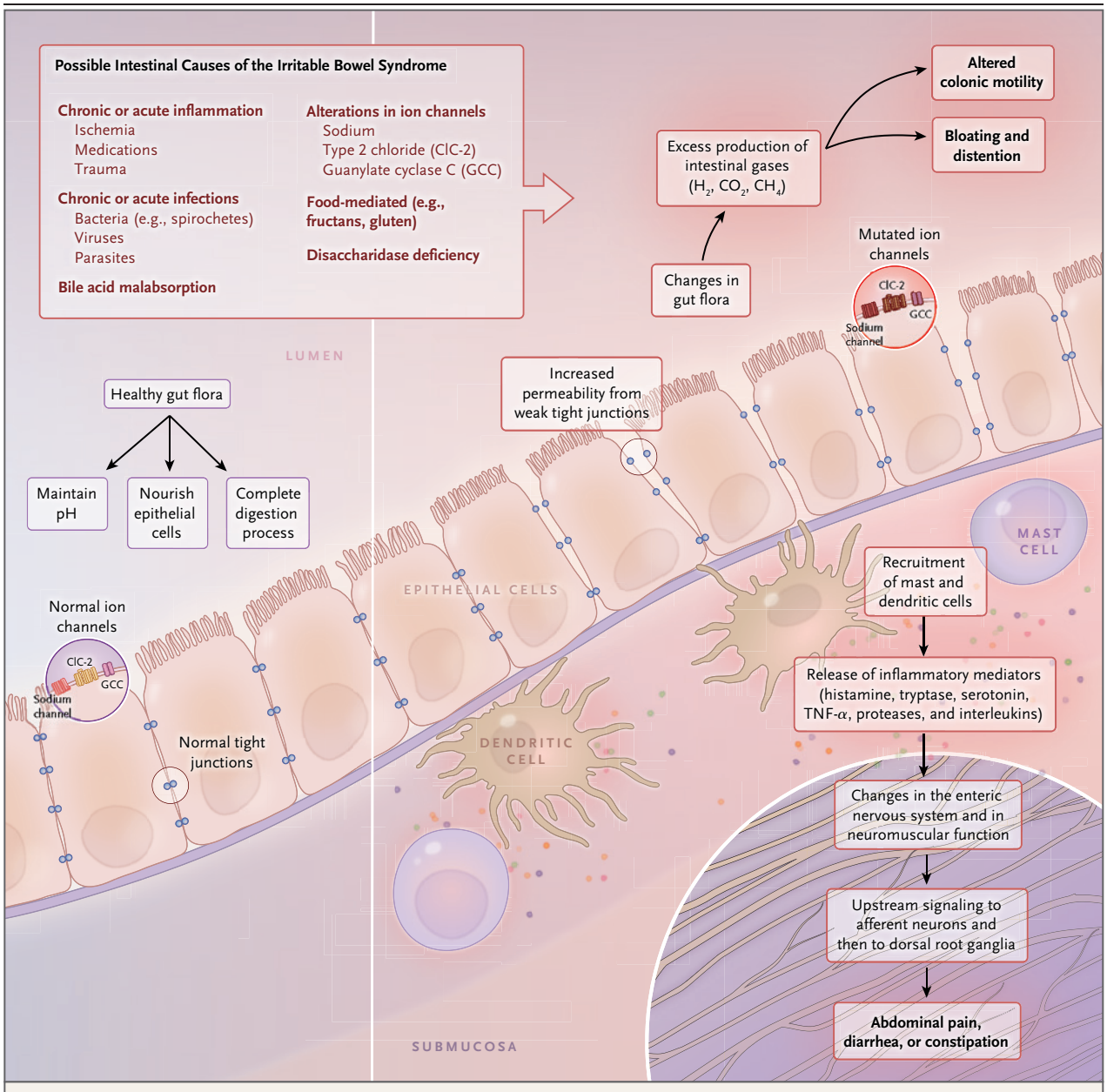


Figure 3. Theoretical Model of the Pathophysiology of IBS.

In healthy persons, tight junctions prevent luminal gastrointestinal tract material (e.g., chemicals, bacteria, medications, and food antigens) from entering the subepithelial space, and intestinal flora play a critical role in maintaining pH and nourishing epithelial cells, as well as completing the process of digestion, which results in the production of intestinal gas (e.g., hydrogen, carbon dioxide, and methane). In susceptible persons, however, it is postulated that infection or consumption of certain foods (e.g., foods containing fructans or gluten) increases intestinal permeability by altering tight junctions. Localized inflammation then develops, with a subsequent influx of inflammatory cells. Inflammatory mediators are released, altering neuromuscular function within the luminal gastrointestinal tract. This may lead to symptoms of abdominal pain and accelerated or delayed transit through the gastrointestinal tract with consequent diarrhea or constipation, respectively. Symptoms of bloating and distention may develop, in part because of changes in the normal gut flora and excess gas production, with abnormal intestinosomatic reflex responses. Disaccharidase deficiency (e.g., congenital sucrose–isomaltase deficiency) and alterations in normal ion-channel function may lead to IBS symptoms in some patients. Not all the pathophysiological processes shown occur in all patients with IBS or in all IBS subtypes. Rather, the wide range of pathophysiological abnormalities identified to date in patients with IBS are shown. TNF-α denotes tumor necrosis factor α.

Table 2. Interventions for Patients with the Irritable Bowel Syndrome, According to Efficacy, Level of Evidence, Side Effects, and Cost.*

Therapy†	Study Outcomes	Reported Efficacy	Quality of Evidence	Limitations of Data	Side Effects	Monthly Cost without Insurance (U.S. $)
Soluble fiber (e.g., psyllium, one sachet three times daily)	Global symptoms	Effective; start at a low dose and increase slowly	Moderate	Only one trial of high quality, and no FDA-approved end points	Diarrhea, constipation, bloating, and flatulence	$15–$30
Low-FODMAP diet	Global symptoms, abdominal pain, bloating	May be effective; nutritionist's guidance helpful	Very low	Few RCTs, many of crossover design with a small number of participants, and no FDA-approved end points	Potential effect on the colonic microbiome, with unknown long-term consequences	NA
Gluten-free diet	Global symptoms, abdominal pain, bloating	May be effective	Very low	Only one placebo-controlled trial, with a small number of participants and no FDA-approved end points; no additive effect over that of a low-FODMAP diet in another small RCT	Potential effect on the colonic microbiome, with unknown long-term consequences	NA
Antispasmodic drugs (e.g., dicyclomine, 20–40 mg four times daily)	Global symptoms, abdominal pain, diarrhea	May be effective but class-dependent	Low	No high-quality trials, only a small number of RCTs assessing each drug, and few trials with FDA-approved end points; none of the drugs identified as effective are available in the U.S.	Abdominal pain, constipation, dry mouth, and dry eyes	$50
Peppermint oil (e.g., Colpermin [McNeil Products], two capsules three times daily)	Global symptoms	Effective	Moderate	Few RCTs and no FDA-approved end points.	Heartburn, dyspepsia, headache, and dry mouth	$9–$19
Lubiprostone, 8 μg twice daily	Global symptoms, abdominal pain	Effective	Moderate	Only a modest benefit over placebo, particularly for abdominal pain	Nausea, diarrhea, and abdominal distention	$348–$358
Linaclotide, 290 μg once daily	Global symptoms, abdominal pain, bloating	Effective	High	Few RCTs	Diarrhea, abdominal pain, and headache	$350
5-HT_3 receptor antagonists (e.g., alosetron, 0.5–1 mg once daily)	Global symptoms, abdominal pain	Effective	High	Only one crossover RCT of ondansetron, which may have no benefit over placebo for abdominal pain; potentially serious side effects with alosetron	Constipation, abdominal pain, nausea, and ischemic colitis	$360–$1,100
Eluxadoline, 75–100 mg twice daily	Global symptoms	Effective	High	Only a modest benefit over placebo for global symptoms, and no benefit over placebo for abdominal pain; potentially serious side effects	Constipation, nausea, abdominal pain, sphincter of Oddi spasm, and pancreatitis	$1,076
Rifaximin, 550 mg three times daily	Global symptoms, abdominal pain, bloating	Effective	Moderate	Few RCTs and only a modest benefit over placebo	Headache, abdominal pain, nausea, and diarrhea	$1,400–$1,900

Probiotics (e.g., *Bifidobacterium infantis* 35624, one capsule daily)	Global symptoms, abdominal pain	May be effective	Low	Few high-quality trials and no FDA-approved end points; bacterial species or strains that are of benefit is unclear	Poorly reported‡	$21
Tricyclic antidepressants (e.g., amitriptyline, 25 mg once daily; if tolerated, can increase dose to 50–75 mg once daily)	Global symptoms, abdominal pain	Effective	Moderate	Few high-quality trials and no FDA-approved end points	Sedation, dry mouth, dry eyes, orthostatic hypotension, arrhythmias, and sexual dysfunction	$4–$9
Psychological therapies	Global symptoms, abdominal pain	Effective	Low	Few high-quality trials and no FDA-approved end points	Poorly reported‡	NA

* Treatment information is adapted from Ford et al.[6] FDA denotes Food and Drug Administration, FODMAP fermentable oligosaccharides, disaccharides, and monosaccharides and polyols, 5-HT_3 5-hydroxytryptamine type 3, NA not applicable, and RCT randomized, controlled trial.
† We recommend 1 month of therapy initially, with the exception of rifaximin, which is licensed for 2 weeks, although retreatment is permitted if symptoms recur.
‡ For probiotics, total numbers of side effects are well reported in available randomized trials, but individual side effects are poorly reported. For psychological therapies, total numbers of side effects and individual side effects are poorly reported in available randomized trials.

and Drug Administration (FDA), whereas new drugs have been assessed in large, rigorous, randomized trials with end points that are FDA-approved.

DIETARY MODIFICATIONS

Many patients with IBS identify specific dietary triggers for their symptoms. Increasing dietary fiber intake is a traditional first-line treatment for patients with IBS, but insoluble fiber, such as bran, can exacerbate abdominal pain and bloating. A systematic review and meta-analysis of seven placebo-controlled trials, involving a total of 499 patients, showed that soluble fiber (psyllium husk) was beneficial in the management of IBS.[6]

There has been a recent resurgence of interest in diet as a treatment for IBS. The recognition that fermentable oligosaccharides, disaccharides, and monosaccharides and polyols (FODMAPs), which are present in stone fruits, legumes, lactose-containing foods, and artificial sweeteners, exacerbate symptoms in some patients because of their fermentation and osmotic effects[42] has led to the use of a low-FODMAP diet as a therapeutic maneuver. In a crossover randomized trial comparing a low-FODMAP diet with a normal local diet,[43] global IBS symptom scores and bloating and pain were significantly reduced with the low-FODMAP diet. Two randomized trials comparing a low-FODMAP diet with conventional dietary recommendations (e.g., eating small, regular meals and avoiding insoluble fiber, fatty foods, and caffeine) showed no significant difference between the two approaches in the overall response to therapy.[44,45] However, in one of these trials, significantly greater improvements in abdominal pain, bloating, stool frequency and consistency, and urgency were noted with the low-FODMAP diet.[45]

Some patients with IBS attribute symptoms to gluten ingestion, despite an absence of immunologic, serologic, and histologic markers of celiac disease. In one small randomized trial, 39 patients with IBS who tested negative for celiac disease and who had had a response to a gluten-free diet continued the diet but were also randomly assigned to receive gluten-containing or placebo muffins and bread.[46] Overall, 68% of those assigned to gluten reported inadequate symptom control, as compared with 40% of those assigned to placebo ($P<0.001$). Since wheat

contains high levels of fructan, a polysaccharide, part of the explanation for the benefit of a gluten-free diet in patients with IBS could be reduced intake of FODMAPs. A trial in which a diet that was both low in FODMAPs and gluten-free was compared with a low-FODMAP diet alone showed no additive benefit of a gluten-free diet,[47] a finding that supports this theory. Although dietary interventions are considered low risk, they rapidly and markedly alter the colonic microbiome; the long-term effects are unknown.[48]

PLACEBO OR REASSURANCE

The placebo response rate in IBS treatment trials is 30 to 40%.[49] In a trial that randomly assigned patients with IBS to a placebo, which they were told had "mind-body self-healing" effects, or to no treatment, 59% of those assigned to the placebo reported adequate relief of symptoms, as compared with 35% of those receiving no treatment ($P=0.03$).[50] We are unaware of any randomized trials that have investigated reassurance as a treatment strategy (i.e., randomized trials that involve reassuring patients of the chronic but benign nature of IBS), although in an uncontrolled study, an explanation of the disease and reassurance were provided, leading to a reduction in patients' perceptions of the degree of impairment in daily functioning.[51] However, any reassurance derived from colonoscopy to rule out organic disease in patients with IBS is short-lived,[52] further supporting recommendations to use diagnostic tests judiciously.

ANTISPASMODIC AGENTS AND PEPPERMINT OIL

Some patients with IBS have abnormal gastrointestinal motility and abnormal contractility of smooth muscle. In a meta-analysis of 23 randomized trials of antispasmodic drugs, involving a total of 2154 patients, hyoscine, pinaverium, and otilonium all appeared to be more effective than placebo, although the numbers of patients in these subgroup analyses were small.[6] None of these agents are available in the United States. One subsequent trial of pinaverium, involving 427 Chinese patients who had IBS with diarrhea, showed that the drug was more efficacious than placebo in reducing abdominal pain and improving stool consistency at 4 weeks.[53] Peppermint oil, which has antispasmodic properties due to smooth-muscle relaxation through blockade of calcium channels, was more effective than placebo in a meta-analysis.[6] A novel formulation of peppermint oil, designed for sustained release in the small intestine, is available for use in the United States.[54]

INTESTINAL SECRETAGOGUES

Lubiprostone and linaclotide are novel drugs that act on intestinal enterocytes to increase fluid secretion into the gastrointestinal tract, through chloride and bicarbonate secretion, accelerating gastrointestinal transit. Both drugs are approved by the FDA for use in patients who have IBS with constipation. Lubiprostone, a prostaglandin derivative, acts on chloride channel protein 2 (ClC-2). In two large randomized trials, involving a total of 1171 patients, a pooled analysis showed that 18% of patients receiving lubiprostone had an improvement in global symptoms, as compared with 10% of patients receiving placebo ($P=0.001$).[55] The effect of the drug on abdominal pain scores in these two trials was statistically significant but modest, and its use may be limited by nausea, which was reported by 8% of treated patients.

Linaclotide is a minimally absorbed, 14-amino-acid peptide that acts on the guanylate cyclase C receptor. In addition to accelerating gastrointestinal transit, the drug inhibits pain fiber activity. In two phase 3 trials of linaclotide, involving a total of 1604 patients, the rate of response (defined as a reduction of ≥30% in abdominal pain and an increase of ≥1 in the number of stools per week) was 33% with linaclotide in each study, as compared with 14% and 21% with placebo.[56,57] Diarrhea was reported by almost 20% of patients taking the drug in each study, although the rate of dropout due to diarrhea was lower, at 5%. Plecanatide, another guanylate cyclase C agonist, was approved in January 2017 by the FDA for the treatment of chronic idiopathic constipation, and phase 3 trials involving patients with IBS with constipation have been completed (ClinicalTrials.gov numbers, NCT02387359 and NCT02493452).

DRUGS ACTING ON 5-HYDROXYTRYPTAMINE TYPE 3 RECEPTORS

Abnormal 5-hydroxytryptamine (5-HT) expression is implicated in the pathophysiology of IBS. Drugs acting on 5-HT type 3 receptors slow co-

lonic transit. In a meta-analysis,[58] alosetron was more effective than placebo in patients who had IBS with diarrhea, for both reduction of global symptoms in four randomized trials, with a total of 1732 patients, and reduction of abdominal pain or discomfort in six trials, with a total of 2830 patients. Adverse events associated with the drug, which is approved in the United States for use in women who have severe IBS with diarrhea, include constipation and, in rare cases, ischemic colitis.[59] Ondansetron, used as an antiemetic agent for 30 years, has a well-established safety profile. In a crossover randomized trial involving 98 patients, treatment with ondansetron led to significant improvements in stool consistency, with a response rate of 80% while patients were taking the drug, as compared with 41% while they were taking placebo. Abdominal pain was not reduced.[60]

DRUGS ACTING ON OPIOID RECEPTORS

Opioid receptors are found throughout the gastrointestinal tract, and drugs that act on them reduce pain perception and slow intestinal transit. Loperamide acts solely on μ-opioid receptors and is often used by patients who have IBS with diarrhea, although evidence of its efficacy is limited.[6] Eluxadoline is a novel drug that acts on δ-, κ-, and μ-opioid receptors. In two phase 3 randomized trials, involving a total of 2427 patients, the drug was more effective than placebo for the treatment of IBS with diarrhea, with response rates of 27% in a pooled analysis, versus 17% with placebo ($P<0.001$).[61] However, no benefit with respect to abdominal pain was noted. Five cases of pancreatitis (0.3%) and eight cases of sphincter of Oddi spasm (0.5%) were documented; patients who had previously undergone cholecystectomy were at increased risk. The drug is approved by the FDA for the treatment of IBS with diarrhea but is not recommended in patients with alcohol dependence or preexisting pancreaticobiliary disease.

ANTIBIOTICS AND PROBIOTICS

The minimally absorbed antibiotic agent rifaximin has been studied in two phase 3 randomized trials, involving a total of 1260 patients who had IBS without constipation.[62] The drug was more effective than placebo for global symptoms and bloating in pooled analyses ($P<0.001$ for both comparisons), although its efficacy was modest. Another large prospective trial showed that repeat dosing with rifaximin was safe and effective.[63] Although rifaximin is FDA-approved for the treatment of IBS with diarrhea, relapse among patients who have a response is usual, and the mode of action is unclear, given evidence that the microbiome is not altered.[64]

Probiotics are attenuated bacteria, or bacterial products, that are beneficial to the host. A meta-analysis suggested that bifidobacterium species may be of benefit as measured by global symptom scores or abdominal pain scores in three randomized trials involving a total of 501 patients, and *Lactobacillus plantarum* (strain DSM 9843) was superior to placebo with respect to the global response in three trials involving a total of 314 patients.[6]

ANTIINFLAMMATORY DRUGS

The observation of low-grade inflammation in a subset of patients with IBS, particularly those with a postinfectious cause, has led to trials of antiinflammatory agents. However, prednisolone and 5-aminosalicylates have not shown superiority over placebo in randomized trials.[65,66]

HISTAMINE RECEPTOR ANTAGONISTS

Mucosal mast-cell activation, with the release of tryptase and histamine, has been implicated in the visceral hypersensitivity observed in a subset of patients with IBS.[67] In a small, placebo-controlled trial, ebastine, a histamine H_1 receptor antagonist, led to reductions in visceral hypersensitivity, and 46% of patients reported symptom relief, as compared with 13% of patients receiving placebo ($P=0.004$).[68]

ANTIDEPRESSANTS AND PSYCHOLOGICAL THERAPIES

Antidepressant agents and psychological therapies may be beneficial in patients with IBS because of the potential role of the brain–gut axis and abnormal central pain processing. A meta-analysis showed that tricyclic antidepressants were more effective than placebo in 11 randomized trials involving a total of 744 patients.[6] Tricyclic antidepressants have anticholinergic properties and slow intestinal transit. These drugs were also more effective than placebo for abdominal pain. The efficacy of other antidepres-

sants, including selective serotonin-reuptake inhibitors, is unclear.[6]

Psychological therapies, such as cognitive behavioral therapy and hypnotherapy, appeared to be beneficial in a meta-analysis,[6] but their efficacy may have been overestimated because of the lack of blinding and the use of a waiting list for receipt of the active intervention as a comparator in some of the studies. A randomized trial showed that the efficacy of hypnotherapy was similar to that of a low-FODMAP diet, but there was no additional benefit of hypnotherapy plus a low-FODMAP diet as compared with either therapy alone.[69] Whether there is a benefit of early use of psychological therapies in the management of IBS is unclear, especially given the difficulty many patients have finding an appropriate provider.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

Many patients with IBS are dissatisfied with conventional medical therapies and seek other forms of treatment. Any benefit of herbal therapies remains unclear, since few studies have been conducted. St. John's wort and a combination of plant extracts known as STW5 (Iberogast, Bayer) have both been tested in patients with IBS.[70,71] STW5 showed superiority over placebo, but St. John's wort was of no benefit. Melatonin has been reported to reduce abdominal pain in patients with IBS.[72]

AN INDIVIDUALIZED APPROACH TO MANAGEMENT

An effective doctor–patient relationship, which requires an empathetic stance on the part of the physician, increases patient satisfaction and reduces the number of subsequent consultations.[73] Reassurance, explanation, and a positive diagnosis are essential steps in management. We recommend starting with dietary modifications (slowly increasing soluble fiber if the patient has IBS with constipation or instituting a low-FODMAP diet temporarily if the patient has IBS with diarrhea or the mixed subtype of IBS). We also recommend increased exercise[74] and stress reduction. A probiotic may be added, especially if bloating is prominent. Pain may be ameliorated with an antispasmodic agent or a tricyclic antidepressant, diarrhea with loperamide or a bile acid sequestrant (e.g., colestipol), and constipation with polyethylene glycol. A 1-month trial of therapy is reasonable before it is stopped. For patients with persistent and troublesome IBS symptoms, linaclotide or lubiprostone may help those who have constipation, and alosetron, eluxadoline, or rifaximin may help those who have diarrhea.

Refractory IBS refers to continuing symptoms, impaired quality of life, and repeated consultations despite medical therapy; pain is often a predominant concern, and at least one psychiatric disorder is usually present. Cure of refractory IBS is generally not possible, but patients can be helped to manage and live with their symptoms. A multidisciplinary team approach to providing patient support is ideal. Opiates should be avoided, since their use increases the risk of the narcotic bowel syndrome, a variant of opioid-induced bowel dysfunction in which recurrent abdominal pain develops with increasing doses of opioid drugs.[75] A combination of gut-directed and central drug treatment, plus psychological therapy, appears to be helpful in minimizing key symptoms.[76] Patients with symptoms that are difficult to manage may request fecal microbial transfer. The efficacy of this approach to the treatment of IBS is unclear, although randomized trials are in progress.

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