Review Article

Current Concepts

The Irritable Bowel Syndrome

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In 1849, Cumming[1] said of the irritable bowel syndrome, "The bowels are at one time constipated, another lax, in the same person. How the disease has two such different symptoms I do not profess to explain." Over the years, the unexplained gastrointestinal symptoms of the irritable bowel syndrome have been described in various terms, including mucous colitis, spastic colitis, nervous colon, and irritable colon. The irritable bowel syndrome and nonulcer dyspepsia are the most common functional gastrointestinal disorders.

The irritable bowel syndrome is defined on the basis of the recently modified Rome criteria as the presence for at least 12 weeks (not necessarily consecutive) in the preceding 12 months of abdominal discomfort or pain that cannot be explained by structural or biochemical abnormalities and that has at least two of the following three features: pain is relieved with defecation, its onset is associated with a change in the frequency of bowel movements (diarrhea or constipation), or its onset is associated with a change in the form of the stool (loose, watery, or pellet-like).[2] The syndrome can be divided into four subcategories according to whether the predominant symptom is abdominal pain, diarrhea, constipation, or constipation alternating with diarrhea.

Epidemiologic Features

Approximately 15 percent of U.S. adults report symptoms that are consistent with the diagnosis of the irritable bowel syndrome[3]; the disease affects three times as many women as men. Whether this difference reflects a true predominance of the disorder among women or merely the fact that women are more likely to seek medical care has not been determined. The irritable bowel syndrome is the most common diagnosis made by gastroenterologists in the United States[4] and accounts for 12 percent of visits to primary care providers.[5] It is estimated that only 25 percent of persons with this condition seek medical care for it, and studies suggest that those who seek care are more likely to have behavioral and psychiatric problems than are those who do not seek care.[6] In addition, patients with a diagnosis of the irritable bowel syndrome are at increased risk for other, nongastrointestinal functional disorders such as fibromyalgia and interstitial cystitis.[7,8] The irritable bowel syndrome accounts for an estimated $8 billion in direct medical costs and $25 billion in indirect costs annually in the United States.[9]

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Pathophysiologic Features

Altered bowel motility, visceral hypersensitivity, psychosocial factors, an imbalance in neurotransmitters, and infection have all been proposed as playing a part in the development of the irritable bowel syndrome (Fig. 1).

Altered Bowel Motility

Over the past 50 years, alterations in the contractility of the colon and small bowel have been described in patients with the irritable bowel syndrome. Psychological or physical stress[10] and ingestion of food[11] may alter the contractility of the colon. Abnormal motility of the small intestine during fasting, such as loss of the migrating motor complex[12] and the presence of both discrete, clustered contractions and prolonged, propagated contractions,[13] has been described in patients with the irritable bowel syndrome. In addition, an exaggerated contractile response to a high-fat meal has been reported.[13] Pain is more frequently associated with irregular motor activity of the small intestine in patients with this syndrome than in normal controls or patients with inflammatory bowel disease.[12]

Visceral Hypersensitivity

Balloon-distention studies of the rectosigmoid[14] and the ileum[15] have shown that patients with the irritable bowel syndrome experience pain and bloating at balloon volumes and pressures that are significantly lower than those that induce pain in control subjects, a phenomenon referred to as visceral hypersensitivity. One possible explanation is that the sensitivity of receptors in the viscus is altered through the recruitment of silent nociceptors in response to ischemia, distention, intraluminal contents, infection, or psychiatric factors.

There may be increased excitability of the neurons in the dorsal horn of the spinal cord, an area rich in neurotransmitters such as catecholamines and serotonin. Centrally, there may be differences in the way

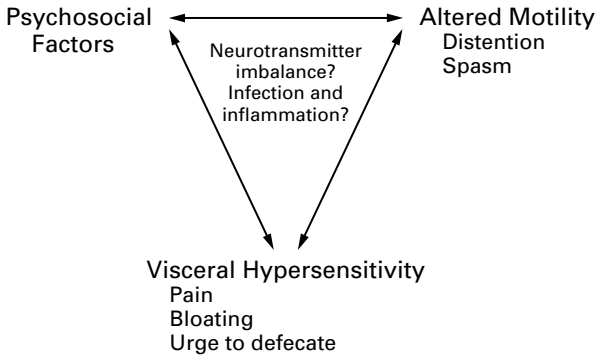

Figure 1. Pathophysiologic Factors in the Development of the Irritable Bowel Syndrome.

The double-headed arrows indicate an interaction.

the brain modulates afferent signals from the dorsal-horn neurons through the ascending pathways. Functional magnetic resonance imaging[16,17] and positron-emission tomography[18,19] of the brain show different levels of activation in the thalamus and the anterior cingulate cortex after balloon distention of the rectum in patients with the irritable bowel syndrome, as compared with normal subjects.

These findings, although controversial, suggest a primary central defect of visceral pain processing. Some authors have suggested that hypervigilance rather than true visceral hypersensitivity may be responsible for the low pain threshold in patients with the irritable bowel syndrome.

Psychosocial Factors

Psychological stress can alter motor function in the small bowel[11] and colon,[20] both in normal subjects and in patients with the irritable bowel syndrome. Up to 60 percent of patients seen at referral centers have psychiatric symptoms such as somatization, depression, and anxiety, and patients with a diagnosis of the irritable bowel syndrome are more likely to have these symptoms than are persons who have never sought medical care for bowel problems.[21,22] When present, psychiatric disturbances influence overall use of health care services and the ability to cope with symptoms. The presence or absence of a history of abuse in childhood (sexual, physical, or both) is correlated with the severity of symptoms in patients with the irritable bowel syndrome.[23] It has even been proposed that experiences early in life may affect the central nervous system and confer a predisposition to a state of hypervigilance.

Neurotransmitter Imbalance

Recent studies have suggested that neurotransmitters are involved in the pathogenesis of the irritable bowel syndrome. Five percent of serotonin is located in the central nervous system, and the remaining 95 percent is in the gastrointestinal tract, within enterochromaffin cells, neurons, mast cells, and smooth-muscle cells. When released by enterochromaffin cells, serotonin stimulates extrinsic vagal afferent nerve fibers and intrinsic enteric afferent nerve fibers, resulting in such physiological responses as intestinal secretion and the peristaltic reflex and in such symptoms as nausea, vomiting, abdominal pain, and bloating.[24] Preliminary evidence suggests that patients with the irritable bowel syndrome have increased serotonin levels in plasma and in the rectosigmoid colon.[25,26]

Other neurotransmitters that may have an important role in functional gastrointestinal disorders include calcitonin gene–related peptide, acetylcholine, substance P, pituitary adenylate cyclase–activating polypeptide, nitric oxide, and vasoactive intestinal peptide. These neurotransmitters may provide links not only between bowel contractility and visceral sensitivity, but also between the enteric and central nervous systems.

Infection and Inflammation

There is compelling evidence that inflammation of the enteric mucosa or neural plexuses initiates or contributes to symptoms associated with irritable bowel syndrome.[27-29] Mucosal inflammatory cytokines may activate peripheral sensitization or hypermotility. Gwee et al. reported that in patients with infectious enteritis, the presence of hypochondriasis and stressful life events at the time of the acute infection predicted the subsequent development of the irritable bowel syndrome.[30] To date, no single conceptual model can explain all cases of the syndrome.

DIAGNOSIS

After a complete history has been obtained, all patients with lower gastrointestinal tract symptoms should undergo a complete physical examination and laboratory testing, including a complete blood count, blood-chemistry tests, liver-function tests, and measurement of thyrotropin. The diagnosis of the irritable bowel syndrome is suggested when a patient's symptoms meet the Rome criteria. In the majority of cases, there are no abnormalities on physical examination or laboratory testing and there are no findings suggestive of a structural disorder — so-called alarm symptoms. Therefore, the irritable bowel syndrome can be reasonably diagnosed on the basis of flexible sigmoidoscopy alone, in patients who are less than 50 years old, or colonoscopy, in those who are 50 or older; barium enema and flexible sigmoidoscopy are often substituted for colonoscopy. In patients with diarrhea, a biopsy specimen should be obtained from the mucosa of the descending colon to rule out microscopic colitis.

If there are abnormalities on physical examination or laboratory testing or if an alarm symptom is present,

the irritable bowel syndrome is a diagnosis of exclusion after reasonable diagnostic testing has been performed, such as colonoscopy, computed tomographic scanning of the abdomen and pelvis, and radiographic evaluation of the small intestine. Alarm symptoms include evidence of gastrointestinal bleeding such as occult blood in the stool, rectal bleeding, or anemia; anorexia or weight loss; fever; persistent diarrhea causing dehydration; severe constipation or fecal impaction; a family history of gastrointestinal cancer, inflammatory bowel disease, or celiac sprue; and the onset of symptoms at the age of at least 50 years. In 1985, the American College of Physicians recommended the use of alarm symptoms to guide treatment[31]; however, the validity of this approach has never been established in rigorous, randomized, prospective clinical studies.

A number of structural or metabolic disorders that are responsive to specific treatment cause symptoms similar to those of the irritable bowel syndrome. Lactase deficiency is a common culprit. Other such disorders include cancer of the colon, diverticulitis, mechanical obstruction of the colon or small intestine, inflammatory bowel disease, enteric infection, ischemia, maldigestion or malabsorption, and endometriosis (suggested by the presence of pelvic pain at the time of the menstrual period). In the absence of alarm symptoms, the presence of one of these structural or metabolic disorders is very unlikely.

Table 1. Symptom-Guided Treatment of the Irritable Bowel Syndrome.*

Pain predominant
Change in diet
Anticholinergic agent
Nitrate
Tricyclic compound
Visceral antinociceptive agent (alosetron† or tegaserod‡)
Selective serotonin-reuptake inhibitor
Nonsteroidal antiinflammatory drug
Opioid
Diarrhea predominant
Change in diet
Loperamide
Diphenoxylate
Cholestyramine
Alosetron†
Constipation predominant
Change in diet
Osmotic laxative
Other laxatives
5-HT_4–receptor agonist (tegaserod‡ or prucalopride§)

*None of the drugs listed in this table are approved by the Food and Drug Administration (FDA) for treatment of the irritable bowel syndrome. 5-HT_4 denotes 5-hydroxytryptamine$_4$.

†The FDA initially approved this use of the drug but subsequently withdrew its approval.

‡An application for approval has been submitted to the FDA.

§The FDA has suspended its investigation of this use of the drug (see text).

TREATMENT

Whether the irritable bowel syndrome is diagnosed on the basis of the history, physical examination, and laboratory tests or after extensive testing (because of the presence of an alarm symptom), the establishment of trust in the physician–patient relationship should be given a high priority in order to maximize the efficacy of treatment and minimize "doctor shopping." A diary of food intake and symptoms can be useful in identifying foods that may be associated with symptoms of the irritable bowel syndrome. Patients often report an exacerbation of symptoms after the consumption of certain foods. Some patients benefit from avoiding or limiting their intake of caffeine, alcohol, fatty foods, gas-producing vegetables, or products containing sorbitol, such as sugarless gum and dietetic candy. The avoidance of constipating foods and the addition of 20 to 30 g of fiber per day either in the diet or in the form of supplements such as bran, polycarbophil, or a psyllium derivative may help relieve constipation[32-35] and may occasionally improve diarrhea.

A rational approach to treating the irritable bowel syndrome uses the patient's symptoms as a guide (Table 1). For patients in whom the disorder is manifested predominantly as abdominal pain, a variety of medications have been used, and several new agents are under development. Antispasmodic agents may reduce abdominal pain or bloating through anticholinergic pathways; in refractory cases, nitrates are occasionally useful for direct relaxation of smooth muscles. A recent meta-analysis suggested the effectiveness of antispasmodic agents and tricyclic compounds in treating selected patients with the irritable bowel syndrome.[36] Unfortunately, many of these agents are not available in the United States, and large-scale, stand-alone studies have not been performed. Small studies have shown that tricyclic compounds in low doses relieve unexplained abdominal pain.[37] Side effects — sedation, dry mouth and eyes, and weight gain — limit the use of primary tricyclic amines. Secondary tricyclic amines such as nortriptyline and desipramine may be less likely to have side effects.[38]

Despite speculation that 5-hydroxytryptamine (5-HT), or serotonin, receptors may be involved in the pathogenesis of the irritable bowel syndrome, the results of treatment with selective serotonin-reuptake inhibitors have been disappointing. Nevertheless, serotonin has been implicated in the modulation of visceral nociception, especially through the 5-HT_3 and 5-HT_4 pathways. Two new agents — alosetron, a 5-HT_3–receptor antagonist, and tegaserod, a 5-HT_4 agonist — have been shown to diminish visceral sensitivity to rectal distention in women who

have diarrhea as the predominant symptom of the irritable bowel syndrome and in those who have constipation as the predominant symptom, respectively.[39,40] Fedotozine, a kappa-opioid agonist,[41] has shown promise as a visceral antinociceptive agent, and other kappa-opioid agonists are being developed. Finally, in some patients who have abdominal pain that is refractory to all these therapeutic agents, treatment with classic analgesics such as nonsteroidal antiinflammatory agents (perhaps with an initial trial of a cyclooxygenase-2 inhibitor) or, in extreme cases, opioid analogues may control the pain and improve the quality of life. The addictive potential of opioid analogues makes them the last choice for long-term therapy.

For patients in whom diarrhea is the predominant manifestation of the irritable bowel syndrome, classic antidiarrheal agents such as loperamide[42] and diphenoxylate may help decrease the frequency of bowel movements and improve the consistency of stool. In a study of women with this form of the irritable bowel syndrome, alosetron prolonged colonic transit, reduced the frequency of bowel movements and the urge to defecate, improved the consistency of stool, and decreased abdominal pain.[43] However, this drug has been removed from the market because of side effects such as severe constipation, ischemic colitis, and bowel perforation. In cases of diarrhea that cannot be controlled, cholestyramine has been used to bind bile acids that may be responsible for increased secretion and decreased absorption of water in the colon.[44] In some refractory cases, a short course of antibiotics may reduce the diarrhea, presumably by altering the intestinal flora.[45]

For patients in whom constipation is the predominant manifestation of the irritable bowel syndrome, consumption of fiber may alleviate constipation and related symptoms such as abdominal pain, tenesmus, and dyschezia.[32] Constipation can also be safely treated with osmotic laxatives such as nonabsorbable carbohydrates (lactulose and sorbitol), milk of magnesia or magnesium citrate, or a polyethylene glycol solution. Two new classes of compounds, aminoguanidine indoles such as tegaserod and benzofurans such as prucalopride, act specifically on 5-HT_4 receptors. These agents shorten the transit time in the colon and small intestine, increase the frequency of bowel movements, and increase the softness of stools.[46-49] Studies of prucalopride have been suspended because of concern about tumorigenic effects in animals. Derivatives of anthraquinones (senna and cascara), which act as strong laxatives, may be used as a last resort, but their use is limited by the frequent development of tachyphylaxis. The question of whether anthraquinones and their derivatives damage the enteric nervous system has not been resolved.

Although many pharmacologic agents have been used to treat the irritable bowel syndrome, few have been tested in controlled, double-blind studies with adequate statistical power. The doses of some commonly used agents are shown in Table 2.

TABLE 2. DOSAGE GUIDELINES FOR DRUGS COMMONLY USED TO TREAT THE IRRITABLE BOWEL SYNDROME.

DRUG	DOSE
Anticholinergic agents	
Dicyclomine hydrochloride	20 mg every 6 hr; can be increased to 40 mg every 6 hr if tolerated
Hyoscyamine sulfate	0.125–0.25 mg sublingually every 4 hr (0.375-mg extended-relief tablets: 1 or 2 tablets every 12 hr)
Antidiarrheal agents	
Loperamide	4 mg/day initially, with a maintenance dose of 4–8 mg/day, in a single or divided dose
Diphenoxylate (2.5 mg) plus atropine sulfate (0.025 mg)	2 tablets 4 times a day
Cholestyramine resin	1 packet (9 g) mixed with fluid and taken once or twice a day
Osmotic laxatives	
Lactulose	10 mg/15 ml of syrup; 15–30 ml/day (usual dose), up to 60 ml/day
Polyethylene glycol solution	17 g dissolved in 240 ml (8 oz) of water, taken daily
Tricyclic compounds	
Amitriptyline	25–75 mg/day
Nortriptyline	25–75 mg/day
Desipramine	25–75 mg/day

The interaction between psychosocial factors and the genesis of all forms of the irritable bowel syndrome is poorly understood. The most provocative observations in this respect are that persons with the syndrome who seek care are those in whom the syndrome is accompanied by a psychiatric disorder and that the syndrome may develop in patients who have both infectious gastroenteritis and a psychiatric disorder. The potential benefits of supportive therapy, relaxation exercises, hypnosis, cognitive behavioral therapy, and psychodynamic interpersonal psychotherapy are well recognized.[50]

The irritable bowel syndrome is a common disorder that has a pronounced effect on the quality of life and that accounts for a large proportion of health care costs. Common pitfalls in diagnosing and treating this disorder include unnecessary repetition of tests, failure to establish trust in the physician–patient relationship, and failure to provide the patient with realistic expectations regarding the efficacy of medications. A concise diagnostic evaluation and prompt institution of symptom-guided therapy can help alleviate the pain and suffering experienced by patients with the irritable bowel syndrome.

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