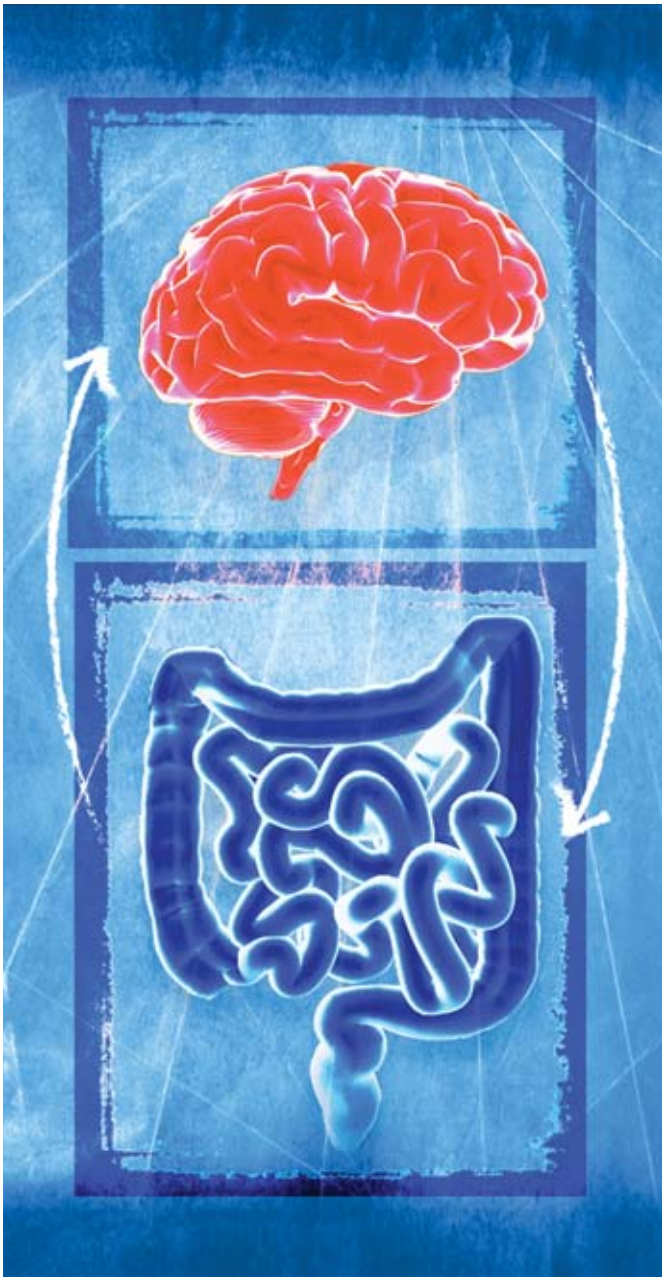
Diagnosis and Treatment of Irritable Bowel Syndrome



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Irritable bowel syndrome (IBS) is one of the most common medical conditions diagnosed today. In the Western world, IBS accounts for up to 33% of referrals to gastroenterologists.[1,2] Although first recognized nearly 2 centuries ago, IBS remains widely misunderstood by both patients and physicians.

For example, 15% of patients with IBS mistakenly believe that IBS eventually develops into cancer, whereas another 30% believe that IBS increases the risk for developing inflammatory bowel disease (IBD).[2] Health care providers also struggle with this complicated disorder as evidenced by a national survey showing that many physicians cannot accurately define IBS.[3] Over the last 2 years, several significant changes related to the diagnosis and treatment of IBS have taken place. This review provides an overview of evolving issues in the diagnosis and treatment of IBS.

Definition

A syndrome is defined as a group of signs or symptoms that characterize a specific disorder. Although the phrase *irritable bowel syndrome* leads many patients and physicians to believe that this disorder is simply a vague amalgamation of nonspecific complaints, IBS remains an appropriate description for a number of reasons. First, this disorder is truly a collection of symptoms rather than just a single, isolated complaint. Second, IBS can affect multiple areas of the gastrointestinal (GI) tract and is not just limited to the colon (ie,

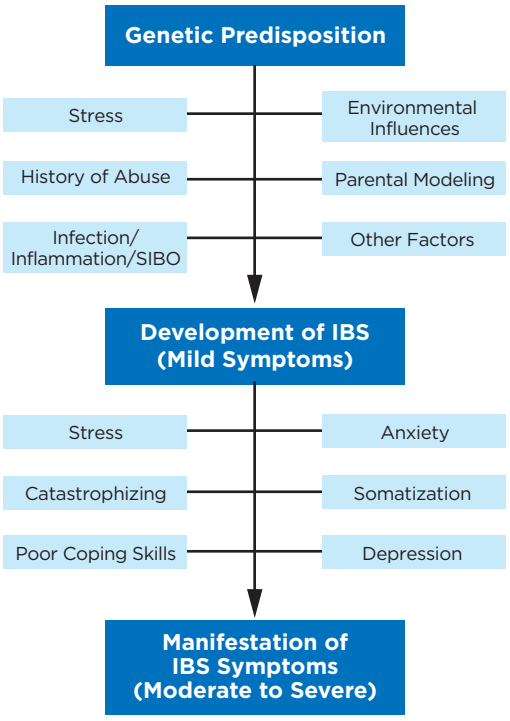

Figure 1. Proposed etiology of IBS.

IBS, irritable bowel syndrome; **SIBO,** small intestinal bacterial overgrowth

the term *irritable colon* should be discarded). Third, at times the intestinal tract does seem "irritable" because of underlying abnormalities in visceral sensitivity.

IBS is defined as a functional GI disorder. Functional bowel disorders are chronic disorders of the GI tract in which an organic or structural lesion responsible for symptom development cannot be identified. Although the lack of objective findings can be frustrating and sometimes confusing to both patients and physicians, a concise definition of IBS does exist, having evolved considerably during the last 30 years. The Manning criteria, published in 1978,[4] were followed by the Rome criteria in 1989,[5] and then the Rome II criteria in 1999.[6] The most recent version of the Rome criteria (Rome III) defines IBS as a chronic disorder characterized by abdominal pain or discomfort associated with disordered defecation (either constipation [IBS-C], diarrhea [IBS-D], or mixed symptoms of alternating constipation and diarrhea [IBS-M]). Symptoms should have developed at least 6 months before the patient first presents for formal evaluation. Abdominal pain or discomfort should be present at least 3 days per month for 3 months and should be associated with 2 or more of the following: improvement with defecation, onset associated with a change in stool frequency, and/or onset associated with a change in stool form.[7]

Prevalence and Epidemiology

IBS is found worldwide, with approximately 4% to 35% of the adult population affected. Several studies from the United States have demonstrated a prevalence of 10% to 15%.[8,9] Although the cause is not known, IBS appears to be slightly more prevalent in women than in men.[8-10] Most studies show that the largest group of patients with IBS are those whose symptoms alternate between constipation and diarrhea, followed closely by IBS-D, and then IBS-C. In most patients with IBS, typical symptoms begin to develop during the late teenage years or early 20s, although the problem may not be diagnosed for many years. The peak prevalence of IBS occurs in the third and fourth decades of life, and the prevalence decreases in the sixth and seventh decades of life. Although IBS can be diagnosed at any age, a new diagnosis of IBS should be made cautiously in patients older than age 60 because other diseases (eg, colon cancer, diverticulitis) may present with similar symptoms. It is important to note that in most patients, IBS is a chronic disorder. Once IBS has been diagnosed, nearly 75% of patients still carry the diagnosis 5 years later.[11]

Etiology

The precise etiology of IBS is not known, although multiple theories abound. One current theory is that some patients are genetically predisposed to develop IBS. An insult or injury, such as an infection, medication, trauma, surgery, or inflammation, then occurs, disrupting normal GI homeostasis (Figure 1). Typical IBS symptoms then develop, and these are generally mild. Concurrent and/or persistent stress, depression, anxiety, somatization, and catastrophizing behavior coupled with poor coping skills may exacerbate and intensify IBS symptoms.

Pathogenesis

Overview

Our understanding of the pathophysiology of IBS has changed considerably during the past 50 years, when it was originally thought to represent a nervous disorder of the GI tract. Almy and Mullin were among the first to propose a connection between the brain and the GI tract when they directly observed changes in colonic motility in patients given stressful information.[12] More recently, research has shown that patients with IBS process sensory information from the GI tract differently. These experiments have demonstrated that IBS is not caused by a single factor; rather, it is a complex disorder in which a number of physiologic processes are involved. These may include abnormalities in intestinal motility, alterations in visceral sensory function, changes in central nervous system (CNS) processing of sensory information, inflammation in the GI tract, alterations in GI flora, and food allergies and sensitivities. These processes are reviewed below.

Altered Gut Motility

Technologic advances in the 1970s enabled researchers to measure motility patterns of the stomach and small intestine directly. When patients with IBS undergo specialized gastric and small bowel motility studies (antroduodenal manometry), discrete clustered contractions are observed in the small intestine. These are bursts of rhythmic contractions and may be associated with episodes of abdominal pain in some patients with IBS.[13] In other patients with IBS, very prolonged contractions are seen within the colon or small intestine, or very high-amplitude propagating contractions within the colon, especially in the postprandial period[14]; these also may be associated with episodes of abdominal pain. Furthermore, in some patients, alterations in the migratory motor complex may either delay (constipation) or accelerate (diarrhea) intestinal transit.[15] Although a number of different patterns of abnormal GI motility have been described in patients with IBS, no single pattern is pathognomonic for IBS. In general, the signs and symptoms of IBS and the underlying alterations in GI motility appear to reflect an exaggeration of the normal patterns of GI motility.

Enhanced Visceral Sensitivity

Abdominal pain is a critical part of the definition of IBS. For years, clinicians have been unable to find an organic reason for the chronic abdominal pain that characterizes patients with IBS. A number of studies now have demonstrated that patients with IBS are more sensitive to pain within the GI tract.[5,16] Many of these research protocols have involved balloon distention of the GI tract to measure this heightened sensitivity.[17] In this procedure, a balloon is placed in the GI tract (rectum, sigmoid colon, ileum) and gradually inflated. Patients with IBS perceive balloon distention at much lower levels of inflation than normal subjects, and they also describe the distention as more painful. Additionally, some patients with IBS suffer from allodynia, in which normal physiologic events are mistakenly interpreted as painful.

Central Nervous System Influences

Sensory processing also may be altered outside the GI tract in patients with IBS. In one study, patients with IBS underwent positron emission tomography scanning of the CNS during rectal balloon distention.[18] The images obtained were compared with images from participants without IBS who underwent similar testing. In comparing the 2 groups, patients with IBS had increased activity in the prefrontal cortex, an area associated with anxiety and hypervigilance, and reduced activity in the anterior cingulate cortex, an area important for opioid binding. A second study that used functional magnetic resonance imaging also reported differences in CNS activity in patients with IBS relative to participants without the disorder.[19] These findings have not been confirmed in larger studies; however, they suggest that patients with IBS may process sensory information from the GI tract differently from individuals without IBS. Additionally, other stimuli, such as stress, anxiety, and depression, may modulate sensory processing and influence the perception of pain. As well, some patients with IBS may be hypervigilant and attend to their symptoms more than healthy volunteers. These findings have significant implications, especially concerning IBS treatment. Therapy that is focused only on the GI tract may not be nearly as successful as a multisystem approach that treats both the GI tract and the CNS.

Other Factors

Several studies have demonstrated that a previous history of infectious gastroenteritis increases the likelihood that IBS will develop in a patient later in life.[20-22] Clinically, many patients recall the persistence of bloating, abdominal pain, and altered bowel habits after an acute infectious illness (eg, traveler's diarrhea). The precise mechanism for this type of IBS (ie, postinfectious IBS) is unknown; however, several possibilities exist. An infectious process may transiently or permanently injure the enteric nervous system, the intrinsic nerve supply responsible for coordinating peristaltic activity within the GI tract. Another possibility is the development of immune hypersensitivity, in which recurrent exposure to a previously benign substance induces inflammation and alters GI motility. Some experts also believe that an infectious agent can initiate a cycle of chronic mucosal inflammation that eventually alters gut motility.

A history of abuse also may play a role in the development of IBS. Several studies have shown a higher prevalence of physical or sexual abuse in patients (primarily women) with IBS than in control groups without IBS.[23] A history of abuse is an important factor to consider in patients with functional bowel disorders, and this issue should be raised during the initial evaluation. The timing of the discussion depends on both the patient and the physician.

The prevalence of celiac disease in the United States is estimated to be 0.75% or 1 in 133.[24] Symptoms of celiac disease can mimic IBS—bloating, abdominal distention, and diarrhea.[25] Several years ago, there was a flurry of interest in what appeared to be a much higher than normal overlap of IBS and celiac disease. However, larger prospective studies have not confirmed these preliminary results.[26,27] Rather than screening all patients with IBS for celiac disease, a commonsense approach (described below) would be to focus on patients with the disorder, primarily those with IBS-D, with persistent symptoms who fail standard therapy.

Small intestinal bacterial overgrowth (SIBO) is defined as the presence of excessive bacteria in the upper GI tract. SIBO is frequently implicated as the cause of chronic diarrhea and malabsorption, and its symptoms (bloating, distention, abdominal cramps,

and diarrhea) can frequently be confused with those of IBS. Several years ago, in an uncontrolled study, Pimentel and colleagues found that 78% of 202 patients who met Rome I criteria for IBS had an abnormal lactulose breath test suggestive of SIBO.[28] This study generated a considerable amount of excitement in the field of IBS because the findings raised the possibility that IBS could be "cured" with antibiotics. Furthermore, a blinded randomized study then found that 84% of patients who met Rome I criteria for IBS had an abnormal lactulose breath test consistent with SIBO, compared with 20% of healthy volunteers,[29] whereas another group reported a prevalence rate of 65% in 98 consecutive patients with IBS.[30] However, other research groups have failed to replicate these preliminary findings. In one study of 85 consecutive patients who met Rome II criteria for IBS, none had SIBO using glucose breath testing,[31] whereas another study found that only 10% of patients with IBS (Rome II criteria) had SIBO using the lactulose breath test.[32] Two recent studies failed to find any significant association of IBS with SIBO.[33,34] In summary, some patients with IBS likely have an imbalance in their indigenous colonic flora that could produce symptoms of gas, bloating, and distention; however, as a group, patients with IBS are no more likely than healthy volunteers to suffer from SIBO.

Diagnosis

Diagnosing IBS need not be a difficult or prohibitively expensive process. With a thorough interview and careful physical examination, most providers can diagnose IBS at the first office visit.[35] IBS should not be a diagnosis of exclusion, nor should the patient be told, or led to believe, "It is all in your head."

The Rome III guidelines are recommended to identify patients both in clinical practice and for inclusion in research studies.[7] The American College of Gastroenterology (ACG) recommends that clinicians use a broad definition for IBS—abdominal pain or discomfort associated with altered bowel habits and the absence of warning signs or "red flags" suggestive of organic disease.

When a patient with IBS is first evaluated in the office, the differential diagnosis seems incredibly broad (Table 1). However, a careful history revealing chronic symptoms coupled with a normal physical examination narrows the differential diagnosis considerably. Finally, if simple laboratory tests are required, normal results may help to further reassure the patient of the diagnosis. When these simple rules are followed, the accuracy of the diagnosis is 97%.[36]

Many health care providers are uncomfortable making a positive diagnosis of IBS and are concerned about missing an underlying organic disorder.[3] Additionally, many patients with IBS initially seem to be reassured by objective testing showing that a serious organic disorder is not present. A serologic test to help diagnose IBS has been on the market since May 2008. This test was developed by Prometheus Laboratories after an exhaustive review of the medical literature to identify serologic biomarkers that could potentially differentiate IBS from other medical disorders. A large number of biomarkers were initially chosen and evaluated in patients with IBS and non–IBS conditions.[37] From this group, a smaller number of biomarkers were then tested in a larger group of patients, resulting in the identification of 10 separate biomarkers. These were carefully evaluated in a large group of patients (n=1,721) including healthy volunteers (n=235); those who met current Rome criteria (as diagnosed by a gastroenterologist) for IBS (n=876) or other functional GI disorders including dyspepsia, chronic constipation, and functional diarrhea (n=155); and those with organic disorders including IBD (n=398) and celiac disease (n=57). Further testing of this panel revealed a sensitivity of 50%, specificity of 88%, and a positive predictive value of 81%. The clinical utility of this test needs to be assessed further.

Patient History

The 2 most common complaints in patients with IBS are abdominal pain and altered bowel habits; which of the complaints is emphasized depends on which is most disturbing to the patient at the time of presentation. The symptom pattern varies considerably from person to person but remains fairly consistent in a given patient, with symptoms fluctuating in intensity and frequency. Typically, symptoms are intermittent, with symptom-free periods lasting days or rarely a week. Some patients will have daily symptoms without remission.

The presence of abdominal pain or discomfort is required for a diagnosis of IBS.[7] Symptoms of abdominal pain or discomfort should have developed at least 6 months before evaluation. These symptoms should be present at least 3 days per month for the prior 3 months and should be associated with disordered defecation (as noted previously). Abdominal pain should be temporally related to defecation in some way; pain related to urination, menstruation, or exertion suggests an alternative diagnosis. The quality of pain varies among patients, although it remains fairly stable over time in individual patients. Some describe the pain as "crampy," whereas others describe it as sharp or burning. The location of the pain also varies from person to person but remains fairly consistent over time in individuals.

The normal pattern of defecation ranges from 3 bowel movements per week to 3 per day.[38] The pattern of defecation is altered in patients with IBS, and although the altered pattern varies from patient to patient, it is fairly consistent in a given individual. Patients with IBS are usually considered to have any 1 of 3 predominant patterns of altered defecation: IBS-C, IBS-D, or IBS-M. Additionally, a fourth category, labeled unsubtyped IBS, is now recognized. These patients do

not have stool characteristics that fit any of the 3 predominant groups described previously. Many patients prone to diarrhea find that the first stool in the morning is of normal consistency; however, subsequent bowel movements become increasingly loose and are associated with significant urgency, abdominal cramps, and flatulence. The urgency and cramps are temporarily relieved by the passage of stool, but they quickly return and precipitate yet another bowel movement. As bowel evacuation ends, the stools are primarily liquid or mostly mucus, and some patients are left feeling drained. Patients with IBS-C often report the passage of rocky hard, pellet-like stools (scybala). Additionally, they may describe straining and incomplete evacuation. Mucus may cover the stools or be passed alone.

Fecal incontinence (usually slight staining of the undergarments) is more common in patients with IBS compared with the general population and may result from reflex relaxation of the sphincter muscles in association with repetitive colonic contractions. Although not well studied, fecal incontinence is more likely to occur in patients with IBS-D or alternating constipation and diarrhea than in those with IBS-C.

Bloating and abdominal distention are common in patients with IBS and may reflect increased amounts of abdominal gas or, more likely, increased sensitivity to normal amounts of intestinal gas. Gas production may be increased in patients with lactose or fructose intolerance (which can exacerbate underlying visceral hypersensitivity), patients who ingest large amounts of fiber, and patients who ingest legumes (eg, beans) that contain stachyose or raffinose. More recently, SIBO has been invoked as a cause of bloating in patients with IBS.[28,39] However, this area is quite controversial, as other investigators have been unable to replicate the initial impressive findings (see above).[33,34] Although gaseous distention is a frequent complaint, patients with IBS generally do not have more intestinal gas than normal subjects. Instead, their tolerance to distention from normal amounts of intestinal gas is decreased.

Weight loss is not associated with IBS and warrants a more thorough investigation. The patient should be questioned carefully about warning signs, or "red flags." Anemia, occult blood in the stool, and GI bleeding also are not directly associated with IBS, and any evidence of bleeding or anemia, in particular, warrants a thorough investigation. A travel history should be elicited to look for evidence of a recent bacterial or parasitic infection, including giardiasis and amebiasis. Patients with IBS may have constitutional symptoms, such as fatigue, myalgia, arthralgia, fever, chills, and night sweats, although these symptoms more commonly are the result of another disorder, such as fibromyalgia, arthritis, or hypothyroidism, rather than IBS. Attention should be paid to family history, and specific questions should be asked about IBS, celiac disease, and any type of GI malignancy.

Physical Examination

A thorough physical examination serves several purposes and should be performed at the time of the initial evaluation. It assures patients that their complaints are being taken seriously, even if their symptoms are classic of IBS and have been present for many years and no other warning signs exist. Also, multiple disease processes may be present. Although most physicians prefer a single unifying diagnosis for each patient, it is not uncommon for several processes to be ongoing

Table 1. Differential Diagnosis Of Irritable Bowel Syndrome

Inflammatory bowel disease
Crohn's disease
Ulcerative colitis
Nonspecific colitis
Collagenous colitis
Lymphocytic colitis
Malabsorption
Amyloidosis
Bacterial overgrowth
Celiac disease
Lymphoma
Pancreatic insufficiency
Tropical sprue
Lactose/fructose intolerance
Food sensitivities
Food allergies
Urogenital sources of pain in women
Endometriosis
Interstitial cystitis
Ovarian cysts
Pelvic inflammatory disease
Uterine fibroids
Other disorders
Colonic inertia
Diabetic diarrhea
Eosinophilic enteritis
HIV enteropathy
Intestinal ischemia
Malignancy
Mastocytosis
Pelvic floor dysfunction
Viral gastroenteritis
Whipple's disease

simultaneously. Hence, a thorough examination will help uncover possible secondary diagnoses.

In patients with IBS, the findings on physical examination are generally quite normal. The vital signs should be taken and recorded. The results of an examination of the head and neck region, heart, lungs, skin, and cranial nerves should be normal. Examination of the lower abdomen may reveal some tenderness or firmness, especially in the left lower quadrant over the sigmoid colon. The sigmoid colon often contains stool, regardless of whether the patient has IBS, and this can usually be palpated. Signs of rebound and guarding should not be present; if they are, an alternative diagnosis should be sought. The physician also should look for evidence of masses in the abdomen, check for bruits, listen for a succussion splash (heard in patients with gastroparesis), and carefully examine the liver and spleen.

A digital rectal examination should be performed in all patients. An anal fissure may explain a history of rectal bleeding, especially in patients with constipation and straining. A fistula or significant perianal disease raises the possibility of Crohn's disease. Some tenderness is often noted in the rectum of patients with IBS as a consequence of visceral hypersensitivity, rectal spasms, and muscular contractions; however, significant tenderness, evidence of a mass, or blood in the rectum warrants further investigation.

Testing

In patients with IBS, the goals of testing are to establish the diagnosis as early as possible, look for coexisting/alternative diagnoses, and avoid performing unnecessary tests. Although extensive testing has been recommended in the past, it is now recognized that no testing is necessary in younger patients who meet the system-based criteria for IBS and have normal examination findings and no "red flags" uncovered during the history.[1,35,36] Many physicians are concerned, however, about diagnosing IBS confidently without performing any objective tests, especially in an era in which medical malpractice suits are increasing. A complete blood cell count should be obtained and the erythrocyte sedimentation rate (or C-reactive protein level) measured if it has not been recently. If constipation is the predominant complaint, the thyroid-stimulating hormone level also should be checked. If diarrhea is the patient's primary complaint, stool samples should be tested for fecal leukocytes. If fecal leukocytes are present, then stool samples should be tested for routine culture, ova and parasites, and *Clostridium difficile.* Serologic tests for celiac disease also should be performed in patients with persistent IBS symptoms (especially those with diarrhea predominance). A cost-effective approach is to begin by checking serum immunoglobulin A and serum tissue transglutaminase antibody. Flexible sigmoidoscopy is usually recommended for patients younger than 40 years with a change in bowel habits or rectal discomfort, and colonoscopy is warranted in all patients 50 years of age or older (45 and older in African Americans), and in those who have a strong family history of inflammatory bowel disease or colorectal cancer, or who are anemic.

Treatment

General Principles

Because the precise etiology of IBS is not completely known, treatment has focused primarily on the relief of symptoms, which can be achieved through a number of modalities. These include patient education and reassurance, diet, supportive and behavioral therapy, and pharmacotherapy aimed at the underlying pathophysiology of altered GI motility, visceral hypersensitivity, and CNS modulation (Table 2). The successful management of IBS requires that the physician be interested in both the patient and the underlying disorder, that both the patient and the physician have a clear understanding of the current state of knowledge of IBS, and, above all, that both parties recognize the chronic nature of the disorder. This last point implies the acceptance of a prolonged cooperative therapeutic endeavor on the part of the patient and the physician.

Treatment begins with the initial interview and physical examination. This thorough examination should demonstrate to the patient that the physician is taking his or her complaints seriously and sets the stage for a productive, interactive working relationship.[40] The variety of important contributing factors (the patient's diet, emotional state, professional and interpersonal relationships, and fears and concerns) provides ample evidence that they all must be included in the overall treatment plan.

The pathophysiology of IBS and the factors that influence it must be explained to the patient. This helps to emphasize that the disorder is chronic and usually can be managed successfully through the cooperation of the patient and the physician. The ability of the physician to predict the course of the disorder increases the patient's confidence. Furthermore, if patients know what to anticipate and also understand that treatment relieves, rather than eliminates, symptoms of IBS, they are better prepared to face recurrent episodes or flares, which can otherwise be frustrating, disappointing, and even frightening.

Diet

Many patients with IBS believe that their symptoms are the result of food allergies; however, true food allergies are quite uncommon. Instead, in most cases of IBS, it is not what the patient eats that causes symptoms; rather, the simple act of eating precipitates bloating, gas, and abdominal discomfort. Some patients find that they react to certain types of foods, such as carbonated beverages, caffeine, fatty or greasy foods, alcohol,

and certain spices, although no convincing data indicate that these particular foods as a group are more likely to produce problems than any others. Patients may wish to abstain from these foods for a time and note whether their symptoms recur on at least 2 occasions when each food is reintroduced. Any food that appears to precipitate symptoms obviously should be avoided, although clinicians should be careful not to place excessive limitations on the patient's diet.

Lactase deficiency is the most common genetic disorder worldwide; many patients with IBS also are lactose-intolerant. Expensive tests are not required to diagnose this common disorder; the simplest test is to have the patient drink a quart of low-fat milk. If symptoms of bloating, distention, flatulence, and diarrhea do not occur, the patient does not have any significant degree of lactose intolerance. Alternatively, because a lactose-free diet can provide dramatic relief for patients who are lactose-intolerant, it is worthwhile for nearly every patient with bloating, distention, gas, and diarrhea to try such a diet. Patients who improve on a 10- to 14-day trial may slowly add small amounts of lactose-containing foods until symptoms reappear. Alternatively, patients may be counseled to use lactose-free milk, rice milk, almond milk, or soy milk.

Many patients with IBS, especially those with predominant symptoms of diarrhea and bloating, also are fructose-intolerant. Symptoms of fructose intolerance are virtually identical to those of lactose intolerance. Patients should review their intake of beverages and foods containing large amounts of fructose (juices, soft drinks, sports drinks, fresh fruits), and eliminate those items for a 7- to 10-day trial period to see if those items are associated with their symptom complex.

Fiber is routinely used to treat all IBS symptoms. However, excessive fiber, whether dietary or as a supplement, often worsens gas and bloating, and can exacerbate symptoms of diarrhea in patients with IBS-D or those with alternating symptoms. Many patients with IBS-D note a significant improvement in their symptoms of gas, bloating, and diarrhea by reducing their fiber intake.

Pharmacotherapy

Given the complexity of the pathophysiology of IBS and the interplay among the gut, enteric nervous system, and brain, it really is not surprising that during the past 50 years, no single agent has been able to "cure" IBS.[41-43] Historically, the treatment for patients with IBS has focused on individual symptoms of abdominal pain, constipation, diarrhea, or bloating, with available therapies targeting only 1 specific symptom and not addressing the multiple symptoms of IBS. However, over the last several years, the FDA has approved 3 drugs to treat the multiple (global) symptoms of IBS. These drugs—alosetron (Lotronex, GlaxoSmithKline), lubiprostone (Amitiza, Sucampo/Takeda) and tegaserod (Zelnorm, Novartis; now available only for emergency use) are discussed below. Selected medications are also outlined in Table 2.

Constipation. For patients with very mild symptoms, initial treatment involving lifestyle modifications, reassurance, changes in diet, and the use of fiber supplements often is all that is required. Patients should be counseled to increase their daily fluid intake, consume foods with natural fiber (at a goal of 25 g/d), and try to use the bathroom at a set time each day. Many patients find that a daily morning regimen of fiber cereal along with fruit high in fiber and fructose and strong coffee or tea is all that is required. Fiber supplements (methylcellulose, psyllium, polycarbophil, coarse bran, or ispaghula husk), act as hydrophilic agents to bind water and prevent excess dehydration. Although they have been widely used in the treatment of IBS for nearly 30 years, only 3 studies have demonstrated any significant benefit—1 for polycarbophil and 2 for ispaghula husk.[42] However, these agents do not relieve abdominal pain, and at least 30% of patients taking them experience significant bloating and abdominal distention. Magnesium hydroxide, in either liquid or pill form, is also an option for mild cases of constipation, but abdominal pain and bloating are generally not relieved. It is important to note that the long-term use of magnesium hydroxide can be dangerous in patients with renal insufficiency or renal failure.

Prescription medications are available when dietary supplements and over-the-counter medications fail. These include the nonabsorbable sugar lactulose and polyethylene glycol formulations. For example, lactulose may improve symptoms of constipation but will not help abdominal pain or discomfort and may worsen bloating. Although some practitioners use misoprostol or colchicine for the treatment of IBS with constipation, there are no data to support the use of either of these agents and thus they cannot be recommended.

Tegaserod was approved for the treatment of women with IBS-C in July 2002. It selectively stimulates serotonin type 4 (5-HT_4) receptors in the GI tract and helps to initiate the peristaltic reflex. Additionally, tegaserod stimulates fluid secretion into the GI tract.[44] Results from 4 large, randomized controlled trials demonstrated that this medication relieved symptoms of constipation, accelerated orocecal transit, and improved symptoms of bloating and abdominal pain in a significant number of women with IBS-C.[35,44-46] In a consensus statement published by a panel of experts from the ACG, tegaserod was given the highest recommendation available (grade A) for the treatment of women with IBS-C.[35] Additionally, a review published by the American Gastroenterological Association found that tegaserod significantly relieved the global symptoms (ie, abdominal pain, bloating, constipation) of women with IBS-C.[1] The FDA removed tegaserod from the market in March 2007 after a retrospective review determined that tegaserod may have

Table 2. Selected Medications Used in the Treatment of Irritable Bowel Syndrome

Treatment		Dosing	Common Side Effects	Comments
Constipation				
Fiber products	Coarse bran	1-2 tsp/d; advance as tolerated	Bloating, abdominal distention	Anecdotal; few controlled trials
	Ispaghula husk	20 g/d		
	Methylcellulose	0.5-1 T (1-2 g) qd-tid		
	Polycarbophil	625 mg qd-tid		
	Psyllium	3.4 g qd-tid		
Osmotic agents	Lactulose	15-30 mL (10-20 g) qd-bid	Bloating, cramps, flatulence	Few controlled trials; off-label use
	Polyethylene glycol	17 g/d	Nausea, bloating, cramps, flatulence	
5-HT_4 agonist	Tegaserod (Zelnorm, Novartis)	6 mg bid ac for 4-6 wk; if response positive, can consider additional 4-6 wk	Headache, diarrhea	Emergency use only; removed from US market in March 2007
Others	Lubiprostone (Amitiza, Sucampo/Takeda)	8 mcg bid	Nausea, vomiting, diarrhea	Approved by the FDA for chronic constipation and for women with IBS-C
	Magnesium hydroxide	622-1,244 mg qd-qid	Diarrhea, cramps	Mild constipation only; avoid long-term use in patients with renal insufficiency
Diarrhea				
Anti-diarrheals	Diphenoxylate HCl–atropine	5 mg tid-qid	Bloating, constipation, loss of appetite, abdominal pain, nausea, vomiting	Discontinue as soon as diarrhea is controlled
	Loperamide	2-4 mg qid, up to 16 mg/d	Abdominal pain and distention, constipation, dry mouth, nausea, vomiting	
Resin-binding agent	Cholestyramine	4 g qd-bid	Constipation, flatulence, can decrease absorption of other drugs	No controlled trials; off-label use
Opioid	DTO	0.6 mL qid, up to 2.4 mL/d	Sedation, constipation	No controlled trials; off-label use; do not confuse with paregoric—DTO contains 25 times more morphine than paregoric
5-HT_3 antagonist	Alosetron (Lotronex, GlaxoSmithKline)	1 mg qd for 4 wk; if tolerated, can be increased to 1 mg bid	Constipation	Grade 1B-2A recommendation by ACG; discontinue immediately if constipation or signs of ischemic colitis develop; restricted management program; efficacy not well established in men

ac, before meals; **ACG,** American College of Gastroenterology; **bid,** twice daily; **DTO,** deodorized tincture of opium; **GI,** gastrointestinal; **hs,** at bedtime; **5-HT,** serotonin; **IBS-C,** constipation-predominant irritable bowel syndrome; **IBS-D,** diarrhea-predominant irritable bowel syndrome; **IR,** immediate release; **OTC,** over-the-counter; **prn,** as needed; **qd,** once daily; **qid,** 4 times daily; **SR,** sustained release; **SSRIs,** selective serotonin reuptake inhibitors; **T,** tablespoon; **TCAs,** tricyclic antidepressants; **tid,** 3 times daily; **tsp,** teaspoon

[a] *Saccharomyces boulardii* lyo; [b] *Lactobacillus acidophilus, Bifidobacterium, Lactobacillus paracasei, Streptococcus thermophilus;* [c] *Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus casei, Lactobacillus bulgaricus, Streptococcus thermophilus*

Treatment		Dosing	Common Side Effects	Comments
Diarrhea (cont'd)				
Probiotics	*Lactobacillus plantarum, Bifidobacterium infantis,* Florastor[a] (Biocodex), Flora-Q[b] (Kenwood), VSL#3[c] (VSL Pharmaceuticals)	Depends on specific agent used	Generally well tolerated	Off-label use; large, double-blind, placebo-controlled studies needed; if patients use these products, make sure supplements are active
Others	Amoxapine; TCAs: amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline (Vivactil, Odyssey), trimipramine	Various	Dry mouth, dry eyes, sedation, weight gain, cardiac arrhythmias, hypotension, constipation	Small studies have shown reduction of abdominal pain
Abdominal Pain				
Anticholinergic agent	Glycopyrrolate (Robinul, Sciele Pharma; various)	1 mg tid	Fatigue, dry mouth, constipation, urinary retention	No controlled trials; off-label use
Antispasmodic agents	Dicyclomine HCl	Start with 10 mg qid; can increase to 40 mg qid	Dry mouth, dry eyes, mild sedation, urinary retention	High incidence of side effects at high dose; tachycardia and orthostatic hypotension occur uncommonly
	Hyoscyamine	0.125-0.25 mg tid-qid or 0.375-0.75 mg SR bid or 0.125 mg IR/0.25 mg SR bid	Dry mouth, dry eyes, fatigue, urinary retention	No controlled trials; off-label use
Others	Acetaminophen	325 mg q4-6 h prn; 4,000 mg/d maximum	Liver injury when used at high doses, especially if taken in combination with alcohol	Included in this table because commonly used OTC, but generally not effective; no controlled trials
	Carbamazepine	100 mg bid on day 1; can increase by up to 100 mg bid prn; 1,200 mg/d maximum	Anorexia, drowsiness, nausea, elevated hepatic enzymes	No controlled trials; off-label use; black box warning for aplastic anemia and agranulocytosis
	Gabapentin	300 mg/d; can titrate to 1,800 mg/d in divided doses	Dizziness, somnolence, peripheral edema	No controlled trials; off-label use
	Pregabalin (Lyrica, Pfizer)	75-100 mg qd-tid		
	SSRIs: citalopram (Celexa, Forest; various), escitalopram (Lexapro, Forest), fluoxetine, fluvoxamine, paroxetine, sertraline (Zoloft, Pfizer; various)	Various	Sedation, fatigue, sexual dysfunction, weight gain	Off-label use; efficacy in IBS not well established; published reports are conflicting; may prove most efficacious in treating coexisting depression, anxiety, and somatization, rather than abdominal pain per se; more expensive but fewer side effects than TCAs
	Tramadol	After titration, 50 mg q4-6 h prn; 400 mg/d maximum	Dizziness, nausea, constipation, headache, somnolence	No controlled trials; off-label use; possible addiction potential
	Amoxapine; TCAs: amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline (Vivactil, Odyssey), trimipramine	Various	Dry mouth, dry eyes, sedation, weight gain, cardiac arrhythmias, hypotension	Small trials; abdominal pain may be relieved

Table 2. Selected Medications Used in the Treatment of Irritable Bowel Syndrome (cont'd)

Treatment		Dosing	Common Side Effects	Comments
Bloating				
Antispasmodic agents	Clidinium	2.5-5 mg tid-qid ac, hs	Fatigue	No controlled trials; off-label use
	Dicyclomine HCl	Start with 20 mg qid; can increase to 40 mg qid	Dry mouth, dry eyes, mild sedation, urinary retention	High incidence of side effects at this dose; tachycardia and orthostatic hypotension occur uncommonly
	Glycopyrrolate	1 mg tablet tid	Drowsiness, dizziness, blurry vision	No controlled trials; off-label use
	Hyoscyamine	0.125-0.25 mg tid-qid or 0.375-0.75 mg SR bid or 0.125 mg IR/0.25 mg SR bid	Dry mouth, dry eyes, fatigue, urinary retention	
	Methscopolamine (Pamine/Pamine Forte, Kenwood; various)	12.5 mg/d	Drowsiness, dizziness, blurry vision	
	Phenobarbital-hyoscyamine-atropine-scopolamine (Donnatal Extentabs, PBM Pharmaceuticals)	1–2 tablets bid-qid	Fatigue, sedation, blurry vision	
Antiflatulence agents	Simethicone	2–4 125-mg tablets ac	Rare side effects	No controlled trials; off-label use; safe; efficacy not established
	Activated charcoal	1–2 125-mg tablets ac and hs	Altered absorption of other medications; discoloration of stool	No controlled trials; off-label use; efficacy not established
5-HT_4 agonist	Tegaserod (Zelnorm, Novartis)	6 mg bid ac for 4-6 wk; if response, can consider additional 4-6 wk	Headache, diarrhea	Emergency use only; removed from US market in March 2007
5-HT_3 antagonist	Alosetron (Lotronex, GlaxoSmithKline)	1 mg qd for 4 wk; if tolerated, can be increased to 1 mg bid	Constipation	Currently available under a restricted management program for women with IBS-D who fail standard therapy
Antibiotic	Rifaximin (Xifaxan, Salix)	400 mg bid	Generally well tolerated; headache, dizziness, constipation	Off-label use; rifamycin derivative; minimally absorbed from GI tract; small studies have shown improvement in bloating; ACG Grade 1B recommendation
Probiotics	*Lactobacillus plantarum, Bifidobacterium infantis,* Florastor[a] (Biocodex), Flora-Q[b] (Kenwood), VSL#3[c] (VSL Pharmaceuticals)	Depends on specific agent used	Generally well tolerated	Off-label use; large, double-blind, placebo-controlled studies needed; if patients use these products, make sure supplements are active

ac, before meals; **ACG,** American College of Gastroenterology; **bid,** twice daily; **DTO,** deodorized tincture of opium; **GI,** gastrointestinal; **hs,** at bedtime; **5-HT,** serotonin; **IBS-C,** constipation-predominant irritable bowel syndrome; **IBS-D,** diarrhea-predominant irritable bowel syndrome; **IR,** immediate release; **OTC,** over-the-counter; **prn,** as needed; **qd,** once daily; **qid,** 4 times daily; **SR,** sustained release; **SSRIs,** selective serotonin reuptake inhibitors; **T,** tablespoon; **TCAs,** tricyclic antidepressants; **tid,** 3 times daily; **tsp,** teaspoon

[a] *Saccharomyces boulardii* lyo; [b] *Lactobacillus acidophilus, Bifidobacterium, Lactobacillus paracasei, Streptococcus thermophilus;* [c] *Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus casei, Lactobacillus bulgaricus, Streptococcus thermophilus*

been associated with an increased risk for cardiovascular events in some patients. The analysis showed that 13 of 11,614 patients (0.11%) treated with tegaserod had a cardiovascular event compared with 1 of 7,031 patients (0.014%) treated with placebo. It is important to note that most, if not all, of the 13 patients who had a cardiovascular event and were treated with tegaserod had known risk factors for coronary artery disease and were older than age 50. Unfortunately, tegaserod is now only available for emergency use, which places the drug beyond the reach of most health care providers. The withdrawal of tegaserod from the market is concerning because it may limit or halt further research of serotoninergic agents.

Lubiprostone, a bicyclic fatty-acid derivative that activates chloride channels within the lumen of the GI tract, improves symptoms of chronic constipation in both men and women and was approved for the treatment of chronic constipation by the FDA in January 2006.[47] The encouraging results in patients with chronic constipation naturally led to lubiprostone being studied in patients with IBS and constipation, and in April 2008, the drug was approved for the treatment of women with IBS-C. Earlier Phase II dose-ranging studies had determined that 8 mcg of lubiprostone twice daily improved IBS symptoms; however, the sample size was small.[48] In a 2007 study, 1,171 adults diagnosed with IBS-C using the Rome II criteria were randomized to receive either 12 weeks of lubiprostone (8 mcg) given twice daily or placebo given twice daily.[49] Most patients were women (91.6%), and most were between the ages of 18 and 65 (91.7%). The primary efficacy variable was a global question rating overall IBS symptoms, while a 7-point balanced scale was used to rate changes in individual symptoms. Patients reporting at least moderate relief for 4 of 4 weeks, or patients reporting significant relief for 2 of 4 weeks were considered monthly responders, and patients had to be a monthly responder for at least 2 of the 3 months in order to qualify as an overall responder. The authors reported that patients receiving lubiprostone were nearly twice as likely as those receiving placebo to achieve overall response (17.9% vs 10.1%; P=0.001). Secondary end points, including abdominal pain, bloating, straining, stool consistency, and constipation all were significantly improved in the lubiprostone group compared with the placebo group (P<0.05 for all end points). Lubiprostone was generally well tolerated. The most common treatment-related side effects were nausea (8% vs 4% in placebo) and diarrhea (6% vs 4% in placebo). Of note, it is thought that the low placebo rate in this study is the result of the much stricter standards for determining whether a patient is classified as a responder. Also, the lower dose (8 mcg) was chosen based on prior dose-ranging studies and may reflect the fact that patients with IBS often respond to medications at lower doses than other patients. Further trials are planned to assess the long-term benefits of lubiprostone in patients with IBS-C.

Diarrhea. Patients with loose, poorly formed stools may respond to diphenoxylate hydrochloride–atropine or loperamide. Loperamide increases intestinal transit time, thereby allowing more fluid to be absorbed. It also increases external anal sphincter tone and may decrease incontinence and soiling in some patients. Care should be taken to discontinue these medications as soon as diarrhea is controlled to avoid inducing constipation, especially in patients who are prone to alternating constipation and diarrhea. Low doses of tricyclic antidepressants (TCAs) can also decrease the frequency of diarrhea. Some clinicians have prescribed calcium channel blockers to decrease gut motility, although large clinical trials are necessary to confirm their efficacy and safety.

Probiotics are defined as organisms that, when administered in adequate amounts, exert a positive influence on the health of the host animal. Although the precise therapeutic mechanism is unknown, it is theorized that probiotics may ameliorate IBS symptoms by stimulating an immune response, reducing inflammation, or altering the composition of gut flora. Although frequently used by patients with IBS, objective data supporting the efficacy of probiotics is limited. A preliminary report noted that *Bifidobacterium infantis* improved some IBS symptoms, although the sample size was small (n=75).[50] A 2006 study evaluated the efficacy of *B. infantis* in a large group (n=362) of all subtypes of patients with IBS.[51] Women between the ages of 18 and 65 who met Rome II criteria were included. Subjects were randomized in a blinded fashion to placebo or 1 of 3 daily doses of *B. infantis* for the 4-week trial period: 1×10^6 colony-forming units (cfu), 1×10^8 cfu, or 1×10^{10} cfu. The primary efficacy end point was daily abdominal pain and discomfort; secondary end points included individual symptoms of bloating, straining, bowel dysfunction, and incomplete evacuation. *B. infantis,* at a dose of 1×10^8 cfu, improved abdominal pain and discomfort significantly more than placebo (P=0.023), although the other two doses were not better than placebo. Analysis of secondary symptoms (bloating, passage of gas, straining, feelings of incomplete evacuation) demonstrated that *B. infantis* at 1×10^8 cfu daily was significantly better than placebo (P<0.05 for all), although doses of 1×10^6 and 1×10^{10} were not better than placebo. Of note, no dose was associated with a significant change in stool frequency. Adverse events were few in number and not different between *B. infantis* and placebo. Post hoc analysis found that the high-dose capsules (1×10^{10}) coagulated, thus preventing adequate release of the bacterium. In summary, this well-designed, multicenter study is the largest to date to evaluate the safety and efficacy of a probiotic for the treatment of IBS. Further studies are needed to better define the mechanism of action of probiotics and to identify

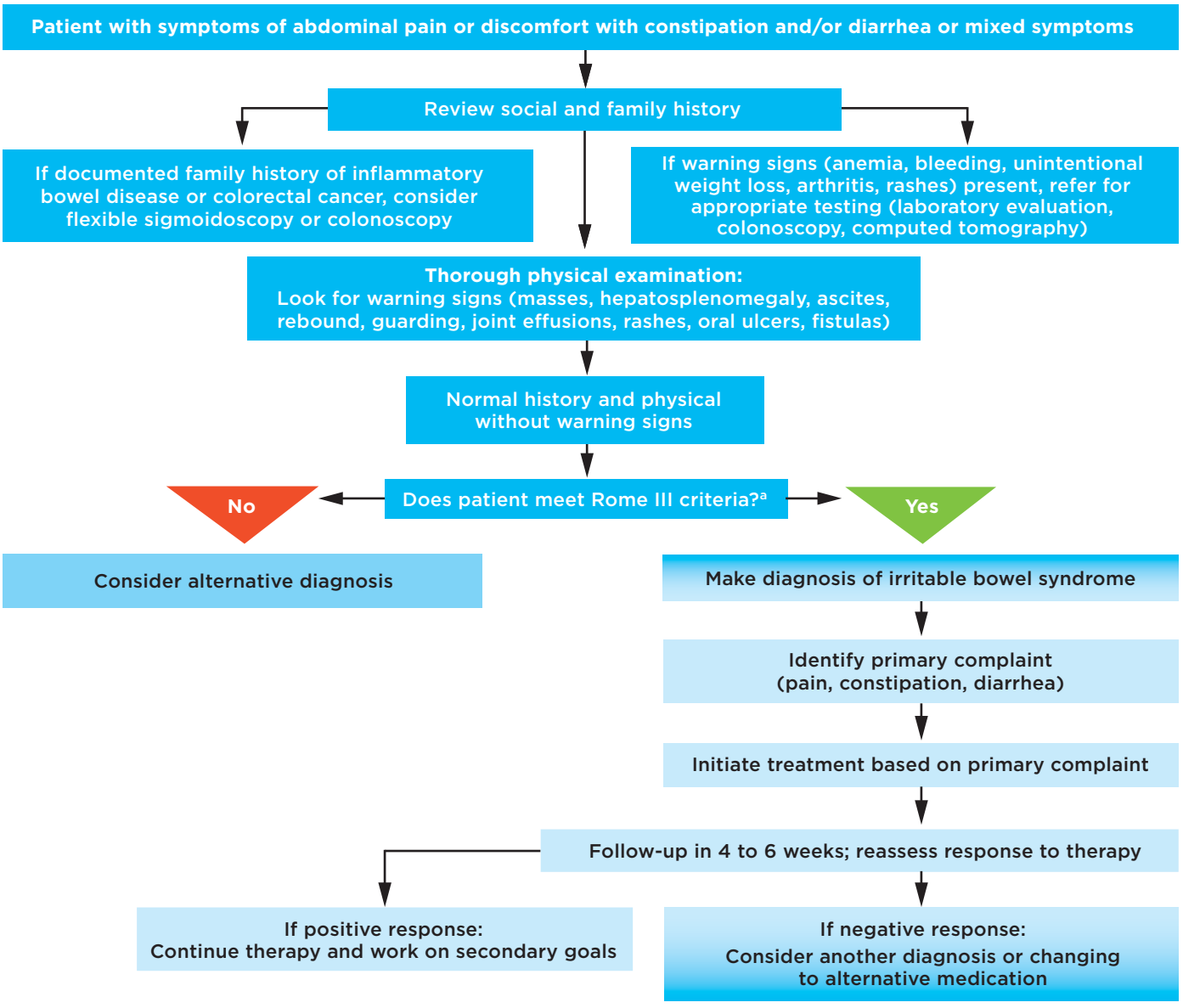

Figure 2. Management algorithm for patients with irritable bowel syndrome.

[a]Symptoms should have developed at least 6 months before the patient first presents for formal evaluation. Abdominal pain or discomfort should be present at least 3 days per month for 3 months, and should be associated with 2 or more of the following: relief with defecation, onset associated with a change in stool frequency, and onset associated with a change in stool form.

which IBS patients might respond with the greatest efficacy. Based on these results, the ACG task force gave probiotics a Grade 2C recommendation.[35]

Patients who do not respond to these medications may benefit from deodorized tincture of opium. Patients can start with 1 or 2 drops each morning in a small amount of water or juice and slowly increase the dose as necessary.

In women with IBS-D who have failed standard therapy, the 5-HT_3–receptor antagonist alosetron is now approved under a limited-use program. A panel of experts from the ACG found that alosetron significantly reduces the global symptoms of diarrhea, abdominal pain, and bloating in patients with IBS-D.[35] Based on several large prospective studies, the ACG task force recently gave alosetron a Grade 1B recommendation for women who have not responded to conventional therapy.[35] After its initial approval, alosetron was withdrawn from the market in November 2000 because of its association with several cases of severe ischemic colitis, some of which were fatal. Additionally, alosetron led to severe constipation in some patients. However, this drug was subsequently allowed to re-enter the US market in November 2002 under a restricted

management plan, and is again available for women with IBS-D. More recent data have demonstrated that long-term use (48 weeks) of alosetron is both safe and efficacious in women with IBS-D.[52] Additionally, since the management plan was instituted, no serious adverse events have been reported with use of alosetron. It is also important to note that patients with IBS are at an overall increased risk for developing ischemic colitis, although the etiology is not known.[53]

Abdominal Pain. Heightened visceral sensitivity and abnormal contractions within the GI tract are considered the underlying cause of abdominal pain in patients with IBS. Therapy for pain during the past 2 decades has consisted mainly of smooth muscle antispasmodic agents. Although there are ample theoretical grounds for prescribing these medications, clinical experience has been disappointing. Most studies that have looked at antispasmodic medications have been poorly designed and poorly controlled and have not shown significant benefits for these agents in comparison with placebo.[42] Nevertheless, some patients improve with antispasmodic drugs, particularly those whose symptoms are induced by meals or who experience tenesmus. When used to prevent meal-induced symptoms, anticholinergics should be taken 30 to 60 minutes before meals so that peak serum levels of the drug coincide with peak symptoms. A meta-analysis has shown that smooth muscle antispasmodics relieve symptoms of abdominal pain in patients with IBS; however, none of the medications tested are available in the United States.[54] As an example, otilonium bromide has been shown to improve symptoms of IBS in several European studies, however, it is not approved by the FDA.[54]

Several TCAs (amitriptyline, nortriptyline, desipramine) have been studied in patients with IBS and have been shown to be effective,[42] but side effects can limit their therapeutic potential. Preliminary data indicate that selective serotonin reuptake inhibitors may relieve chronic abdominal pain.

Analgesic medications should be avoided if possible; if used, they should be prescribed at the lowest dose possible. Aspirin and acetaminophen are safe but not beneficial. Narcotics should not be prescribed.

Bloating. Bloating is one of the most difficult GI complaints to treat. Most medications designed to alleviate gaseous distention have proved to be disappointing. Simethicone and activated charcoal provide some benefit in a limited number of patients, although no controlled studies have been performed. As previously noted, tegaserod and alosetron have been shown to relieve symptoms of bloating.[1,35]

Two therapies have been advocated for the treatment of bloating in patients with IBS. One is the nonabsorbable antibiotic rifaximin (Xifaxan, Salix). Rifaximin is a semisynthetic antibiotic derived from rifamycin, which is effective at treating both gram-positive and gram-negative aerobes and anaerobes. Rifaximin was approved by the FDA in 2004 for the treatment of traveler's diarrhea in patients 12 years of age and older. Two studies have evaluated the safety and efficacy of rifaximin in the treatment of patients with IBS. In the first study, 87 patients with IBS were randomized to receive either rifaximin (400 mg) or placebo 3 times daily for 10 days.[55] At the 10-week follow-up appointment, symptoms of bloating were significantly better in the rifaximin group than in the placebo group (P=0.02). Abdominal pain and diarrhea were not improved however, and the percentage of patients with SIBO was not given. A second study focused on patients with functional bloating (n=124), approximately half of whom met Rome II criteria for IBS.[56] Patients were randomized to either twice-daily rifaximin (400 mg) or placebo for 10 days. At the 10-day follow-up evaluation, global IBS symptoms were better in the group treated with rifaximin (P=0.04), as were symptoms of bloating. Of note, none of these patients had an abnormal hydrogen breath test at baseline. This study is limited by its very short follow-up period. In summary, these results are intriguing and certainly warrant further study with a larger number of patients, longer follow-up periods, and hydrogen breath tests performed at baseline and at the conclusion of therapy. Although several authorities have advanced the idea that this medication treats SIBO in patients with IBS, it is more likely that the transitory benefits result from the suppression of colonic bacteria.[57] Based on these and other studies, the ACG task force gave rifaximin a Grade 1B recommendation.[35]

Probiotics are a second potential new therapy for improving symptoms of bloating associated with IBS. It is believed that probiotics normalize the ratio of anti-inflammatory to proinflammatory cytokines in the gut, thereby alleviating symptoms (see above).

Psychological Management

Psychological management begins with the recognition of depression, anxiety, panic disorder, or a somatization disorder. The symptoms of IBS are often anxiety-provoking and sometimes are perpetuated by social reinforcement (secondary gain). Psychological evaluation and management can usually be conducted effectively by the interested physician without the need for a psychiatric referral. IBS by itself is not an indication for psychiatric consultation. Referral should be reserved for patients who require expert psychotherapy whether or not they have IBS.

Psychological management is dictated by answers to the following questions: Is there evidence of anxiety and are the symptoms aggravated by stress? If so, what are the specific stressors? Is the patient depressed? Does gratification from illness behavior reinforce the illness? What misconceptions does the patient have about IBS? Treatment usually requires a multifocal approach that includes making the patient aware of the problem through counseling sessions,

cognitive-behavioral therapy, stress management, and the use of medications to treat the associated/underlying psychological disorder. Several studies have now demonstrated that this multifocal approach can be very successful.[58]

Alternative Medicines

Many patients with IBS believe that peppermint oil minimizes symptoms of pain and bloating, although a 1998 meta-analysis does not support this view.[59] In contrast, a more recent meta-analysis pointed out that there is some evidence that peppermint oil is more effective than placebo in relieving some symptoms of IBS.[60] Some patients use acupuncture and hypnotherapy with success, although this is patient-dependent. Many patients resort to natural remedies and herbal medications after traditional medications have failed to provide relief. In these cases, the physician should ask the patient to bring the medications or labels into the office to ensure that the patient is not ingesting a toxic or dangerous substance.

New Directions

Linaclotide is a novel peptide that stimulates intestinal guanylate cyclase type-C receptors. Early Phase I studies demonstrated that it improved visceral pain in animals, whereas a Phase II study showed that it improved symptoms in patients with chronic constipation. In a recent multicenter, double-blind, placebo-controlled, dose-ranging study, 420 patients with IBS-C (modified Rome II criteria; <3 complete spontaneous bowel movements per week) were randomized to 1 of 4 different daily doses of linaclotide (75, 150, 300, or 600 mcg) or placebo for 12 weeks after a 2-week baseline period during which symptoms were monitored.[61] The primary end point was the change in complete spontaneous bowel movements; secondary end points were abdominal pain, other symptoms of constipation (eg, straining), and bloating. In all, 337 patients (80%) completed the entire study; 13 of those patients who took the study medication, but none of those on placebo, discontinued the study due to significant diarrhea. Using a strict intention-to-treat analysis (in which patients who dropped out were considered treatment failures), linaclotide—at all study doses—was shown to significantly improve stool frequency ($P<0.023$ or better, for all doses), in addition to symptoms of straining and abdominal pain ($P<0.05$ for all). Linaclotide also significantly relieved bloating in these patients at all doses ($P<0.05$) except the 150-mcg dose, which was not statistically better than placebo. Additionally, patients treated with linaclotide (all doses) were more likely than those treated with placebo to report adequate relief of global IBS symptoms for at least 6 of the 12 weeks in the study period. These promising results have led to the initiation of a large Phase III clinical trial, which is currently ongoing.

Summary

In most cases, IBS is a chronic disorder in which relatively symptom-free periods may alternate with exacerbations of abdominal pain, bloating, constipation, or diarrhea. Longitudinal studies have shown that more than 75% of patients in whom IBS is initially diagnosed retain that diagnosis for 5 years after the initial diagnosis has been made.[11]

Figure 2 provides an algorithm for the management of patients with IBS. The diagnosis of IBS should be straightforward and based on the Rome III criteria in conjunction with a thorough history and physical examination. Extensive testing is generally not required. Treatment should be initiated as early as possible and should focus on the predominant symptom reported by the patient. The standard therapies commonly used to treat IBS are not effective in reducing global complaints of abdominal pain, bloating, and constipation. Medications that target the serotonin system have been shown to significantly relieve symptoms in patients with IBS-C (tegaserod) and patients with IBS-D (alosetron), although the use of these agents is restricted under a management plan (alosetron) or for life-threatening emergencies only (tegaserod). Newer agents that stimulate chloride channels (lubiprostone) or that modulate colonic flora (probiotics and antibiotics) may improve symptoms in some patients and warrant further study.

Physicians may wish to direct patients with IBS who are interested in learning more about testing and treatment options to the American College of Gastroenterology Web site, www.ibsrelief.org.

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