Clinical Roundtable Monograph

The ACG Evidence-Based Review on the Management of Irritable Bowel Syndrome: Recommendations from Bench to Bedside

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Abstract

Irritable bowel syndrome (IBS) is a common, though incompletely understood, functional bowel disorder. A systematic review, released in early 2009 by the American College of Gastroenterology IBS Task Force, provides a more practical definition of IBS for the clinical setting as well as a summary of current evidence pertaining to diagnosis and treatment. The Task Force review of current therapeutic options employed evidence-based methodology to examine historic efficacy and safety data and a formalized grading system to evaluate evidence quality. Translating and applying the concepts described in the Task Force review into clinical practice requires careful interpretation of the grading system and individualization of therapy based on specific patient symptomology and history. The following roundtable discussion provides insights into IBS pathophysiology and the clinical adoption of the Task Force analyses and recommendations, with the goal of helping clinicians to maximize outcomes of global symptom relief in the IBS population.

Sponsored by Postgraduate Institute for Medicine.

Target Audience: This activity has been designed to meet the educational needs of gastroenterologists involved in the management of patients with irritable bowel syndrome.

Statement of Need/Program Overview: Many potential mechanisms have been proposed to explain the pathophysiologic symptoms of IBS, including genetic predisposition; food intolerance; social, environmental, or behavioral factors; and previous enteric infections. The complex nature of IBS pathology makes optimal treatment challenging. There are multiple examples of the pathogenic role of bacteria in IBS, which suggest that therapeutic approaches that affect gut bacteria and the respective host responses to these pathogens might alleviate symptoms in patients with functional gastrointestinal symptoms. This notion is supported by observations from several open-label investigations as well as randomized, double-blind, controlled studies that have characterized the therapeutic benefit of antibiotics in the treatment of functional gastrointestinal symptoms in patients with or without a diagnosis of IBS. In January 2009, an evidence based review of the management of IBS was published by the ACG in order to update the 2002 guidelines on IBS treatment, in light of new data.

Educational Objectives: After completing this activity, the participant should be better able to:
1. Explain the complex nature of IBS pathology and how it effects treatment.
2. Describe the role of bacteria in IBS including the use of antibiotics for treatment.
3. Identify the medical options for direct treatment of IBS to relieve symptoms, such as bloating, abdominal pain, constipation, diarrhea, and flatulence.
4. Outline the ACG guidelines for the treatment of patients with IBS.

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Introduction

Irritable bowel syndrome (IBS), a common disorder managed by primary care physicians and gastroenterologists, is characterized by recurrent abdominal pain and abnormal bowel habits.[1] To provide physicians with an up-to-date analysis of the epidemiology, diagnosis, and treatment of IBS, the American College of Gastroenterology (ACG) IBS Task Force convened and published the monograph entitled "An Evidence-Based Systematic Review on the Management of Irritable Bowel Syndrome" in 2009.[1]

The task force provided a practical definition of IBS for the clinician: abdominal pain or discomfort associated with altered bowel habits occurring for at least 3 months.[1] Notably, there are 3 subtypes of IBS, based on stool consistency: diarrhea-predominant IBS (IBS-D); constipation-predominant IBS (IBS-C); and mixed-symptom IBS (IBS-M), in which patients may alternate between diarrhea and constipation. The task force also provided recommendations for the treatment and management of IBS, using a formalized grading system and reported the results of a series of systematic reviews on the value of diagnostic tests and the efficacy of the various therapies for IBS.[1]

Grading System

To grade their findings, the task force employed a grading system for evidence-based guidelines that is commonly used by other organizations (Table 1).[1,2] This system provides a numerical score for the strength of a treatment recommendation and a lettered designation for the quality of available evidence. The strength of a recommendation was graded as strong (Grade 1) or weak (Grade 2) and was dependent upon a risk-benefit comparison, the burden of adhering to the recommendation, and, sometimes, cost. The quality of evidence was graded as high (Grade A), moderate (Grade B), or low (Grade C). Factors that may have negatively influenced the quality of evidence included poor study design, unexplained heterogeneity of results, indirectness of evidence, imprecise results, and reporting

Table 1. ACG IBS Task Force Grading System[1,2]

Grade	Strength of recommendation	Quality of evidence	Implications
1A	Strong	High	• Benefits clearly outweigh risks and burden, or vice versa • Recommendation is applicable to patients in most circumstances • Further evidence is unlikely to alter confidence in the estimate of effect
1B	Strong	Moderate	• Benefits clearly outweigh risks and burden, or vice versa • Recommendation is applicable to patients in most circumstances • Additional high-quality evidence may alter confidence in the estimate of effect and may change the estimate
1C	Strong	Low or very low	• Benefits clearly outweigh risks and burden, or vice versa • Recommendation is applicable to patients in most circumstances • Additional high-quality evidence will likely alter confidence in the estimate of effect and may change the estimate
2A	Weak	High	• Benefits are closely balanced with risks and burden • Suggests that the best action may differ, depending on circumstances, patients, or societal values • Further evidence is unlikely to alter confidence in the estimate of effect
2B	Weak	Moderate	• Benefits are closely balanced with risks and burden • Suggests that the best action may differ, depending on circumstances, patients, or societal values • Additional high-quality evidence may alter confidence in the estimate of effect and may change the estimate
2C	Very weak	Low or very low	• Benefits may be closely balanced with risks and burden, but there may be uncertainty in the estimates of benefits, risks, and burden • Suggests that other alternatives may be equally reasonable • Additional high-quality evidence will likely alter confidence in the estimate of effect and may change the estimate

Table 2. ACG Recommendations for Diagnostic Testing in Patients With Symptoms of IBS[1]

Test recommendation	Grade	Comment
No routine colonic imaging	1B	Applies to patients <50 years of age with typical symptoms of IBS and no alarm features
Routine screening for celiac sprue	1B	Applies to patients with IBS-D or IBS-M
No routine diagnostic testing*	1C	Applies to patients with no alarm features with typical symptoms of IBS
Routine colonic imaging	1C	Applies to patients with alarm features and for routine screening for colon cancer in patients >50 years of age
Lactose breath testing	2B	Applies to patients in whom lactose maldigestion is a concern despite modification of diet
Breath testing for SIBO	2C	Evidence is insufficient to recommend routine breath testing for SIBO
Random colonic biopsies to rule out microscopic colitis	2C	Applies to patients with IBS-D who undergo colonoscopy

IBS=irritable bowel syndrome; IBS-D=diarrhea-predominant IBS; IBS-M=mixed-symptom IBS; SIBO=small intestinal bacterial overgrowth.

*Includes complete blood count, serum chemistries, thyroid function studies, stool for ova and parasites, and abdominal imaging.

bias.[2] Positive factors for the quality of evidence may have included a large treatment effect, plausible bias, and the presence of a dose-response effect.[2]

The highest recommendation was Grade 1A, reflecting a "strong recommendation that can apply to most patients in most circumstances and further evidence is unlikely to change confidence in the estimate of effect."[1] In contrast, the lowest recommendation, Grade 2C, reflected a "very weak recommendation where other alternatives may be equally reasonable and higher quality evidence would likely change confidence in the estimate of effect."[1]

Recommendations for Diagnosis of IBS

With few exceptions, the task force concluded that diagnosis of IBS in patients with no alarm features can be made with only limited diagnostic testing, if the patient fulfills the symptomatic criteria spelled out in the task force's practical definition of IBS. Alarm features include rectal bleeding; weight loss; iron deficiency anemia; nocturnal symptoms; and a family or personal history of colorectal cancer, inflammatory bowel disease, or celiac sprue. Based on a review of available evidence, the task force made specific recommendations for clinical testing in patients with symptoms of IBS (Table 2). In fact, strong recommendations were made against routine diagnostic testing in patients with typical symptoms of IBS with no alarm features (Grade 1C) and against colonic imaging for patients less than 50 years of age without alarm symptoms (Grade 1B).

In contrast, the task force made strong recommendations in favor of routine screening for celiac sprue in patients with IBS-D and IBS-M (Grade 1B) and colonic imaging for patients older than 50 years of age or with

alarm symptoms (Grade 1C). The task force made weak or very weak recommendations for breath testing (Grade 2B for patients with suspected lactose maldigestion; Grade 2C for routine testing for small intestinal bacterial overgrowth) and for random colonic biopsies to rule out microscopic colitis in patients with IBS-D who undergo colonoscopy (Grade 2C).

Treatment of IBS

The task force rated numerous therapies that have been evaluated for the treatment of IBS (Table 3). To date, the selective C-2 chloride channel activator, lubiprostone, for IBS-C in females, is the only approved therapy indicated for IBS. Lubiprostone was given a favorable rating by the task force for relief of global IBS symptoms in females with IBS-C (Grade 1B). Other therapies, including antibiotics (ie, rifaximin, neomycin; Grade 1B), antidepressants (Grade 1B), and psychological therapies (Grade 1C), have shown efficacy for relief of symptoms of IBS and were given a favorable rating by the task force. The 5-HT$_4$ agonist, tegaserod, was also favorably rated by the task force (Grades 1A-1B); however, this agent is only available through an emergency investigational drug program. The 5-HT$_3$ antagonist, alosetron, was awarded a favorable grade for the risk versus benefit in females with refractory IBS-C (Grade 1B), but was given weaker grades for efficacy for relief of global IBS symptoms in females (Grade 2A) and males (Grade 2B) with IBS-D. Notably, alosetron is only available through a regulated prescribing program. Weak ratings (Grades 2B-2C) were given for the use of antispasmodics; probiotics; the antidiarrheal loperamide; fiber; polyethylene glycol laxatives; and exclusion diets for IBS.

Table 3. ACG Recommendations for the Treatment of IBS

Treatment	Grade	Comments
5-HT4 receptor agonists (ie, tegaserod)[1,3] • Efficacy for relief of global IBS symptoms in females with IBS-C • Efficacy for relief of global IBS symptoms in patients with IBS-M • Most common AE is diarrhea	1A 1B 1A	May be associated with cardiovascular AEs. Only available from the FDA through an emergency investigational drug protocol. NNT=10
Nonabsorbable antibiotics (ie, rifaximin, neomycin)[1]	1B	Short-term treatment effective for improvement of global symptoms of IBS and relief of bloating. Rifaximin most likely to benefit patients with IBS-D or patients with IBS with the primary symptom of bloating. Efficacy of neomycin demonstrated only in 1 study. Long-term safety and efficacy data needed.
Selective C-2 chloride channel activators (ie, lubiprostone)[1]	1B	Efficacy for relief of global IBS symptoms in females with IBS-C. FDA approved for use in females IBS-C.
Antidepressants[1,4]	1B	Efficacy for relief of global IBS symptoms and abdominal pain. Limited safety and tolerability data. NNT=4 for all antidepressants; NNT=4 for TCAs; NNT=3.5 for SSRIs
5-HT3 receptor antagonists (ie, alosetron)[1,3] • Risk/benefit balance favorable for females with IBS that has not responded to conventional therapy • Effective for relief of global IBS symptoms in females with IBS-D • Effective for relief of global IBS symptoms in males with IBS-D • Associated with serious AEs, including constipation and colonic ischemia	1B 2A 2B 2A	Only available through a regulated prescribing program for females with chronic and severe IBS-D who have not responded to conventional therapy. NNT=8
Psychological therapies[1,4]	1C	Relief of global IBS symptoms with cognitive-behavioral therapy, dynamic psychotherapy, and hypnotherapy, but not with relaxation therapy. NNT=4

Antispasmodic agents[1,5]
• For short-term relief*
• For long-term relief*
    Evidence for safety and tolerability*
    Peppermint oil
	
	2C
	2B
	2C
	2B
		AEs have not been fully defined
		NNT=5 for antispasmodics†
		NNT=2.5 for peppermint oil

Probiotics[1,6]	2C	Meta-analysis revealed statistically significant reduction in IBS symptoms. Most effective species and strains remain unknown. NNT=4; however, because of publication bias, this may be an overestimate of efficacy
Antidiarrheals (ie, loperamide)[1]	2C	Effective for improving stool frequency and consistency, but not for improving global symptoms of IBS or relieving abdominal pain. Safety and tolerability data needed.
Dietary fiber[1,5] • Ispaghula husk • Bran	 2C 2C	Safety issues and AEs have not been formally assessed for bulking agents. NNT=11 for all fiber; NNT=6 for ispaghula husk
PEG laxative[1]	2C	Efficacy in IBS demonstrated in only 1 study.
Exclusion diets[1]	2C	Routine use outside of clinical trials is not recommended.

5-HT=serotonin; AE=adverse event; IBS=irritable bowel syndrome; IBS-C=constipation-predominant IBS=IBS-D, diarrhea-predominant IBS; IBS-M=mixed-symptom IBS; FDA=US Food and Drug Administration; NNT=number needed to treat; PEG=polyethylene glycol; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant.

*For the antispasmodics hyoscine, cimetropium, and pinaverium. †Includes studies with otilonium, cimetropium, hyoscine, pinaverium, trimebutine, rociverine, alverine, dicyclomine, mebeverine, pirenzepine, prifinium, and propinox.

Summary

The following monograph summarizes the clinical insights of three leading physicians in the IBS community following a roundtable discussion of the ACG IBS Task Force recommendations. The goal of this monograph is to aid clinicians in implementing these recommendations into clinical practice. The first chapter by Dr William Chey defines IBS and discusses its pathophysiology and diagnosis. In the second chapter, Dr Mark Pimentel summarizes current therapies for IBS-D and IBS-M. In the third chapter, Dr Jennifer Christie reviews current therapies for IBS-C, while also providing her clinical perspective on therapies for IBS and her views on the patient-doctor relationship. Hopefully, the 2009 ACG IBS Task Force recommendations will provide guidance for clinicians in the diagnosis and management of IBS, a common condition that can have substantial impact on patient quality of life and healthcare economics.

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IBS Diagnosis and Confirmation

William D. Chey, MD

IBS is a common but incompletely understood bowel disorder defined by the Rome committee, a group of international experts who meet every 7–8 years to develop a set of consensus criteria to define functional bowel disorders. The main purpose of the Rome criteria are to guide clinical research.[1] However, an increasing need for a practical definition in the clinical and community setting has been noted. In early 2009, the American College of Gastroenterology (ACG) IBS Task Force released guidelines on IBS[2] that offer a simplified definition of IBS, as well as recommendations for diagnosis and treatment. The guidelines serve to summarize the latest evidence and to provide guidance on the selection of treatment options to practicing physicians.

A Working Definition of IBS Disease Behavior

The Rome III consensus document defines IBS by the presence of recurrent abdominal pain or discomfort for at least 3 days per month in the last 3 months, plus at least 2 of the following features: the improvement of symptoms with defecation, the onset of symptoms associated with a change in the frequency of stool, or the onset of symptoms associated with a change in the stool form.[2] The onset of symptoms should be at least 6 months prior to the evaluation of the patient.

These criteria are somewhat complicated, and have not been widely accepted on the part of clinicians. To address this, the ACG review on IBS offers a simplified definition of abdominal pain or discomfort that is associated with altered bowel habits over the course of at least 3 months. This definition is one that clinicians can more easily utilize in day-to-day practice.

One important component of the working definition of IBS is the clinical phenotype of the disease. By definition, all patients with IBS have abdominal pain or discomfort, but bowel habits can vary among patients: some patients may have primarily diarrhea (IBS-D), whereas others may experience primarily constipation (IBS-C). A significant proportion of patients will have a mixture of diarrhea and constipation (IBS-M). The Rome III committee suggested that patients be phenotyped for the purposes of clinical research, diagnostic testing, and treatment. Diagnostic testing and selection of specific therapies are predicated on these differences in symptoms. Rome III moved away from stool frequency as an indicator of disease phenotype (which was a component of the Rome II guidelines[3]), and focused on stool consistency alone. The reason for this shift is evidence suggesting that frequency is not a reliable surrogate for diarrhea or constipation when patients are asked about their symptoms. What a patient means by "diarrhea" may be very different from what a physician means. Therefore,
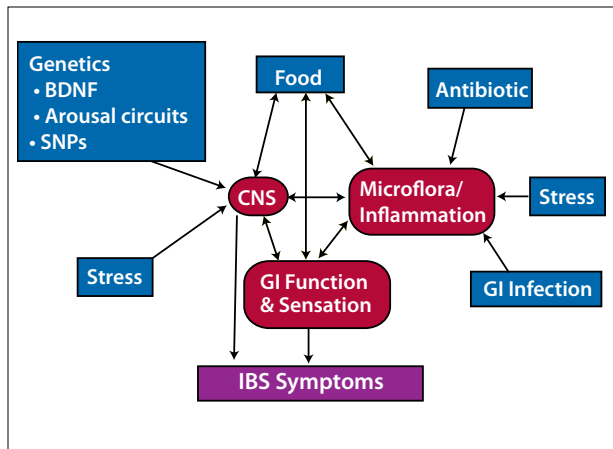
Figure 1. Evolving conceptual model of irritable bowel syndrome (IBS).

BDNF=brain-derived neurotrophic factor, CNS=central nervous system, GI=gastrointestinal, SNPs=single nucleotide polymorphisms.

physicians need to be specific about the information they need—in terms of urgency, consistency, and/or frequency—when classifying patients into IBS subtypes.

It is also important to realize that there is a dynamic element to groupings of patients with different subtypes of IBS. Patients do not necessarily stay in the subgroup in which they are placed at the time of initial evaluation. They will often move from IBS-C or IBS-D into the IBS-M or mixed group. However, few patients will move fully across the spectrum between IBS-D and IBS-C .

Current Understanding of IBS Pathophysiology

Understanding of IBS pathophysiology remains incomplete. Researchers believe that a genetic predisposition may interact with a number of environmental factors to lead to changes in physiology, such as abnormalities in motor function and visceral sensation (Figure 1). In addition to general stress, some of the key life events that can influence the development of IBS include sexual, physical, and verbal abuse. Experience of acute gastroenteritis can also lead to the development of IBS. Another rapidly growing area of research is the impact of food on IBS. Food can change both motor function and sensation within the gastrointestinal tract, leading to the development of IBS symptoms.

One interesting area of research is the role of low-grade inflammation as a cause of symptoms in IBS patients. In a histologic study, IBS patients were shown to have higher lymphocyte counts per ganglion, and more inflammation of lymphocytes within the mesenteric plexus than control subjects.[4] A study by Liebregts and colleagues[5] found increased levels of certain proinflammatory cytokines,

including tumor necrosis factor (TNF)-alpha, interleukin (IL)-1-beta, and IL-6, in patients with IBS compared with healthy controls.

In a study by Dinan and colleagues,[6] the cytokines IL-6 and IL-8 were elevated in patients with all subtypes of IBS compared with healthy controls. The researchers concluded that IBS patients have a proinflammatory cytokine profile and an exaggerated muscarinic receptor-mediated IL-6 response.

Mast cell numbers and function are also abnormal in IBS patients. Mast cells are located at the host/environment interface, in close proximity to sensory nerves. They are activated by factors such as stress, mechanical irritation, toxins, and a variety of peptides. In animal models, degranulation of mast cells has induced visceral hypersensitivity.[7] Indeed, mast cells may play a role in the pathogenesis of IBS, at least in some patients. Guilare and associates[8] found abnormal mast cell numbers and function among IBS-D patients compared with healthy volunteers. The IBS patients showed a marked increase in the number of degranulating mast cells, as well as increased tryptase levels in the jejunal fluid.

Two studies by Barbara and colleagues examined the role of mast cells in IBS patients. In a 2004 study,[9] the researchers identified colonic mucosal mast cells and their release of tryptase and histamine in 44 IBS patients. Among these IBS patients, 77% exhibited a greater area of colonic mucosa occupied by mast cells than healthy controls. The mast cells in close proximity to gut nerves were significantly correlated with the severity and frequency of abdominal pain symptoms. In another study,[10] the researchers found that mast cell mediators released from colonic mucosa of IBS patients, but not from healthy controls, increased the firing of rat nociceptive visceral sensory nerves in vitro.

Finally, abstract data from 2007[11] suggest that the mast cell degranulation inhibitor sodium cromoglycate may improve symptoms in some patients with IBS. Two earlier studies[12,13] also found a beneficial effect of this agent on IBS, which provides compelling data to support the role of mast cells in the pathophysiology of some patients with IBS.

A rapidly evolving area of research involves the role of gut microbiome in the pathogenesis of IBS. There are three examples from both literature and clinical observation to support the connection between alterations in the gut microbiome and the development of IBS. First, some patients develop IBS after an acute gastrointestinal infection. Second, there is literature to suggest that small intestinal bacterial overgrowth (SIBO) may play a role in the development of IBS-like symptoms. Third, some studies suggest that the intestinal flora may differ between IBS patients and otherwise healthy individuals. A meta-analysis by Halvorsen and colleagues[14] found that individuals who had experienced acute gastroenteritis were 7 times more likely to develop IBS than those who had not. Of the patients with gastroenteritis,
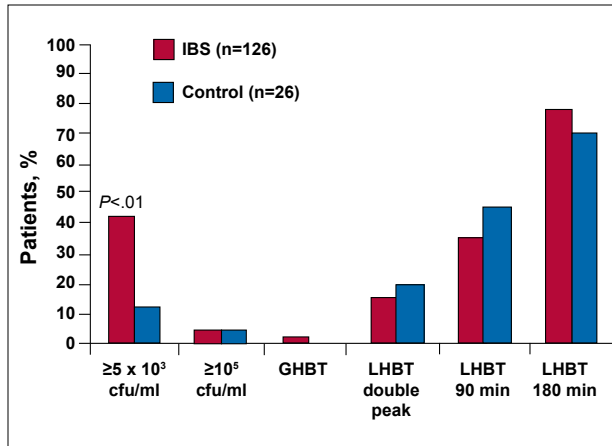
Figure 2. Results of testing for small intestinal bacterial overgrowth in irritable bowel syndrome (IBS).

cfu=colony forming units, GHBT=glucose hydrogen breath test, LHBT=lactulose hydrogen breath test.

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several groups were more likely to develop postinfectious IBS: women, patients with severe diarrheal illness, those who lost more than 10 pounds during their illness, and those who had bloody diarrhea during their acute infection. In addition, individuals with pre-existing anxiety or depression were more likely to develop postinfectious IBS.[15] Perhaps more important is the issue of increased life stress. Gwee and associates[16] found that individuals with acute gastroenteritis increased life-event scores (a surrogate measure for life stress) during the previous year were more likely to develop postinfectious-IBS than those with lower scores.

Most of the studies suggesting a role for SIBO in IBS used either lactulose or glucose hydrogen breath testing as a measure of SIBO and there are many problems with the use of these techniques as a surrogate measure of SIBO. The lactulose hydrogen breath test is likely sensitive but not specific for SIBO.[17] On the other hand, the glucose hydrogen breath test is likely specific but not sensitive for SIBO.[18] Jejunal aspiration for quantitative culture is often held up as the gold standard for the diagnosis of SIBO. Unfortunately, jejunal aspiration for quantitative culture is difficult to perform properly, uncomfortable for the patient, requires specialized infrastructure and is expensive. A 2007 study (Figure 2) found no significant differences in results of lactulose breath testing, glucose breath testing, or jejunal aspiration for quantitative culture (SIBO ≥10^5 CFU/mL) between IBS patients and controls.[19] Though these authors did not identify a difference in SIBO using the standard definition of 10^5 CFU/mL or more jejunal aspirate, they did identify differences between groups when lower bacterial thresholds were considered. This suggests that more subtle

levels in bacterial contamination of the small intestine may be present in some IBS patients when compared to controls.

It is important to realize that there is tremendous variability in the constituent bacterial flora within IBS and control populations. As yet, a consistent microbiome fingerprint that identifies patients with IBS has not been identified. However, quantitative PCR assays suggest that there may be decreased amounts of *Lactobacillus* species in IBS-D and increased *Veillonella* species in IBS-C, although there is considerable overlap among IBS patients and controls.[20] It is conceivable that differences in the location, quantity and constituent species of bacteria may underlie the development of IBS, presumably due to changes in the physiology of the gastrointestinal tract.

Patient Populations Requiring Further Diagnostic Investigation

Additional diagnostic tests may be required in certain subsets of patients presenting with IBS-like symptoms, in order to rule out possible organic causes such as colorectal cancer, inflammatory bowel disease, and celiac sprue. Because IBS is diagnosed most commonly in patients under the age of 50 years, further diagnostic testing may be warranted in older patients exhibiting new-onset IBS-like symptoms. The ACG guidelines[2] list several "alarm features" that may increase the physician's concern for the existence of organic disease. These include rectal bleeding, weight loss, iron deficiency anemia, nocturnal symptoms, and a personal or family history of colorectal cancer, inflammatory bowel disease, or celiac disease. For patients with these clinical features, further testing should be performed based upon the nature and severity of the patient's most bothersome symptoms. It is, however, important to remember that most patients with an alarm feature will eventually wind up with a diagnosis of IBS. In other words, the real value of alarm features is in their high negative predictive value for organic disease. The absence of alarm features in a patient with typical IBS symptoms makes it highly likely that the correct diagnosis is indeed IBS.

The ACG guidelines state that in younger patients with no alarm features, the diagnosis of IBS can usually be based on symptoms alone. The guidelines urge physicians to consider the pretest probability of other conditions before testing for them (Table 1). For example, serum chemistries, complete blood count, thyroid function tests, stool testing, and abdominal and colonic imaging are not recommended in IBS patients without alarm features, as these tests have a low likelihood of uncovering organic disease. One exception to this rule is the ACG recommendation to routinely screen IBS-D and IBS-M patients for celiac sprue, as emerging evidence suggests a higher prevalence of this condition among IBS patients than among controls. Although there is a great

Table 1. Pretest Probability of Organic Diseases in Irritable Bowel Syndrome Versus Controls

Organic GI Disease	IBS Patients (pretest probability %)	General Population (Prevalence %)
Colitis/IBD	0.51–0.98	0.3–1.2
Colorectal cancer	0–0.51	0–6
Gastrointestinal infection	0–1.5	n/a
Thyroid dysfunction	4.2	5–9
Celiac disease	3.6	0.7
Lactose malabsorption	38	26

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deal of research interest in the concept of SIBO in IBS, the ACG guidelines suggest that the current available evidence is insufficient to recommend testing for it in the clinical setting. The guidelines also mention the potential overlap between the symptoms of IBS-D and microscopic colitis. When a patient with IBS-D undergoes a colonoscopy, the guidelines suggest that the endoscopist obtain random colonic mucosal biopsies to rule out microscopic colitis.

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Treatment of Diarrhea-Predominant or Mixed-Symptom IBS

Mark Pimentel, MD

In the treatment of IBS in general, there are many strategies available to physicians. Considering both the severity and the persistence of symptoms, as well as the success or failure of patients' prior treatment attempts, will allow physicians to individualize therapy and develop realistic goals for long-term disease management. Although the 2009 guidelines provide evidence of efficacy for a variety of treatment strategies, in order to provide comprehensive therapy, both symptom relief and resolution of the underlying causes need to be considered.

Addressing IBS Symptoms

One of the mainstays of therapy in new IBS patients is dietary modification, which has been used for many gastrointestinal disorders. Adding a fiber supplement is one dietary approach that has the potential for treating both constipation and diarrhea. The mechanism of diarrhea is believed to be at least partially related to the absorptive capacity of nondigestible carbohydrates. However, fiber has side effects that offset its benefits, including bloating, gas, and distension. In particular, bloating has been the Achilles heel in the use of fiber. In the 2009 ACG guidelines[1], the dietary approach has not found much favor in the setting of IBS-D or IBS-M, because fiber and other forms of dietary manipulation have provided only modest efficacy and only in IBS-C. In most cases, clinicians rarely view fiber as an option, particularly in IBS-D and IBS-M.

Another avenue of therapy targeting specific IBS symptoms is the administration of antispasmodic therapy (eg, hyoscine). Although antispasmodics are used to alleviate the abdominal discomfort symptoms of IBS, their efficacy has been challenged in recent years. The majority of antispasmodic agents available in the United States are poorly studied, and those that have been studied have not shown significant efficacy.

The use of antidiarrheals such as loperimide or other antipropulsive agents is effective for most cases of diarrhea, irrespective of cause. Antidiarrheals are one of the most common classes of agents prescribed to address symptoms of intractable diarrhea. However, one of the challenges of IBS is that although we have drugs that can manipulate transit, they are not always used on a mechanistic basis. In other words, antidiarrheals slow transit in anyone with diarrhea, without necessarily addressing the cause of the diarrhea or the other symptoms in the patient who has IBS-D.

Addressing IBS Pathophysiology

Probiotics have become a source of much enthusiastic research in IBS over the last decade. The principle behind the use of probiotics is that certain bacteria have beneficial effects on motility, inflammation, and epithelial health in the digestive tract. Unfortunately, multiple double-blind studies have been completed with various probiotics, alone and in combination, and almost none of these studies have met primary endpoints in treating IBS. Further, negative publication bias in the scientific literature, which discourages the publication of studies with negative outcomes, could further cloud this issue. Regardless, there are a host of published, controlled studies showing a failure of probiotics to improve IBS.

Only one probiotic has demonstrated some benefit, reported in two studies. The first, a study by O'Mahoney and associates[2], showed that *Bifidobacterium infantis* in a daily malted milk drink for 8 weeks showed a reduction in symptom scores for abdominal pain/discomfort, bloating/distension, and bowel movement difficulty, compared with patients who received a placebo. Although this trial was successful, the product is not currently available to patients. A subsequent study of a *Bifidobacterium infantis* daily capsule for 4 weeks performed by Whorwell and colleagues[3] demonstrated success at improving abdominal pain and bloating, bowel dysfunction, incomplete evacuation, straining, and the passing of gas. Another challenge in the use of probiotics to treat IBS lies in determining their long-term role. In published studies, patients were treated for a limited number of weeks, with benefits in only 1 or 2 weeks of treatment duration. Finally, the mechanism of probiotic therapies remains unclear. If researchers can identify the pathway by which probiotics work, it will lead to targeted research of the most efficacious agents in the future.

Another strategy to address the underlying causes of IBS is the prescription of low-dose antidepressants. As with many IBS therapeutic options, antidepressant use has limited positive data. The most comprehensive study to date[4], using the tricyclic desipramine, failed to detect a significant benefit over placebo in the intention-to-treat analysis, although the study was adequately powered. However, several meta-analyses[5,6] have shown that low-dose antidepressants do have some success in improving IBS symptoms. The question that remains is that of their mechanism of action. Most investigators believe that the anticholinergic effects of tricyclic antidepressants are the primary pathway for IBS-D improvement. Low-dose antidepressants can also help modify visceral afferent pain sensations and the combination of these two mechanisms may ultimately provide benefit.

Encouraging results continues to accrue in the research of antibiotics for IBS. Breath-test–based research has suggested that IBS patients may have excessive bacteria in the small intestine. Not all researchers agree that breath testing truly represents bacterial overgrowth, rather than colonic overexpansion of bacteria. However, all of the controlled studies[7-14] published thus far have demonstrated the efficacy of antibiotics over placebo in IBS patients. The most widely studied antibiotic therapy for IBS is the gut-specific agent rifaximin. Rifaximin has shown efficacy in normalizing lactulose breath test results in both IBS and non-IBS subjects, and in the global relief of IBS symptoms (Figure 1). Thus, it is a prime therapeutic target for IBS. Currently, rifaximin is approved for treatment of travelers' diarrhea caused by noninvasive strains of *Escherichia coli*. However, phase III trials of rifaximin (1,650 mg daily for 14 days, utilizing a newly developed 550 mg tablet) have recently been completed and hold promise of an expanded indication for nonconstipation forms of IBS.

Figure 1. Overall improvement of irritable bowel syndrome symptoms with rifaximin (1,200 mg/day for 10 days) during 10 weeks of posttreatment follow-up.

Reproduced with permission from Pimentel et al.[10]
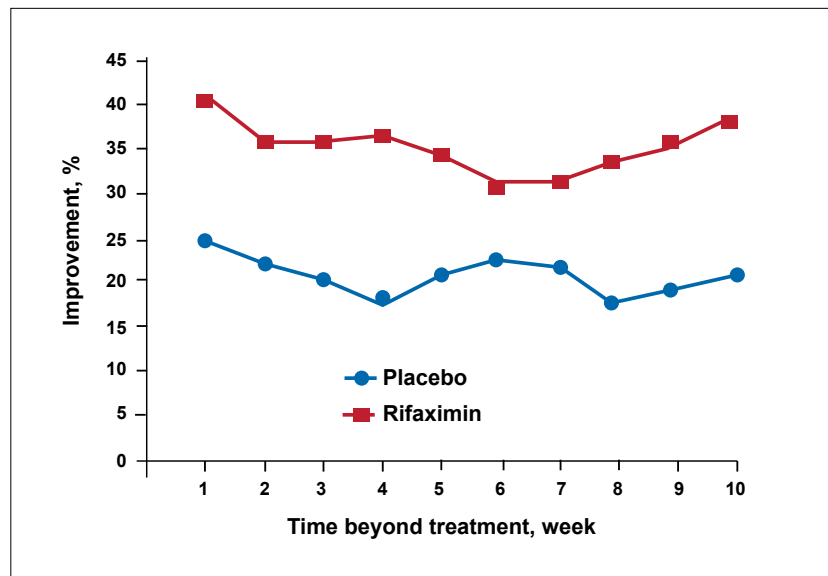
IBS-D and IBS-M have also been treated with serotonin-regulating agents, principally the 5HT receptor antagonists. The first of these agents was alosetron, a $5HT_3$ receptor antagonist, which demonstrated a substantial slowing of intestinal transit in IBS patients[15] and a significant effect in improving the symptoms of patients with refractory diarrhea. Due to the adverse effect of rare but serious cases of ischemic colitis, alosetron was subsequently removed from the market. However, in post-marketing analysis, the rate of ischemic colitis associated with alosetron was found to be lower than was initially described[16] and it was reintroduced as a last-line option for patients who have not responded to other therapies and who have severe symptoms.

Tegaserod is an agonist of the $5HT_4$ receptor that has been shown to provide some efficacy in reducing the symptoms of IBS-M.[17] Currently, there is no full understanding of its mechanism but some researchers suggest that tegaserod may normalize intestinal motor function, because serotonin is instrumental in the correct motor function of the gastrointestinal tract. However, due to postmarketing observation of a slightly raised incidence of cardiovascular events in patients taking tegaserod, is not currently approved for IBS-M and is no longer available in the United States, aside from an emergency investigational drug protocol.[18]

Conclusion

One of the great challenges in treating IBS is that outcome measures are, for the most part, subjective. Physicians who treat IBS, like those who treat many other gastrointestinal disorders, rely on global symptom relief as the targeted outcome of treatment. Large-scale studies have demonstrated that the majority of agents used for IBS do demonstrate some measure of global symptom relief. At this time, this is our best benchmark for the success of IBS management.

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Treatment of Constipation-Predominant IBS

Jennifer A. Christie, MD

Treatment options for IBS-C comprise a variety of therapies, including dietary modification, laxatives, antibiotics, chloride channel activators, and $5HT_4$ receptor agonists. The drugs used to treat IBS-C have demonstrated varying levels of success in improving individual patients' symptoms. Further, any approach needs to be tailored to the patient's individual symptom profile, symptom severity, and response to therapy. The ACG guidelines[1] have helped to quantify the efficacy of the therapies available, and to provide a systematic review of those options with the highest potential to deliver safe and effective symptom relief for IBS.

Dietary Strategies to Control IBS Triggers and Relieve Constipation

Patients with IBS-C will often report that specific food products will trigger their IBS symptoms, which include constipation, bloating, and abdominal discomfort. In fact, one randomized study revealed that specific food triggers could be isolated by IBS patients. Observational studies have reported a number of potential dietary triggers, the most common being dietary carbohydrates such as fructose. A double-blind, randomized, placebo-controlled crossover study[2] in 25 patients with IBS and fructose malabsorption, exposed subjects to graded dosing of either fructose, fructans, a combination of fructose and fructans (mix), or glucose for two weeks each, with at least a 10-day washout period between treatment phases. The researchers found that patients receiving glucose reported a significant reduction in overall IBS severity (Figure 1) and individual symptoms compared with periods in which they received other sugar solutions.

Other foods that have been implicated in the worsening of constipation and bloating symptoms are dairy products, alcohol, and fatty foods. Although studies excluding these foods show modest efficacy in reducing IBS symptoms, data are insufficient at this time to make any generalized recommendations regarding dietary changes.

Common bulking agents used in the treatment of IBS-C include the fiber supplements psyllium and calcium polycarbophil. Although bulking agents may help regulate bowel function, scientific evidence for efficacy in IBS is lacking. Most of the clinical trials testing fiber are poorly designed, with a small sample size and a short follow-up period. However, one 2009 study[3] compared psyllium (a soluble fiber) and bran (an insoluble fiber) with placebo (rice flour), twice daily for three months, in a group of IBS patients that was not divided into symptom subgroups. Of the 275 patients enrolled in the study, 111 (40%) dropped out. The dropout rate was highest among patients who were taking bran supplements (44% of 97) versus psyllium (36% of 85) or placebo (40% of 93). Treatment with psyllium resulted in a significantly greater percentage of patients with adequate symptom relief and significantly greater reduction in the severity of their IBS symptoms compared with placebo.

Several other trials have studied the use of various fiber supplements in the treatment of IBS. In the current ACG guidelines,[1] 12 randomized clinical trials were evaluated.[4] Most of the trials were poorly designed and did not differentiate among the subtypes of IBS. Although the outcomes were varied, 4 of the 6 trials studying psyllium demonstrated an improvement in global IBS symptoms versus placebo. Interestingly, treatment with wheat bran in the trials that were evaluated showed no improvement in IBS symptoms. The difference in effect between soluble and insoluble fiber is not completely clear. However, it is possible that soluble fiber, which mixes with water, may form bulkier stools that help to stimulate peristalsis and produce more effective defecation.

Despite the lack of good evidence, many gastroenterologists still recommend fiber to their patients. However, quite often, fiber intake can worsen the symptoms of bloating and flatulence, particularly in patients who are already present-
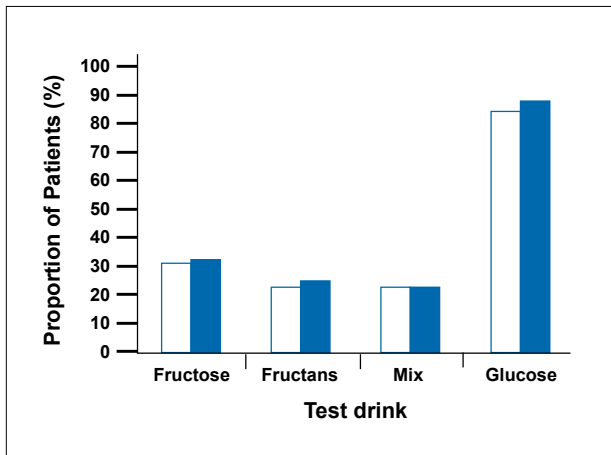
Figure 1. Proportion of patients whose overall IBS symptoms remained adequately controlled (patient response to question "were your symptoms adequately controlled in this phase?") after challenge with designated carbohydrate solution (per protocol=blue; intent to treat=white). $P \leq .002$ for glucose versus other test drinks for per protocol population.

Adapted with permission from Shepherd et al.[2]

ing with these symptoms. For many of my IBS patients experiencing bloating, I discontinue fiber recommended by previous physicians. Regardless, if physicians recommend fiber, it is very important that the dose be titrated and that adequate fluid intake be emphasized.

Medical Options to Relieve Constipation

IBS-C is often associated with a significant reduction in health-related quality of life (HRQOL). This connection has been described in several publications, including those by El-Serag[5] and Gralnek and colleagues.[6] Patients who experience a reduction in HRQOL describe severe, debilitating constipation, bloating, abdominal pain, and a low overall sense of well-being. Fiber and dietary change are frequently not sufficient to manage these symptoms. Therefore, additional pharmacologic therapies for IBS-C are warranted. Some of the drugs that have been examined for use in IBS-C include laxatives, antibiotics, chloride channel activators, and $5HT_4$ agents.

The data for the use of osmotic laxatives in the treatment of IBS-C are weak, at best. However, a small randomized trial of polyethylene glycol (PEG) laxative treatment in 48 adolescents with IBS-C by Khoshoo and associates[7] found that stool frequency, but not abdominal pain, improved in patients taking PEG alone compared with PEG plus tegaserod. Often, patients will benefit from medications like PEG solution, but if they are still experiencing discomfort, it is acceptable to use a stimulant laxative once or twice per

week without any adverse effects. However, patients who use stimulant laxatives such as bisacodyl, senna, and sorbitol, commonly have mixed results. Over-the-counter stimulant laxatives can be associated with abdominal pain, cramping, and urgency, which will worsen a patient's overall sense of well-being. They can also lead to electrolyte disturbances if overused. Although there is no real danger of colonic inertia, patients can build a tolerance to stimulant laxatives, and they may need increasingly higher doses to achieve an effect over time.

Lubiprostone is a chloride-channel activator that was initially investigated for the treatment of chronic idiopathic constipation (CIC), a condition that is differentiated from IBS-C by a relative lack of pain symptoms. Although CIC patients may have some abdominal discomfort due to constipation, pain is not the predominant symptom. However, lubiprostone was found to reduce abdominal discomfort in CIC patients, prompting further investigation into its use in IBS-C. In combined phase III studies,[8] the use of 8 mcg of lubiprostone twice daily resulted in an 18% response rate, versus 10% for placebo (P=.001). Patients in the two phase III trials were predominantly female, and the drug was approved only for use in women with IBS-C. The most common side effects associated with lubiprostone were nausea (which occurred in 8% of patients), diarrhea (6%), and abdominal distension (2%).

Currently, no $5HT_4$ receptor agonists are readily available for use in patients with IBS-C, despite these agents' known efficacy. Tegaserod is an agonist of the $5HT_4$ receptor that was initially approved for use in women with IBS-C but was withdrawn from the market after combined data from 29 randomized controlled trials showed adverse cardiovascular events in 0.11% of tegaserod-treated patients, compared with 0.01% in patients who received placebo.[9] Based on the meta-analysis performed by the ACG task force on the management of IBS,[10] tegaserod at 6 mg twice daily was superior to placebo in the global improvement of IBS symptoms. Tegaserod is available through an emergency investigational drug protocol of the USFDA.

Overall Strategies for Global Symptom Relief

The approach to the management of patients with IBS-C must be multipronged. The primary objective is to reduce the frequency and severity of the primary symptom of each patient, be it constipation, bloating, or abdominal pain (Figure 2). In some cases, focusing on the primary symptom, and treating accordingly, will result in the improvement of secondary symptoms as well. The overall objective is to improve the patient's quality of life, as it relates to IBS symptoms.

Additional therapies such as centrally acting agents (including selective serotonin reuptake inhibitors [SSRIs]
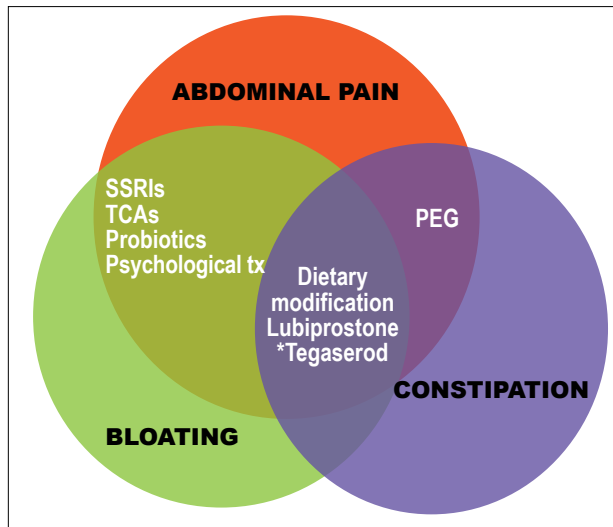
Figure 2. Major symptoms of constipation-predominant irritable bowel syndrome and therapies for symptom management.

*Tegaserod is only available through an emergency investigational new drug protocol.

PEG=polyethylene glycol, SSRIs=selective serotonin reuptake inhibitors, TCAs= tricyclic antidepressants; tx=treatment.

and, occasionally, tricyclic antidepressants) may prove useful. I use tricyclic antidepressants with caution in patients with IBS-C, as the anticholinergic effect and slowing of intestinal transit associated with these agents may worsen constipation and bloating symptoms. Patients with abdominal pain as a major symptom often respond positively to SSRIs because these drugs can alter the visceral hypersensitivity that contributes to abdominal pain in patients with IBS. Though the results are variable, probiotics are also used very commonly in the management of IBS. Regimens that include *Bifidobacterium* have shown the greatest efficacy. Other potentially helpful therapies for IBS-C include psychological therapies such as cognitive behavioral therapy, dynamic psychotherapy, and hypnosis.

In my practice, I generally see three categories of IBS patients, across all IBS subtypes. First, there are patients who are comfortable with the diagnosis of IBS but feel they have been inadequately treated. They are in search of better treatment options. Second, there are patients who believe they may have IBS, but because of the severity of their symptoms are looking for other possible diagnoses. These patients require reassurance of their diagnosis as well as relief of their symptoms. Third, there are patients who, despite being diagnosed with IBS by primary care physicians and/

or gastroenterologists, are convinced that they have been dismissed and given an IBS diagnosis because their doctors cannot figure out the true cause of their symptoms. I have actually had patients tell me that they are looking for a physician like certain characters from dramatic television series. I often ask these patients for their perspective on their illness, as well as offering them mine. I then try to rationalize both perspectives with the patient, explaining to them why IBS is the most likely diagnosis. Quite often, I find that explaining (in laymen's terms) the pathophysiology of IBS, including serotonin pathways and their effect on motility and gut sensation as a real physical and clinical condition, helps to validate their symptoms and gives the patient insight into what may be happening in their gut. It is important to recognize patient attitudes and consider their symptoms, in order to set realistic treatment goals, as the establishment of a solid physician-patient relationship is of utmost importance in the management of IBS. Patients need to feel reassurance, as they often perceive that they are not taken seriously with regard to the nature and severity of their symptoms. Therefore, acknowledging their symptoms as real, addressing components that significantly affect overall quality of life, and treating them accordingly, is crucial to a successful patient-physician relationship. Ultimately, although gradually in many cases, patients will experience symptom improvement and a better overall quality of life.

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The ACG Evidence-Based Review on the Management of Irritable Bowel Syndrome: Recommendations from Bench to Bedside

CME Post-Test: *Circle the correct answer for each question below.*

1. What class of drug is sodium chromoglycate?

    a. Mast cell granulation inhibitor
    b. Anticholinergic
    c. Antidepressant
    d. Selective C-2 chloride channel activator

2. The American College of Gastroenterology (ACG) review defines IBS as follows:

    a. Abdominal pain or discomfort that is associated with altered bowel habits over the course of at least 6 months
    b. Abdominal pain or discomfort that is associated with altered bowel habits over the course of at least 3 months
    c. Altered bowel habits over the course of at least 3 months, with or without abdominal pain or discomfort
    d. Altered bowel habits over the course of at least 6 months, with or without abdominal pain or discomfort

3. A study by Liebregts and colleagues found increased levels of certain proinflammatory cytokines, including tumor necrosis factor (TNF)-alpha, interleukin (IL)-1-beta, and IL-6 levels in patients with IBS compared with healthy controls. Which patients showed increased levels of these cytokines?

    a. IBS-C
    b. IBS-D
    c. IBS-M
    d. All IBS patients

4. According to Dr. Pimentel, which side effect has most limited the utility of fiber in the treatment of IBS patients?

    a. Gas
    b. Increased bowel frequency
    c. Increased urgency
    d. Bloating

5. Which antibiotic has shown the most promise in the treatment of IBS-D?

    a. Neomycin
    b. Rifaximin
    c. Clarithromycin
    d. Cefaclor

6. According to Dr. Pimentel, what is the best benchmark for IBS improvement?

    a. Global symptom relief
    b. Regulation of motor function
    c. Normalization of lactulose breath testing
    d. Decrease in the number of stools per day

7. What associated effect led to the withdrawal of tegaserod for the treatment of IBS?

    a. An increased risk of cardiovascular events
    b. A lack of efficacy in IBS patients
    c. An increase in bloating
    d. An increased risk of ischemic colitis

8. What class of drug is lubiprostone?

    a. A 5HT 3 receptor antagonist
    b. A 5HT 4 receptor agonist
    c. A chloride channel activator
    d. A probiotic

9. A 2008 study by Shepherd and colleagues evaluated 25 patients who were randomized in a crossover design to receive either fructose, fructans, a combination of fructose and fructans, or glucose for two weeks each. The group receiving which sugar solution showed an improvement in IBS severity?

    a. Fructose
    b. Fructans
    c. A combination of fructose and fructans
    d. Glucose

10. TRUE or FALSE: SSRIs can alter the visceral hypersensitivity component of IBS.

    a. True
    b. False

Evaluation Form The ACG Evidence-Based Review on the Management of Irritable Bowel Syndrome: Recommendations from Bench to Bedside

PIM is committed to excellence in continuing education, and your opinions are critical to us in this effort. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. **You must complete this evaluation form to receive acknowledgment for completing this activity.**

Please rate your level of agreement by circling the appropriate rating:
1 = Strongly Disagree   2 = Disagree   3 = Neutral   4 = Agree   5 = Strongly Agree
Learning Objectives
After participating this activity, I am now better able to:

1. Explain the complex nature of IBS pathology and how it effects treatment.	1 2 3 4 5
2. Describe the role of bacteria in IBS including the use of antibiotics for treatment.	1 2 3 4 5
3. Identify the medical options for direct treatment of IBS to relieve symptoms, such as bloating, abdominal pain, constipation, diarrhea, and flatulence.	1 2 3 4 5
4. Outline the ACG Guidelines for the Treatment of Patients with IBS.	1 2 3 4 5

Based upon your participation in this activity, choose the statement(s) that apply:
❐ I gained new strategies/skills/information that I can apply to my area of practice.
❐ I plan to implement new strategies/skills/information into my practice.

What strategies/changes do you plan to implement into your practice? _____

_____

What barriers do you see to making a change in your practice? _____

_____

Which of the following best describes the impact of this activity on your performance?
❐ I will implement the information in my area of practice.
❐ I need more information before I can change my practice behavior.
❐ This activity will not change my practice, as my current practice is consistent with the information presented.
❐ This activity will not change my practice, as I do not agree with the information presented.

Please rate your level of agreement by circling the appropriate rating:
1 = Strongly Disagree   2 = Disagree   3 = Neutral   4 = Agree   5 = Strongly Agree
The content presented:

Enhanced my current knowledge base	1 2 3 4 5
Addressed my most pressing questions	1 2 3 4 5
Promoted improvements or quality in health care	1 2 3 4 5
Was scientifically rigorous and evidence-based	1 2 3 4 5
Avoided commercial bias or influence	1 2 3 4 5

Would you be willing to participate in a post-activity follow-up survey?   ❐ Yes   ❐ No

Please list any topics you would like to see addressed in future educational activities: _____

_____

If you wish to receive acknowledgment for completing for this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876.

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

Request for Credit

Name _____ Degree _____

Organization _____ Specialty _____

Address _____

City, State, Zip _____

Telephone _____ Fax _____ E-mail _____

Signature _____ Date _____

For Physicians Only: I certify my actual time spent to complete this educational activity to be: _____
❐ I participated in the entire activity and claim 1.0 credits.
❐ I participated in only part of the activity and claim _____ credits.