Irritable bowel syndrome (IBS) is recognized as one of the most commonly encountered functional gastrointestinal disorders, affecting an estimated one in five adult Americans. It is characterized by a symptom complex that includes chronic abdominal pain and discomfort that is relieved with defeation, abnormal stool frequency, and a change in stool form. Although the etiology of this disorder continues to remain elusive, this article reviews the current theory of the pathophysiologic mechanisms and reports on diagnostic and management principles for the primary care provider.

(Key words: irritable bowel syndrome, gut motility, visceral hypersensitivity, brain-gut axis, alternating diarrhea and constipation)

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Epidemiology
Irritable bowel syndrome is diagnosed most frequently in young adults who have recurrent or chronic gastrointestinal symptoms, usually consisting of abdominal pain and altered bowel habits. Classic features of IBS include triggering of symptoms caused by stress or diet, relief of pain with defeation, and irregularity of bowel movements. In the United States annually, IBS accounts for 3.5 million physician visits, predominantly by adult female patients. It is the most common cause for referral to gastroenterologists, constituting 20% to 50% of referred patients. In one study, researchers estimate the healthcare cost of IBS in the United States to be $8 billion per year.

Pathophysiology
Numerous mechanisms have been purported to explain the cause of disease. The failure of laboratory studies to show any morphologic, histologic, microbiologic, or biochemical abnormalities in patients with IBS previously supported the concept that IBS was primarily a disorder of gastrointestinal motility. More current theory suggests that the syndrome represents a multitude of aberrations. Dysmotility, visceral hypersensitivity, abnormal brain-gut responses, psychosocial factors, sensorimotor dysfunction, and alterations in local reflex mechanisms or extrinsic and central neural connections have been postulated as the basis for disease.

Altered gut motility
There have been many reports, often conflicting, of abnormal motility in IBS. In healthy persons, high-amplitude peristaltic contractions are seen six to eight times in 24 hours. These contractions tend to cluster around meals and bowel movements. The frequency of these contractions appears to be markedly diminished in constipation-predominant IBS. Some studies have demonstrated hypermotility and high-amplitude contractions over long segments of intestine in patients with IBS during episodes of crampy abdominal pain. Other studies have not found these differences and were unable to show correlation between symptoms, including diarrhea, and motor abnormalities.

Visceral hypersensitivity
In the majority of patients with IBS, sensory perception of pain is abnormal. In their article appearing in Lancet in 1997, Maxwell and colleagues cite Accarino and colleagues’ finding that patients with IBS had pain at lower volumes of visceral balloon distension. Increasing evidence suggests that long-term changes in the thresholds and gain of the visceral afferent pathways are present in patients with functional bowel disorders; this type of change is referred to as visceral hyperalgesia. This exaggerated sensory perception may explain the symptoms that are produced in IBS even with small volumes of gas or stool.

Psychosocial factors
Psychologic disorders are frequently seen concomitantly in patients with IBS. In fact, several studies have demonstrated that approximately 50% of patients with IBS have a coexisting psychiatric disorder at the time of presentation. Recent survey of 206 female patients with IBS reported a 44% incidence of physical or sexual abuse in childhood, a rate that was 3 to 11 times higher than in control patients. Although no specific personality profile appears to be associated with IBS, certain psychiatric disorders are increasingly prevalent with IBS. Panic disorder, characterized by paroxysmal attacks of
intense fear and autonomic arousal, has been associated with IBS. Other studies have shown that patients with IBS tend to be more preoccupied with illness than healthy subjects; they report more illness not related to IBS and more debilitation from other illness than a control group. This association may suggest that illness behavior persists because it has been supported by social reinforcement, which provides secondary gain.

**Brain-gut axis**

The enteric nervous system (ENS) is a diffuse network of ganglia running from the smooth muscle of the esophagus to the rectum. It independently controls gut function, including the migrating motor complex and peristalsis. Neural transmission within the ENS is controlled by a plethora of neurotransmitters and neuromodulatory peptides. It is the integration of intestinal motor, sensory, autonomic, and central nervous system activity interacting through the brain-gut axis that is responsible for normal gastrointestinal function. The numerous neu-

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**Figure 1. Algorithmic guide to diagnosis of irritable bowel syndrome based on positive findings.** (Adapted from Rothstein RD. Irritable bowel syndrome. Med Clin North Am 2000;84:1247-1257.)
Transmitters found in the brain and gut which link visceral afferent sensation and intestinal motor function with higher cortical centers include enkephalins, substance P, calcitonin gene-related polypeptide, nitric oxide, cholecystokinin, and 5-hydroxytryptamine (5-HT).

The gut contains more than 95% of the body’s 5-HT, and concentrations of 5-HT in the bowel is on an order of magnitude higher than that in the brain. Depending on conditions, 5-HT can make the bowel contract or relax, secrete or not secrete. It appears that 5-HT stimulates both vagal and enteric afferent nerve fibers, initiating responses as diverse as nausea, vomiting, intestinal secretion, and the peristaltic reflex. Recent studies have shown that 5-HT3 receptors exist on gut afferent neurons and that their activation by locally released 5-HT leads to visceral nociceptive stimulation in addition to increased neuronally mediated motor and secretory activity.

**Diagnosis**

The differential diagnosis of IBS is distinctive (Figure 2). Therefore, diagnosis of IBS should be one based on positive findings rather than a diagnosis of exclusion (Figure 1). Application of the Rome II criteria (Figure 3) allows a positive

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**Table**

<table>
<thead>
<tr>
<th>Predominant symptom and agent*</th>
<th>Dosage</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Constipation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psyllium fiber (Metamucil, Konsyl, long-acting formula)</td>
<td>1 T once, twice, or three times daily</td>
<td>Bloating/flatulence</td>
</tr>
<tr>
<td>Polycarbophil (Citruce1, FiberCon)</td>
<td>1 T once, twice, or three times daily</td>
<td></td>
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<tr>
<td><strong>Diarrhea</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loperamide (Imodium)</td>
<td>4 mg after first loose bowel movement, then 2 mg after each subsequent loose bowel movement</td>
<td>Constipation, nausea, central nervous system depression</td>
</tr>
<tr>
<td>Cholestyramine (Questran)</td>
<td>One packet (4 g) once or twice daily</td>
<td>Constipation, abdominal discomfort/pain, flatulence, nausea, vomiting, diarrhea, indigestion, decreased appetite, hiccups, sour taste in mouth, headache, dizziness, drowsiness</td>
</tr>
<tr>
<td><strong>Postprandial pain</strong></td>
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<td></td>
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<tr>
<td>Dicyclomine (Bentyl)</td>
<td>Start at 10 mg to 20 mg four times a day (if not effective in 2 weeks or side effects occur with doses &lt;80 mg, discontinue use)</td>
<td>Dry mouth, dizziness, blurred vision, nausea, lightheadedness, drowsiness, weakness, nervousness, rash or itching, difficulty urinating, decreased sweating</td>
</tr>
<tr>
<td>Hyoscyamine sulfate (Levsin)</td>
<td>0.125 mg to 0.25 mg three or four times daily</td>
<td>Dry mouth, urinary hesitancy/retention, blurred vision, eye sensitivity to bright light, tachycardia, nausea, bloating, heartburn, constipation, weakness or nervousness, changes in taste, headache, dizziness, lightheadedness</td>
</tr>
<tr>
<td>Hyoscyamine sulfate (Levbid)</td>
<td>0.375 mg twice daily</td>
<td></td>
</tr>
<tr>
<td><strong>Chronic pain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline hydrochloride (Elavil)</td>
<td>25 mg to 50 mg at bedtime</td>
<td>Arrhythmias, tachycardia, palpitations, tremors, weight gain, fatigue, dry mouth, nausea, diarrhea</td>
</tr>
</tbody>
</table>

*By generic name, with brand name in parentheses.

diagnosis of IBS to be made with confidence.14 A thorough detailed history and physical examination are essential in establishing the diagnosis. The most common presentation of IBS is abdominal pain associated with altered bowel habits (that is, constipation, diarrhea, or alternating constipation and diarrhea).7 Clinical features that argue against the diagnosis are

- the appearance of the disorder for the first time in old age;
- a steady, progressive course from time of onset;
- nocturnal symptoms that frequently awaken the patient;
- fever;

- significant weight loss not attributable to associated depression;
- rectal bleeding; or
- steatorrhea stools.10

Although no laboratory study is diagnostic of IBS, the complete blood cell count is reassuring if the hemoglobin value and leukocyte counts are normal. Patients 50 years of age or older with IBS symptoms of recent onset should have a colon examination.2 Other testing should be ordered as indicated. A study involving 196 patients with IBS found that the erythrocyte sedimentation rate, thyroid profiles, and parasitic examinations had no diagnostic yield in the routine evaluation of patients with IBS.26

Management

The most effective approach to the management of IBS is a patient-centered interview,27 which encourages the patient to discuss his or her function, ideas, fears, and expectations in relation to symptoms experienced. Owens and associates28 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. Patients should be reminded that like hypertension and diabetes, IBS can only be managed, not cured.7

Dietary modification

A high-fiber diet helps to prevent both excessive hydration and dehydration of stool. Clinical trials have also demonstrated placebo responses of 63% to 71% in patients with IBS who used different fiber preparations.29 Thus, a trial of fiber seems appropriate in all patients with IBS given the large placebo response and safety profile. Gradual introduction of fiber may diminish the common complaint of gas and bloating from these agents.5

Pharmacologic treatment

Drug treatment should be directed toward the most troublesome symptoms (Table).

- **Antispasmodic agents**—Anticholinergic drugs may be beneficial for painful cramps, fecal urgency, and diarrhea. Dicyclomine and hyoscine have been the cornerstone of therapy for many patients.

- **Antidiarrheals**—Loperamide hydrochloride and diphenoxylate have been found effective in patients with painless diarrhea and IBS. Patients with suspected lactase deficiency should exclude lactose-containing items from their diet to assess if there is a clinical response. Some patients note improvement with avoidance of other forms of sugar, including sorbitol and fructose.5

- **Psychotropic agents**—Tricyclic antidepressants are beneficial in patients with pain-predominant IBS and increased bowel frequency. These agents should be used cautiously in patients with heart disease and in elderly patients. They are

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**Checklist**

- **Drug-induced**
  - Constipation, such as from use of:
    - calcium channel blockers,
    - antidepressants,
    - aluminum-containing antacids
  - Diarrhea, such as from:
    - laxatives,
    - antibiotics,
    - magnesium-containing antacids
- **Lactase deficiency**
  - Endocrine-producing tumors — gastrinoma
  - — carcinoid
  - — vasoactive intestinal peptide-secreting tumor
- **Inflammatory bowel disease**
  - Crohn’s disease
  - Ulcerative colitis
- **Other types of colitis**
  - Infectious colitis
  - Diverticulitis
  - Ischemic colitis
  - Radiation colitis
- **Psychiatric disease**
  - Depression
  - Panic disorder
  - Somatization
- **Intestinal parasites**
  - *Giardia spp*
  - *Strongyloides spp*
  - *Entamoeba histolytica*
- **Metabolic disorders**
  - Thyroid disease
  - Diabetes mellitus
- **Malabsorption**
  - Chronic pancreatitis
  - Celiac sprue
  - Postgastrectomy syndromes
- **Intestinal pseudo-obstruction**
  - Primary visceral myopathy/neuropathy
  - Secondary myopathy/neuropathy (scleroderma, diabetes)
- **Miscellaneous**
  - Posthysterectomy diarrhea
  - Mast cell disease
  - Villous adenoma
  - Opportunistic infections in immunocompromised host

**Figure 2.** Differential diagnoses. (Source: Drossman DA. American College of Gastroenterology Postgraduate Course: Advancing GI into the Next Century, 2C-265, October 2000.)
not appropriate for initial treatment of IBS. The use of more contemporary antidepressants, the selective serotonin reuptake inhibitors, require further study and are not considered standard of care unless psychologic features predominate.

Alosetron hydrochloride—Alosetron hydrochloride (Lotronex), a potent and highly selective serotonin 5-HT3 receptor antagonist, was shown to be more effective than placebo in relieving abdominal pain and improving bowel functions in women with diarrhea-predominant IBS. Because of serious postmarketing adverse events, including severe constipation, ischemic colitis, and death, alosetron was voluntarily withdrawn from the market in November 2000.

Comment
Irritable bowel syndrome is a complex disorder with both physiologic and psychosocial components. The most important aspects of treatment are listening, validating, educating, and identifying and reinforcing coping strategies in a long-term therapeutic alliance with each patient. A strong physician-patient relationship is paramount in the successful management of the patient with irritable bowel syndrome.

References