

Irritable Bowel Syndrome: Current Concepts and Future Prospects

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Irritable bowel syndrome (IBS) is the most common gastrointestinal disorder seen by physicians. IBS is characterized by chronic or recurrent abdominal pain and disturbed bowel habits in the absence of structural or biochemical abnormalities. Because of significant overlap of functional gastrointestinal symptoms representing different anatomic regions, a patient with IBS may manifest esophageal, gastroduodenal, biliary, or anorectal symptoms.^{1,2}

The diagnosis of IBS depends primarily on established clinical criteria rather than on laboratory data. The absence of a specific confirming study, heterogeneity of symptoms, and fear of missing an underlying organic disease make this syndrome a diagnostic dilemma in routine medical practice. In addition, IBS has a significant economic impact, consuming an estimated \$8 billion in health care costs annually.³ A systematic and cost-effective approach is therefore required for its diagnosis and management.

EPIDEMIOLOGY

IBS occurs in 10% to 22% of adults in the United States;⁴ however, only 10% of patients with IBS seek medical attention. In the United States annually, IBS accounts for 3.5 million physician visits, predominantly by adult female patients. In India and Sri Lanka, men are more likely than women to present for treatment. Classically, IBS is considered a disorder of the young, especially in white persons. However, recent epidemiologic studies suggest that the prevalence of IBS in elderly persons is similar to that in younger persons.⁵ In fact, the majority of elderly patients who are diagnosed with "painful diverticular disease" may actually have IBS. Another study indicated that IBS is also very common in the African population.⁶

PATHOPHYSIOLOGY

The precise mechanisms involved in the pathogenesis of IBS are still unclear. At least three mechanisms interact: psychosocial factors, altered gut motility, and

visceral hypersensitivity or disturbed intestinal perception of pain. Luminal irritants also may affect these mechanisms (Table 1). The predominance of any of these factors varies among patients.

Psychosocial Factors

Emotional stress is known to affect intestinal motility and transit time.⁷ Several studies have demonstrated that approximately 50% of patients with IBS have a coexisting psychiatric disorder at the time of presentation. These psychiatric illnesses may modulate symptoms of IBS (Table 2).⁸ A recent survey of 206 female patients with IBS reported a 44% incidence of physical or sexual abuse in childhood, a rate which was three to 11 times higher than in control patients.⁹ Patients with IBS view minor illnesses such as colds and the flu more seriously and consult physicians more frequently than patients who do not have IBS. As children, patients with IBS were more likely than other individuals to have received gifts or remained home from school when ill.¹⁰ One study found a significant correlation between morning IBS symptoms and the quality of prior night's sleep.¹¹ Symptomatic constipation was noted more frequently in women with IBS after hysterectomy, whereas the rectum was found to be more irritable in patients with IBS after cholecystectomy.¹²

Altered Gut Motility

Before the 1980s, abnormalities in intestinal motility were considered the usual explanation for symptoms of IBS. Snape et al¹³ described a predominant 3-cycles-per-second slow-wave pattern in patients with IBS compared to control patients. Later, inflated balloons were used to

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Table 1. Pathogenesis of Irritable Bowel Syndrome

Psychological distress
Abnormal gut motility
Abnormal visceral perception
Luminal factors irritating the small bowel or colon
Lactose, other malabsorbed sugars, or complex carbohydrates
Bile acids, short chain fatty acids
Food allergens
Drugs

Adapted with permission from Camilleri M, Choi MG: Review article: irritable bowel syndrome. *Aliment Pharmacol Ther* 1997;11:3–15.

Table 2. Psychological Features of Irritable Bowel Syndrome

Somatization
Obsessive-compulsive behavior
Interpersonal sensitivity
Depression
Anxiety
Hostility
Phobia
Paranoia
Psychosis

Adapted with permission from Misra SP, Thorat VK, Sachdev GK, et al: Long-term treatment of irritable bowel syndrome: results of a randomized controlled trial. *Q J Med* 1989;73:931–939.

identify trigger points that can reproduce abdominal pain in patients with IBS.¹⁴ Rogers et al¹⁵ noticed that patients with IBS exhibit both an increased amplitude and prolonged duration of the gastrocolonic response. However, these findings were not reproducible by other investigators. More recently, a selective acceleration in right colon transit has been demonstrated in some diarrhea-predominant patients with IBS with the help of colonic scintigraphy.¹⁶ In summary, there is no diagnostic marker of motor activity in patients with IBS, although some abnormal patterns have been described under simulated conditions.

Visceral Hypersensitivity

Studies performed over the past 20 years show strong evidence for hypersensitivity of mechanoreceptors and chemoreceptors of the gut in the etiology of IBS. Patients with visceral hypersensitivity have a lower pain threshold than control patients in response to intestinal distension simulated with a balloon barostat.¹⁷ This exaggerated sensory perception may explain the symptoms that are produced in IBS even with small volumes of gas or stool. Almy¹⁸ reinforced the importance of the brain-gut axis in the regulation of colonic activities and described the colonic response of various somatic and psychological stresses during proctoscopy. Using cerebral evoked potential recording in noncardiac chest pain, investigators have shown that the peripheral afferent pathways stimulated by esophageal distention are not abnormal and that the perceptual disturbances result from abnormalities in the central nervous system.¹⁹ Aggarwal et al²⁰ suggested specific associations between the autonomic nervous system, predominant physical symptoms, colon transit time, and psychological factors in patients with IBS. These researchers found that constipation in IBS is asso-

ciated with a cholinergic abnormality whereas diarrhea is associated with an adrenergic abnormality.

At present, whether primary sensory abnormalities occur at a peripheral or central level is not definitely established. According to the hypothesis of Mayer and Gebhart, an initial local event at the periphery (eg, irritation, inflammation, damage, infection, or stress) produces primary hyperalgesia in the gut. The increased sensory input to spinal interneurons can result in secondary visceral hyperalgesia. Adjacent, undamaged tissue develops sensitivity to normally innocuous stimuli and a central sensitization with long-lasting changes in the synaptic circuitry of dorsal horn.²¹ This pain memory also may be affected by descending pain modulatory systems such as stress. The concept of pain memory provides an integrated view of IBS. This concept is further supported by a recent study by Munakata et al,²² in which repeated stimulation of sigmoid splanchnic afferents in patients with IBS resulted in the development of central sensitization that caused rectosigmoid hyperalgesia in the absence of applied stimuli as compared with control patients.

Luminal Factors

Various digested and undigested components of food (eg, lactose, fructose) have been shown to aggravate symptoms of IBS. Similarly, food allergens may be important in exacerbation of IBS. Bile acid malabsorption may account for unexplained functional diarrhea in up to 10% of patients whose diarrhea is attributed to IBS. A clinical trial of dietary exclusions involving 189 patients with IBS demonstrated an improvement in 91 patients that persisted during a mean follow-up of 15 months.²³

Table 3. Criteria for Diagnosis of Irritable Bowel Syndrome

Continuous or recurrent symptoms for at least 3 months consisting of abdominal pain or discomfort that is:

Relieved by defecation

Associated with a change of stool frequency

Related to a change in stool consistency

—AND—

Two or more of the following symptoms during at least one quarter of the episodes or days:

Altered stool frequency (> 3 bowel movements/day or < 3 bowel movements/week)

Altered stool form (lumpy/hard or loose/watery)

Altered stool passage (straining, urgency, or a feeling of incomplete evacuation)

Passage of mucus

Bloating or feeling of abdominal distention

Adapted with permission from Thompson WG: Functional bowel disease and functional abdominal pain. *Gastroenterol Int* 1992;5:75-91.

DIAGNOSTIC APPROACH

Patient History and Physical Examination

Because no pathognomonic abnormalities have been identified in IBS, the differential diagnosis of this disorder is extensive. A careful history and physical examination are essential in establishing the diagnosis. The modified version of Manning's criteria for diagnosis of IBS is described in **Table 3**.²⁴ The most common presentation of IBS is abdominal pain associated with altered bowel habits (ie, constipation, diarrhea, or alternating constipation and diarrhea). Constipation is the most common presenting complaint. Various extraintestinal symptoms in patients with IBS are summarized in **Table 4**.

Physicians who consider IBS a diagnosis of exclusion are often compelled to exclude all organic diseases, leading to an extensive, costly work-up. Symptoms of anemia, bleeding, fever, weight loss, or a recent change in bowel habit should not be attributed to IBS. Pain and diarrhea that awaken the patient at night are suggestive of organic disease. A history of sexual or physical abuse or a psychiatric illness is common in IBS. Fibromyalgia frequently coexists with IBS.²⁵ The quality, location, and timing of abdominal pain may suggest a specific disorder. A careful review of the patient's medications is also very important, particularly with reference to drugs with gastrointestinal toxicity or side effects.

Table 4. Extraintestinal Symptoms in Patients with Irritable Bowel Syndrome

Back pain

Constant tiredness/Lethargy

Bad breath/Unpleasant taste in mouth

Frequent headaches

Urinary frequency

Urinary urgency

Nocturia

Incomplete emptying of bladder

Dyspareunia

Thigh pain

Adapted with permission from Whorwell PJ: Extraintestinal manifestations of the irritable bowel syndrome. In *Irritable Bowel Syndrome*. Reed NW, ed. Cambridge, MA: Blackwell Science, 1991:43-47.

The patient's dietary history is important. The patient should be asked about symptoms of lactose intolerance, and a 3-week trial of a lactose-free diet can be used to rule out lactose intolerance. In confusing cases, a hydrogen breath test after lactose challenge should be ordered.

Pressure pain over the abdominal aorta may be provoked in some patients with IBS,²⁶ but this pain is not a proven physical finding. The presence of a mass lesion, lymphadenopathy, hepatosplenomegaly, jaundice, ascites, a succussion splash, specific skin lesions, and evidence of peripheral or autonomic neuropathy are indicative of organic disease.

Laboratory Evaluation

Stool examination for leukocytes and parasites and *Clostridium difficile* toxin assay may be helpful in select patients with possible inflammatory bowel disease, history of antibiotic use, or recent travel. In a recent study involving 196 patients with IBS, researchers found that erythrocyte sedimentation rates, thyroid profiles, and parasitic examinations had no diagnostic yield in the routine evaluation of patients with IBS.²⁷ A sigmoidoscopy should be performed in younger patients who do not meet the IBS diagnostic criteria. Colonoscopy should be reserved for patients older than age 40 years or for patients who have symptoms of obstruction, bleeding, or family history of colon cancer or polyps. A gynecologist should be consulted for cases in which a woman with chronic pelvic pain has IBS symptoms that worsen during menstruation.²⁸ Ultrasonography, computed tomography or upper endoscopy should be

used only when a patient's symptoms are strongly suggestive of biliary or upper gastrointestinal pathologies.

STRATEGIES FOR OPTIMAL MANAGEMENT

Reassurance and Education

The most important step in the management of IBS is to establish a good therapeutic relationship with the patients and to gain their confidence. Patients should be educated about the functional nature of the disease. A simplified explanation of bowel motility can be very helpful. Patients should be reminded that, similar to high blood pressure, arthritis, and diabetes, IBS can only be managed, not cured. Physicians should identify the patient's concerns, discover the precipitating factors that caused the patient to consult the physician, set consistent limits about diagnostic procedures, respond realistically to the patient's expectations, and involve the patient in the treatment to optimize results.²⁹ Owens et al³⁰ found a clear association between the strength of the physician-patient interaction and a reduction in the number of return visits for IBS-related symptoms.

Diet Modification

Dietary modifications are popular in patients with IBS. A high-fiber diet helps prevent both excessive hydration or dehydration of stool. Lactose, fructose, or sorbitol may induce symptoms in diarrhea-prone IBS and should be discontinued. In patients with pain-gas-bloat symptoms, the foods associated with increased flatulence (eg, milk products, beans, onions, carrots, raisins, bananas, apricots, prunes, brussels sprouts wheat, pretzels, bagels) should be reduced or avoided. In 20% of patients with IBS, a high-fiber diet can actually aggravate symptoms of bloating and distention.

Stool-Bulking Agents

The United States has one of the lowest per capita intakes of fiber in the world. Therefore, increasing daily fiber intake is recommended for most Americans, particularly those with IBS. The hydrophilic property of fiber increases fecal output and enhances the colonic transit time in many constipated patients. In patients with diarrhea-predominant IBS, dietary fiber can delay transit. However, clinical trials using different preparations of fiber in patients with IBS reported placebo responses of 63% to 71%.³¹ In one study, polycarbophil was found to be effective in patients with IBS and alternating diarrhea and constipation and in patients with constipation-predominant IBS alone.³² Because of the large placebo response and safety, a trial of fiber seems appropriate in all patients with IBS.

Table 5. Pharmacologic Agents for Irritable Bowel Syndrome Based on Predominant Symptom

Predominant symptom	Agent	Dosage
Constipation	Psyllium	1 tbs qd/bid/tid
	Polycarbophil	500–1000 mg bid/tid
	Cisapride	10–20 mg tid/qid
Diarrhea	Loperamide	2 mg tid
	Cholestyramine	4 g qd/bid
Postprandial pain	Dicyclomine	10–20 mg qid
	Hyoscyamine	0.125–0.25 mg tid/qid
Chronic pain	Amitriptyline	25 mg/hr
	Desipramine	50 mg/hr
Flatulence/Bloating	Simethicone	40–80 mg tid/qid

bid = twice per day; hs = bedtime; qd = every day; qid = four times per day; tbs = tablespoon; tid = three times per day

Adapted with permission from Thompson WG: Pathogenesis and management of the irritable bowel syndrome. In *Evolving Concepts in Gastrointestinal Motility*. Champion MC, Orr WC, eds. Cambridge, MA: Blackwell Science 1996:200–220.

Pharmacologic Agents

No drug has a proven efficacy in IBS because of the complex symptomatology of the illness.³¹ The physician therefore should avoid chronic prescriptions of expensive and potentially harmful drugs. Drug therapy is best used in patients with severe symptoms who are refractory to physician's counseling and dietary manipulations. Camilleri and Prather³³ recommend a pathophysiologic approach based on alleviating the predominant symptom. These symptoms and their therapeutic options with doses are summarized in **Table 5**. Several classes of pharmacologic agents have been proposed for the treatment of IBS, including antispasmodic, anti-diarrheal, antiafferent, prokinetic, and psychotropic agents. Many of these agents are still experimental.

Antispasmodic agents. Anticholinergic drugs may be beneficial for painful cramps and fecal urgency in patients with IBS. Dicyclomine and hyoscyamine sulfate are used most commonly. These medications most effectively manage postprandial pain when given 30 minutes before meals. Tincture of belladonna may cause mouth dryness and thus requires dose titration. Cimetropium may cause improvement in the global sense of well-being in addition to its antispasmodic effect.³⁴ Mebeverine is a very popular papaverine derivative in Europe. This drug is a potent smooth muscle relaxant without anticholinergic and calcium-blocking

properties, which can inhibit ileal peristalsis and colon motility in patients with IBS.³⁵ Calcium blockers (verapamil, nifedipine, octylonium bromide, peppermint oil, pinaverium bromide) have been used in patients with IBS because of the smooth muscle relaxant properties of these drugs. However, no studies to date have demonstrated the clinical efficacy of these drugs for IBS. In two controlled studies, pinaverium bromide (50 mg orally three times per day) was found to be more effective than placebo for abdominal pain and constipation.³⁶ Loxiglumide, a cholecystokinin antagonist, slows the proximal colon transit in patients with IBS, but not in healthy control patients.³⁷ This local action on proximal colon supports the hypothesis that cholecystokinin acts through the afferent fibers of the vagus nerve.

Antidiarrheal agents. In patients with IBS and painless diarrhea, loperamide and diphenoxylate have been found to be effective. These agents are most useful if taken on a short-term basis prior to a stressful event. Cholestyramine may be helpful in patients with IBS who have idiopathic bile acid malabsorption.

Antiafferent agents. Reduction of intestinal perception by blocking the afferent nerve receptors is a new way to treat patients with IBS. Serotonin-3 receptors are widely distributed in the gut at postsynaptic vagal and sympathetic nerve endings as well as within the enteric nervous system. Ondansetron, a selective serotonin-3 antagonist, has been found to improve diarrhea, stool consistency, postprandial epigastric discomfort, flatulence, and heartburn.³⁸ Similarly, intravenous granisetron was found to reduce postprandial motility and rectal sensitivity in 12 patients with IBS.³⁹ Octreotide, a somatostatin analog, has been shown to significantly increase threshold for visceral perception in patients with IBS without modifying smooth muscle tone.⁴⁰ Fedotozine, a kappa opioid agonist, has been found to be more effective than placebo in relieving abdominal pain. This agent has a peripheral mechanism of action and has no central nervous system side effects.^{41,42}

Recently the effects of leuprolide acetate, a gonadotropin-releasing hormone analog, have been tested in female patients with IBS. The study found that nausea, abdominal pain, early satiety, anorexia, and abdominal distension improved significantly in these subjects.⁴³ Three mechanisms of action of leuprolide acetate are still under discussion: the inhibition of the release of the ovarian hormones that affect gut motility through their action on the enteric nervous system, the direct effect on neurons in the brain or the spinal cord, and the direct effect on the enteric nervous system.⁴⁴

Prokinetic agents. Prokinetic agents proposed for IBS include dopamine antagonists, such as domperidone and metoclopramide, and serotonin-4 agonists, such as cisapride. Domperidone has been found to reduce diarrhea, flatulence, borborygmus, and pain as effectively as placebo.⁴⁵ Cisapride facilitates acetylcholine release from myenteric plexus and enhances propulsive motor activity of the gastrointestinal tract. This drug is significantly more effective than placebo in increasing the number of bowel movements per week in constipation-predominant IBS, and cisapride also lowers abdominal pain.⁴⁶ Laxatives generally should be avoided in patients with IBS because these agents cause undesirable side effects and may exaggerate the swings from constipation to diarrhea.

Psychotropic agents. Tricyclic antidepressants are beneficial in patients with pain-predominant IBS and increased bowel frequency.⁴⁷ The anticholinergic and analgesic effects of the tricyclic antidepressants on the gastrointestinal tract occur within 24 to 48 hours. However, these agents should be used cautiously in patients with heart disease and in elderly patients. Tricyclic agents also are not appropriate for initial treatment of IBS.⁴⁷ In one study, 54% of patients reported global improvement during desipramine treatment compared with 18% with placebo. A new antidepressant, mianserin (combined serotonin-2+3 and alpha2 antagonist), recently was found to control abdominal pain and functional disability in patients with IBS with no clinical psychopathology.⁴⁸

Anxiolytic agents are of limited benefit in patients with IBS. These drugs can cause drowsiness, impaired judgment and coordination, rebound effect on withdrawal, and serious drug interactions. However, anxiolytic agents may be used for brief periods to treat stress-related exacerbations of IBS.²⁹

Psychological Treatments

Psychological treatments have been reported to be of value in a select motivated group of patients with IBS. These treatments included cognitive-behavioral therapy, dynamically oriented psychotherapy, hypnotherapy, biofeedback, and relaxation techniques alone or in combination. These psychological treatments may help to reduce anxiety levels, encourage health-promoting behaviors, and give the patient greater responsibility and control in treatment. However, no trial to date has provided unequivocal evidence that psychological treatment is efficacious in IBS.⁴⁹

Therapy for Intractable Symptoms

Approximately 15% of patients with IBS do not

Table 6. Evaluation of Intractable Symptoms

Constipation

Rule out metabolic problems (hypothyroidism, hypercalcemia, hypokalemia, diabetes), chronic laxative abuse, drugs causing constipation, poor diet, pelvic floor dysfunction, and neurogenic disorders

Rule out organic diseases with sigmoidoscopy and barium enema if patient < age 40 years or colonoscopy if patient > age 40 years

Consider functional studies:

Colonic transit test to identify patients with colonic inertia

Anorectal manometry to evaluate abnormalities of sphincter tone and rectal sensation or compliance

Defecography and balloon expulsion to evaluate functional outlet obstruction

Electromyography to evaluate skeletal muscle activation and denervation

Diarrhea

Rule out laxatives, antacids, and poorly absorbed carbohydrates (lactulose, sorbitol, fructose)

Weigh 24-hour stool and send for examination for ova and parasites, leukocytes, and laxatives, measurement of electrolytes and hydrogen ion concentration, and Sudan B fat stain

Trial of cholestyramine

Hydrogen breath test after lactose challenge

Colonoscopy with biopsies

Upper endoscopy with small bowel biopsies

Transit test to evaluate small bowel and colon motility

Abdominal pain

Plain abdominal radiography

Pelvic examination in women

Trial of amitriptyline

Small and large bowel barium series

Gastrointestinal manometry, endoscopy, right upper quadrant ultrasound, and endoscopic retrograde cholangiopancreatography in select cases

respond to routine treatment and may need further evaluation as outlined in **Table 6**. This subgroup of patients with IBS needs an ongoing relationship with a physician to provide psychosocial support and to prevent "doctor shopping" and further expensive work-up. Antidepressants should be considered for unremitting pain and impaired daily functioning. These agents also may alleviate major or atypical depression or panic attacks. Treatment should be

Table 7. Experimental Pharmacotherapy in Irritable Bowel Syndrome

Selective muscarinic M3 receptor anticholinergic agents

Cholecystokinin antagonists

Somatostatin analogs

Gonadotropin-releasing hormone analogs

Serotonin-3 and serotonin-4 receptor type antagonists

Kappa opioid agonists

Substance P antagonists

Calcium channel blockers

Adapted with permission from Camilleri M, Choi MG. Review article: irritable bowel syndrome. *Aliment Pharmacol Ther* 1997;11:3-15.

given for 3 to 4 weeks, and if found effective, can be continued for 12 months.

Narcotics or nonsteroidal anti-inflammatory drugs are not indicated for IBS. Mental health consultation should be obtained with ongoing medical care. Cognitive behavioral treatment is the most commonly recommended psychological treatment in the United States.⁵⁰ This treatment involves identifying maladaptive thoughts, perceptions, and behaviors and using this information to develop new ways to control intractable symptoms. Dynamic psychotherapy is popular in Europe for refractory cases.⁵¹ Relaxation training may help to counteract the physiologic effects of stress or anxiety. Patients with chronic pelvic pain should be referred to interdisciplinary pain management centers.⁵² Biofeedback techniques were found to be effective in patients with IBS presenting with fecal incontinence as well as chronic constipation.^{53,54}

PROGNOSIS

IBS may persist in a waxing and waning fashion indefinitely and cause serious socioeconomic problems for the affected patient. However, when diagnosed according to current criteria and treated appropriately, IBS carries a good prognosis.⁵⁵ Ongoing counseling, reassurance, education, and judicious use of medications all contribute to a successful outcome. In a retrospective study involving 112 patients with IBS, Svendsen et al⁵⁵ found 51% of the patients showed improvement at a 5-year follow-up examination. Previous abdominal surgery was associated with a poor prognosis. In a prospective study involving 104 patients who were followed for 5 to 7 years, 39% of the patients improved and 24% were completely symptom-free. The outcome was worse in women, in patients with

diarrhea-predominant IBS, and in patients who had IBS for more than 2 years.⁵⁶

FUTURE PROSPECTS

The management and prognosis of IBS will continue to depend on the knowledge and skill of the treating physician. The demand for psychological treatment will probably increase in the coming years. It is recommended that the physicians who handle patients with IBS frequently should become versed in psychotherapy for their patients. To date, psychotropic agents have not been adequately assessed, particularly antidepressants. Attempts currently are being made to identify more suitable pharmaceutical agents that modulate gastrointestinal transit and visceral perception. The data currently available clearly indicate that several pharmaceutical targets are potentially involved in IBS physiopathology. In the next 5 years various new agents (Table 7) affecting different levels of brain-gut axis will likely impact the management of IBS. Until then, the practicing physician should follow the empirical approach of empathy, education, reassurance, high-fiber diet, and symptomatic pharmacotherapy. HP

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