Irritable Bowel Syndrome

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Learning Objectives

1. Review the epidemiology and pathophysiology of irritable bowel syndrome (IBS).
2. Diagnose IBS using the Rome IV criteria.
3. Utilize targeted diagnostic testing in patients presenting with symptoms consistent with IBS.
4. Manage IBS utilizing evidence-based nonpharmacological and pharmacological therapies in a stepwise approach.
5. Design an appropriate interdisciplinary management plan or care team for patients with IBS.

Sloane is a 32-year-old gender-nonconforming natal female (uses they/them/their pronouns) who presents to establish care. They report a 5-year history of intermittent abdominal pain and diarrhea. Five years ago, they had a bout of traveler's diarrhea while on a trip to Mexico. After the initial resolution of symptoms, they began experiencing episodic diarrhea and abdominal cramping.

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Epidemiology

Irritable bowel syndrome (IBS) is a symptom-based condition defined by abdominal pain with altered bowel habits in the absence of demonstrable organic disease. The prevalence is between 10% and 15% in North America and is equally distributed between subtypes: constipation predominant (IBS-C), diarrhea predominant (IBS-D), mixed type (IBS-M), and un-subtyped [1]. Women are 1.5–2 times more likely to be affected than males, and the prevalence of IBS decreases with age [2]. IBS is commonly encountered in the primary care setting and accounts for 25–50% of all referrals to gastroenterology. The burden of disease accounts for 3.1 million ambulatory care visits and up to 5.9 million dollars in prescriptions annually [3, 4].

Pathophysiology

The pathophysiology of IBS remains elusive. Traditionally, IBS has been theorized as being a gastrointestinal tract (GI) manifestation of primary brain dysfunction. However, newer epidemiologic studies have noted that GI symptoms may precede mood symptoms, which suggests a dual directionality of gut-brain axis dysfunction. Serotonin (5-HT) is an important and ubiquitous neurotransmitter in the central as well as enteric nervous systems, playing an integral role in GI motility and communication with the brain. Studies have found reduced postprandial 5-HT release in patients with IBS-C compared with those patients with postinfectious IBS and healthy individuals [5]. However, others have shown that alterations in 5-HT metabolism in patients with IBS did not have associations with GI or mood symptoms [6].

Acute enteric infections often precede the onset of IBS, especially IBS-D, and may serve as a trigger for immune activation that is mechanistically different from that of non-infectious IBS. A prospective controlled cohort study of 19,000 individuals exposed to drinking water contaminated with known GI pathogens such as *Norovirus*, *Giardia*, and

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Campylobacter jejuni showed increased risk of developing IBS-D symptoms in those with preexisting anxiety mediated by T-cell immune activation [7]. Separately, studies have shown increased concentration of cytokines in colonic mucosa as well as peripheral blood of patients with IBS-D [8]. This increased concentration of proinflammatory cytokines was also associated with mood disorders such as anxiety and depression [9].

Many patients with IBS also report diet triggers that initiate or exacerbate their symptoms. Though these are not usually reproducible when rechallenged in a double-blinded manner, certain foods seem to be implicated in the alteration of the gut microbiome and generation of IBS symptoms. Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) have been reported to exacerbate symptoms in a subgroup of patients due to proposed fermentation and osmotic effects [10]. In fact, follow-up studies have shown increased small bowel distension and increased water content on MRI when FODMAPs are administered to healthy individuals [11].

Sloane describes experiencing watery bowel movements up to three times a day on at least 3 out of 7 days of the week. They do have occasional normal stools. The diarrhea is accompanied by crampy diffuse abdominal pain that is improved with defecation. They believe intake of certain foods may correlate to timing of their symptoms and have been trialing elimination of dairy products and gluten with limited improvement. Their symptoms have been getting slightly worse over the past year.

Clinical Manifestations and Diagnostic Criteria

Clinical manifestations of IBS encompass a wide range of symptoms including abdominal cramping, bloating, and changes in bowel habits from loose/frequent stools to constipation. Symptoms often change over time and can mimic other disorders. Therefore, diagnosis is usually based on a combination of characteristic symptoms over time and the exclusion of organic diseases. The current diagnostic standard, the Rome IV criteria, describes IBS as recurrent abdominal pain associated with two or more of the following characteristics: abdominal pain related to defecation, abdominal pain associated with changes from baseline stool frequency, and/or abdominal pain associated with a change from baseline stool appearance or form. These criteria should be fulfilled at least 1 day a week for at least 3 months with symptom onset of more than 6 months prior to diagnosis [12].

Classification of a patient's predominant bowel complaint plays an important role in determining further diagnostic testing as well as treatment. As described previously, IBS is classified into four subtypes: IBS-D, IBS-C, IBS-M, or un-subtyped IBS based on stool consistency as assessed by the Bristol Stool Form Scale (BSFS), a validated tool that categorizes stool appearance from a score of 1 (hard and lumpy) to 7 (entirely liquid). This tool can easily be accessed for free on the internet.

It is important to note that the Rome IV updated subtype criteria is explicitly based on *predominant* bowel habits on days with abnormal bowel movements, and not an average of all days. For example, a patient who experiences >25% of abnormal bowel movements consistent with BSFS 6 or 7 can be considered to have IBS-D, while another patient who experiences 25% of abnormal bowel movements consistent with BSFS 1 or 2 has IBS-C. Moreover, another subset of patients may have alternating constipation and diarrheal symptoms (IBS-M) or symptoms that do not fit into any of the other three categories (IBS-un-subtyped). Many IBS-M patients may report extended periods of constipation followed by multiple watery bowel movements only later to be diagnosed with IBS-C with progressive stool accumulation then resulting in eventual bowel purging. A stool diary in these cases can be particularly helpful to elucidate patterns within the chaotic bowel habits these patients may experience [13].

Sloane denies any nocturnal stools, weight loss, rectal bleeding, or family history of gastrointestinal issues. They state they were previously diagnosed with IBS-D. They are wondering if any additional testing should be done at this point.

Differential Diagnosis and Diagnostic Strategies

For patients who present to primary care with symptoms of abdominal pain, constipation, and/or diarrhea, a detailed history and physical exam play a key role in the diagnostic process; oftentimes, no further testing is needed to confidently make a diagnosis of IBS. The differential diagnosis and subsequent diagnostic strategies for IBS are largely dictated by the predominant symptom subtype; however, it is important to keep in mind that conditions can sometimes fall into more than one category. The presence of any alarm features in a patient's medical history including symptom onset after age

50, severe and progressive symptoms, unexplained weight loss, vomiting, nocturnal diarrhea, rectal bleeding, unexplained iron deficiency anemia, or family history of colon cancer, celiac disease, or inflammatory bowel disease indicate the need to exclude organic disease. For patients who fit the Rome IV criteria for IBS without any alarm features, guidelines recommend no further diagnostic workup as it is low yield and unlikely to uncover a new diagnosis [14–16]. However, even in the absence of alarm features, a limited evaluation may still be appropriate to exclude the presence of illnesses that may cause similar symptoms.

Diarrhea-Predominant Symptoms

Table 27.1 outlines the major categories to consider when evaluating a patient with IBS-D [17, 18]. Categorizing diarrhea as inflammatory, malabsorptive/fatty, or watery is a useful framework to navigate the lengthy differential diagnosis for chronic diarrhea and guide additional workup. The first step is to assess for features of inflammatory diarrhea, which include constitutional symptoms, fever, weight loss, and bloody diarrhea. Inflammatory bowel disease, invasive infections, and malignancy all fit into this category. Inflammatory

Table 27.1 Differential diagnosis of IBS-D [17, 18]

Differential diagnoses	Distinguishing features from IBS-D
1. Inflammatory diarrhea – characterized by constitutional symptoms (fever, weight loss) and bloody diarrhea	
Inflammatory bowel disease (IBD)	Family history of IBD Progressive symptoms Extraintestinal manifestations Nutritional deficiencies (iron, vitamin B12, folate, zinc, vitamin D) Elevated inflammatory markers (CRP, ESR) Elevated fecal calprotectin and lactoferrin
Invasive Infections (i.e., *Campylobacter*, *Salmonella*, *Shigella*, enterohemorrhagic *E. coli*)	Historical risk factors: immunocompromised state, travel, animal contact, contaminated food or water ingestion
Malignancy	Older age (but young age does not exclude!) Family history of cancer or familial cancer syndrome
2. Malabsorptive diarrhea – characterized by foul-smelling, fatty, floating, pale, large volume stools; weight loss, + fecal fat, and nutritional deficiencies (iron, vitamin B12, folate, zinc, vitamin D)	
Celiac disease	Dermatitis herpetiformis Responsive to gluten avoidance
Diet-induced	Diet history: symptoms exacerbated by consumption of lactose, high-fructose corn syrup, sugar alcohol additives – sorbitol, mannitol, and xylitol – which are frequently found in sugar-free products such as gum, candy, or soda
Chronic pancreatitis	Historical risk factors: alcohol use, history of recurrent acute pancreatitis
Bile acid malabsorption	Postcholecystectomy Responsive to bile acid sequestrants Difficult to test for outside of research settings; consider empiric treatment
Small bowel bacterial overgrowth (SIBO)	Historical risk factors: anatomic or functional abnormalities including strictures, surgically altered anatomy, motility disorders (DM, scleroderma), systemic disorders (immunocompromised state, chronic pancreatitis, cirrhosis, ESRD)
3. Watery diarrhea – characterized by frequent liquid stools, nocturnal stools, systemic symptoms depending on etiology	
Infectious (i.e., *C. difficile*, *Giardia*, enterotoxigenic *E. coli*, *Cryptosporidium*, *Listeria*, viral)	Historical risk factors: antibiotic use, daycare centers, immunocompromised state/HIV, extremes of age
Drug-induced	Common culprit medications: laxatives, proton pump inhibitors, antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), antineoplastic agents, immunosuppression agents, metformin
Metabolic Hyperthyroidism Adrenal insufficiency Neuroendocrine tumors (VIPoma, carcinoid syndrome)	Systemic symptoms related to the metabolic abnormality (i.e., flushing, palpitations, weight loss)
Microscopic colitis	Middle-aged to older patients Can present with large stool volumes (up to 2 L/day) and nocturnal diarrhea May be associated with medication use (i.e., NSAIDs, SSRIs, PPIs)

bowel disease (IBD) may initially present with subtle symptoms such as IBS-D with more than a third of IBD patients also fulfilling Rome criteria for IBS [19]. However, patients with IBD usually experience symptom progression over time underscoring the importance of follow-up and reassessment. Fecal calprotectin is a noninvasive marker of intestinal inflammation that can be used to monitor disease activity in patients with IBD and help differentiate IBD from IBS-D. A complete blood count (CBC) and iron studies can be used to look for subacute blood loss from the GI tract commonly seen in IBD. Serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) should also be considered to evaluate for underlying inflammation; these markers are nonspecific but can indicate underlying inflammation that needs further attention. The probability of active IBD is <1% with fecal calprotectin levels <40 ug/g or with a CRP level <0.5 mg/L [20]. Patients with an invasive infection may have an exposure or travel history. To evaluate for infection, stool studies for bacterial culture, parasites, *Clostridium difficile*, leukocytes, and fecal lactoferrin should be sent. Patients with a strong family history of colon or rectal cancers or cancer syndromes who present with bloody diarrhea/stools should be evaluated early for malignancy regardless of age or accompanying symptoms.

Celiac disease, pancreatic insufficiency, diet-induced bile acid malabsorption, and small bowel bacterial overgrowth (SIBO) are the main causes of malabsorptive diarrhea. Malabsorptive diarrhea can present with foul-smelling "floating" or "greasy" stools, weight loss, and vitamin deficiencies. Checking a fecal fat can help identify malabsorptive diarrhea due to chronic pancreatitis. Celiac disease shares a significant overlap with IBS-D. A recent meta-analysis of 36 studies with 15,256 individuals found an increased likelihood of biopsy-proven celiac disease in patients with IBS with a pooled odds ratio of near 4.5 compared to non-IBS controls [21]. Given its prevalence, serum testing for tissue transglutaminase (tTG) antibodies and total IgA levels for celiac disease should be considered in all IBS-D patients. Total IgA deficiency may affect the validity of antibody testing as tTG antibodies are IgA antibodies. There may also be an overlap between IBS-D and bile acid diarrhea as a systematic review and meta-analysis found positive SeHCAT (23-seleno-25-homotaurocholic acid) testing, which measures radiolabeled bile acid retention, to be present in up to 25% of individuals with IBS-D [22]. Additional testing for lactose intolerance, pancreatic insufficiency, small bacterial overgrowth, tumor syndromes, and bile acid diarrhea is usually carried out after consultation with a gastroenterologist.

Patients presenting with frequent, watery diarrhea should be evaluated for noninvasive infectious causes, microscopic colitis, thyroid disease, endocrinopathies, metabolically active tumors, and medication side effects. A TSH and free T4 level can be checked to evaluate for thyroid disease; if adrenal insufficiency is entertained, the patient can undergo a cosyntropin (ACTH) stimulation test. Stool studies for bacterial culture, parasites, *C. difficile*, leukocytes, and fecal lactoferrin can be helpful if there is clinical suspicion for infectious diarrhea. Microscopic colitis might be considered in older patients with nocturnal stools and comorbid autoimmune disease [23]. Testing for metabolically active tumors such as a VIPoma or carcinoid tumor is most often done under the direction of a specialist. As always, a full medication reconciliation is key to determining any GI medication side effects.

In general, if there is any concern for an underlying IBD, microscopic colitis, or gastrointestinal malignancy, an immediate referral to a gastroenterologist for an endoscopy and/or colonoscopy should be placed as these diseases are most readily diagnosed under direct visualization and biopsy.

Constipation-Predominant Symptoms

The differential diagnosis for patients suffering from IBS-C differs from those who have primary diarrhea symptoms, but the diagnostic strategy is similar. Table 27.2 provides a

Table 27.2 Differential diagnosis of IBS-C [24, 25]

Differential diagnoses	Distinguishing features from IBS-C
1. Primary constipation (also known as chronic idiopathic constipation or functional constipation) – abdominal pain is NOT a prominent complaint	
Normal transit constipation	Regular bowel movements, but subjective complaints of hard stools, difficult evacuation
Slow transit constipation	Defecation may be dramatically infrequent (≤1 bowel movement (BM)/week) May be associated with a pelvic floor injury – childbirth, pelvic surgery
Rectal evacuation disorder Dyssynergic defecation Structural abnormality Functional defecation disorders	Straining even with soft stools, digital manipulation to pass BM
2. Secondary constipation	
Metabolic Hypothyroidism Diabetes mellitus Electrolyte imbalances	Associated signs/symptoms of hypothyroidism, diabetes mellitus Review basic screening lab work: TSH, BMP, Ca
Drug-induced	Common culprit medications: opioids, antihypertensives, antidepressants, antihistamines, and anticholinergics
Neurologic disorders Neuropathy Parkinson's disease Spinal cord injury Multiple sclerosis	Associated neurologic symptoms
Malignancy	Family history Weight loss Bloody stools Change in stool caliber related to structuring

framework of differential diagnoses and distinguishing features to consider in the evaluation of a patient with suspected IBS-C [24, 25]. Again, taking a detailed history assessing for any alarm features as well as performing an appropriate physical exam will help guide whether any additional workup is necessary.

Constipation may be a result of primary, or chronic idiopathic constipation, or secondary to metabolic, drug-induced, neurologic, or malignant etiologies. If a rectal evacuation disorder is suspected such as dyssynergic defecation, we suggest referral to a gastroenterologist for more specialized diagnostic testing. Checking a TSH, free T4, and electrolytes is reasonable to ensure there is not a secondary metabolic condition contributing to constipation. A full medication reconciliation should be performed looking for offending medications as constipation is a common, but often overlooked, side effect of many medications, including many over-the-counter preparations.

While colonic malignancy remains a common concern, meta-analyses of several cross-sectional studies and limited prospective studies have found no increased colon cancer risk in patients with typical IBS-C symptoms when compared to healthy controls [26]. Nevertheless, all patients should be up-to-date with age-appropriate colorectal cancer screening.

You order bloodwork and a stool sample given Sloane's report of slightly worsening diarrhea. CBC, CRP, thyroid testing, and fecal parasite testing all return within normal limits. You call Sloane on the phone to update them about the results. Sloane is relieved to hear that their tests were normal. They would like to avoid taking a medication if possible and asks what you would recommend.

Treatment Strategies

General Considerations

IBS patients frequently report dissatisfaction with their healthcare, particularly in relation to a delay in diagnosis, inadequate education, being perceived by physicians as problematic patients, and a lack of validation of their symptoms or suffering. A positive patient-physician relationship improves both IBS symptoms as well as patient satisfaction [27–29]. Establishing a firm, prompt diagnosis of IBS and educating the patient regarding etiology, diagnosis, and prognosis is an important first step in establishing a working relationship [30–33]. Providers should be aware of patients' potentially prior negative interactions with the healthcare system, validate their symptoms, and display active listening skills and empathy [28, 29]. It is important to set realistic patient expectations and treatment goals, specifically that IBS is not curable, but rather a chronic condition that can be well managed through individualized lifestyle modifications and, at times, medication. Patients should be made aware that although IBS may have a negative impact on their quality of life, this illness is not life-threatening and will not transform into a malignant condition. Continued reassurance provides positive reframing for patients to help patients cope with their symptoms.

There are several nonpharmacological and pharmacological therapies available for IBS. Treatment recommendations should be based on IBS subtype, comorbid conditions, patient preference, and provider expertise/comfort. Given the heterogeneity of IBS, it is important to tailor therapy recommendations to each individual patient through shared decision-making.

Nonpharmacological Interventions

Diet and Exercise

In patients with IBS, true food allergies are rare; however, many patients, regardless of subtype, have food sensitivities or intolerances and benefit from dietary modification. Some patients may independently identify food intolerances. Patients should be asked about dietary triggers and any dietary modifications they have already instituted. For others, maintaining a food/symptom diary can help identify intolerances. Traditional dietary advice includes increasing dietary fiber, taking probiotics, as well as limiting caffeine, alcohol, spicy foods, fatty foods, carbonated drinks, chewing gum, and artificial sweeteners. Fiber can provide relief of diarrhea but is most effective at treating constipation. Soluble (psyllium) fiber should be recommended as insoluble (bran) fiber may exacerbate bloating and gas [34]. A meta-analysis suggests probiotics are beneficial in the treatment of IBS; however, study heterogeneity makes it difficult to give a specific recommendation regarding preparations, species, or strains [35]. Although traditional dietary advice does provide symptom improvement, specialized diets, such as a diet low in FODMAPs, appear to be more effective at reducing gastrointestinal symptoms [36].

Systematic reviews and meta-analyses demonstrate a low-FODMAP diet is effective in reducing gastrointestinal symptoms in most patients with IBS [36, 37]. FODMAPs exacerbate IBS symptoms as they are poorly absorbed by the gastrointestinal tract leading to increased luminal water content, increased fermentation by gut bacteria, and excess gas production. Examples of foods high in FODMAPs can be seen in Table 27.3. A low-FODMAP diet should be initiated with the help of an experienced dietician. Initially, patients are instructed to eliminate all foods high in FODMAPs.

Table 27.3 Examples of high-FODMAP foods versus low-FODMAP foods [35–42]

	High-FODMAP foods	Low-FODMAP foods
Fruits	Avocados, apples, apricots, dates, cherries, figs, mango, pears, peaches, plums, watermelon	Bananas, blueberries, cantaloupe, grapefruit, grapes, kiwi, lemon, lime, mandarin, oranges, passion fruit, pineapple, tangerine
Vegetables	Artichokes, asparagus, beets, broccoli, cabbage, cauliflower, mushrooms, okra, onions, peas	Bell peppers, carrots, corn, cucumbers, eggplant, lettuce, leafy greens, potatoes, pumpkin, tomatoes, zucchini
Grains	Wheat/rye/barley-based breads, cereal, pasta, crackers, cookies	Gluten-free or spelt products, oats, quinoas
Protein	Cashews, legumes, baked beans, kidney beans, lentils	Almonds, eggs, tofu, plain cooked meats, and seafood
Dairy	Cow's milk, soft cheese, margarine	Lactose-free products, hard cheeses
Sweeteners	Honey, high-fructose corn syrup, sorbitol	Maple syrup, table sugar (sucrose), dark chocolate

Symptom improvement is generally seen around 3–4 weeks, although individual response times may be variable. After 4–6 weeks, the patient can reintroduce one high-FODMAP subgroup at a time while monitoring symptoms. Most patients will be able to tolerate some high-FODMAP subgroups and can follow a modified low-FODMAP diet based on individual tolerances. The rechallenge phase and relaxation of dietary restrictions are important as there are concerns about the long-term impact of a low-FODMAP diet on the gut microbiome, nutritional adequacy, and patient compliance [38, 39].

Several randomized double-blind placebo-controlled trials implicate wheat in exacerbating IBS symptoms. Most patients with IBS, even without evidence of celiac disease, experience improvement in gastrointestinal symptoms while on a gluten-free diet [40]. Wheat contains both gluten and high levels of fructans raising the possibility that the improvement achieved on a gluten-free diet may be due to the elimination of high-FODMAP foods rather than the elimination of gluten itself [41]. There is currently stronger evidence to support the efficacy of a low-FODMAP diet; however, a gluten-free diet is also a reasonable recommendation and may be easier for some patients to follow given the availability of products and the clear packaging of gluten-free foods [40, 42]. Moreover, patients should be instructed to avoid gas-producing foods, and in some, avoidance of lactose-rich foods may be needed.

In addition to dietary modifications, exercise is another component of lifestyle modification for patients with IBS. There is limited data that low- to moderate-intensity exercise can be beneficial for IBS symptoms [43–45].

Psychological and Alternative/Complementary Therapies

Underlying gut-brain axis dysfunction can respond to psychological and alternative/complementary therapies. Cognitive behavioral therapy (CBT), hypnotherapy, interpersonal therapy, multicomponent therapy, and dynamic psychotherapy all appear to be effective treatments for IBS [34, 46]. The strongest evidence exists for CBT, and a meta-analysis demonstrated a number needed to treat (NNT) of three [34, 46]. CBT is a highly structured psychotherapy that focuses on identifying and correcting maladaptive information processes and behavioral response patterns. Despite positive treatment outcomes with CBT, access to a psychologist may be difficult or limited for many patients. Thus, researchers are currently investigating the efficacy of psychological care delivered through minimal-contact methods utilizing technology (internet, phones, smartphone apps) and self-help strategies [47].

Two systematic reviews found that CBT-based minimal-contact treatment strategies significantly reduce IBS symptoms as compared to usual care, waitlists, online discussion forums, and symptom monitoring [48, 49]. It is unclear, however, how CBT-based minimal-contact treatment strategies compare to traditional CBT. Data remain limited with regard to relaxation therapy, stress management, and mindfulness training [34, 46]. Chinese herbs and other homeopathic regimens are frequently advertised as treatment for IBS; however, they have not been rigorously studied and cannot yet be recommended as effective treatments for IBS. In several randomized controlled trials, acupuncture compared to sham acupuncture did not improve IBS symptoms [50–52].

In summary, we first recommend nonpharmacological interventions including dietary modification, particularly a low-FODMAP diet, exercise, and, if appropriate, psychological therapy, as first-line treatment to all patients with IBS (Table 27.4). Most patients will achieve satisfactory and adequate relief of symptoms with the nonpharmacological interventions provided.

Sloane decides to try a low-FODMAP diet and start exercising regularly. They return to your office in 3 months and state that these interventions have not helped with symptoms. Sloane is ready to try a medication as they are tired of dealing with frequent diarrhea. At this appointment, Sloane also discloses that they have been struggling with mood symptoms over the past 6 months. They report low energy, difficulty concentrating at work, and difficulty falling asleep.

Table 27.4 Stepwise approach to treatment of IBS [13, 16, 34, 46]

Nonpharmacological Interventions

- Establish a trusting patient-physician relationship
- Set realistic patient expectations and treatment goals
- Dietary Modification(Low FODMAP Diet)
- Exercise
- Psychological (Cognitive Behavioral Therapy)

Pharmacological Management

	IBS-C	IBS-D		Pain
Medications that improve stool frequency/ consistency	**Polyethylene Glycol** 17gm daily - TID	**Loperamide** Initial: 4 mg, followed by 2 mg after each loose stool; Maintenance 4 to 8 mg/day single dose or divided doses; max 16 mg/day		• **Hyoscyamine** 0.125-0.25 mg q4 hrs PRN; max: 1.5 mg/day • **Dicyclomine** 20 mg QID x 7 days; then ↑ to 40 mg QID • **Peppermint Oil** 187-225 mgTID
FDA approved medications that improve global IBS symptoms	**Lubiprostone*** 8 mcg BID **Linaclotide*** 290 mcg daily	**Rifaximine*** 550 mg TID × 14 days; may be retreated 2 times with the same dosing regimen	+	**TCAs** • **Amitriptyline** 10-25 mg QPM; may ↑ up to 75 mg • **Nortriptyline** 10 mg daily **SSRIs** • **Citalopram** 40 mg daily • **Fluoxetine** 20 mg daily • **Paroxetine** 40 mg daily
		Eluxadoline* 75-100mg BID		

*FDA approved for females 18 years or older; Pharmacological management: green = first-line; yellow = second-line; purple = third-line

Pharmacological Interventions

Pharmacological management should be based on the subtype of IBS and the presence of other prominent symptoms such as pain, gas, and bloating, as well as comorbid conditions.

IBS-C

Along with nonpharmacological therapies, we recommend a trial of polyethylene glycol as first-line treatment for IBS-C given its availability and excellent safety profile. Polyethylene glycol 3350, an osmotic laxative, is frequently used to treat constipation. Two small randomized controlled trials in IBS-C patients found that polyethylene glycol improved stool consistency and the number of spontaneous bowel movements per week as compared to placebo; however, these studies failed to show improvement in abdominal discomfort and pain symptoms in the polyethylene glycol arm, and the sample sizes were not clearly adequate [53, 54]. Polyethylene glycol is readily available over the counter, can be easily titrated based on the patient's symptoms, and is generally well-tolerated. There is minimal systemic absorption, and the most frequent side effects associated with its use include abdominal discomfort, bloating, nausea, and diarrhea. The role of polyethylene glycol in the treatment of IBS-C has been questioned by some; however, there is a paucity of evidence that recommends against its use [55]. Other laxatives, especially bowel stimulants, should be avoided as these will likely exacerbate abdominal pain and have a higher risk of leading to dependence.

We recommend intestinal secretagogues as second-line treatment for patients with IBS-C who have failed lifestyle interventions and polyethylene glycol. Intestinal secreta-

gogues, lubiprostone and linaclotide, are FDA approved for the treatment of IBS-C. Both lubiprostone and linaclotide stimulate receptors in the intestinal mucosa that lead to an influx of water into the gut lumen promoting transit. Several randomized clinical trials demonstrate that both drugs significantly improve IBS symptoms compared to placebo with an NNT of 12.5 and 6, respectively [34]. Many of the primary end points of the clinical trials reflect partial improvement in overall IBS symptoms rather than complete resolution of symptoms, so it is important to counsel patients that these medications will not "cure" IBS, but rather mitigate the symptoms. In addition, it is essential to counsel patients about potential side effects related to the use of these secretagogues including nausea and diarrhea. Approximately twice as many patients taking lubiprostone report nausea when compared to placebo [56, 57]. Diarrhea is common with both lubiprostone and linaclotide with a number needed to harm (NNH) of 10 and 6, respectively [34]. Apart from the abovementioned side effects, lubiprostone and linaclotide are generally well-tolerated and have a favorable safety profile; the occurrence of serious adverse events are rare [56–59].

IBS-D

Along with nonpharmacological therapies, we recommend a trial of loperamide as first-line treatment for IBS-D. A trial of ondansetron and a trial of bile acid sequestrants are also reasonable alternatives for symptom control in patients with IBS-D. Medications such as ondansetron (a selective 5-HT3 receptor antagonist), loperamide (a gut-directed opioid-receptor agonist), and bile acid sequestrants are frequently recommended for IBS-D given their antidiarrheal properties, availability, and tolerability; however, the evidence base supporting their use in IBS-D is weak. One randomized controlled trial demonstrated that ondansetron as compared to placebo improves stool frequency and consistency, but does not improve pain scores [60]. Two small randomized controlled trials (n = 20 and n = 90) and one prospective trial examining loperamide compared to placebo found improvement in stool frequency and consistency with mixed effects on pain scores [61–63]. The data is not overwhelming, but loperamide is a reasonable first-line option. Bile acid sequestrants may be beneficial in IBS-D as there appears to be an overlap between IBS-D and bile acid malabsorption; however, formal evidence supporting the uses of bile acid sequestrants in the treatment of IBS-D is currently limited [64].

We recommend rifaximin as second-line therapy in patients with IBS-D who fail nonpharmacological therapy and a trial of symptomatic management with loperamide. There are two FDA-approved treatments for IBS-D: rifaximin, a gut-specific minimally absorbed antibiotic, and eluxadoline, a mixed μ-opioid receptor agonist and δ-receptor antagonist. Rifaximin is FDA-approved as a 14-day treatment course. Presumably, rifaximin alters the gut microbiome to decrease the symptoms of IBS. Compared to placebo, rifaximin provides significant relief of global IBS symptoms; however, approximately two-thirds of patients experience a relapse of symptoms after drug discontinuation [65–67]. Retreatment with another course of rifaximin appears to be both safe and effective, and the FDA has approved up to two repeat courses of rifaximin [67].

We reserve eluxadoline as a third-line agent given the safety concerns. Eluxadoline is an opioid receptor agonist; it acts to decrease intestinal motility and the visceral pain response. Compared to placebo, it is also effective at improving global IBS symptoms; however, sphincter of Oddi dysfunction and pancreatitis can rarely occur (0.5% and 0.4%, respectively) with the use of this drug and have resulted in hospitalization in some patients, specifically those with prior cholecystectomy [68, 69]. Eluxadoline is currently contraindicated in patients with prior cholecystectomy, those with other structural biliary or pancreatic disease, and those with heavy alcohol use.

Pain

In addition to considering subtype-specific therapies, there are several medications that target abdominal pain associated with IBS. Selection of an appropriate agent should be made by considering patient comorbidities and individual patient preferences and by engaging the patient in shared decision-making.

Antispasmodics, peppermint oil, and antidepressants including tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitor (SSRIs) are effective at reducing both pain and overall IBS symptoms compared to placebo A meta-analysis found that antispasmodics, as a class, are effective at improving IBS symptoms when compared to placebo [33]. However, there was significant heterogeneity among the studies regarding individual antispasmodics. Of all the drugs evaluated, hyoscyamine and dicyclomine are the only agents available in the United States. This meta-analysis included three trials evaluating hyoscyamine with an NNT of 3, while only one trial evaluated dicyclomine with an NNT of 4. Unfortunately, antispasmodics as compared to placebo also have a higher rate of adverse events. There were no serious adverse events; however, anticholinergic side effects including dry mouth, dizziness, and blurred vision were frequent with the use of antispasmodics [34].

Peppermint oil is an attractive alternative to antispasmodics for treating the pain associated with IBS as it is effective (NNT = 3) and has minimal side effects. Heartburn is the most common side effect reported; however, sustained released preparations and enteric-coated preparations of peppermint oil may reduce the frequency of heartburn [34, 70, 71]. In patients with comorbid anxiety or depression, the use of either TCAs or SSRIs may improve both IBS symptoms

and mood symptoms. A meta-analysis demonstrated that TCAs and SSRIs are effective at reducing abdominal pain and overall IBS symptoms as compared to placebo, but these medications were more likely to produce adverse events, particularly dry mouth and drowsiness with the use of TCAs [34, 46]. Some gastroenterologists suggest preferentially starting TCAs for IBS-D and SSRIs for IBS-C because constipation and diarrhea are respective class side effects; however, this is not supported by the IBS-specific literature [13]. Serotonin norepinephrine reuptake inhibitors (SNRIs) have a place in some chronic pain conditions but have not been thoroughly studied in patients with IBS.

When to Refer

IBS tends to be a chronic illness, and patients should be educated that there will be periods of time with varying control of symptoms. Most patients treated with the nonpharmacological and pharmacological strategies tend to do well and are happy with their symptom control, but for those who fail to improve despite adherence to diet and medications, referral to a specialist should be considered. Specialists may try different treatment options and often conduct a more extensive evaluation including endoscopy, cross-sectional imaging, and/or more comprehensive laboratory blood testing to exclude other organic diagnoses. In tertiary care centers, IBS patients are often seen in conjunction with a dietician and if need be a psychotherapist. Patients who remain refractory to the treatments prescribed by their primary care physician and the gastroenterologist often benefit from referral to a psychiatrist.

Summary Points

1. IBS is a common clinical condition characterized by abdominal pain associated with altered bowel habits. IBS has four clinical subtypes: IBS-D, IBS-C, IBS-M, and IBS un-subtyped or unclassified. The pathophysiology of IBS is likely multifactorial and is an area of ongoing research.
2. In patients presenting with typical IBS symptoms, no alarm features, and a normal physical exam other than abdominal tenderness, Rome IV criteria can be used to diagnose IBS without additional diagnostic testing.
3. The need for additional diagnostic testing should be tailored to the individual patient based on patient characteristics, IBS subtype, and physician discretion. Red flag symptoms should prompt further evaluation for systemic disease.
4. A stepwise approach is recommended for the treatment of IBS. First-line therapies include nonpharmacological therapies and agents aimed at symptom management such as polyethylene glycol 3350 for IBS-C and loperamide for IBS-D. Several other pharmacological agents are available for second-line therapy including linaclotide or lubiprostone for IBS-C and rifaximin for IBS-D. Antispasmodics, antidepressants, and peppermint oil are helpful in mitigating pain associated with IBS. Patients with refractory IBS or those who develop alarm features should be referred to gastroenterology for additional evaluation.
5. Interdisciplinary support including a dietician and mental health provider should be considered in the management of patients with IBS.

You recommend a trial of a tricyclic antidepressant and close follow-up. Sloane reports an improvement in both their mood and gastrointestinal symptoms at their 6-week follow-up appointment. You recommend continuing the medication for the next several months. Sloane asks you, however, if irritable bowel syndrome can be cured by the medication.

Review Questions

1. A 25-year-old female presents to your clinic with complaints of intermittent abdominal pain associated with diarrhea for the past 6 months. She states she has abdominal pain and loose stools multiple times a day about twice a week. She denies any GI bleeding, nocturnal symptoms, weight loss, or family history of inflammatory bowel disease but notes that her symptoms seem to be worse during times of increased stress. On physical exam, she is afebrile, HR: 70 beats/min, BP: 110/65 mmHg. Abdominal exam reveals normoactive bowel sounds, diffuse mild tenderness, no rebound or guarding, and no masses. Which of the following is the next best diagnostic step?
   A. Colonoscopy
   B. Fecal leukocytes
   C. CT abdomen and pelvis
   D. Apply Rome IV criteria
   E. Watchful waiting

   The correct answer is D. This patient displays no "red flag" features that would indicate underlying GI tract or systemic pathology. The Rome IV criteria can be applied to this patient to facilitate a clinical diagnosis without additional diagnostics as she is presenting with complaints consistent with irritable bowel syndrome without alarm features [16]. Early diagnosis helps accelerate a treatment plan and increases patient satisfaction. Should this patient not respond

to first-line treatment or her symptoms progress, additional workup should be pursued.

2. A 51-year-old Caucasian female presents to the clinic to establish care. She reports intermittent abdominal pain and bloating associated with diarrhea. The symptoms have been present for several years, and she denies rectal bleeding, weight loss, and nocturnal symptoms. On average, the symptoms occur once a week. She has a copy of prior medical evaluations which reveal normal thyroid function tests, normal IgA levels, negative celiac disease panel, and normal fecal calprotectin level. She has never had a colonoscopy. She uses loperamide as needed, and this adequately controls her symptoms. Which of the following is the next best step?
   A. No further testing is required.
   B. C-reactive protein.
   C. Colonoscopy.
   D. Fecal elastase.
   E. Stool ova and parasite.

   The correct answer is C. All patients with IBS should undergo age-appropriate colorectal cancer screening. In this Caucasian female with no family history of colon cancer, screening for colon cancer should start at 50 years of age [72].

3. A 45-year-old female with depression and constipation-predominant irritable bowel syndrome returns to your clinic for follow-up. She reports exercising regularly and staying hydrated. Her depression is well controlled with sertraline and cognitive behavior therapy. She has previously tried taking polyethylene glycol twice a day to help with her constipation without significant relief. Most recently, she tried linaclotide for 6 weeks, again, without relief of her symptoms. What is the next best step in management?
   A. Referral to gastroenterology
   B. Switch linaclotide to lubiprostone
   C. Start a gluten-free diet
   D. Start senna

   The correct answer is A. Patients who fail nonpharmacological and pharmacological management should be referred to gastroenterology for further evaluation including other possible etiologies of constipation and/or additional management considerations [24, 25].

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