Uma Mahadevan MD, Series Editor
guildconference.com

Irritable Bowel Syndrome

Elizabeth J. Videlock

Lin Chang

Irritable bowel syndrome (IBS) is a prevalent chronic functional gastrointestinal disorder characterized by the presence of chronic or recurrent abdominal pain associated with altered bowel habits. It is a multifactorial condition that has been recently redefined as a disorder of gut-brain interaction. The diagnosis is based on symptom criteria and limited diagnostic testing. In recent years, there have been significant advances in developing efficacious dietary, pharmacologic and non-pharmacologic approaches in the treatment of IBS. Management should focus on a patient-centered approach, reducing cost, continuity of care, and improving patient satisfaction and health related quality of life. This review discusses the epidemiology, clinical symptoms, and evidence-based and practical approaches to diagnostic evaluation and treatment of IBS.

Irritable bowel syndrome (IBS) is a functional bowel disorder (FBD) that is characterized by abdominal pain associated with diarrhea and/or constipation. IBS is one of the most common gastrointestinal disorders diagnosed in primary care and gastroenterology practices.[1] In IBS, the gastrointestinal (GI) tract is grossly and histologically normal. For this reason, it has been referred to as a "functional" GI disorder. However, there is increasing evidence of distinct pathophysiologic mechanisms underlying IBS. Thus, IBS has now been redefined as a disorder of gut–brain interaction that is classified by GI symptoms related to any combination of the following: motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and altered central nervous system (CNS) processing.[2]

Elizabeth J. Videlock, MD Lin Chang, MD Vatche and Tamar Manoukian Division of Digestive Diseases, David Geffen School of Medicine at UCLA, Los Angeles, CA

EPIDEMIOLOGY

Prevalence and Impact

A recent population-based study found that 30% met criteria for ≥1 FBD and 4.6% met Rome IV criteria for IBS (Table 1).[3] Using the less stringent Rome III criteria (Table 1),[4] the prevalence was 9%. IBS is subtyped by predominant bowel habit. Based on Rome IV subclassification criteria (Table 2), the prevalence of IBS with diarrhea (IBS-D), IBS with mixed symptoms (IBS-M), and IBS with constipation (IBS-C) are similar and < 5% are unsubtyped (IBS-U).[3,5] IBS is more prevalent in women and younger individuals.[1,6] Up to 50% individuals with IBS symptoms do not seek healthcare, and those who do have symptoms for an average of 7 years prior to being diagnosed with IBS.[7] IBS is associated with a poorer health-related quality of life (HRQOL)[8] and significant healthcare utilization and costs. It accounts for 10% to 15% of primary care visits and 25% to 50% of gastroenterology visits.[9] The combined indirect and direct costs for IBS has been estimated to be $1.01 billion.[10]

Risk Factors

Post-infection IBS (PI-IBS) is defined as the onset of IBS symptoms following resolution of acute infectious gastroenteritis, characterized by two or more of the following: fever, vomiting, diarrhea, or a positive bacterial stool culture, in an individual without a history of IBS.[11] GI infection is associated with about a 4-fold increase in risk of IBS-symptoms at twelve months in comparison to uninfected individuals.[12] Risk factors for PI-IBS include a preexisting GI condition, a history of more severe diarrheal illness, younger age, female gender, chronic stressful life events, or psychological disorders.[13]

There is an association between having IBS, including PI-IBS, and stressful life events in childhood and/or adulthood.[14,15] A history of early adverse life events (EALs) or traumatic experiences during childhood increases an individual's risk for IBS by at least 2-fold. These EALs include, but are not limited to, maladjusted relationships with a parent or primary caregiver, severe illness or death of a parent, a mentally ill or incarcerated household member, and physical, sexual, or emotional abuse.[16] Two survey studies found that the majority of IBS patients believe that stress causes and triggers their symptoms.[7,17]

DIAGNOSIS

The differential diagnosis for the symptoms of IBS is shown in Table 3. The use of the Rome diagnostic algorithm (Figure 1)[18] which is comprised of a medical history and physical examination, evaluation of GI symptoms and alarm signs or symptoms, limited diagnostic testing and use of symptom-based Rome IV criteria (Table 1),[1] which are sufficient to make the diagnosis of IBS. Alarm features include rectal bleeding, weight loss, iron deficiency anemia, nocturnal diarrhea, and a family history of colon cancer, inflammatory bowel disease (IBD) or celiac disease.[19] The presence of "red flags" or alarm features may indicate a need for further diagnostic tests but it should not exclude a patient from being diagnosed with IBS.[19]

The Rome IV criteria are currently the most widely used criteria for diagnosis of IBS and are accepted by regulatory agencies including the Food and Drug Administration (FDA). Symptom frequencies in the Rome IV criteria were based on US normative data. The purpose of the Rome criteria and the modifications in Rome IV are to improve the specificity (although this reduced the sensitivity) for the purposes of clinical research studies.[20] However, in clinical practice, patients meeting Rome III or IV criteria can and should be diagnosed with IBS.

Recent AGA guidelines for the diagnostic evaluation of patients with IBS-D or chronic diarrhea recommend a fecal calprotectin or fecal lactoferrin to screen for IBD.[21] A normal level is associated with a <1% chance that symptoms are due to IBD. In individuals with IBS symptoms, it is

Table 1. Rome III and IV (urrent) Criteria and Supportive Symptoms for IBS
Source: Longstreth et al. 2006 [4] and Lacy et al. 2016.[1] Reproduced with permission from Elsevier

Rome IV[1]	Rome III[4]
Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with 2 or more of the following criteria: 1. Related to defecation 2. Associated with a change in frequency of stool 3. 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.	Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months that is associated with 2 or more of the following: 1. Improvement with defecation 2. Onset associated with a change in frequency of stool 3. Onset associated with a change in form (appearance) of stool Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

Symptoms supportive of the diagnosis of IBS are abnormal stool frequency (< 3 bowel movements per week or > 3 bowel movements per day), abnormal stool form (lumpy/hard stool or loose/watery stool), defecation straining, urgency or a feeling of incomplete evacuation, and passing mucus.

cost-effective to obtain celiac serologies when the prevalence of celiac disease is at least 1%.[22] Serum IgA tissue transglutaminase (tTG) and an IgA level should be ordered. Because IgA deficiency can lead to a false-negative result, a test for IgG deaminated gliadin peptides can be ordered in IgA-deficient patients.[21] While Giardia antigen and polymerase chain reaction (PCR) tests are recommended in patients with IBS-D symptoms, conventional ova and parasite stool testing is not recommended unless there is a history of recent travel to endemic areas.[21] In 25-30% of patients with IBS-D symptoms, there is evidence of bile acid diarrhea[23] and therefore, testing for bile acid diarrhea or an empiric trial of bile acid sequestrants is recommended.[21] A blood test measuring circulating antibodies to cytolethal distending toxin B and vinculin (anti-CdtB, anti-vinculin) have been shown to be increased in IBS-D and possibly IBS-M.[24] However, this test has a low sensitivity (<50%), and the major societies did not issue recommendations for or against the use of these serologic tests.[21,25,26]

Other routine blood tests, such as a metabolic panel and thyroid function tests, are rarely abnormal in patients with symptoms of IBS, and typically do not lead to an alternative diagnosis.[27] Abdominal imaging such as a CT scan or ultrasound is not recommended in IBS patients without alarm signs or symptoms.

A colonoscopy should be performed according to the guidelines for colon cancer screening and surveillance in the general population in patients with IBS symptoms without alarm features.[19] There is a low pretest probability of IBD and colonic neoplasia in these patients. However, if a colonoscopy is performed in a patient with diarrheal symptoms, colon biopsies should be taken in the right and left colon to rule out microscopic colitis and collagenous colitis.

The association between small intestinal bacterial overgrowth (SIBO) and IBS remains controversial. With the possible exception of predicting response to rifaximin in patients with IBS-D,[28] there is limited clinical utility of testing for SIBO (e.g., lactulose hydrogen breath test) in patients with IBS. Society guidelines currently do not recommend testing for evaluation of IBS.[19,25,26,29]

Routine testing for carbohydrate malabsorption is generally not recommended in individuals with IBS symptoms.[19,25,26,29] However, lactose breath testing can be considered when lactose maldigestion remains a concern despite avoiding dairy products. Similarly, fructose breath testing can be considered in patients suspected of having fructose

Table 2. Irritable Bowel Syndrome (IBS) Subtypes by Bowel Habit

	Percent [b] of stools that meet the criteria (over the preceding 3 months) on days with abnormal stools (i.e. types 1-2 and/or 6-7)	
Subtype [a]	**Hard or lumpy stools (Bristol type 1–2)**	**Loose or watery stools (Bristol type 6–7)**
IBS with constipation (IBS-C)	≥25%	<25%
IBS with diarrhea (IBS-D)	<25%	≥25%
Mixed IBS (IBS-M)	≥25%	≥25%
Unclassified IBS (IBS-U)[c]	<25%	<25%

a The word *with* is preferred to predominant due to symptom instability.

b on days with at least one abnormal bowel movement

c Patients who meet diagnostic criteria for IBS but whose bowel habits cannot be accurately categorized into 1 of the 3 groups above should be categorized as having IBS unclassified.

Patients with both diarrhea and constipation that may alternate within hours or days, were previously classified as IBS-A according to the Rome II criteria, but should now be referred to as IBS-M. The category of alternating IBS (IBS-A) should be reserved for patients with bowel habits that have changed over time, e.g., weeks to months.

maldigestion. Adult Sucrase Isomaltase Deficiency has been recognized in a very small subgroup of IBS-D patients and can be considered especially if there is no response to a low fermentable oligo-saccharides, di-saccharides, and mono-saccharides, and polyols (FODMAP) diet.[30,31]

TREATMENT

Overall Approach

It is important to assess the severity and impact of symptoms on the patient's HRQOL as they guide treatment. Patients with mild symptoms (i.e., do not impact daily activities) can be managed with providing a positive diagnosis of IBS, reassurance, education, and dietary guidance. Pharmacotherapy may not be required or can be used on an as needed basis. However, patients with moderate to severe symptoms (i.e., moderate to severe impact on daily activities) will benefit from the approaches used in patients with mild disease activity but also often require pharmacological and/or psychological therapies.

Understanding the biopsychosocial model of functional GI disorders which integrates clinical experience, pathogenesis with the bidirectional influence of psychologic and physiologic factors (brain-gut/mind-body interactions), and impact and clinical outcomes helps to guide management (Figure 2).[2] The biopsychosocial model provides a clinical framework for the physician to integrate the broad range of biomedical and psychosocial factors that explain the illness experience.[2]

A successful healthcare provider–patient relationship is the foundation of effective care of IBS patients. The quality of this relationship improves patient outcomes. Components of a therapeutic provider–patient relationship include a nonjudgmental patient-centered communication, a careful and cost-effective evaluation, inquiry into the patient's understanding of the illness, patient education, and involvement of the patient in treatment decisions which can empower them.

As many treatments target normalization of bowel habits, treatment approaches can differ based on IBS bowel habit subtype. The Rome algorithms for IBS-C and IBS-D are shown in Figures 3 and 4, respectively. The individual treatments are described below. References to primary literature can be found in the American College of Gastroenterology (ACG) monograph[32] unless cited directly.

Figure 1. Diagnostic Algorithm for IBS[18]

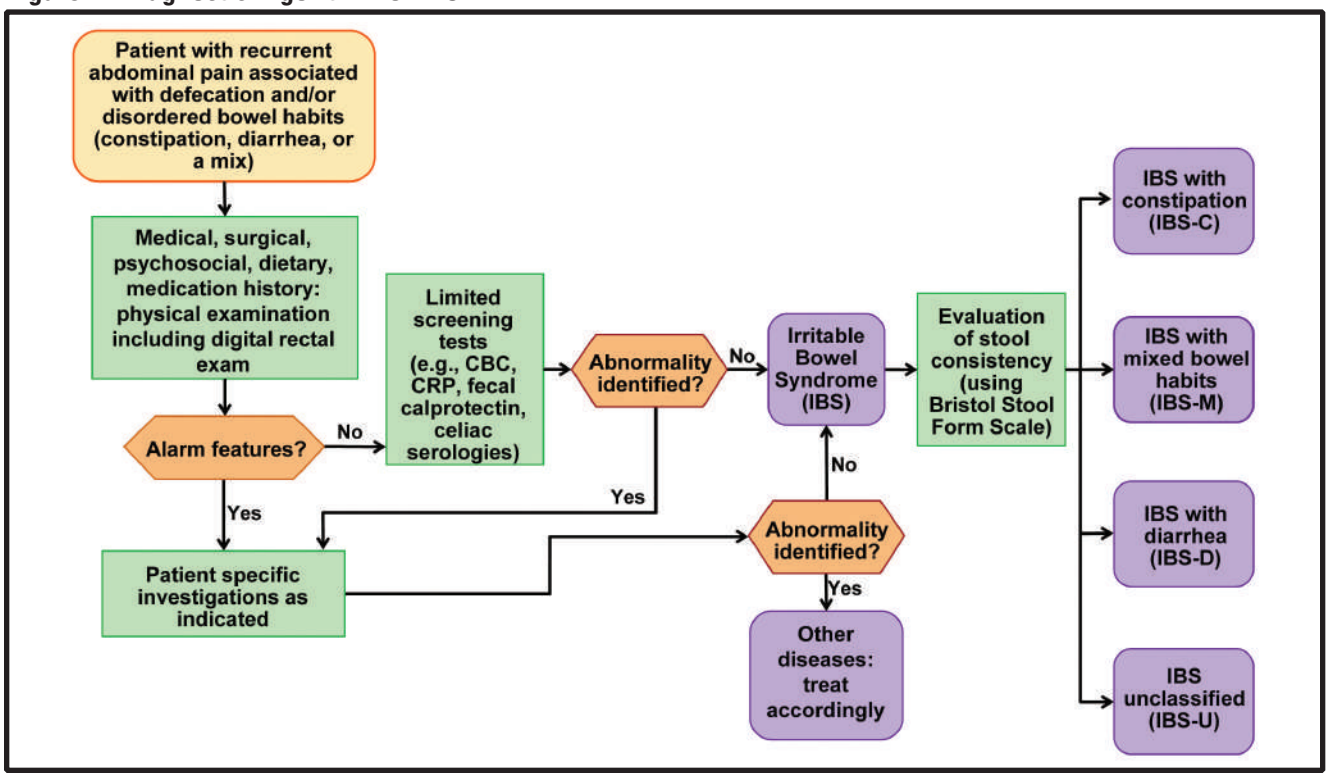
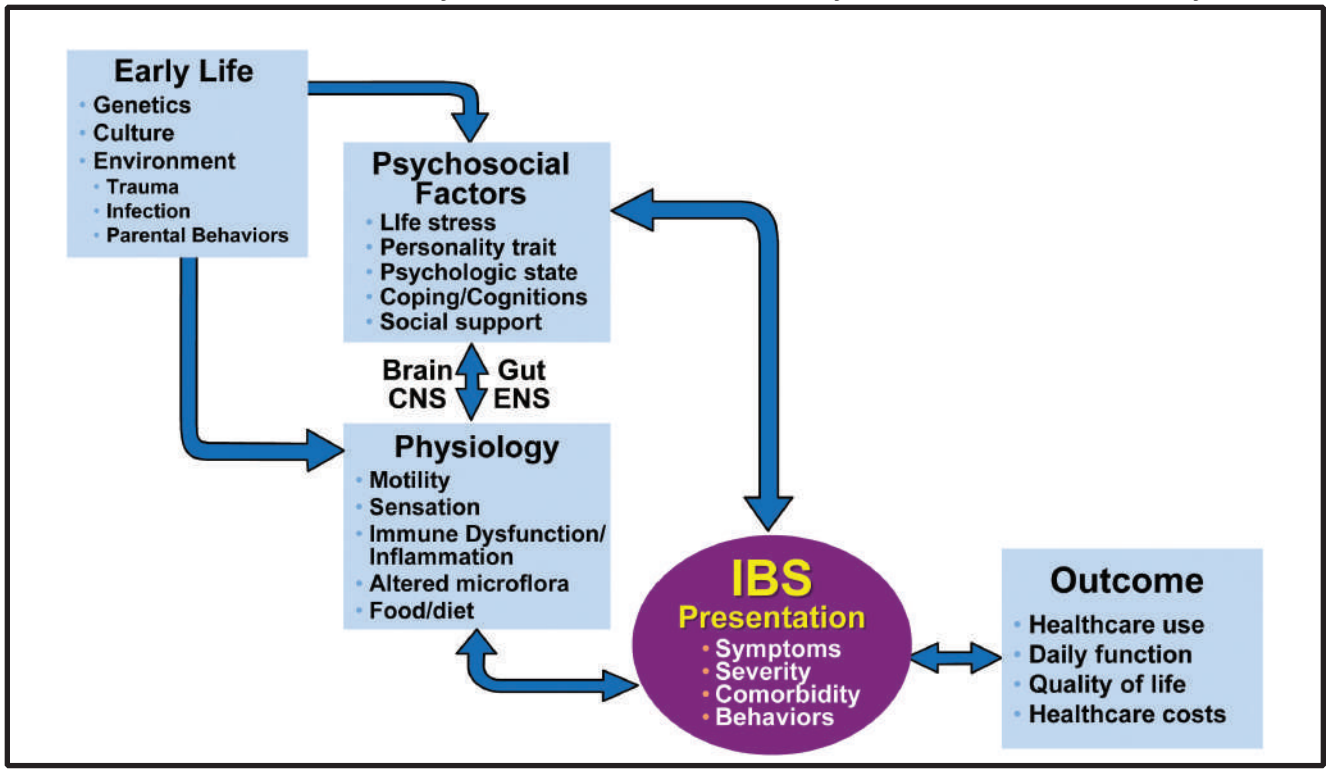


Figure 2. Biopsychosocial Model of IBS[2]
Abbreviations: IBS, irritable bowel syndrome; CNS, central nervous system; ENS, enteric nervous system



Diet and Lifestyle Changes

The majority of IBS patients perceive that symptoms are exacerbated by meals and that they have food allergies or intolerances.[33] There is more evidence that food intolerance rather than food allergies contributes to IBS symptoms. However, there is currently not strong evidence that food panels, which measure IgG levels to certain foods, predict food intolerance in IBS. A 1- to 2-week food and symptom diary can help determine consistent food triggers that can guide dietary modification and avoid eliminating more foods than necessary. Controlled trials have demonstrated that a low FODMAP diet is efficacious in reducing overall and individual symptoms of IBS. Although a low FODMAP diet was recommended by GI societies, the quality of evidence was considered very low. Although efficacy is thought to extend to all bowel habit subtypes, there appears to be more evidence to support its efficacy in patients with non-constipating IBS. Success of the low FODMAP diet is more likely if the patient works with a dietitian.

While there are studies that demonstrate a reduction in IBS symptoms with a gluten free diet, the evidence is of low quality and it is not recommended by GI societies.

Bulking agents, namely soluble fiber such as psyllium, have been shown to be efficacious in IBS. All studies were conducted in IBS, and not specifically IBS-C, and no study reported data by predominant bowel habit. However, anecdotal experience suggests that bulking agents are more effective in IBS-C than other subtypes.

Physical activity is beneficial in reducing IBS symptoms compared to usual activity.[34] Improving sleep may also be helpful as poor sleep quality correlates with worse IBS-related abdominal pain, distress and HRQOL.[35]

Pharmacological Therapies

Pharmacologic therapies and associated doses to treat IBS symptoms are listed in Table 5.

IBS-C

Laxatives

Osmotic laxatives, such as polyethylene glycol (PEG) or magnesium-containing products, are

(continued on page 18)

(continued from page 16)

generally safe and well tolerated and can be considered in patients with mild IBS-C. In IBS-C, PEG has been shown to relieve constipation symptoms but not abdominal pain. Other osmotic laxatives, such as lactulose and sorbitol, are frequently associated with bloating and/or cramping in IBS patients. Stimulant laxatives (senna, bisacodyl) have been studied more in chronic (functional) constipation than IBS-C. They can be used if more effective than other therapies or on an as needed basis, but may cause abdominal cramping, urgency and loose stools.

Lubiprostone

Lubiprostone is a chloride channel (ClC-2) activator increases luminal chloride secretion. In randomized controlled trials (RCTs), lubiprostone improved stool consistency, straining, abdominal pain/discomfort and constipation severity. The most common side effects of lubiprostone are nausea and diarrhea. Taking lubiprostone with food helps to decrease nausea. Lubiprostone should be considered in patients with mild to moderate symptoms of IBS-C and when pain is not a predominant and persistent symptom.

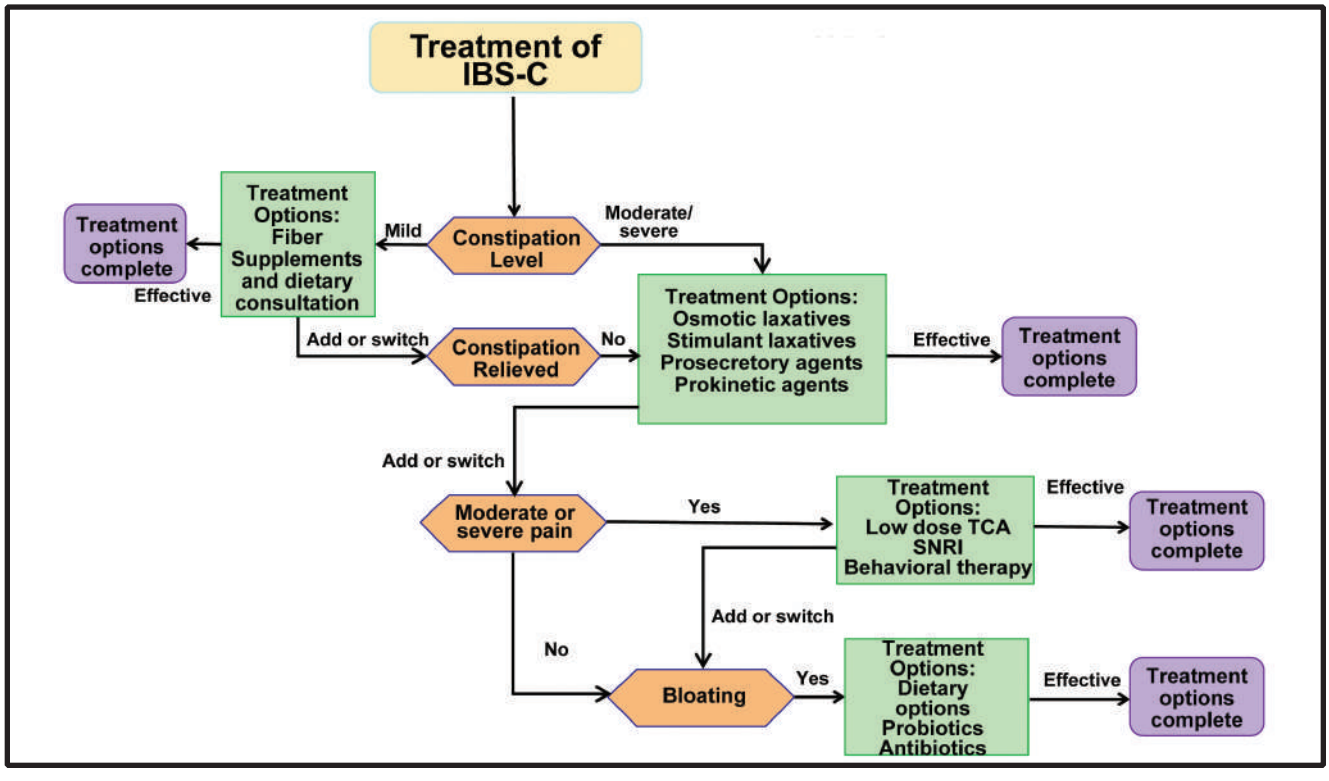
Linaclotide and Plecanatide

Linaclotide is a minimally absorbed, guanylate cyclase C (GC-C) agonist that increases luminal secretion of chloride and bicarbonate via the cystic fibrosis transmembrane conductance regulator. In multiple clinical trials conducted in IBS-C patients, linaclotide at a dose of 290 µg per day has been associated with significant improvement of abdominal pain, bloating and constipation symptoms.

Plecanatide is a similar to uroguanylin, which is a natural ligand of the GC-C receptor that acts in a pH-dependent manner. Three RCTs showed that plecanatide significantly relieved abdominal pain and constipation symptoms compared to placebo. The main side effect of both GC-C agonists was diarrhea.

Based on their efficacy profile, these medications should be a mainstay in the treatment of IBS-C, particularly in patients with moderate to severe symptoms or when pain or bloating is

Figure 3. Treatment Algorithm for IBS-C
Abbreviations: IBS-C, IBS with predominant constipation; TCA, tricyclic antidepressant; SNRI, serotonin and norepinephrine reuptake inhibitor ***Printed with permission from Rome Foundation***



a predominant symptom despite improvement in bowel habits.

Tenapanor

Tenapanor is a minimally absorbed, inhibitor of the GI sodium/hydrogen exchanger isoform 3 (NHE3) that increases excretion of sodium and water in stool. Tenapanor significantly improved abdominal pain and constipation symptoms and was approved by the FDA for IBS-C in 2019. It is not yet available.

Tegaserod

Several RCTs have demonstrated the efficacy of tegaserod, a selective 5-HT_4 partial agonist, in improving symptoms of IBS-C and IBS-M compared to placebo.[36] Tegaserod was suspended by the FDA in 2007 because of the higher incidence of cardiovascular ischemic events in patients compared to placebo (0.11% vs 0.01%). However, in 2019, the FDA approved the reintroduction of tegaserod for treatment of IBS-C in adult female patients <65 years of age with low cardiovascular risk. Tegaserod is contraindicated in patients with a history of myocardial infarction, stroke, transient ischemic attack, angina, ischemic colitis or other forms of intestinal ischemia.

IBS-D

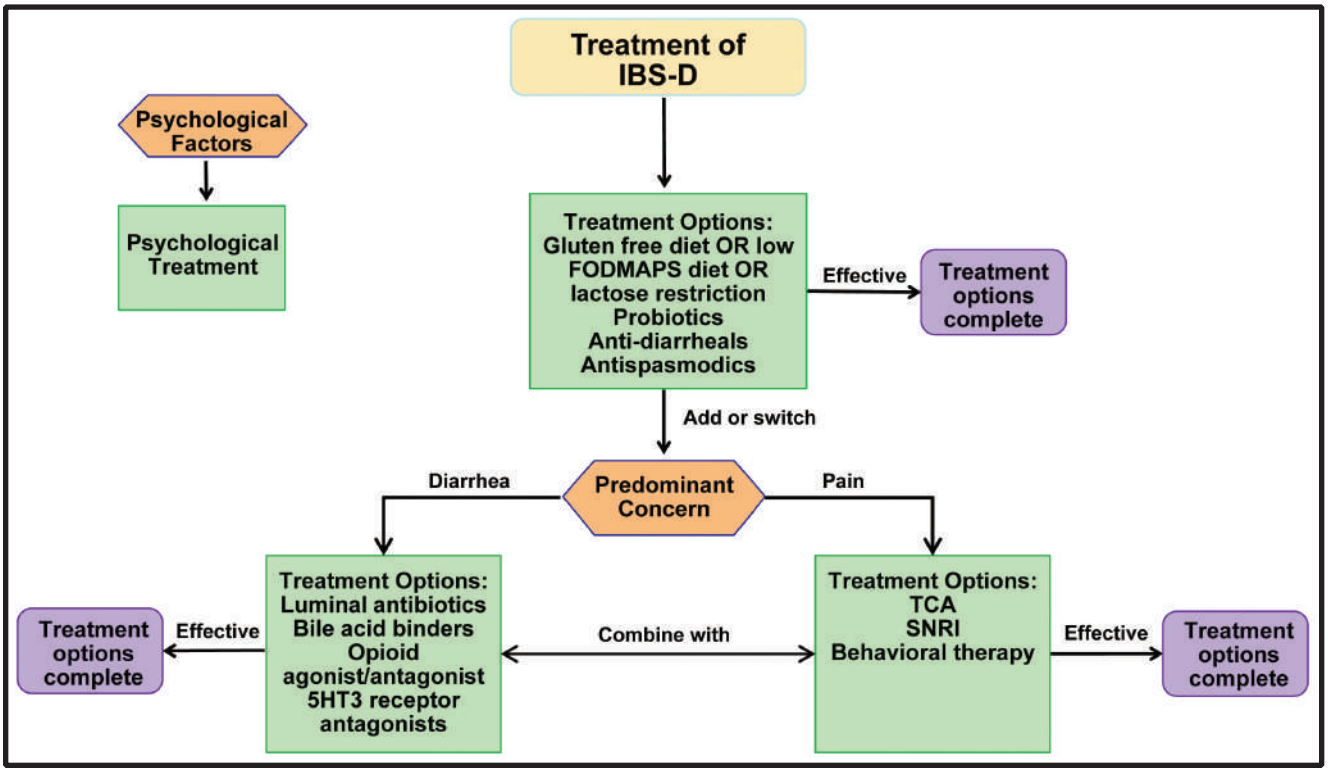
Loperamide

Loperamide reduces diarrhea by acting directly on the intestinal smooth muscle via the μ-opioid receptor. Two small RCTs showed that it did not have a beneficial effect on global IBS symptoms or abdominal pain but reduced stool frequency. Although antidiarrheals can be used regularly, they are more commonly used on an as-needed basis (e.g., leaving the house, a long car trip, a meal, or a stressful event).

Eluxadoline

Eluxadoline is a mixed agonist of both μ- and a κ-opioid receptors and an antagonist of δ-opioid receptors and was approved by the FDA for IBS-D

Figure 4. Treatment Algorithm for IBS-D
Abbreviations: IBS-D, IBS with predominant diarrhea; FODMAP; fermentable oligo- di- and mono-saccharides and polyols; TCA, tricyclic antidepressant; SNRI, serotonin and norepinephrine reuptake inhibitor, $5HT_3$, serotonin type 3
Printed with permission from the Rome Foundation



in 2015. RCTs demonstrated efficacy of both doses of eluxadoline in improving overall symptoms and stool consistency, frequency, urgency. The effect on abdominal pain was not as consistent. Due to an associated increased risk of pancreatitis, contraindications of using eluxadoline include lack of a gallbladder, known or suspected biliary duct obstruction, or sphincter of Oddi disease, alcohol intake of more than 3 drinks/day, a history of pancreatitis, structural diseases of the pancreas.

Rifaximin

Rifaximin is a broad-spectrum, minimally absorbed antibiotic that is approved to treat IBS-D. It has been shown to be superior to placebo in improving global symptoms, abdominal pain, diarrhea and bloating. Symptoms can return over time following treatment (e.g. within 3-6 months), but retreatment can be prescribed with up to two additional times for recurrent symptoms. Rifaximin is generally well tolerated.

Table 3. Differential Diagnosis of Irritable Bowel Syndrome (IBS)

IBS with constipation (IBS-C)
- Hypothyroidism

IBS with diarrhea/mixed symptoms (IBS-D/M)
- Celiac disease
- Carbohydrate maldigestion
- Bile acid malabsorption
- Chronic pancreatitis
- Gastrointestinal infection
- Inflammatory bowel disease (IBD)
- Hyperthyroidism
- Carcinoid tumor

IBS-multiple subtypes
- Food intolerance
- Small intestine bacterial overgrowth
- Enteric neuropathy or myopathy
- Malignancy
- Medication side effects
- Gynecological conditions (e.g., endometriosis)
- Psychological conditions (e.g., depression, anxiety)
- Other functional gastrointestinal disorders (e.g., functional abdominal pain syndrome, functional dyspepsia)
- Connective tissue disease

Bile Acid Sequestrants

As previously mentioned, bile acid diarrhea is part of the evaluation of suspected IBS-D. Thus, an empiric trial of bile acid sequestrant therapy, such as cholestyramine (powder) or colesevelam (tablets) can be considered and may be effective in a subset of patients.

Alosetron and Ondansetron

5-HT_3 receptor antagonists can slow gut transit and reduce visceral hypersensitivity and have been shown to be efficacious in treating IBS-D symptoms compared to placebo. RCTs demonstrated that alosetron significantly improved abdominal pain, diarrheal symptoms, and urgency in IBS-D. It is currently available under a risk evaluation and mitigation strategy for women with severe IBS-D who have failed traditional treatment. This restriction is due to the occurrence of rare GI-related serious adverse events including ischemic colitis and serious complications of constipation (rate of 1.1 and 0.66 per 1000 patient years, respectively).

The $5HT_3$ antagonist ondansetron is approved to relieve nausea and is currently being studied in IBS-D. A relatively smaller, placebo-controlled, crossover clinical trial with 3-week treatment periods demonstrated that ondansetron (4 mg tablets that could be titrated up to 8 mg three times daily) significantly reduced diarrhea but not abdominal pain.[37]

Multiple Subtypes

Antispasmodics

Antispasmodics are smooth muscle relaxants and significantly improve IBS symptoms including abdominal pain compared to placebo. They are commonly used in IBS, particularly to relieve postprandial GI symptoms. Hyoscyamine and dicyclomine area most commonly prescribed for IBS in the US.

Compared to placebo, peppermint oil, a smooth muscle relaxant, overall reduces IBS symptoms.

(continued on page 22)

(continued from page 20)

Peppermint oil is available in a small-intestinal-release formulation, which can reduce abdominal pain, discomfort and severity of IBS symptoms.[38]

Probiotics

There is considerable heterogeneity among probiotic RCTs in IBS. Many studies are small or of poor quality. In general, *Bifidobacteria* demonstrated some efficacy in reducing overall symptoms in IBS.[19] *Bifidobacteria animalis* subsp. *lactis* DN-173 010, *Bifidobacterium bifidum* MIMBb75 and *Escherichia coli* DSM17252 have been recommended for relief of bloating, distension, and overall symptoms in IBS.[32]

Central Neuromodulators

Centrally acting agents, such as antidepressants, have been relabeled as gut-brain neuromodulators as they work both in the brain and the gut.[2] The rationale for using central neuromodulators in IBS is that they may reduce visceral perception and potentially treat coexistent psychological symptoms. Tricyclic antidepressants (TCAs),

Table 4. Diagnostic Testing in the Evaluation of IBS Symptoms

	AGA (IBS-D only)[42]	CAG[25]	NICE[43]	UEG Algorithm[26]
Complete blood count			Yes	
Erythrocyte sedimentation rate	No		Yes	
C-reactive protein	No	No	Yes	Yes
Thyroid function			No	
Fecal calprotectin/lactoferrin	Yes	No		Yes
Celiac serologies	Yes	Yes	Yes	Yes
Giardia (PCR or antigen test)	Yes			
Ova and parasites without history of travel to high risk regions	No		No	No
Fecal occult blood			No	
Colonoscopy in <50 years of age without alarm features		No	No	No
Colonoscopy in new-onset IBS symptoms at ≥50 years of age		Yes		Yes
Food allergy testing		No		
Lactose hydrogen breath tests		No	No	No
Glucose hydrogen breath tests		No		
Bile acid diarrhea (fecal bile acid testing or empiric trial)	Yes			
SeHCAT or C4 testing		Yes		

Table 5. Pharmacological Treatment of IBS	
Agent (class)	**Dose**
IBS-C	
Psyllium/ispaghula (bulking agent)	20–25 g/day
Polyethylene glycol (PEG; osmotic laxative)	13.8 g PEG 3350+E in 125 mL water, 1–3 times/day
Lubiprostone (chloride channel activator)	8 µg twice daily
Linaclotide (guanylate cyclase C agonist)	290 µg daily
Plecanatide (Guanylate cyclase C agonist)	3 mg daily
Tenapanor (Na+-H+ exchange inhibitor)	50 mg twice daily
Tegaserod (5-HT_4 agonist)	6 mg twice daily
IBS-D	
Loperamide (antidiarrheal peripheral μ-opioid antagonist)	Up to 4 mg four times daily
Rifaximin (antibiotic)	550 mg 3 times daily for 14 days
Eluxadoline (μ-and κ-opioid receptor agonist and δ-opioid antagonist)	100 mg twice daily is recommended dose 75 mg twice daily available for those unable to tolerate 100 mg, are receiving concomitant OATP1B1 inhibitors, or have mild or moderate hepatic impairment.
Alosetron (5-HT3 antagonist)	0.5–1 mg twice daily
Bile acid sequestrants	
Cholestyramine	Start 2-4 g/d and titrate to response (max 24 g/d)
Colestipol	1g twice daily, increase of 1 g/d every other day
Colesevelam	2 tablets (625 mg) 3 times per day
Various IBS Bowel Habit Subtypes	
Tricyclic antidepressants (TCAs) (e.g. amitriptyline, imipramine, doxepin, desipramine, nortriptyline)	10–200 mg daily
Selective serotonin reuptake inhibitors (SSRIs) (e.g., fluoxetine, sertraline, paroxetine, citalopram)	10–100 mg daily
Selective serotonin reuptake inhibitors (SNRIs) (e.g., duloxetine)	30 mg twice daily
Delta ligand agent (e.g., pregabalin)	Escalating doses for the first week (75 mg twice daily for 3 days, then 150 mg twice daily for 3 days), 10 weeks of 225 mg twice daily and tapering doses for week 12 (150 mg twice daily for 3 days, then 75 mg twice daily for 3 days).
Antispasmodics (all pooled)	
Hyoscine/scopolamine (antispasmodic)	10 mg three times daily
Dicyclomine hydrochloride	20-40 mg four times daily
Peppermint oil (antispasmodic)	~200 mg three times daily
Probiotics	Variable
Lactobacillus plantarum DSM 9843	10^7-10^{10} cfu
Bifidobacterium infantis 35624 (probiotic)	1×10^8 CFU daily
Psychological Therapy	
Cognitive behavioral therapy (CBT)	1 hr/wk 6-12 wks
Hypnotherapy	30 min/wk for 6 wks to 1 hr/wk for 12 wks

IBS, irritable bowel syndrome; 5-HT_4, serotonin type 4; 5-HT3, serotonin type 3

selective serotonin reuptake inhibitors (SSRIs), and to a lesser extent serotonin–norepinephrine reuptake inhibitors (SNRIs) have been studied in IBS.

TCAs can be considered first-line treatment for IBS patients with predominant pain, especially if they have IBS-D since TCAs have anticholinergic effects and can reduce diarrhea. They can be started at 10-25 mg qhs and gradually increased to the lowest, most effective and tolerated dose (e.g., up to 75 or 100 mg). Because desipramine and nortriptyline have less anticholinergic and antihistaminic side effects compared with amitriptyline and imipramine, they are favored if constipation or sedation is a concern.

Most RCTs of SSRIs in IBS have been small. While SSRIs may improve global symptoms of IBS, they are not efficacious in relieving abdominal pain. They are generally tolerated better than TCAs. However, diarrhea may be a side effect and therefore they may be more useful in patients with constipation. They should be considered in patients with significant psychologic symptoms which can amplify IBS symptoms and/or negatively impact coping of symptoms.

SNRIs, such as duloxetine has only been assessed in a small IBS study,[39] but there is substantial evidence of their pain inhibitory properties. Therefore, they may be efficacious in patients with chronic abdominal pain, particularly if TCAs are not effective or well tolerated. SNRIs have been approved to treat fibromyalgia and depression, which are often coexistent in IBS and thus may be an ideal agent in these overlap patients.

Psychological Therapies

The rationale of using psychological treatment for IBS is that symptoms can be triggered by stressful life events, there is a notable coexistence with psychiatric disorders, and central-acting therapies can reduce visceral perception. Cognitive behavioral therapy, relaxation therapy, multicomponent psychological therapy, hypnotherapy, and dynamic psychotherapy have been found to be effective in IBS. There are emerging studies demonstrating similar efficacy of internet based behavioral treatment, which may be more convenient and accessible than in-person treatments.

Fecal Microbiota Transplantation (FMT)

FMT has been assessed for the treatment of IBS. A recent meta-analysis of four studies showed no benefit of FMT for global IBS symptoms,[40] but another meta-analysis found a beneficial effect for FMT from donor stool delivered via colonoscopy vs autologous stool based.[41] Larger and higher quality studies are needed.

CONCLUSION

IBS is a common chronic GI disorder characterized by alterations in gut-brain interaction. It is a multifactorial, complex disorder that can be conceptualized using a biopsychosocial model. There are society guidelines for the diagnostic testing and treatment efficacy and safety in IBS which can help guide management, however, a patient-centered approach that considers multiple factors that affect treatment response are recommended. These factors include patient-related factors (comorbidities, treatment preferences, insurance, etc.), provider factors (past experience, knowledge and expertise, comfort and access to certain treatments, etc.) and system level factors (practice setting, location, reimbursement, etc.). Although beyond the scope of this review, we can look forward to emerging scientific data that will help enhance our understanding of IBS pathophysiology as well as advances in drug development for IBS. ■

References

1. Lacy BE, Mearin F, Chang L, et al. Bowel Disorders. Gastroenterology. 2016.
2. Drossman DA, Chang L, Chey WD, et al. Rome IV Functional Gastrointestinal Disorders – Disorders of Gut-Brain Interaction. 4 ed. Raleigh, NC: Rome Foundation; 2016.
3. Palsson OS, Whitehead W, Tornblom H, et al. Prevalence of Rome IV Functional Bowel Disorders Among Adults in the United States, Canada, and the United Kingdom. Gastroenterology. 2020.
4. Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. Gastroenterology. 2006;130(5):1480.
5. Black CJ, Yiannakou Y, Houghton LA, Ford AC. Epidemiological, Clinical, and Psychological Characteristics of Individuals with Self-reported Irritable Bowel Syndrome Based on the Rome IV vs Rome III Criteria. Clin Gastroenterol Hepatol. 2019.
6. Camilleri M. Sex as a biological variable in irritable bowel syndrome. Neurogastroenterol Motil. 2020:e13802.
7. Sayuk GS, Wolf R, Chang L. Comparison of Symptoms, Healthcare Utilization, and Treatment in Diagnosed and Undiagnosed Individuals With Diarrhea-Predominant Irritable Bowel Syndrome. Am J Gastroenterol. 2017;112(6):892.

8. El-Serag HB, Olden K, Bjorkman D. Health-related quality of life among persons with irritable bowel syndrome: a systematic review. Aliment Pharmacol Ther. 2002;16(6):1171.
9. Talley NJ, Zinsmeister AR, Van Dyke C, Melton LJ, 3rd. Epidemiology of colonic symptoms and the irritable bowel syndrome. Gastroenterology. 1991;101(4):927.
10. Everhart JE. Functional Intestinal Disorders. Washington, DC: US Government Printing Office: US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.; 2008. Contract No.: NIH Publication No. 09-6443.
11. Barbara G, Grover M, Bercik P, et al. Rome Foundation Working Team Report on Post-Infection Irritable Bowel Syndrome. Gastroenterology. 2019;156(1):46.
12. Klem F, Wadhwa A, Prokop LJ, et al. Prevalence, Risk Factors, and Outcomes of Irritable Bowel Syndrome After Infectious Enteritis: A Systematic Review and Meta-analysis. Gastroenterology. 2017;152(5):1042.
13. Ruigomez A, Garcia Rodriguez LA, Panes J. Risk of irritable bowel syndrome after an episode of bacterial gastroenteritis in general practice: influence of comorbidities. Clin Gastroenterol Hepatol. 2007;5(4):465.
14. Whitehead WE, Crowell MD, Robinson JC, et al. Effects of stressful life events on bowel symptoms: subjects with irritable bowel syndrome compared with subjects without bowel dysfunction. Gut. 1992;33(6):825.
15. Parker CH, Naliboff BD, Shih W, et al. Negative Events During Adulthood are Associated With Symptom Severity and Altered Stress Response in Patients With Irritable Bowel Syndrome. Clin Gastroenterol Hepatol. 2019.
16. Bradford K, Shih W, Videlock EJ, et al. Association between early adverse life events and irritable bowel syndrome. Clin Gastroenterol Hepatol. 2012;10(4):385.
17. Halpert A, Dalton CB, Palsson O, et al. What patients know about irritable bowel syndrome (IBS) and what they would like to know. National Survey on Patient Educational Needs in IBS and development and validation of the Patient Educational Needs Questionnaire (PEQ). Am J Gastroenterol. 2007;102(9):1972.
18. Kellow JE, Guest Editor in Drossman DA, Chang L, Chey WD, Kellow JE, Tack J, Whitehead WE (Eds). Rome IV Diagnostic algorithms for common GI symptoms. 2nd ed. Raleigh, NC: Rome Foundation; 2016.
19. Brandt LJ, Chey WD, Foxx-Orenstein AE, et al. An evidence-based position statement on the management of irritable bowel syndrome. Am J Gastroenterol. 2009;104 Suppl 1:S1.
20. Lin L, Chang L. Benefits and Pitfalls of Change From Rome III to Rome IV Criteria for Irritable Bowel Syndrome and Fecal Incontinence. Clin Gastroenterol Hepatol. 2019.
21. Smalley W, Falck-Ytter C, Carrasco-Labra A, et al. AGA Clinical Practice Guidelines on the Laboratory Evaluation of Functional Diarrhea and Diarrhea-Predominant Irritable Bowel Syndrome in Adults (IBS-D). Gastroenterology. 2019;157(3):851.
22. Spiegel BM, DeRosa VP, Gralnek IM, et al. Testing for celiac sprue in irritable bowel syndrome with predominant diarrhea: a cost-effectiveness analysis. Gastroenterology. 2004;126(7):1721.
23. Wedlake L, A'Hern R, Russell D, et al. Systematic review: the prevalence of idiopathic bile acid malabsorption as diagnosed by SeHCAT scanning in patients with diarrhoea-predominant irritable bowel syndrome. Aliment Pharmacol Ther. 2009;30(7):707.
24. Pimentel M, Morales W, Rezaie A, et al. Development and validation of a biomarker for diarrhea-predominant irritable bowel syndrome in human subjects. PLoS One. 2015;10(5):e0126438.
25. Moayyedi P, Andrews CN, MacQueen G, et al. Canadian Association of Gastroenterology Clinical Practice Guideline for the Management of Irritable Bowel Syndrome (IBS). J Can Assoc Gastroenterol. 2019;2(1):6.
26. Moayyedi P, Mearin F, Azpiroz F, et al. Irritable bowel syndrome diagnosis and management: A simplified algorithm for clinical practice. United European Gastroenterol J. 2017;5(6):773.
27. Tolliver BA, Herrera JL, DiPalma JA. Evaluation of patients who meet clinical criteria for irritable bowel syndrome. Am J Gastroenterol. 1994;89(2):176.
28. Rezaie A, Heimanson Z, McCallum R, Pimentel M. Lactulose Breath Testing as a Predictor of Response to Rifaximin in Patients With Irritable Bowel Syndrome With Diarrhea. Am J Gastroenterol. 2019.
29. The National Institute for Health and Care Excellence (NICE) Surveillance report 2017 - Irritable bowel syndrome (2008) NICE guideline CG61. London2017.
30. Henstrom M, Diekmann L, Bonfiglio F, et al. Functional variants in the sucrase-isomaltase gene associate with increased risk of irritable bowel syndrome. Gut. 2018;67(2):263.
31. Zheng T, Eswaran S, Photenhauer AL, et al. Reduced efficacy of low FODMAPs diet in patients with IBS-D carrying sucrase-isomaltase (SI) hypomorphic variants. Gut. 2019.
32. Ford AC, Moayyedi P, Chey WD, et al. American College of Gastroenterology Monograph on Management of Irritable Bowel Syndrome. Am J Gastroenterol. 2018;113(Suppl 2):1.
33. Eswaran S, Tack J, Chey WD. Food: the forgotten factor in the irritable bowel syndrome. Gastroenterol Clin North Am. 2011;40(1):141.
34. Zhou C, Zhao E, Li Y, et al. Exercise therapy of patients with irritable bowel syndrome: A systematic review of randomized controlled trials. Neurogastroenterol Motil. 2019;31(2):e13461.
35. Ballou S, Alhassan E, Hon E, et al. Sleep Disturbances Are Commonly Reported Among Patients Presenting to a Gastroenterology Clinic. Dig Dis Sci. 2018;63(11):2983.
36. Chey WD, Pare P, Viegas A, et al. Tegaserod for female patients suffering from IBS with mixed bowel habits or constipation: a randomized controlled trial. Am J Gastroenterol. 2008;103(5):1217.
37. Garsed K, Chernova J, Hastings M, et al. A randomised trial of ondansetron for the treatment of irritable bowel syndrome with diarrhoea. Gut. 2014;63(10):1617.
38. Weerts Z, Masclee AAM, Witteman BJM, et al. Efficacy and Safety of Peppermint Oil in a Randomized, Double-Blind Trial of Patients With Irritable Bowel Syndrome. Gastroenterology. 2020;158(1):123.
39. Brennan BP, Fogarty KV, Roberts JL, et al. Duloxetine in the treatment of irritable bowel syndrome: an open-label pilot study. Hum Psychopharmacol. 2009;24(5):423.
40. Xu D, Chen VL, Steiner CA, et al. Efficacy of Fecal Microbiota Transplantation in Irritable Bowel Syndrome: A Systematic Review and Meta-Analysis. Am J Gastroenterol. 2019;114(7):1043.
41. Ianiro G, Eusebi LH, Black CJ, et al. Systematic review with meta-analysis: efficacy of faecal microbiota transplantation for the treatment of irritable bowel syndrome. Aliment Pharmacol Ther. 2019;50(3):240.
42. Weinberg DS, Smalley W, Heidelbaugh JJ, et al. American Gastroenterological Association Institute Guideline on the pharmacological management of irritable bowel syndrome. Gastroenterology. 2014;147(5):1146.
43. The National Institute for Health and Care E. Surveillance report 2017 - Irritable bowel syndrome (2008) NICE guideline CG61. London2017.