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Diagnosing and Treating IBS: Translating Rome IV for GI and Primary Care Teams CME / ABIM MOC / CE

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Educational Impact Challenge

The goal of this activity is to improve the knowledge and competence of clinicians who manage patients with IBS regarding their use of the Rome IV criteria to appropriately diagnose IBS subtype and select optimal treatments.

Before you begin this activity, please assess your clinical knowledge by completing this brief survey. Answering these questions again after the activity will allow you to see what you learned and to compare your answers with those of your peers.

Introduction

Gastrointestinal symptoms are among the leading causes for consulting a physician.[1] In a majority of patients, routine diagnostic investigations, if performed, fail to demonstrate an underlying structural abnormality as a cause for the symptoms. These patients are often referred to as having 'functional' gastrointestinal disorders.[2] Although this term refers to disturbances in function -- alterations in gut motility, visceral sensitivity, or secretion not readily identified by routine clinical evaluation -- clinicians and patients may interpret this term as 'psychiatric' or as a 'wastebasket' definition where nothing is found. However, a variety of physiological disturbances, including visceral hypersensitivity, where discomfort or pain is generated by physiological events in the gastrointestinal tract; abnormal motility; altered gut microflora; and dysregulation of neural interaction between the central and enteric nervous systems have emerged as the main factors contributing to symptom generation.[3-5] In line with these mechanisms, the Rome IV consensus has redefined functional disorders as disorders of gut-brain interaction.[3,6]

As a result of their prevalence, functional bowel disorders have a major economic impact and considerable associated health care costs. The Rome consensus process classifies this large and heterogeneous patient group into diagnostic categories, and each diagnosis has specific criteria for use in research and clinical care. For more than 2 decades, the Rome Foundation has supported expert committees to create documents that characterize these disorders, update the known pathophysiology based on current research, and make diagnostic and treatment recommendations.[2] More than 2 dozen disorders are incorporated into anatomic systems: esophageal, gastroduodenal, bowel, biliary, anorectal, and central nervous system (CNS). The most recent update of this diagnostic system, the international Rome IV consensus for the diagnosis of functional gastrointestinal disorders (FGIDs) (disorders of gut-brain interaction;), was published May 2016.[3,4]

One of the most prevalent FGIDs within the bowel classification system is irritable bowel syndrome (IBS). IBS is characterized by abdominal pain related to disordered bowel function (diarrhea, constipation, or both) for at least 3 months in the absence of evidence for other diseases to explain these symptoms.[3,5] Patients with IBS may account for up to 40% of patients seen in gastroenterology practice and 15% of patients seen in primary care. At both the specialist and primary care levels, IBS is considered by clinicians a challenging condition.[1,5,7] The main reasons are diagnostic uncertainty and limitations in the therapeutic options for managing IBS. The Rome criteria divided IBS into 3 main subtypes based on stool consistency: IBS-C (predominant constipation), IBS-D (predominant diarrhea), and IBS-M (IBS with mixed bowel habits). The management approach and treatment options differ according to the IBS subtype.[5]

Epidemiology and Impact of the Irritable Bowel Syndrome

The estimated prevalence of IBS globally is 11%, ranging between 10% and 15% in studies in North America.[8,9] IBS affects both men and women, and young as well as older adults. In epidemiological surveys, however, IBS affects about 65% of women and 35% of men and up to 80% in women in clinical referral populations, possibly reflecting gender-related differences in healthcare seeking.[5] The peak prevalence is in the third and fourth decade of life. The impact of this disorder, ie, having symptoms of pain and bowel difficulties at least 3 days a week, needing to frequent toilet facilities, and even the stigma of having a bowel disorder, leads to greater healthcare seeking, reduced school and social activities, work absenteeism, and disability compared with most chronic medical disorders. An internet survey in nearly 2000 patients with IBS found that most reported moderate to severe symptoms, restricted activities on 20% of days in the past year, 3 physician visits, and work absenteeism in 13% because of health reasons.[10] Additionally, patients reported that they would give up 15 years (25% of remaining life) to be in perfect health. IBS is often associated with other comorbid conditions and symptoms, such as fibromyalgia, chronic fatigue syndrome, chronic back pain, chronic pelvic pain, and chronic headache. Therefore, IBS symptoms have a major impact on patients' quality of life.[1,5,10]

Pathophysiology of the Irritable Bowel Syndrome

The pathophysiology of IBS is poorly understood but appears to be heterogeneous and includes influencing factors from both the gastrointestinal tract and the brain -- hence the term 'disorders of gut-brain interaction.' Relevant factors include altered gastrointestinal motility, visceral hypersensitivity, increased mucosal permeability, low-grade immune activation, reactions to food components, dysregulation of the brain-gut axis, and altered gut microbiota.

Disordered motility. Disordered motility is closely related to the stool pattern in IBS. As a group, IBS-C patients have slower transit times, while IBS-D patients have faster transit compared with healthy controls. However, most patients with IBS have a colonic transit time that is within the normal range.[11]

Visceral hypersensitivity. Visceral hypersensitivity is the phenomenon of increased sensitivity of the bowel, allowing normally silent physiological processes to be perceived by the patient (visceral hypersensitivity) and normal intestinal function to cause pain (allodynia). Visceral hypersensitivity is a major determinant of pain severity in IBS.[4] The underlying mechanism is sensitization of gut-brain afferent pathways. The primary site of sensitization may be peripheral, in the bowel wall, or central, in the brain. Upregulation of receptors and sensitization by mast cell products have been identified as peripheral mechanisms of sensitization.[12] In the brain, changes in pain-processing and pain-suppressing pathways have also been implicated in the pathogenesis of pain in IBS, termed central hypersensitivity. The latter phenomenon may occur more readily in cases of psychological comorbidities such as anxiety, depression, and somatization.[13,14]

Gut microbiota. Recent studies focusing on gut microbiota have found less diverse gut microbiota in patients with IBS compared with controls.[15] The role of microorganisms is best established in so-called postinfectious IBS. In an important subset of patients with IBS, symptoms begin and persist following an acute episode of infectious gastroenteritis, which can be bacterial, viral, or amebic in origin. Besides the severity of the acute infection, younger age, female sex, and anxiety and stress are associated with a higher risk of postinfectious IBS.[16]

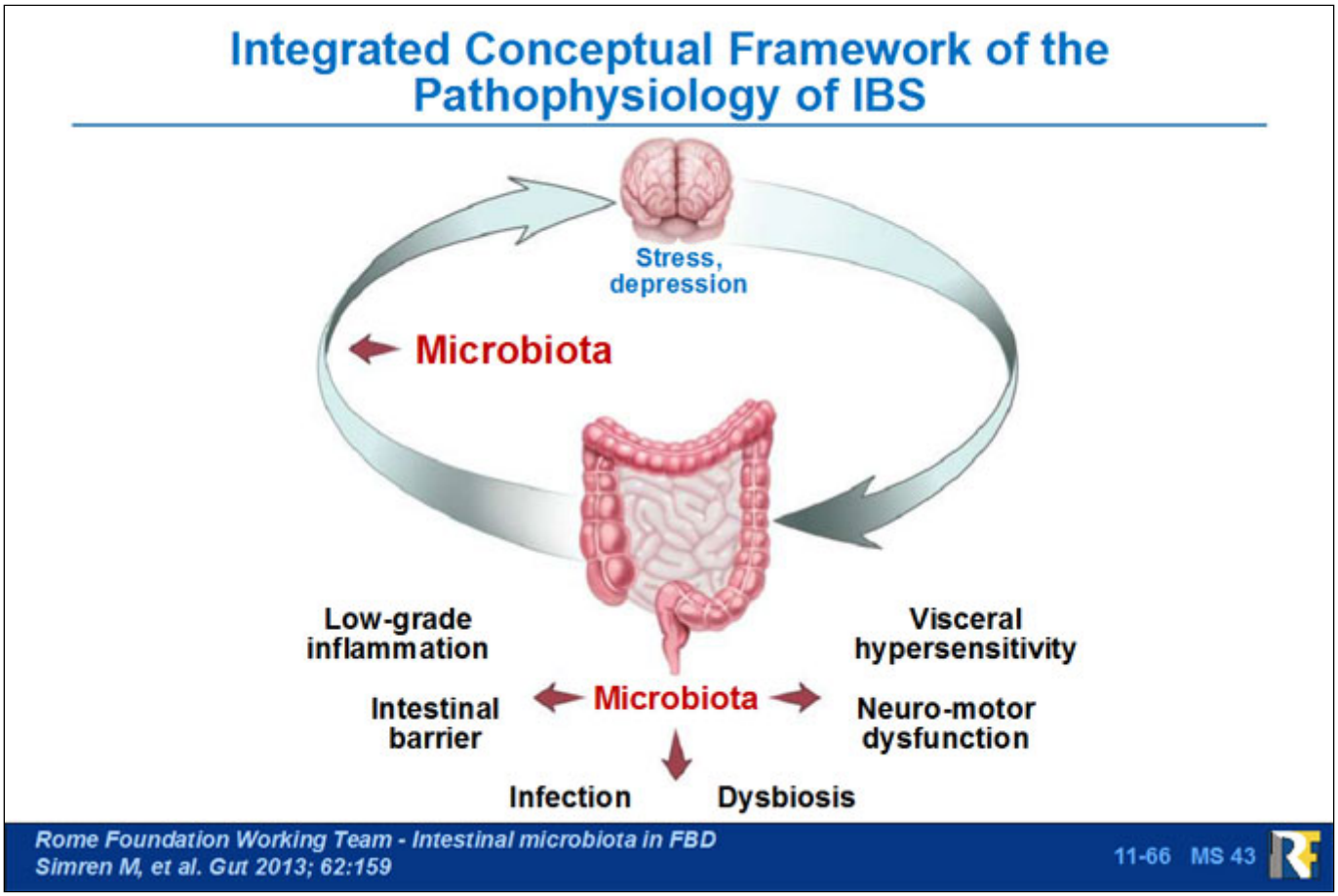
Changes in gut mucosa. Discrete changes in the gut mucosa are also present in patients with IBS, including low-grade inflammation, immune activation, and mucosal barrier dysfunction. Low-grade inflammation and immune activation are present in the form of mild increases in the number of mast cells and lymphocytes and signs of activation of these inflammatory cells.[17] Additionally, and closely associated with the immune activation, there is evidence of increased mucosal permeability as a consequence of altered expression of tight junction proteins.[18] These changes are thought to contribute to peripheral mechanisms of hypersensitivity. Whether the low-grade inflammation is a primary event, eg, persisting after acute gastroenteritis, or whether it is secondary to increased mucosal permeability, eg, allowing food or other luminal antigens to reach the submucosal compartment and trigger immune activation, remains to be determined.

Food and intraluminal factors. Food and intraluminal factors are increasingly important in our evolving understanding of IBS symptom generation and is mainly driven by the recognition that specific dietary alterations may improve symptoms (discussed in section on treatment with dietary interventions).[19] Additionally, the bile acid pool and bile acid metabolism have been identified as key determinants of bowel transit times and is therefore linked to the predominant stool pattern.[20]

Disorders of gut-brain interaction. In Rome IV, the so-called FGIDs are grouped as disorders of gut-brain interaction. The common denominator is evidence that central processing of afferent information from the gastrointestinal tract is altered in IBS

and other disorders, contributing to the generation of visceral hypersensitivity. The underlying neural substrate is probably a lower threshold for excitability in dorsal horn neurons or a deficient activity of descending antinociceptive pathways, promoting increased visceral pain sensitivity. The concept of gut-brain interactions also takes into account the frequent psychosocial comorbidities such as anxiety, depression, and somatization, which may in fact be associated with central mechanisms of hypersensitivity generation.[21] Finally, there is evidence for a vicious circle in which bowel symptoms may trigger anxiety and depression that in turn may maintain or worsen bowel symptoms.[22]

Figure 1. Integrated Conceptual Framework of the Pathophysiology of IBS



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Diagnosing IBS

The Rome IV Diagnostic Criteria for IBS

The Rome IV diagnostic criteria for IBS are summarized in the Table shown.[5] IBS is identified as a functional bowel disorder (ie, a disorder of gut-brain interaction) in which recurrent abdominal pain is associated with defecation or a change in bowel habits. Disordered bowel habits are typically present (constipation, diarrhea, or a mix of both), as well as symptoms of abdominal bloating/distension.

The principal updates to Rome IV from Rome III are (1) the elimination of discomfort as a defining symptom; (2) the use of a frequency threshold of once weekly instead of 3 times per month; and (3) an association of pain with defecation, and to include worsening instead of only improvement with defecation.[6] The definition of IBS was changed from symptoms of pain or discomfort in Rome III to pain alone in Rome IV because the notion 'discomfort' is unclear, inconsistently interpreted, or even nonexistent in many languages and cultures.[5,6]

Table. Irritable Bowel Syndrome: Rome IV Diagnostic Criteria*

Recurrent abdominal pain on average at least 1 d/wk in the last 3 mo, 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 mo with symptom onset at least 6 mo prior to diagnosis

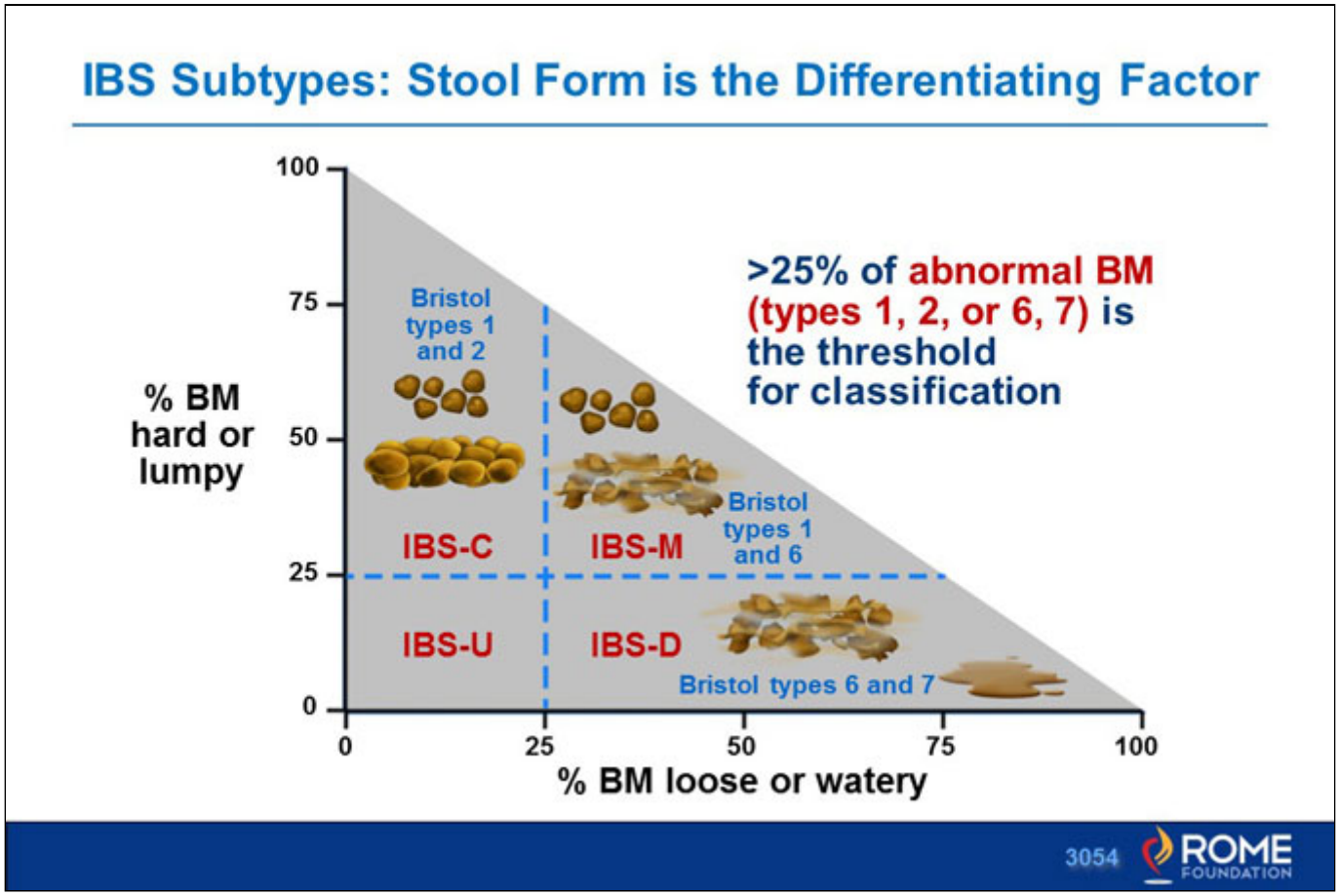
In all preceding iterations of the Rome definitions, symptom frequency thresholds were based on expert opinion. The new symptom frequency threshold is based on the 90th percentile limits of prevalence in a survey of 1600 subjects in the US general population.[22,23] This assures that the currently used criteria have a solid scientific foundation.

Additionally, Rome IV recognizes that several of the functional bowel disorders exist on a spectrum, with transitions from one entity to another over time. IBS is therefore now put into a continuous spectrum with other functional bowel disorders such as chronic constipation, functional bloating and distension, and functional diarrhea.[5,24]

IBS Subtypes

As described earlier, the 3 main IBS subtypes are IBS-C, IBS-D, and IBS-M.[5] Based on normative data in the general population, abnormal bowel movements are those that can be classified as Types 1 and 2 or Types 6 and 7 on the Bristol Stool Form Scale. IBS-C is present when 25% of all *abnormal* bowel movements are Types 1 or 2; IBS-D is present when 25% of all abnormal bowel movements are Types 6 or 7; and IBS-M is present when both criteria are fulfilled. All other patients are labeled as irritable bowel syndrome unclassified (IBS-U).

Figure 2. IBS Subtypes



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Medical History

A careful medical history should include an assessment of whether the symptom pattern corresponds to IBS. Following are key history elements for diagnosing IBS[5,24-26]:

1. Presence of abdominal pain. The pain is usually vague, located to the lower abdomen, and is either relieved or, more rarely, worsened by passage of a bowel movement.
2. Disordered bowel movements. Typically in IBS, stool passage and abnormalities of bowel pattern, ie, constipation, diarrhea, or both, need to be present. Stool frequency is determined by asking simple questions. In the West, normal stool frequency ranges between 3 per week to 3 per day. Stool consistency can be assessed using the Bristol stool form scale. Associated symptoms may also be present. Urgency and, at times, stool leakage or incontinence, is prevalent in patients with IBS-D much like straining or incomplete evacuation is prevalent with IBS-C.
3. Bloating or distention. Although not listed as a 'diagnostic' symptom in the Rome criteria, bloating/distention is almost invariably present in patients with IBS. It may be a sense of gaseous distention (bloating) or a truly visible increase in abdominal girth (distention), or both. Typically, bloating worsens after meals, tends to be maximal toward the evening, and improves overnight.

Fulfilling diagnostic criteria is mandatory to diagnose IBS; but it is sometimes not sufficient, as some structural disorders may present with similar symptoms.[5,24,25]

Assessment of Symptoms and Symptom Severity

Symptoms supportive for an IBS diagnosis also include (1) additional aspects of bowel function, eg, straining; urgency; feeling of incomplete evacuation; mucus in feces; and unpredictable bowel pattern with 3 or more different stool form types per week; (2) the presence of other digestive symptoms often associated with IBS, eg, heartburn; epigastric pain; early satiety; postprandial fullness; nausea; and (3) extraintestinal symptoms associated with IBS, eg, fibromyalgia; chronic fatigue; chronic pelvic pain; anxiety; depression; temporomandibular joint disorders; headache; neck and back pain; migraine; dyspareunia; urinary symptoms; sleep problems; palpitations; chest pain.[5]

It is also helpful to evaluate the severity of the symptoms, which can lead to a more focused plan of care and treatment. IBS symptoms may be classified as mild, moderate, or severe.[24-26]

Mild symptoms. Patients with mild or infrequent symptoms comprise about 40% to 45% of patients with IBS. They are seen more often in primary care than in gastroenterology practices and do not have major impairment in daily functioning or psychological distress. Symptoms are often based on gastrointestinal dysfunction, ie, vomiting, diarrhea, constipation. Abdominal pain is minimal or mild and without other comorbid physical symptoms. While these patients usually do not have dominant psychiatric diagnoses and their quality of life is generally good, they may report concerns about the effects of their symptoms on their daily lives. These patients do not make frequent medical visits and usually maintain normal activity levels without restriction.

Moderate symptoms. A smaller proportion of patients, about 30% to 35%, seen in primary or secondary care report moderate symptoms and have intermittent disruptions in activity, eg, missing social functions, work, school. They may identify a close relationship between symptoms and inciting events such as dietary indiscretion, travel, or distressing experiences. These patients may have abdominal pain that is more moderate in intensity and be more psychologically distressed than patients with mild symptoms. Other medical or psychological comorbidities may be present. These patients are also more likely to lose time from work or need to curtail usual activities.

Severe symptoms. Approximately 20% to 25% of patients with FGIDs have severe symptoms and a smaller proportion have very severe and refractory symptoms. These patients, who are often seen in referral practices, have a high frequency of associated psychosocial difficulties, including anxiety, depression or somatization, personality disturbance, and chronically impaired daily functioning; another 10% will have major work disability. There may be a history of major loss or abuse, poor social networks or coping skills, and 'catastrophizing' behaviors. These patients may visit gastroenterology consultants frequently and hold unrealistic expectations to be ''cured.' Perhaps from earlier experiences in the health care system, they may feel stigmatized by their condition and deny or not consider a role for psychosocial factors in their illness. As a result, they may be unwilling to engage in psychological or psychopharmacological treatment but will more often seek further diagnostic studies to legitimize their complaints and prefer pharmacological treatments directed at the gut.

Alarm symptoms. The history should also address alarm symptoms, which are a positive family history of colorectal cancer; inflammatory bowel disease (IBD) or celiac disease; a history of blood in the stools or anemia; fever; nocturnal diarrhea; or weight loss. The presence of 1 or more alarm features increases the likelihood of organic disease and may prompt additional investigations.

Finally, as psychosocial comorbidity is prevalent in IBS and may determine treatment choices, it is important to inquire about symptoms suggesting anxiety, depression, or a history of trauma.[5]

As dietary factors can cause or exacerbate symptoms, physicians should investigate whether some foods lead to worsening pain, bloating gaseousness or other discomfort. The clinician should evaluate for lactose intolerance, gluten sensitivity or other FODMAPs (discussed below).

Physical Examination

A complete physical examination is also mandatory. This is generally normal in patients with IBS symptoms, with the exception of mild tenderness over the lower abdomen occurring not infrequently. The anorectal examination is a crucial aspect in any patient with bowel symptoms. While the primary purpose of the physical examination is to identify other causes for the symptoms and to reassure the patient, some findings can be associated with IBS, though they are not specific. These include increased nonobstructive bowel sounds, tenderness overlying the sigmoid colon, and a negative Carnett test that excludes abdominal wall pain.[27,28] The anorectal examination should be performed to exclude a weak anal sphincter if incontinence is occurring in IBS-D, or to evaluate for dyssynergia -- paradoxical levator contraction with straining as in IBS-C. Any abnormalities on physical examination, such as masses or unexpected severe tenderness or pain upon palpation, unusual bowel or vascular sounds, should prompt additional technical examinations such as ultrasound, complemented with computed tomography (CT) scan if necessary.

Tests for IBS

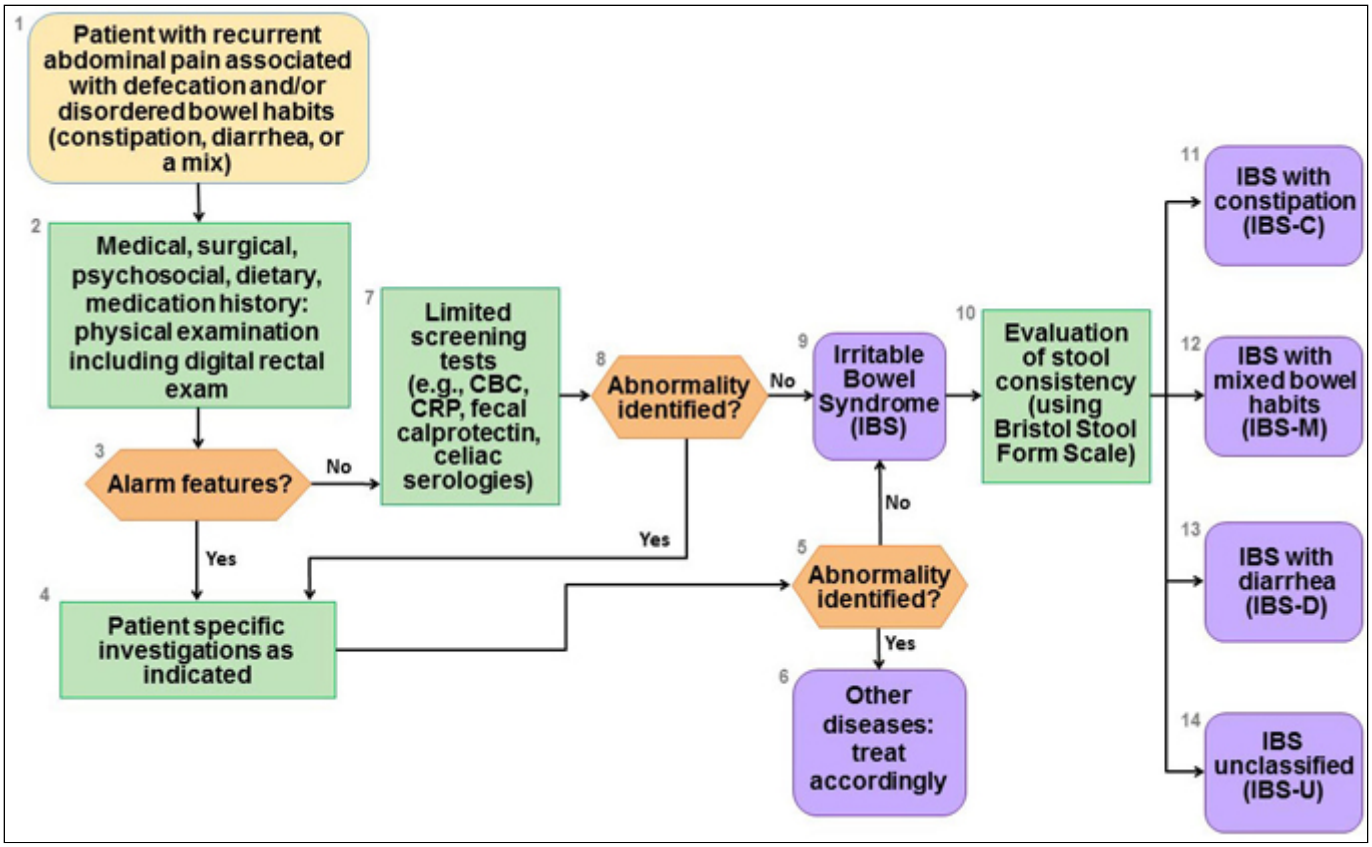
The medical history and physical examination are often complemented with limited laboratory tests, such as blood cell count and C-reactive protein (CRP), which can be considered in all patients with suspected IBS. Thyroid tests can be added if there is clinical suspicion of abnormal thyroid function. In patients with diarrhea, stool calprotectin assay is useful to screen for IBD, and serology (tissue transglutaminase antibodies) to test for celiac disease. Hence, laboratory tests mainly serve to help exclude other diagnoses.

There is an ongoing effort to identify laboratory tests that can help in diagnosing IBS. Both a panel of serum tests and a test for antibodies against vinculin/cytolethal distending bacterial toxin B (cdtB) have been shown to associate with presence of, respectively, IBS and IBS-D in selected study populations.[29,30] Presently, the performance of these tests in contributing to a diagnosis of IBS is preliminary, and their impact on management at the primary care level still needs confirmation with larger well-designed studies.

Referral for colonoscopy is indicated in case of a positive or borderline calprotectin test, severe watery diarrhea (with biopsies to rule out microscopic colitis), and in all patients ≥50 years in the absence of warning signs (45 years in African Americans). Stool examination is mainly useful in high-prevalence areas for infectious gastroenteritis. Carbohydrate (eg, lactose, fructose, sorbitol) malabsorption is another cause of diarrhea, cramps, and bloating, for which specialized breath tests can be used. However, empirical elimination from the diet for a few weeks is often more practical.

A diagnostic and management algorithm for IBS (and other functional disorders) was developed by the Rome foundation and can be found as 'Rome IV interactive clinical decision toolkit' through the Rome Foundation website.[31]

Figure 3. Rome IV Diagnostic Algorithm: Recurrent Abdominal Pain with Disordered Bowel Habits



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Role of the Primary Care Physician in Diagnosis

The primary care physician (PCP) is usually the point of health care access for patients with IBS. Initial diagnostic assessment, communicating the diagnosis to the patient, providing a disease explanatory model to the patient, and determining when a patient should be referred to the gastroenterologist are key tasks for PCPs. Physicians often feel uncomfortable communicating a diagnosis of IBS early in the work-up and tend to defer this until other possible explanations for a patient's symptoms (ie, structural disease) have been ruled out, or until symptoms have responded to initial therapy.[32] However, lack of a diagnosis can have a negative effect on patient confidence in the clinical approach and may increase patients' underlying worries about major undiagnosed disease. Not stating the diagnosis with confidence (ie, based on fulfilling Rome criteria, excluding 'red flags,' and limited diagnostic studies) can lead patients to doubt the diagnosis and continue to seek additional medical opinions and diagnostic tests. Effective management of IBS is therefore reliant on physicians being able to name or provisionally name the condition they think underlies the symptom -- in this case IBS.[33] Any additional tests that are considered can be put in the context of 'confirming this tentative diagnosis.' The expectation that these tests will turn out normal can be expressed to the patient a priori.

Additionally, the physician should provide the patient with a clear explanation of how he or she believes symptoms are generated and how the symptoms can be targeted with specific management strategies.[34] Simple explanatory models incorporating altered motility, sensitivity of the gut, responses to food, gut microbiota, and gut-brain interactions and their modulation by stress or anxiety, can all be used to educate the patient about the nature of the condition and its symptoms. It is also important to clarify that IBS is a chronic disorder and that the focus of care is on management of symptoms, not cure.

Follow-up of response to the initial treatment approach is done by the primary care practitioner or can involve a physician assistant or nurse practitioner. Key factors are confirmation of the initial diagnosis, follow-up of the impact of lifestyle and dietary changes with adjustments if needed, and evaluation of the level of symptomatic response to the initial treatment.

Referral to a specialist for further diagnostic workup or management should be considered in case of alarm or risk symptoms justifying colonoscopy, severe symptoms that interfere with ability to work or study, and lack of response to standard treatments. Referral to a psychiatrist or psychologist should be considered when a clinically relevant comorbid depression or anxiety disorder is present.

Case 1 illustrates the diagnostic and initial therapeutic approach in a patient with IBS-D. It is based on the Rome IV knowledge and also illustrates the use of the guidelines presented in the Rome IV diagnostic algorithms -- the Rome IV Multidimensional Clinical Profile and the Rome IV Interactive Clinical Decision Toolkit https://romeonline.org/?post_type=product.

Case 1: 55-year-old man with 5-year history of abdominal pain and diarrhea

A 55-year-old man sees his PCP for abdominal pain and diarrhea. He is married, has 2 children, and calls his job as a high-ranking government administrator very stressful. He is a nonsmoker and uses alcohol on occasion. He has a history of an appendectomy, nonallergic asthma, and recurrent peptic ulcers that stopped after eradication of Helicobacter in 1993.

During the last 5 years, the patient has experienced increasingly distressing episodes of abdominal cramps and watery diarrhea with urgency that is relieved with each bowel movement. Symptoms *are present at least 2 to 3 days per week and* often develop about 30 minutes after eating; the patient believes they may be more severe after ingesting lactose-containing foods. These symptoms are also associated with dizziness and a feeling of weakness, and exacerbated in stressful episodes. The anticipation of potential diarrheal episodes causes the patient considerable anxiety, with restriction in social activities, and he becomes irritable toward family members and colleagues during symptomatic episodes. There is no incontinence or nocturnal episodes of diarrhea. There is no blood in the stools or weight loss. Family history indicates no evidence for IBD, celiac disease, or gastrointestinal cancer. The patient has tried antispasmodics without beneficial effect. He has taken loperamide with difficulty -- it induces constipation when taken in between episodes and works too late in acute exacerbations.

Clinical examination: Weight and height are 66 kg and 170 cm respectively, and a body mass index of 22.8 kg/m^2. Normal cardiopulmonary examination. Normal abdominal examination apart from appendectomy surgery scar. Empty rectum.

Laboratory studies included a full blood count, CRP, metabolic panel, thyroid function, and celiac screening, which were all normal. Stool culture showed no pathogens. The PCP recommended a lactose-free diet. The patient returns 6 weeks later and is not improved.

Because this patient has never been evaluated for his symptoms, has not responded to lactose restriction, and is older than 50 years, the PCP refers him to a gastroenterologist for a colonoscopy and recommendations for other treatment options.

The gastroenterologist notes the long-standing history of abdominal crampy pain associated with and relieved by the diarrhea, which is highly suggestive of IBS. *There is no history of ingestion of nutrients containing poorly absorbable sugars (e.g. sorbitol in chewing gum).* She agrees that a colonoscopy should be done in addition to routine cancer surveillance to exclude IBD or microscopic colitis. She discusses this tentative diagnosis and diagnostic plan with the patient.

The colonoscopy is normal and the biopsies do not show inflammatory changes.

The patient has observed the relation between meals and symptoms more closely over the past several weeks and declares himself intolerant to fatty foods. He also started a gluten-free diet 3 weeks ago after talking to a colleague at work, but this did not change his symptoms. He is convinced that his symptoms are all attributable to job-related stress and asks for a drug that will calm his bowels.

At this point, the gastroenterologist reaffirms the diagnosis of IBS based on Rome criteria and the negative studies. She communicates this to the patient and the role of stress/anxiety, as well as food. They discuss the options listed below including further dietary intervention (low FODMAP diet), pharmacotherapy, (eluxadoline, alosetron, rifaximin), or central neuromodulator therapy (tricyclic antidepressant). The latter, which may also impact on the (anticipatory) stress related to his condition, is the patient's preferred option. Treatment is started with nortriptyline 25 mg in the evening, with a plan to increase to 50 mg after 3 weeks.

Management of IBS

The cornerstone for effective IBS management is a good physician-patient relationship, which relies to a large extent on the empathy and communication skills of the physician.[35] The choice of a treatment is determined by the severity and impact of symptoms, the stool subtype, the presence of psychosocial comorbidities, and also patient preference (eg, diet vs medication).

Choosing and starting treatment should be preceded by listening actively to the patient about his or her symptoms and concerns, and should be supported by the explanatory model that was used to explain the condition and how symptoms are generated.[32] The communication and treatment proposals should be in line with the patient's concerns and expectations.

When embarking on a treatment plan, it is also useful to set realistic timelines and prospects and to involve the patient in the choice of treatment type. Finally, the physician should show a long-term commitment to care, ie, willingness to see the patient back and adjust treatment as necessary.[35] The latter task can be shared with a PA or nurse with an understanding of the nature of IBS symptoms, their natural history, and expected response to therapy. Treatment strategies can be changed or combined if the initial choice does not generate sufficient symptom control. As discussed previously, referral to a specialist should be considered for severe symptoms that interfere with ability to work or study, or lack of response to standard treatment regimens.

Dietary and Lifestyle Changes

At the outset, patients with IBS get general lifestyle and dietary advice, which includes eating regular meals that are not too large, avoiding caffeine and alcohol, and getting regular physical exercise and sufficient sleep at night.[24,25] In those with constipation, increasing fiber intake may improve stool pattern. Soluble fiber (eg, ispaghula, psyllium) is preferred, as insoluble fiber may worsen bloating. Fiber intake should be started at a modest dose (5 or 7 grams) and slowly increased to a target of 20 to 30 grams per day.

Elimination of potentially poorly digestible sugars, such as lactose or sorbitol, may be beneficial in some patients with IBS-D. As indicated above, while breath tests can aid to establish a diagnosis, empirical elimination from the diet for a few weeks is a more practical approach.

Recently, more complex dietary modifications have been proposed for patients with IBS. The low FODMAP diet aims to eliminate all poorly absorbable substances that are osmotically active or undergo fermentation. Controlled trials have shown benefit of this approach in reducing bloating, pain, and disordered defecation in patients with IBS. However, the low FODMAP diet is complex and requires compensatory measures to avoid calorie restriction and stepwise reintroduction of FODMAPs in case of symptomatic benefit, all through explanation and follow-up visits by a trained dietician. The low FODMAP diet is therefore generally more appropriate in advanced care. Emerging data suggest that a less stringent diet (eg, 'NICE' diet or other rational diets that include avoiding excess fat, frequent small meals) may also be effective in IBS, but additional studies and standardization is required.[5,36,37]

Some patients with IBS without celiac disease have benefited from a gluten-free diet. However, the benefit may result from a nonspecific response to the lowering of FODMAPs that is associated with gluten elimination. Based on current evidence, gluten elimination is not recommended in patients with IBS who have no evidence of celiac disease.[5,36,37]

Regarding diet, it is important to keep in mind that 'effort after meaning' is a common psychological method that patients employ to ease anxiety about their symptoms by attributing them to factors retrospectively. They may then feel more in control of their illness by concurrently altering their dietary behaviors. An example would be to attribute GI symptoms to gluten sensitivity and then avoid eating gluten, even if there is no symptom improvement. Therefore, the clinician needs to guide the patient through diagnostic possibilities while avoiding unnecessarily restrictive behaviors.

Pre- and Probiotics and Other Nutritional Approaches

Probiotics are defined as live microorganisms which, when administered in adequate amounts, confer a health benefit on the host. The effect of probiotics in IBS has been the topic of many clinical trials, with mixed results. The published evidence suggests an overall beneficial effect of probiotics on IBS symptoms vs placebo, but one of limited magnitude compared with pharmacologic agents.[36-38] There is also no clear evidence that one probiotic is better than another.

Prebiotics are ingredients in food that may stimulate either the growth of or the activity of beneficial bacteria. Some prebiotics have been suggested to be beneficial for IBS, but studies show inconsistent results, suggesting a lack of evidence of efficacy.[38]

Medical foods are foods that are formulated to be consumed or administered under the supervision of a physician and are intended for the specific management of a disease or condition for which distinctive nutritional requirements are established by

medical evaluation. Peppermint oil is available as a medical food preparation for the treatment of IBS (discussed below). Serum-derived bovine immunoglobulin/protein isolate is another recently developed medical food that is postulated to bind to microbial products in the lumen and improve immune balance and mucosal barrier function in the gastrointestinal tract. However, controlled efficacy trials are lacking.[37]

Glutamine is an essential amino acid in humans and a regulator of gut barrier integrity. In a small pilot trial in IBS-D, glutamine supplementation reduced IBS symptom severity and normalized intestinal permeability. Palmitoylethanolamide and polydatin are dietary compounds that have a potential to reduce mast cell activation. In a small placebo-controlled trial, palmitoylethanolamide/polydatin improved abdominal pain severity in patients with IBS. Finally, a number of herbal mixtures, such as STW 5 (Iberogast) and aloe vera and curcumin/fennel oil based preparations, have been assessed in relatively small IBS studies and have shown potential for symptom improvement. All these approaches require larger confirmatory studies.[37]

Treatment Options for IBS-C

As discussed previously, soluble fiber may improve constipation in IBS-C but does not address the pain or bloating, which are key features of IBS. Similarly, stimulant laxatives such as senna, cascara, or bisacodyl can also temporarily improve constipation but are more valuable as temporary aids or 'rescue' medications given their limited long-term benefits.

Secretagogues (lubiprostone, linaclotide, plecanatide) soften stools by increasing intestinal chloride secretion from enterocytes, accompanied by efflux of water and sodium. Lubiprostone activates apical type 2 chloride channels and is approved by the US Food and Drug Administration (FDA) for treating IBS-C at a dose of 8 µg twice daily. The main adverse events are nausea and diarrhea. Linaclotide and plecanatide are peptide agonists that act in the lumen to activate guanylate cyclase C receptors. This stimulates intracellular production of cyclic guanosine monophosphate leading to activation of the cystic fibrosis transmembrane conductance regulator (CFTR) channel with chloride and water secretion and may also exert visceral analgesic effects. The main adverse event with these agents is watery diarrhea. The FDA-approved dose of linaclotide for IBS is 290 µg daily. In case of diarrhea, the dose can be decreased to 145 µg or 72.5 µg. For plecanatide, the recommended daily dose is 3 mg.[26,36-37,39]

Drugs under evaluation for the treatment of IBS-C or chronic constipation include tenapanor, an inhibitor of the sodium/hydrogen exchange channel isoform 3, and prucalopride, a serotonin-4 receptor agonist.[37,39]

Case 2 illustrates the diagnostic and therapeutic approach in a patient with IBS-C.

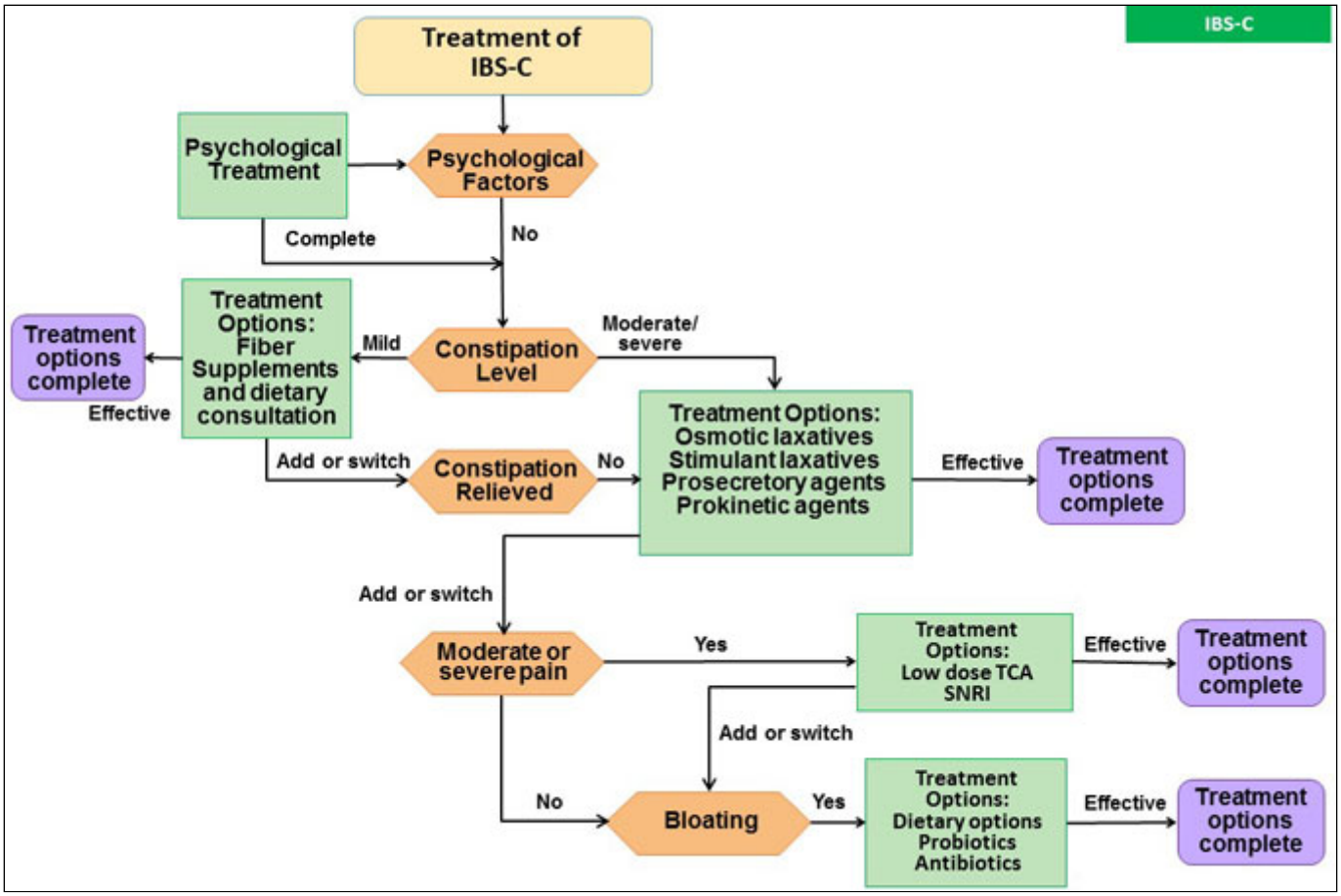
Case 2. 37-year-old woman with long-standing abdominal pain, hard stools, and constipation

A 37-year-old woman who works as a social worker presents to her PCP with long-standing abdominal pain that she describes as feeling like she is being 'torn apart.' The pain may persist for hours, is accompanied by bloating, and is partially relieved by a bowel movement. She has a bowel movement every 2 to 3 days of normal to hard consistency. When the stools are hard she reports needing to strain but does not use manual maneuvers to evacuate the stool.

Her symptoms have been present for more than 5 years and have progressively worsened. Recently, the symptoms have led to repeated absences from work. She also complains of fatigue, which she attributes to the abdominal symptoms. She has been treated for depression and is currently taking venlafaxine. She also takes a proton pump inhibitor for heartburn and uses a peppermint oil preparation occasionally. There is no relevant family history, weight loss, or blood in the stools.

The history is typical of IBS-C. Given the patient's age and lack of alarm or risk factors, there is no need for extensive examinations. Only full blood count, CRP, and thyroid function are checked and found to be normal.

Figure 4. Rome IV Treatment Algorithm for IBS-C



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Treatment options for this patient with IBS-C include laxatives, secretagogues (lubiprostone, linaclotide, plecanatide), or, where available, a prokinetic agent (prucalopride). Laxatives are inexpensive and easy to use but are unlikely to address her pain, which is the predominant feature. The same is true for fiber supplements. Based on these considerations, her PCP proposes treatment with a secretagogue, eg, linaclotide 290 µg daily (dose to be adjusted in case of diarrhea) or plecanatide 3 mg daily or lubiprostone 8 µg twice daily.

Treatment Options for IBS-D

The greatest benefit of dietary interventions, especially elimination of lactose and other poorly absorbable sugars, is in the subgroup of patients with IBS-D . Empirical elimination of lactose from the diet is an obvious and easy initial approach.

Loperamide is an inexpensive and valid initial option to treat diarrhea, but its efficacy for treating pain and other global symptoms is limited based on the available evidence. The magnitude of efficacy of this peripherally acting µ opioid agonist shows high intersubject variability, resulting in a dosage range of 2 mg up to 16 mg daily. Some patients may have difficulty finding the right balance between controlling diarrhea and inducing constipation.[25,26,36,37,39]

Eluxadoline is a recently developed mixed µ receptor agonist/δ opioid receptor antagonist with low bioavailability that is effective in IBS-D and patients who do not respond to loperamide. This agent has less tendency to cause problematic constipation. The starting dose is 100 mg twice daily. The dose should be decreased to 75 mg twice daily for patients who develop side effects from the higher dosage, have liver disease, or are taking OATP1B1 inhibitors that affect CYP metabolism. Eluxadoline has been associated with sphincter of Oddi spasm and pancreatitis, so it should not be used in patients with cholecystectomy or with a history of alcohol abuse (as defined on the product label: alcohol abuse, alcohol addiction, or more than 3 alcoholic drinks a day).[25,36,37,39]

The $5HT_3$-antagonist alosetron has been shown to reduce abdominal pain and diarrhea in women with IBS-D. Its usage has been limited by regulatory authority restrictions because of a risk of inducing severe constipation or ischemic colitis (1/1000 patients treated); however, these restrictions have recently been lifted. Alosetron was initially approved at a dose of 1 mg twice

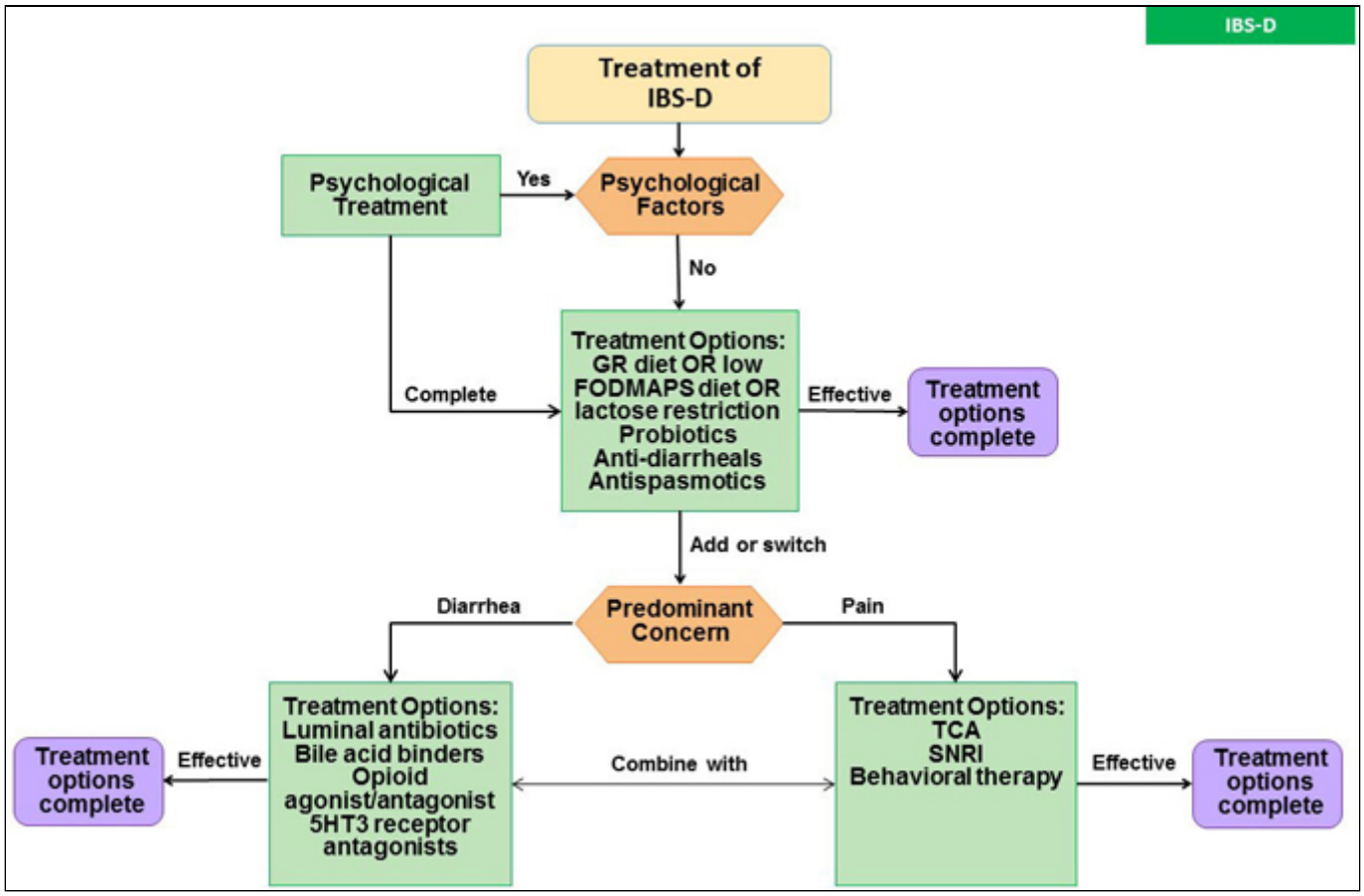
daily, but the current most frequently used dose is 0.5 mg twice daily. Another $5HT_3$-antagonist, ramosetron, was found effective in men and women with IBS-D in Japan. Ondansetron, clinically used as antiemetic during chemo- or radiotherapy, decreases diarrhea in IBS-D at doses of 4 mg or 8 mg daily.[38,39]

In 2 phase 3 clinical trials, 2 weeks of treatment with the poorly absorbable antibiotic rifaximin 550 mg 3 times daily provided adequate relief of symptoms and improved pain and bloating during 10 weeks of posttreatment follow-up in patients with nonconstipated IBS. In a follow-up retreatment trial in IBS-D, with retreatment in case of symptom recurrence within 18 weeks, the efficacy of rifaximin was maintained over time with no signs of adverse events -- notably, no cases of Clostridium difficile infection and no problems of resistance formation.[25,26,36,37,39] Based on this evidence, rifaximin is a safe, moderately effective, but expensive treatment option, FDA- approved for IBS-D, and perhaps most appealing in cases with prominent bloating.

Bile acid malabsorption is a well-known cause of diarrhea after ileal resection, but it may also occur in the absence of surgery because of genetic alterations in the control of bile acid synthesis and reabsorption. Uncontrolled studies suggest that bile acid sequestrants (eg, cholestyramine, colestipol, and colesevelam) improve stool consistency in a subset of patients with IBS-D, although formal controlled trials are currently lacking. Specific tests for bile acid malabsorption exist but are not available in the United States. A course of bile acid sequestrants can be tried empirically when other therapies have failed.[25,37,39]

Finally, low-dose tricyclic antidepressants (TCAs) may be helpful in treating IBS-D through their effects on reducing visceral hypersensitivity and decreasing stool frequency via noradrenergic and anticholinergic effects.[40]

Figure 5. Rome IV Treatment Algorithm for IBS-D



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Treatment Options for IBS-M

The large subgroup of patients with IBS-M has been less well studied, and recent drug development has not been directed to this subpopulation. Treatment is based on the use of older drugs, such as spasmolytics or peppermint oil.[24-26,36,37,39]

Antispasmodics (eg, hyoscyamine, dicyclomine) act on muscarinic receptors to inhibit bowel contractions. A Cochrane meta-analysis showed that antispasmodics as a group improve abdominal pain in IBS.[40] The adverse effects of the older anticholinergic antispasmodics include dry mouth, dizziness, and blurred vision. Peppermint oil has antispasmodic properties acting on transient receptor potential channel melastin type 4. Peppermint oil (3 to 4 capsules per day) is able to improve abdominal distention compared with placebo. Rifaximin may also be useful for IBS-M by reducing bloating and regularizing stool, but there are no confirmatory controlled studies and current approval is only for IBS-D.

Treatment of Refractory Pain in IBS

Although opioids represent the most potent class of analgesics, there is no evidence of efficacy in IBS; and prolonged use of narcotic analgesics is associated with specific complications such as opioid-induced constipation and narcotic bowel syndrome (a condition of opioid-induced visceral pain, which worsens as doses are erroneously increased). The most supported nonopioid alternatives for chronic abdominal pain, including in IBS, are central neuromodulators and, more specifically, antidepressants.[40]

A good therapeutic relationship is essential in managing IBS, especially when prescribing neuromodulator treatment. Meta-analyses suggest efficacy of tricyclic antidepressants (eg, amitriptyline, nortriptyline, desipramine) in IBS; and while not adequately studied, serotonin noradrenergic reuptake inhibitors (eg, duloxetine, venlafaxine) offer potential benefit. TCAs should be started at a low dose (25 mg) and gradually increased (up to 100 mg). While the therapeutic benefit from antidepressants may take 4 to 6 weeks to achieve, side effects may occur rapidly, though patients often adapt to them.[40,41]

In case of refractory pain, psychological treatment may be of benefit. Studies have demonstrated efficacy of hypnotherapy and cognitive behavioral therapy in IBS.[5,24-26,408] However, patients need to be receptive to this centrally targeted approach, and there is a paucity of experienced therapists for IBS and related FGIDs.

Summary and Conclusions

IBS is one of the most common conditions seen in primary care, internal medicine, and gastroenterology clinical practice. The Rome IV consensus has updated definitions and recommendations for diagnosis and management of IBS and other disorders of gut-brain interaction. Key aspects in the management of patients with IBS include a targeted and detailed assessment of symptom pattern and severity, awareness of alarm or risk factors, careful physical examination, and the use of selected additional diagnostic tests, especially in patients with diarrhea or alarm or risk factors. Communicating a clear diagnosis of IBS, a cornerstone for effective IBS management, builds on a good physician-patient relationship that requires empathy and communication skills from the physician.

Patients should be educated about IBS, with a clear explanation of the basis of their symptoms and specific management strategies. A management algorithm, available online as the 'Rome IV interactive clinical decision toolkit' provides guidance for diagnosis and treatment of IBS and other functional disorders in a step-by-step interactive process. The toolkit facilitates selection from a large number of available treatments for IBS, including lifestyle and dietary management, pre- and probiotics, pharmacologic agents for specific stool patterns, and treatment targeting abdominal pain by means of central neuromodulators or behavioral and psychologic therapies.

Educational Impact Challenge

What did you learn from this activity? Please click on the "Next" button to proceed to a brief survey to see how your knowledge improved after the education. You can also see how your answer compares with those of your peers.

Educational Impact Challenge

Abbreviations

CFTR = cystic fibrosis transmembrane conductance regulator
CNS = central nervous system
CRP = C-reactive protein
CT = computed tomography

FDA = US Food and Drug Administration
FGID = functional gastrointestinal disorders
FODMAP = fermentable oligo, di-, monosaccharides, and polyols
IBS = irritable bowel syndrome
IBS-C = irritable bowel syndrome with constipation
IBS-D = irritable bowel syndrome with diarrhea
IBS-M = irritable bowel syndrome with mixed bowel habits
IBS-U = irritable bowel syndrome unclassified
OTC = over-the-counter
PCP = primary care physician
TCA = tricyclic antidepressant

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