CME

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Irritable Bowel Syndrome Overview

Introduction

Irritable bowel syndrome (IBS), not to be confused with inflammatory bowel disease (IBD), is one of the most common gastrointestinal (GI) conditions diagnosed today, accounting for 25 to 50% of referrals to gastroenterologists.[1] While it is reassuring that IBS does not directly cause death, it accounts for a significant number of visits to primary care physicians and is the second highest cause of work absenteeism after the common cold.[2] One estimate suggests that the total direct cost of IBS (including inpatient and outpatient health services) was greater than $1.7 billion in the United States in 2000.[3] It remains a poorly understood chronic disorder despite recent advances in research with its pathophysiology. This review is a summary of the current state of knowledge and management of this common condition that was first recognized two centuries ago.

Definition

IBS is a functional GI disorder characterized by chronic abdominal pain or discomfort and altered bowel habits in the absence of any organic cause. It has been referred to by several labels over the years. These include spastic colitis, nervous colon, irritable colon and unstable colon. These terms should be discarded as they are imprecise and inaccurate. The current understanding of IBS not only encompasses the colon but also the rest of the GI tract and sometimes with extra-intestinal manifestations. Therefore, IBS should be seen in terms of multiple physiological determinants contributing to a common set of symptoms rather than as a single disease entity.

In general, physicians tend to be more comfortable treating known diseases with defined etiologies, pathologic changes and reproducible symptoms, signs and laboratory abnormalities. As such, the absence of objective findings in patients with IBS is not only frustrating for the physician, but also the patient. In an attempt for a more concise definition, and to positively characterize this condition, the Manning criteria were published in 1978, followed by the Rome I criteria in 1989.[4,5] It soon became obvious that these criteria were too cumbersome to use in clinical practice and only suited for research protocols. A revised Rome I criteria became the Rome II criteria in 1978.[6] This is less cumbersome. The Rome II criteria define IBS as a chronic disorder in which abdominal pain or discomfort has been present for at least 12 weeks (need not be consecutive) during the previous 12 months with at least two of the following three features:

1. Relieved by defecation
2. Associated with change in stool frequency
3. Associated with change in stool consistency

Epidemiology

IBS is a worldwide disorder affecting approximately 4 to 35% of the adult population. It is estimated that only 15% of people affected seek medical attention. In North America, the prevalence ranges from 15 to 20% from several studies.[7-10] A population-based study in Europe found an overall prevalence of 11.5%, varying widely among different countries.[11] It is almost twice as common in women as in men. It affects the young and the elderly, although younger patients are more likely to be diagnosed.[12] In most patients, typical symptoms usually start in late teenage years or early twenties. The peak prevalence of IBS is between the third and fourth decades of life decreasing in the sixth and seventh decades. The diagnosis of IBS should be made with caution in patients older than 60 years because of other diseases, such as colon cancer and complicated colon diverticulosis, which can masquerade as IBS.

Pathogenesis

While the pathophysiology of IBS remains uncertain, recent advances in research have led to a number

of theories explaining some of the symptoms experienced by patients. Factors implicated to work in concert to produce the symptom complex of IBS include abnormalities in intestinal motility, alterations in visceral sensory function, and changes in central nervous system (CNS) processing of sensory information. Indeed, a lot of research is now focused on the interaction of the CNS and the GI tract in an attempt to better understand IBS. This is referred to as the brain-gut axis.

Altered Gut Motility

Studies have shown a number of abnormal GI motility patterns in patients with IBS. Discrete clustered contractions have been observed in the small intestine with gastroduodenal manometry. These burst of rhythmic contractions have been associated with abdominal pain in some patients.[13] In others, very prolonged contractions or high amplitude propagating contractions have been observed in the small intestine and colon, correlating with symptoms particularly in the postprandial period.[14] Perhaps a cause-effect explanation for altered bowel habit is seen in some patients with IBS, where alterations in the migratory motor complex (MMC) may either delay (constipation) or accelerate (diarrhea) intestinal transit.[15] These observations of altered GI motility are by no means pathognomonic of IBS as they do occur in normal individuals, although in general they appear to be exaggerated in patients with IBS.

Enhanced Visceral Sensitivity

Several studies have now demonstrated increased sensitivity to pain within the GI tract in patients with IBS.[16] To measure this response, many of the studies have used balloon distension of a part of the GI tract (rectum, sigmoid, colon or ileum).[17] Patients with IBS perceive the distension at much lower levels of inflation and also describe the distension as more painful compared with normal subjects. This possible increase in sensitivity appears to be specific for visceral afferents since patients with IBS have normal or even increased thresholds to somatic pain.

Central Nervous System Influences

It appears patients with IBS process sensory information from the GI tract differently. Two recent studies have shed light on this observation. In the first study, images obtained during positron emission tomography (PET) scanning of the CNS during rectal balloon distention in IBS patients, showed increased activity in the prefrontal cortex (an area associated with anxiety and hypervigilance) and reduced activity in the anterior cingulate cortex (important for opioid binding) compared with normal subjects.[18] A second study found differences in CNS activity in patients with IBS compared to subjects without IBS using functional magnetic resonance imaging (MRI).[19] Emotional stimuli such as stress, anxiety and depression may modulate this sensory processing and the perception of pain. This is the basis for a more holistic approach to IBS management recognizing the interplay between body and mind that almost certainly influences the frequency and severity of IBS symptomatology.

Other Factors

A few studies have demonstrated increased likelihood of symptoms of IBS later in life following an attack of infectious gastroenteritis.[20] The exact mechanism is not fully understood, but one possibility is transient or permanent injury to the enteric nervous system, which is the intrinsic nerve supply coordinating peristaltic activity within the GI tract. Another possibility is the development of immune hypersensitivity, in which recurrent exposure to benign substances in the GI tract induces inflammation and alters GI motility. Multiple reports have also shown a higher prevalence of previous physical and sexual abuse (particularly in women) with IBS than in control groups without IBS.[21]

Diagnosis

The diagnosis of IBS can usually be made with a thorough interview and physical examination. Indeed, most primary care physicians correctly identify the symptom complex particularly once patients are identified with recurring symptoms. The problem is with the possibility of an underlying organic pathology that may be missed. This, in addition to an extensive list of differential diagnosis (Table 1), can lead to a barrage of tests creating a lot of anxiety for the patient. There is no need for extensive testing as through the use of published guidelines such as the Rome II criteria and a few well targeted tests, IBS can be confidently diagnosed. IBS is no longer a diagnosis of exclusion. For practitioners who are unaware or cannot remember the Rome II criteria, the American College of Gastroenterology (ACG) recommends a broader definition of IBS: abdominal pain or discomfort associated with altered bowel habits and the absence of warning signs or "red flags" suggestive of organic disease in making a diagnosis. These warning signs include anemia, bleeding per rectum, weight loss, recurring fever, chronic severe diarrhea and a family history of colon cancer.

Table 1. Differential Diagnosis of Irritable Bowel Syndrome

Inflammatory Disorders
- Inflammatory bowel disease (Crohn's disease and ulcerative colitis)
- Microscopic colitis (collagenous and lymphocytic colitis)
- Eosinophilic enteritis

Infectious Gastroenteritis
- Bacterial overgrowth
- IV enteropathy

Endocrine Disorders
- Diabetic diarrhea
- Thyroid diseases
- Adrenal insufficiency

Malabsorption
- Celiac disease
- Lactose intolerance
- Pancreatic insufficiency
- Whipple's disease
- Lymphoma

Colonic Motility Disorders
- Colonic inertia
- Pelvic floor dysfunction

Urogenital Disorders
- Ovarian cysts
- Endometriosis
- Uterine fibroid
- Pelvic inflammatory disease
- Interstitial cystitis

Others
- Medications
- Laxative abuse
- Malignancy
- Intestinal ischemia
- Amyloidosis
- Mastocytosis
- Food allergies and sensitivities

History

Patients with IBS present with a wide array of symptoms including both GI and extraintestinal complaints. The most typical symptoms, however, are abdominal pain or discomfort and altered bowel habits. The pattern of symptoms varies considerably from person to person but remains fairly constant in a given individual, with the symptoms varying in intensity or frequency.

Abdominal pain is usually described as a crampy sensation, or sharp or burning pain. Others may describe discomfort. The pain varies in intensity with periodic exacerbations. A particular pattern remains fairly stable over time in individual patients. The location of the pain also varies from person to person but seems to be consistent over time in a given patient. Factors that may exacerbate the pain include emotional stress and eating, while defecation usually relieves the pain. Progressive severe abdominal pain that interferes with sleep or associated with anorexia, malnutrition and weight loss are not usual with IBS and should prompt investigations for an organic etiology.

The normal pattern of defecation ranges from three bowel movements per day to three per week.[22] This is altered in patients with IBS. Patients are usually considered to have one of three predominant patterns of altered defecation: diarrhea, constipation, or diarrhea alternating with constipation. Patients prone to diarrhea would describe normal stool consistency with their first bowel movement, usually after meals, becoming looser and eventually turning liquid with mucous subsequently. The looser motions are typically associated with urgency, abdominal cramps and flatulence which are temporarily relieved by passage of stool. Large volume diarrhea, bloody stools, nocturnal diarrhea, and greasy stools are not associated with IBS and suggest an organic disease. IBS patients with constipation often report the passage of rocky hard, pellet-like stools in addition to describing straining and feeling of incomplete evacuation. Stools may be associated with mucus which could also be passed alone.

In addition to characterizing the classical symptoms of abdominal pain and altered bowel habits, dietary pattern with temporal association of symptoms with dairy products should be determined. A careful medication history should be obtained and family history of celiac disease, IBD and colon cancer excluded. Fecal incontinence (usually slight staining of the underpants) occurs in as much as 20% of patients with IBS due to repetitive reflex relaxation of the sphincter muscles in association with repetitive spasm of the colon. This appears to be more common in IBS patients with diarrhea. Bloating and abdominal distension are also common in IBS patients. They reflect more accurately increased sensitivity to normal amounts of intestinal gas. The other GI symptoms, particularly involving the upper GI tract associated with IBS, are gastroesophageal reflux, dysphagia, early

satiety, intermittent dyspepsia, nausea and non-cardiac chest pain.

Extraintestinal symptoms that patients with IBS complain of include impaired sexual function, dysmenorrhea, dyspareunia, and increased urinary frequency and urgency.[23] Patients are also more likely to have hypertension, reactive airway disease, and rheumatologic syndromes, including fibromyalgia.[24, 25]

Physical Examination

Although normal in patients with IBS, a thorough examination serves to reassure patients and physician alike. Abdominal tenderness may be variable and non-specific, sometimes in the left lower quadrant. An alternate diagnosis should be sought if rebound tenderness and guarding is present. Audible bowel sounds (borborygmi) or increased bowel sounds on auscultation are not uncommon. A digital rectal examination should be performed in all patients as anorectal conditions like anal fissure or rectal masses may be easily detected. Tenderness due to visceral hypersensitivity may also be elicited.

Diagnostic Studies

There is no specific test that is diagnostic of IBS. The goal of testing is to exclude alternate or coexisting conditions. Laboratory studies should include complete blood count (CBC), biochemical profile (CMP), thyroid stimulating hormone (TSH) and erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). If diarrhea is the patient's primary complaint, stool samples should be tested for fecal leukocytes (gram staining), routine cultures, ova and parasites, *Giardia* and *Cryptosporidium* screening and, finally, *Clostridium difficile* toxins, especially if fecal leukocytes are present. Persistent diarrhea should provoke serologic markers for celiac disease. Lactose intolerance can be excluded by asking patients to ingest a quart (1L) of milk and observing for symptoms. Bloating, abdominal pain or discomfort and diarrhea occurring within a couple of hours of ingestion of milk may be enough to make this diagnosis. Lower endoscopies are performed quite often in these patients. Although the diagnostic yield is low in those < 40 years, normal flexible sigmoidoscopy may be reassuring to the very anxious patient. For those ≥ 50 years, colonoscopy is recommended not only to obtain mucosal biopsies to exclude microscopic colitis but also for colon cancer screening purposes, emphasized by the ACG position statement. In practice, however, most gastroenterologists would do a complete examination of the colon even if < 50 years for several reasons.

Management

General Principles

There is no medicine or therapy that can cure IBS. The goal of therapy, therefore, is to improve the quality of life. Central to this is establishing a relationship of mutual interest and gaining the confidence of the patient. It is important not to dismiss symptoms as "being in the head;" rather attempts should be made at explaining the pathophysiology of the symptom complex in light of the current knowledge. There should be clear understanding of the chronic nature of the disorder which may be exacerbated, sometimes by known factors and at other times by unknown triggers. Most IBS patients worry about cancer. Education and reassurance serves to reduce anxiety and enhance cooperation from the patient. The other modalities to improve quality of life include dietary manipulation, pharmacotherapy, psychological management and alternative medicine. The cumulative burden for caring for IBS patients may be enormous. However, many patients with symptoms of IBS do not seek medical attention.

Dietary Manipulation

Some patients often relate worsening of their symptoms to certain types of food they eat. While there are no convincing data to prove this it is wise to abstain from these foods, especially if temporal association can be demonstrated on at least two occasions. The likes include spicy foods, fatty or greasy foods, caffeine and dairy products.

Pharmacotherapy

Therapeutic agents have been used historically to target specific complaints or symptoms in patients with IBS. Only two drugs approved by the FDA address global symptoms of IBS (like abdominal pain/discomfort, bloating) in addition to targeting a predominant symptom: tegaserod (Zelnorm, Novartis) improves global symptoms in patients with predominant constipation and alosetron (Lotronex, Glaxo-SmithKline) in patients with diarrhea-predominant IBS. The following is a guide to the application of pharmacologic agents depending on the predominant symptom.

Constipation

Mild cases can be managed simply by lifestyle changes, with increased fiber diet, daily fluid intake of at least 64 oz (2 L) and setting time aside everyday to use the bathroom, preferably after a meal to take advantage of increased colonic motility that occurs

postprandially. Exercise may also increase colonic activity, as such a daily walking or running routine may be suggested. If this is ineffective, over-the-counter (OTC) fiber supplementation (methylcellulose, psyllium, polycarbophil, coarse bran and ispaghula husk) can be added. These agents increase stool volume and diameter, retain fecal water and increase colonic bacterial mass, resulting in shortened transit time. Although they have been widely used for years, only three studies have demonstrated significant benefit; one for polycarbophil and two for ispaghula husk.[26] Common side effects of fiber supplementation are abdominal bloating, distension and flatulence; as such, gradual introduction and increase is advised. Magnesium products are options for mild cases, although should be avoided in patients with renal insufficiency. Other prescription medicines available when dietary fiber supplementation fails include the nonabsorbable sugar lactulose, polyethylene glycol solution, either in liquid form (used as bowel cleansing agent in colonoscopy) or powdered form titrated over time, the prostaglandin agent misoprostol and colchicine.

The FDA approved tegaserod in July 2002 for the treatment of women with IBS and constipation. It is also being increasingly used in men although licensed only to treat constipation in this gender. It has a specific action of selectively binding to serotonin type 4 (5-HT4) receptors in the gut that are directly involved in initiating the peristaltic reflexes (agonist). Results from four large randomized controlled trials have shown that tegaserod accelerates orocecal transit and relieves symptoms of constipation, bloating and abdominal pain from up to two-thirds of women with constipation-predominant IBS.[12,27-29] This medication has received the highest recommendation for the treatment of women with IBS and constipation by a panel of experts with the American College of Gastroenterology (ACG).[12] In addition, a recent review on the subject published by the American Gastroenterology Association (AGA), found that the medication significantly relieves the global symptoms of women with IBS and constipation.[30] Diarrhea is the most common side effect with potential for rare ischemic colitis.

Diarrhea

Patients may respond to loperamide or diphenoxylate hydrochloride-atropine combination. Loperamide increases intestinal transit time with an additional advantage of increasing the external anal sphincter tone thereby decreasing incontinence and soiling in some patients. Constipation may occur rather rapidly if these agents are not stopped soon after the control of diarrhea particularly in those with diarrhea alternating with constipation. Codeine and low doses of tricyclic antidepressants (TCA) have also been shown to decrease the frequency of diarrhea. Constipation is a common side effect of calcium channel blockers. One strategy, although not proven, is to utilize this as part of a management plan in those with hypertension. Some patients may require deodorized tincture of opium (DTO). Starting with 1-2 drops each morning, this can be increased as necessary.

The 5-HT3-receptor antagonist, alosetron, was initially approved for the treatment of women with diarrhea-predominant IBS. Unfortunately, it had to be withdrawn from the market in November 2000 because of several cases of severe ischemic colitis, some of which were fatal. A panel of experts from the ACG concluded that the medication significantly reduces the global symptoms of diarrhea, abdominal pain and bloating in patients with diarrhea-predominant IBS.[12] The medicine is now reapproved by the FDA and is available under a limited-use program for patients with IBS and diarrhea.

Abdominal Pain

Increased visceral perception and abnormal GI contractions are thought to be the underlying cause of abdominal pain. In theory, agents targeted at decreasing GI tract contractions (smooth muscle antispasmodic medications) should ameliorate pain. Unfortunately, currently there is no medicine available that can satisfactorily treat pain in IBS. Most studies looking at agents that can decrease GI tract contractions have not demonstrated any significant benefits in comparison to placebo.[26] Nevertheless, some patients improve with antispasmodic medications, especially in those whose symptoms are induced by meals or who experience tenesmus. Anticholinergics should be given 30 to 60 minutes before meals so that the peak level of the drug coincides with peak symptoms.

Antidepressants like the TCAs in low dose (amitriptyline, nortriptyline, and desipramine), which are the most studied for use in IBS, appear to improve subjective complaints of abdominal pain.[31,32] Global symptoms are usually not relieved. Their therapeutic potential is sometimes limited by their side effects. The selective serotonin reuptake inhibitors (SSRIs) are less studied, although preliminary data suggests some benefit in chronic abdominal pain.

Analgesic medications should be avoided if possible; however, if used they should be prescribed in

low doses. Acetaminophen and aspirin may be tried first, although usually are not beneficial. Addictive narcotics should not be prescribed. Abdominal pain as part of the global symptoms in constipation-predominant IBS patients may derive some relief with tegaserod.

Bloating

This represents one of the most difficult GI complaints to treat. Most medicines designed to treat bloating do not work. Dietary advice may be helpful. Simethicone, activated charcoal and α-galactosidases (Beano) may be beneficial in some patients. Tegaserod has been shown to relieve bloating as well.

Psychological Management

In one study, 18% of IBS patients seen in the community had comorbid psychiatric disorders such as depression and generalized anxiety disorder.[33] A higher percentage (54 to 94%) was seen in those seeking treatment in referral centers.[34,35] Coexisting anxiety, panic disorder, depression and somatization disorders should be recognized and managed appropriately. Some symptoms of IBS are often anxiety-provoking and sometimes perpetuated by social reinforcement (secondary gain). Assessment of stress and aggravation of symptoms with specific stressors should be identified. Misconception about IBS can be dispelled with education and continuous reassurances. Referral should be reserved for patients who need expert psychotherapy. Psychological management appears to be more successful when a multifocal approach is employed.[36] This includes education of patients about the problem, counseling sessions, cognitive behavioral therapy, stress management and use of medication to treat associated or underlying psychological disorders.

Alternative Medicine

A large number of patients do not improve or are not satisfied with traditional available therapies and resort to alternative medicines out of desperation or frustration. Unfortunately, there are few studies available to support or discredit these potential therapies.

Herbal medicines are commonly used in Asia and Africa to treat a variety of ailments. A 16-week double-blind placebo-controlled trial comparing standard Chinese herbal formulation with placebo found significant improvement in global symptoms in the herbal formulation group.[37] Future well-designed clinical research studies will be needed to confirm the efficacy and safety of this approach for treatment of IBS.

Some patients believe peppermint oil minimizes abdominal pain and bloating. Indeed a meta-analysis of five double-blind, placebo-controlled randomized trials showed significant global improvement of IBS symptoms in patients who received peppermint oil, compared with those who received placebo.[38] The authors cautioned that there were strong limitations of their study and that further studies are required to clarify the role of peppermint oil in treatment of IBS.

Others find success with acupuncture and hypnotherapy. Probiotics, which include admixture of yeast or nontoxic bacteria, have enjoyed some success in the treatment of specific GI disorders such as bacterial overgrowth and recurrent *Clostridium difficile* colitis. More attention is being focused on its usefulness in IBS.

Summary

IBS is a non-fatal chronic disorder in which relatively symptom-free periods alternate with exacerbations of abdominal pain, bloating, constipation or diarrhea. More than 75% of patients in whom the diagnosis was initially made retain the diagnosis five years later.[37] The diagnosis of IBS should be based on a thorough history and physical examination, in conjunction with the Rome II criteria. Extensive testing is not required. Treatment should begin with education and reassurance, in addition to focusing on the predominant symptom presented by the patient. Symptoms and demands for attention by individual patients vary widely. Successful management relies on developing a sound doctor-patient relationship based on understanding, trust and compliance. While the standard therapies commonly used are ineffective in reducing global symptoms of abdominal pain, bloating and changes in bowel habits, newer agents targeting the serotonin system have been shown to significantly relieve symptoms in patients with IBS and constipation (tegaserod) and in patients with IBS and diarrhea (alosetron).

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CME Questions 3a-f

Select the correct answer for the following:

3a. Symptoms of irritable bowel syndrome (IBS) account for the second most common reason for work absenteeism in the US.
   a. True
   b. False

3b. A 60-year-old man presenting with a six month history of abdominal pain relieved by defecation associated with constipation and weight loss can be confidently diagnosed with IBS.
   a. True
   b. False

3c. IBS is a stress-related disorder which affects mainly people of North European descent.
   a. True
   b. False

3d. While pharmaceutical agents may be useful in the management of IBS, the mainstay of therapy is to improve symptoms and to establish a working relationship with the patient.
   a. True
   b. False

Please select the best answer to each of the following questions:

3e. The following theories have been proposed to explain the pathogenesis of irritable bowel syndrome except:
   a. Alteration in the perception of visceral stimuli in the gastrointestinal tract.
   b. Injury to the enteric nervous system following an attack of infectious gastroenteritis.
   c. Increased gastrointestinal stimuli with gas production.
   d. Accelerated or delayed intestinal transit due to alteration in the migratory motor complex (MMC).
   e. Abnormal processing of sensory information in the central nervous system (CNS).

3f. Which of the following medicines, approved by the FDA, improves the global symptoms of IBS?
   a. Loperamide
   b. Tegaserod
   c. Amitriptyline
   d. Sertraline
   e. Polycarbophil