Irritable Bowel Syndrome: A Review and Update

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ABSTRACT

Relevance: Irritable bowel syndrome (IBS) is the most common GI disorder (affecting approximately 11% of the population globally) and patients with IBS are frequently seen by primary care physicians and specialists.

Objectives: This article will summarize the existing evidence on epidemiology, pathophysiology, diagnosis, and treatment of IBS and to provide the best evidence in a way that can be practically utilized by providers.

Results/Findings: Irritable bowel syndrome is a Gastrointestinal disorder (GI) characterized abdominal pain and altered bowel movements. It's etiology and pathophysiology differs between individuals with IBS, but include intestinal microflora, GI motility, visceral hypersensitivity, brain-gut interactions, and post-infectious. The evaluation of IBS includes a thorough exam and history and physical exam. Multiple treatments exist for IBS-C and IBS-D and are reviewed in this article.

Conclusion: The diagnosis is based the presence of abdominal pain and bowel changes and the exclusion of other organic diseases. IBS is a clinical diagnosis based on Rome IV Criteria. Successful management of patients with IBS includes dietary and lifestyle changes, medication, and behavioral interventions.

Methodology of the evidence review: A search of Ovid (MEDLINE) and Cochrane Database of Systematic Reviews was performed usingthe terms epidemiology, pathophysiology, diet, therapy, management, etiology, pathogenesis, diagnosis, treatment, irritable bowel syndrome, functional GI disorders, and IBS. Evidence was graded strong, moderately strong, or suggestive. Evidence grading was based on study design, power of results, and the risk of bias. The highest rated evidence was preferentially utilized for each topic area addressed in this review. The database search yielded thousands of articles, of which 58 were selected for inclusion based on the quality of data and relevance.

INTRODUCTION

Irritable bowel syndrome (IBS) is a Gastrointestinal disorder (GI) characterized abdominal pain and altered bowel movements. IBS is the most common GI condition affecting approximately 11% of the population globally [1-3]. Approximately 10-20% of adults in Western countries have symptoms consistent with IBS and a similar prevalence has been reported in Asia [3]. The estimated global prevalence of IBS is around 11%, and the rate has been relatively stable for the last 30 years [3]. Globally, Southeast Asia appears to have the lowest prevalence of IBS (7.0%) and South America has the highest (21.0%) [3]. The prevalence in Africa is unclear due to the paucity of data for this continent [4]. Thirty percent of people who experience the

symptoms of IBS consult physicians for their IBS symptoms, and IBS patients account for as high as 25% to 50% of all GI referrals [1,2]. Patients with IBS, who do seek care, tend to have a lower quality of life [2]. In one study, 76% of patients with IBS reported IBS-related impairment in activities of daily life [5]. Compared with matched controls, IBS patients use a greater amount of medical services and incur significantly more annual all-cause health care costs than those without IBS [6]. IBS is also responsible for a significant economic burden. Inadequate IBS symptom control is associated with increased annual health care costs of $3,065 per patient [6]. Costs of IBS appear to be primarily attributable to an increased use of medical services rather than pharmacy costs [6]. In a study of IBS-D patients, over half (58.4%) of the costs were attributable to office visits and other outpatient services (diagnostic tests) while the remaining costs were attributable to prescriptions (19.5%), inpatient admissions (13.6%), and ED visits (8.5%) [6].

RISK FACTORS

Risk factors for IBS include female sex (2:1 predominance), a family history of IBS, a personal history of sexual abuse, and a medical diagnosis of anxiety or depression [7]. Although anxiety and depression increase the risk of IBS approximately twofold, IBS isn't merely a manifestation of anxiety or depression, and only one-half of patients with lifetime IBS have lifetime mood or anxiety disorders [8,9]. There is conflicting data on the effect of education and socioeconomic status on IBS prevalence [3,4,10]. IBS is also much more common in young patients, with less than 25% of patients presenting after the age of 50 years old [2].

SUBTYPE CLASSIFICATION

Irritable bowel syndrome is classified into subtypes. The subtypes are determined by the percentage of particular stool characteristics on days that the individual has at least one abnormal (loose or hard) bowel movement. Determining the subtype of IBS is important for both diagnosis and treatment. The subtypes include: Diarrhea-predominant (IBS-D), Constipation-predominant (IBS-C), Mixed (IBS-M), or Untyped. Diarrhea predominant IBS is defined as greater than twenty-five percent of stools being loose or watery and less than five percent of hard stools [11,12]. Constipation-predominant IBS is defined as greater than twenty-five percent of stools being hard and less than twenty-five percent of stools being loose or watery [11,12]. Mixed subtype IBS is defined as greater than twenty-five percent of stools being hard and greater than twenty-five percent of stools being loose or watery [11,12]. If information about a patient's stool is not available or it does not fit a subtype criteria, the IBS is classified as Untyped.

Table 1: Subclassification of IBS.

IBS Subtype:	Percent Loose Stools	Percent Hard Stools
IBS-D	≥25%	<5%
IBS-C	≥25%	<25%
Mixed	≥25%	>25%

ETIOLOGY AND PATHOPHYSIOLOGY

The pathophysiology of IBS remains uncertain and the cause may differ between individuals with IBS and similar symptoms. Despite the fact that one etiology has not been determined for all patients with IBS, multiple mechanisms have been proposed based on the current medical literature. Several of the proposed mechanisms for IBS are discussed below.

Altered gastrointestinal reactivity

Traditionally IBS symptoms were thought to be related to colonic motility dysfunction as bowel motility has been linked to symptoms in IBS [13]. Increased distention that can lead to abdominal discomfort has also been associated with delayed transit in IBS-C patients [14]. However, not all patients with IBS have motility changes or reactivity associated with symptoms, so this etiology is likely only relevant to a subset of IBS patients.

Visceral hypersensitivity

A subset of patients with IBS have visceral hypersensitivity. The hypersensitivity is thought to be linked to serotonin dysregulation. Hypersensitivity has been demonstrated in IBS patients through balloon distension analysis [15]. High colon pain perception is perceived by IBS patients with low-volume balloon distention of the descending colon that is present or as severe in controls [15].

Inflammation

Conventionally, IBS was thought of as a non-inflammatory disorder. However, evidence shows that particularly in a subset of patients with IBS-D, inflammation may play a significant role in the pathogenesis of IBS [16,17].

Brain-Gut etiologies

Brain activity alterations may in play a role in IBS including the effect of stress on the hypothalamic–pituitary–adrenal (HPA) axis. A recent study also showed MRI alterations in brain

white mater for patients with IBS which could be a clue to another etiology of IBS [18].

Microflora

Irritable bowel syndrome has been associated with aberrant microbiota [19]. Furthermore, down-regulation of bacterial colonization with Lactobacillus, Bifidobacterium and F. prausnitzii has been observed in IBS patients, particularly in diarrhea-predominant IBS [20]. Microbiota changes participate in the pathogenesis of IBS and may underlie the efficacy of probiotic supplements.

Postinfectious

Patients with a significant Gastroenteritis (GE) are more likely to develop IBS. The rates of IBS development after a severe, acute enteritis may be as high as 20-30%, but is related to the severity of the infection [21]. The more severe the GE, the more likely the person is to subsequently develop IBS. The cause of persistent or new bowel symptoms after an acute GI infection is uncertain, but several mechanisms have been proposed. Mechanisms by which enteritis may increase risk of IBS include: disruption of the mucosal nerves leading to irritability, bile acid dysfunction and malabsorption, and disruption of colonic flora [22-24].

Food allergies

The role of food allergy in IBS is uncertain. There is currently no well-proven mean to identify these individuals and results from serum immunoglobins testing to food allergens has not been associated with IBS symptoms [25].

Clinical presentation

The clinical presentation of IBS is variable, but abdominal pain is the most common. Pain can be cramp-like and is often exacerbated by stressful events or eating certain foods. Pain related to IBS can be associated with menstrual cycles. This correlation can make IBS challenging to differentiate from endometriosis. Patients with IBS may note a mucous discharge with their stools, a feeling of incomplete evacuation, pain with defecation, and/or significant pain relief after a bowel movement. Some patients report a sense of urgency and fecal incontinence. However, nocturnal fecal incontinence that awakens a patient from sleep is an indication that something other than IBS is causing symptoms and is not consistent with IBS [7,25].

Evaluation

Evaluation of IBS starts with consideration of possible differential diagnoses that include malignancy, inflammatory bowel disease, infectious processes, endometriosis, thyroid or parathyroid disorders, laxative abuse, lactose intolerance, and celiac disease [12]. Physicians should also assess the patient for red flag signs and symptoms suggestive of other serious disorders whose diagnosis would require further evaluation. All patients with red flags should be evaluated with a colonoscopy. Red Flags of IBS include [12]:

- Unexplained rectal bleeding
- Fever
- Weight loss
- Anemia
- Nocturnal diarrhea that prevents sleep.
- Onset of symptoms after 50 years of age
- First degree relative with IBD or early colon cancer

The evaluation of IBS is further based on the specific subtype. Patients with IBS-D require investigation for celiac disease, lactose intolerance, and inflammatory bowel disease (IBD). Celiac disease can be screened for with either a serum IgA antibody to tissue transglutaminase or anti-endomysial antibody. If lactose intolerance is suspected based on history, hydrogen breath testing, a lactose avoidance diet, or lactase supplementation can be utilized to help confirm the diagnosis. IBD can be screened for with either a CRP or fecal calprotectin [25]. A complete blood count and guaiac testing typically are obtained to rule out anemia and rectal bleeding [25-27]. If there are no red flags and laboratory testing is normal, there is no need for patients with IBS symptoms to undergo a colonoscopy.

Diagnosis

IBS symptoms can mimic those associated with other disease conditions, posing a challenge for diagnosis. Therefore, ruling out other possible differentials diagnoses is paramount to making an accurate diagnosis of IBS. The diagnosis of IBS is made by performing a careful review of the patient's symptoms, determining the presence or absence of red flags, performing athorough physical examination, andutilizing Rome IV criteria (See Table Two) [11,28]. Rome criteria must be fulfilled for the past 3 months, with symptom onset at least 6 months before diagnosis [11]. Because abdominal pain is a

prerequisite for diagnosis of IBS based on Rome Criteria, the absence of abdominal pain rules out the diagnosis of IBS. Unfortunately, although the majority of patients with IBS are diagnosed and treated in a primary care setting, only a minority of general practitioners appear utilize Rome criteria to diagnose IBS [29].

There are no confirmatory blood tests for IBS. Biomarkers are under investigation, particularly in IBS-D, but do not replace clinical diagnosis [27,30]. Currently, there are no histological criteria to diagnose irritable bowel syndrome, but there are investigative studies that hope to differentiate and diagnose IBS patients based on evaluation of colonic biopsies [31].

Table 2: Rome IV Criteria for Diagnosing IBS [11].

Abdominal pain that occurs, on average, at least 1 day/week over the last 3 months, associated with two or more of the following criteria:
• Related to defecation • Associated with a change in frequency of stool • Associated with a change in form (appearance) of stool.
Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Treatment

Successful treatment of IBS often involves multiple strategies including pharmacologic and non-pharmacologic therapies.

Non-pharmacological treatments

Counseling and educating patients on the etiologies, course, and treatment options for IBSis the first step in treatment and can reduce the anxiety that often triggers IBS exacerbations. Patient perceptions regarding IBS underscore the need for more extensive counseling by providers. In one study, 52% of patients with IBS thought that the disease was caused by a lack of digestive enzymes, 34% thought patients with IBS required surgical intervention, and more than 20% thought IBS could develop into cancer and could shorten their life expectancy [32].

The approach to IBS management depends on the severity of the patients' symptoms. For IBS of mild severity, management can begin with non-medication treatments. Unproven remedies, but with few negative side effects, include: increasing fluid, avoiding caffeine, and losing excess weight [25]. For more severe IBS, medication or a combination of treatments is often utilized.

Exercise was shown in one randomized controlled trial to provide long-term improvement of IBS-related GI symptoms and also improved any associated psychiatric symptoms [33]. Recent systematic reviews indicate that psychological interventions are efficacious and their gains are maintained long-term. Treatment efficacy for psychological therapies do not appear to be directly related to the number of sessions indicating even short sessions of psychological therapy can be effective for IBS [34]. Cognitive behavioral therapy (CBT) is the main psychotherapy option and can reduce abdominal pain and abnormal stools significantly in patients with IBS [34,35]. Combining cognitive behavioral therapy with drug therapy is likely even more effective. Mindfulness and hypnotherapy also may be useful [36].

Dietary changes such as increasing soluble fiber and following a FODMAP diet may improve IBS symptoms, although the evidence is not strong. For IBS-D, some evidence supports the low fermentable oligosaccharides, disaccharides, monosaccharide's and polyols (FODMAP) diet for short-term efficacy [37]. FODMAPs are poorly absorbed short-chain carbohydrates including fructose (in excess of glucose), lactose, polyols, fructans, and galacto-oligosaccharides. The FODMAP diet limits or eliminates foods that are fermentable, oligosaccharides, disaccharides, monosaccharides, and polyols (includes fructans [eg, wheat, garlic, broccoli, legumes, sweeteners] and stone fruits [eg, apricots, peaches]). However, a 2017 systematic review noted high risk of bias in FODMAP diet studies and attributed the effects to a placebo response [38].

Table 3: Summary of Non-Pharmacological Treatments.

TREATMENT	IBS-TYPE
Physician Counseling on IBS	ANY
Psychological Interventions (CBT, hypnosis, mindfulness)	ANY
FOD-MAP DIET	IBS-D, Mixed

MEDICATIONS

Antidepressants

Tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) can be used for relief of abdominal pain and global IBS symptoms. The authors of a recent American Gastroenterological Association (AGA) review concluded that although TCAs and SSRIs appear effective, the evidence is of low quality [39]. Because the anticholinergic properties of TCAs tend to cause constipation, they may be best for patients with IBS-D. Conversely, SSRIs tend to cause

diarrhea and may be the best antidepressant therapy for patients with IBS-C.

Antispasmodics

Antispasmotics available in the Unites States include dicyclomine, hycosamine, and peppermint. Based on low-quality evidence, antispasmodic drugs provide short-term relief of IBS symptoms (3 to 6 weeks) [39-41]. Peppermint is a natural antispasmodic agent that is often well-tolerated and can be consumed as peppermint tea.

Probiotics

There is some evidence that probiotics improve symptoms but studies have not shown improvement in stool frequency [42]. Therefore, probiotics are often combined with a motility medication that either slows or speeds GI transit. Data regarding the ideal composition of bacteria in the probiotic preparation are unclear. A meta-analysis showed that single strains of Lactobacillus had no benefit for IBS symptoms, whereas Bifidobacteria, alone or in combination, were effective. More data are needed to confirm efficacy and the ideal preparation.

Other

Prebiotics are non-digestible, selectively fermented dietary fibers thought to promote the growth of bacteria in the GI tract. However, there is little evidence to support their use for IBS at this time [43]. Glutamine supplementation could be a reasonable option as a recent small RCT of oral dietary glutamine supplements for IBS-D showed a reduction in the severity of IBS symptoms [44]. Data regarding anti-flatulence drugs such as simethicone are conflicting, but due to their low side-effects they may be useful in patients with significant gas, bloating, and flatulence [25].

Table 4: Medication Treatment for IBS.

Treatment	Type of IBS indicated for	Level of Evidence	Source
Antidepressants	IBS-C, IBS-D, Mixed, Untyped	SORT B	Weinberg 2014
Antispasmotics	Any	SORT B	Weinberg 2014
Probiotics	Any	SORT B	Moayyedi 2010
Loperamide	IBS-D	SORT B	Chang 2014
Polyethylene glycol	IBS-C	SORT B	Chang 2014
Rifaxamin	IBS-D	SORT A	Chang 2014
Eluxadoline	IBS-D	SORT A	RIvkin 2016, Chang 2014
Linaclotide	IBS-C	SORT A	Chang 2014
Lubiprostone	IBS-C	SORT A	Chang 2014

MEDICATION TREATMENTS SPECIFICALLY FOR IBS-D

The anti-motility drug loperamide is commonly used to treat loose stools in patient with IBS-D. Loperamide is mildly effective for diarrhea in IBS patients but does not reduce global IBS symptoms or urgency [40]. Bile acid sequestrants such as colesevelam (Welchol) have been shown to improve stool consistency in patients with IBS-D but are not commonly used or FDA approved for this indication [45]. In small recent study, low-dose Bismuth improved symptoms and quality of life in adult patients with IBS-D and may be an option for mild to moderate symptoms [46].

The antibiotic rifaximin (Xifaxan) is a possible initial management for IBS-D that is relatively safe and lacks significant drug-drug interactions because it is not absorbed systemically [40]. Rifaximin is FDA approved for the treatment of IBS-D and treatment can be repeated, if needed, for up to two additional courses.

Eluxadoline (Viberzi), a mixed mu and kappa opioid receptor agonist/delta opioid receptor antagonist, is FDA approved for IBS-D based on studies showing a reduction in abdominal pain and diarrhea [47]. Eluxadoline has drug-drug interactions and drug-disease contraindications that limit use such as cholecystectomy, chronic liver disease, chronic pancreatitis, and alcohol abuse [12,47]. Alosetron is a 5-HT3 antagonist previously restricted because of a risk of ischemic colitis and severe constipation [40]. Those restrictions were removed by the FDA in 2016, but this drug should be administered cautiously and considered last-line treatment.

Table 5: Summary of Key Points.

Key Points:
Diagnosis
Abdominal discomfort is a prerequisite for the diagnosis of IBS
Evaluation of IBS should include a thorough history and identification of any red flags
There are no specific serologic markers or diagnostic tests to confirm IBS
The diagnosis of IBS includes ruling out other diagnoses such as celiac disease, lactose intolerance, and inflammatory bowel disease
IBS is a clinical diagnosis based on Rome IV Criteria
There are no specific serologic markers or diagnostic tests to confirm IBS
Red Flags
IBS should not cause rectal bleeding, fever, weight loss, anemia, or nocturnal diarrhea that prevents sleep.
Red flags are an indication for a colonoscopy
Treatment
Counseling is the first step in the treatment of IBS
Successful treatment of IBS often involves multiple strategies including pharmacologic and non-pharmacologic therapies

MEDICATION TREATMENTS SPECIFICALLY FOR IBS-C

Over the counter medication management for IBS-C includes polyethylene glycol (Miralax). Polyethylene glycol is a laxative effective for increasing the frequency and ease of bowel movements in patients with IBS-C [40]. There also is fair evidence that soluble fiber, such as psyllium, can improve the frequency and consistency of bowel movements in mild to moderate IBS-C [37,48].

Because of cost, FDA approved medications for IBS-C are typically reserved for patients who do not benefit from polyethylene glycol. FDA approved medication for IBS-C include the secretagogues, linaclotide and lubiprostone, that increase secretions in the GI tract to improve intestinal transit in patients with IBS-C. In a pooled analysis of the most frequent adverse events, intestinal secretagogues were shown to be relatively safe drugs. The most common adverse events include diarrhea, abdominal pain, and nausea [49].

Linaclotide (Linzess) has been shown to improve stool consistency and abdominal pain in adults with IBS-C. It improves symptoms in patients who have failed soluble fiber and laxatives [40]. It should not be used for children because of harmful effects in animal studies. Lubiprostone (Amitiza), a locally active chloride channel activator, appears safe and effective for improving stool consistency and degree of straining with bowel movements, but evidence is lacking on long-term effectiveness for abdominal pain or bloating [40,50]. Lubiprostone is approved for women with IBS-C over the age of 18.

PROCEDURAL TREATMENTS

Large high-quality studies on procedures for IBS are lacking. Therefore, procedural treatments for IBS are considered experimental. A small study showed improvement in IBS-associated abdominal pain, bloating, bowel habits, and quality of life with Fecal microbiota transplantation (FMT) [51]. However, a recent randomized double-blinded placebo-controlled study found that FMT did not result in clinical improvement of IBS [52].

Irritable bowel syndrome is not considered a condition that necessitates surgical intervention. However, in a case series of six patients who underwent total colectomy for refractory IBS-C, postoperative physical and mental health scores significantly improved compared with preoperative scores [53]. This small study does not give credible support using this drastic procedure, but with further study, it may become a future option for patients with severe persistent symptoms.

INTEGRATIVE MEDICINE TREATMENTS

Yoga and curcumin-fennel oil have been used by patients with IBS with low-quality evidence of efficacy [54,55]. Limited evidence suggests that biofeedback and hypnotherapy also may be options [56]. Acupuncture studies have shown conflicting results among patients with IBS, but it does appear to have less side effects than medication and is a reasonable option for patients who are willing to try it [57,58].

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