ACG Clinical Guideline: Management of Irritable Bowel Syndrome

Brian E. Lacy, PhD, MD, FACG[1], Mark Pimentel, MD, FACG[2], Darren M. Brenner, MD, FACG[3], William D. Chey, MD, FACG[4], Laurie A. Keefer, PhD[5], Millie D. Long, MDMPH, FACG (GRADE Methodologist)[6] and Baha Moshiree, MD, MSc, FACG[7]

Irritable bowel syndrome (IBS) is a highly prevalent, chronic disorder that significantly reduces patients' quality of life. Advances in diagnostic testing and in therapeutic options for patients with IBS led to the development of this first-ever American College of Gastroenterology clinical guideline for the management of IBS using Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology. Twenty-five clinically important questions were assessed after a comprehensive literature search; 9 questions focused on diagnostic testing; 16 questions focused on therapeutic options. Consensus was obtained using a modified Delphi approach, and based on GRADE methodology, we endorse the following: We suggest that a positive diagnostic strategy as compared to a diagnostic strategy of exclusion be used to improve time to initiating appropriate therapy. We suggest that serologic testing be performed to rule out celiac disease in patients with IBS and diarrhea symptoms. We suggest that fecal calprotectin be checked in patients with suspected IBS and diarrhea symptoms to rule out inflammatory bowel disease. We recommend a limited trial of a low fermentable oligosaccharides, disacchardies, monosaccharides, polyols (FODMAP) diet in patients with IBS to improve global symptoms. We recommend the use of chloride channel activators and guanylate cyclase activators to treat global IBS with constipation symptoms. We recommend the use of rifaximin to treat global IBS with diarrhea symptoms. We suggest that gut-directed psychotherapy be used to treat global IBS symptoms. Additional statements and information regarding diagnostic strategies, specific drugs, doses, and duration of therapy can be found in the guideline.

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/B755.

Am J Gastroenterol 2021;116:17–44. https://doi.org/10.14309/ajg.0000000000001036; published online December 14, 2020

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic, often debilitating, and highly prevalent disorder of gut-brain interaction (previously called functional gastrointestinal [GI] disorders) (1,2). In clinical practice, IBS is characterized by symptoms of recurrent abdominal pain and disordered defecation (1,3). The Rome IV criteria, derived by consensus from a multinational group of experts in the field of disorders of gut-brain interaction, can be used to diagnose IBS for both clinical and research purposes (4). Patients with IBS should report symptoms of abdominal pain at least once weekly (on average) in association with a change in stool frequency, a change in stool form, and/or relief or worsening of abdominal pain related to defecation (Table 1). Although bloating is a commonly reported symptom, its presence is not mandatory to accurately diagnose IBS (4).

IBS is a common source of referrals to gastroenterologists with a prevalence of approximately 4.4%–4.8% in the United States, United Kingdom, and Canada and affects most commonly women and individuals younger than 50 years (5). Symptoms of IBS greatly affect patients' quality of life (6,7), and this marked negative impact is highlighted by 1 study which reported that a majority of patients would give up 10–15 years of life expectancy for an instant cure for their condition and by another study which found that patients with IBS would accept a median risk of sudden death of 1% if a hypothetical medication could cure their IBS symptoms (8,9).

IBS causes a significant burden to health care systems worldwide. As highlighted in a recent review article, direct medical costs attributed to IBS in the United States, excluding prescription and over-the-counter medications, are estimated to be as high as $1.5–$10 billion per year (10). High levels of health care resource utilization, testing that is often unnecessary or performed too frequently, and significant regional variation in testing and treatment further contribute to substantial direct and indirect costs (11,12).

The management of IBS has been examined in several recent monographs, reviews, and position statements (1,3,4). These publications summarize and review data and provide management recommendations based on meta-analysis and/or expert opinion. However, essential diagnostic and treatment recommendations have not been formally evaluated by the American

[1]Division of Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, Florida, USA; [2]Division of Gastroenterology and Hepatology, Cedars-Sinai, Los Angeles, California, USA; [3]Division of Gastroenterology and Hepatology, Northwestern University, Chicago, Illinois, USA; [4]Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, Michigan, USA; [5]Icahn School of Medicine at Mount Sinai, New York, New York, USA; [6]Division of Gastroenterology and Hepatology, University of North Carolina, Chapel Hill, North Carolina, USA; [7]Division of Gastroenterology and Hepatology, University of North Carolina, College of Medicine, Charlotte, North Carolina, USA. **Correspondence:** Brian E. Lacy, PhD, MD, FACG. E-mail: Lacy.Brian@mayo.edu.
Received April 15, 2020; accepted October 8, 2020

© 2020 by The American College of Gastroenterology

Copyright © 2020 by The American College of Gastroenterology. Unauthorized reproduction of this article is prohibited.

Table 1. Rome IV diagnostic criteria for irritable bowel syndrome (4)

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 the frequency of stool
3. Associated with a change in the form (appearance) of stool
These criteria should be fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis. Adapted with permission from Bowel Disorders. *Gastroenterology* 2016;150: 1393–407. ©2016 AGA Institute. Published by Elsevier. All rights reserved.

College of Gastroenterology (ACG) using rigorous Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology. This ACG clinical guideline was developed to provide clinicians with high quality evidence, when available, to support essential clinical questions relevant to the diagnosis and management of IBS (Table 2).

SCOPE OF THE GUIDELINE AND METHODOLOGY

This guideline will focus on key issues related to the diagnosis and management of IBS. Given the complexity of IBS, it is not possible to address all diagnostic and management issues. Clinically relevant questions were developed by a panel of experts who focus their clinical and research efforts on disorders of gut-brain interaction (previously called functional GI disorders). The group formulated 25 key statements that followed the population, intervention, comparator, and outcome format to guide the search for evidence (Table 3). These questions were answered by performing a comprehensive international literature search (see methods below). This guideline focuses primarily on the evaluation and management of patients in North America, as not all diagnostic tools (e.g., 23-seleno-25-homotaurocholic acid [SeHCAT]) and medications for IBS (e.g., pinaverium) are available in North America. Over the past decade the US Food and Drug Administration (FDA) has issued guidelines, suggesting that therapies for IBS symptoms be evaluated with an emphasis on global symptom improvement. As such, when applicable, questions were developed with an emphasis on evaluating global response to IBS symptoms for each therapy. An inherent limitation to this approach is that not all therapies were evaluated in double-blind, randomized, placebo-controlled trials with the primary endpoint being an improvement in global IBS symptoms. Where appropriate, this is mentioned in the text. Finally, it is worth noting that the strength of the recommendation, as described below, is based on an overall review of the literature and does not infer or imply that an individual patient may or may not receive benefits from the specific therapy described.

An individualized literature search was performed for each population, intervention, comparator, and outcome question which involved searching MEDLINE, EMBASE, PubMed, and the Cochrane Controlled Trials Register from inception to February 1, 2020. The search emphasized randomized, placebo-controlled trials with at least 10 subjects and study length ≥4 weeks. Abstracts, case reports, uncontrolled studies, and studies less than 4 weeks in duration were not included. References of articles meeting the search criteria were reviewed for additional relevant studies. Trained GRADE methodologists analyzed the data to assess the quality of evidence and given strength of recommendation. The quality of evidence was expressed as high (estimate of effect is unlikely to change with new data), moderate, low, or very low (estimate of effect is very uncertain). GRADE uses objective reproducible criteria to determine quality of evidence and risk of bias among relevant studies, including evidence of publication bias, unexplained heterogeneity among studies, directness of the evidence, and precision of the estimate of effect (13). A summary of the quality of evidence for the statements is given in Table 4. The strength of recommendation is given as either strong (most patients should receive the recommended course of action) or conditional (many patients will have this recommended course of action, but different choices may be appropriate for some patients). In the case of conditional recommendations, a greater discussion is warranted, so that each patient can arrive at a decision based on their values and preferences. The strength of recommendation is based on the quality of evidence and risks vs benefits (14).

We used a modified Delphi approach to achieve consensus. Each statement was presented during a monthly phone conference and voted on by all expert authors. Statements were revised and then either presented again on a phone conference or circulated by email. One face-to-face meeting was held. The vote on the final recommendation and quality of evidence for each statement was unanimous. A summary of the recommendations is given in Table 2.

Recommendation

We recommend that serologic testing be performed to rule out celiac disease (CD) in patients with IBS and diarrhea symptoms.
Strong recommendation; moderate quality of evidence.

CD is an immune-mediated disease in which foods containing the storage protein gluten lead to enteropathy in genetically susceptible individuals. The clinical presentation of CD is highly variable, ranging from entirely asymptomatic to frank malabsorption. In a meta-analysis of studies conducted in North America, the seroprevalence of CD based on 7 studies including almost 18K subjects was estimated to be 1.4% (95% confidence interval [CI] 0.7%–2.2%), whereas the prevalence of biopsy-proven CD, based on a single study including 200 subjects, was estimated to be 0.5% (15–17). Making a diagnosis of CD is important because untreated persons can develop a myriad of significant downstream consequences including neuropsychiatric disease, other autoimmune diseases, nutritional deficiencies, infertility, as well as GI malignancies (16).

Many patients with CD present with abdominal pain, bloating, and/or altered bowel habits which can be mistaken for IBS (18–21). A recent meta-analysis of 36 eligible studies, including 15,256 persons of which 9,275 fulfilled symptom-based criteria for IBS, was conducted to determine whether patients with IBS symptoms are more likely to test positive for CD (19). The prevalence of positive antiendomysial antibodies and/or tissue transglutaminase antibodies was 2.6% (95% CI 1.6%–3.8%) and of biopsy-proven CD was 3.3% (95% CI 2.3%–4.5%) in patients with IBS symptoms (20). Pooled odds ratios (ORs) from the world's literature showed an increased likelihood of positive antiendomysial antibodies and/or tissue transglutaminase antibodies (2.75, 95% CI 1.35–5.61) and biopsy-proven CD (4.48, 95% CI 2.33–4.60) in patients with IBS symptoms compared with controls. Only a small number of included studies were

Copyright © 2020 by The American College of Gastroenterology. Unauthorized reproduction of this article is prohibited.

Table 2. Summary and strength of recommendations

1	We recommend that serologic testing be performed to rule out celiac disease in patients with IBS and diarrhea symptoms. Strong recommendation; moderate quality of evidence.
2	We suggest that fecal calprotectin (or fecal lactoferrin) and C-reactive protein be checked in patients without alarm features and with suspected IBS and diarrhea symptoms to rule out inflammatory bowel disease. Strong recommendation; moderate quality of evidence for C-reactive protein and fecal calprotectin. Strong recommendation; very low quality of evidence for fecal lactoferrin.
3	We recommend against routine stool testing for enteric pathogens in all patients with IBS. Conditional recommendation; low quality of evidence.
4	We recommend against routine colonoscopy in patients with IBS symptoms younger than 45 years without warning signs. Conditional recommendation; low quality of evidence.
5	We suggest a positive diagnostic strategy as compared to a diagnostic strategy of exclusion for patients with symptoms of IBSs to improve time to initiate appropriate therapy. Consensus recommendation; unable to assess using GRADE methodology.
6	We recommend a positive diagnostic strategy as compared to a diagnostic strategy of exclusion for patients with symptoms of IBSs to improve cost-effectiveness. Strong recommendation; high quality of evidence.
7	We suggest that categorizing patients based on an accurate IBS subtype improves patient therapy. Consensus recommendation; unable to assess using GRADE methodology.
8	We do not recommend testing for food allergies and food sensitivities in all patients with IBS unless there are reproducible symptoms concerning for a food allergy. Consensus recommendation; unable to assess using GRADE methodology.
9	We suggest that anorectal physiology testing be performed in patients with IBS and symptoms suggestive of a pelvic floor disorder and/or refractory constipation not responsive to standard medical therapy. Consensus recommendation; unable to assess using GRADE methodology.
10	We recommend a limited trial of a low FODMAP diet in patients with IBS to improve global IBS symptoms. Conditional recommendation; very low quality of evidence.
11	We suggest that soluble, but not insoluble, fiber be used to treat global IBS symptoms. Strong recommendation; moderate quality of evidence.
12	We recommend against the use of antispasmodics for the treatment of global IBS symptoms. Conditional recommendation; low quality of evidence.
13	We suggest the use of peppermint to provide relief of global IBS symptoms. Conditional recommendation; low quality of evidence.
14	We suggest against probiotics for the treatment of global IBS symptoms. Conditional recommendation; very low quality of evidence.
15	We suggest against PEG products to relieve global IBS symptoms in those with IBS-C. Conditional recommendation; low quality of evidence.
16	We recommend the use of chloride channel activators to treat global IBS-C symptoms. Strong recommendations; moderate quality of evidence.
17	We recommend the use of guanylate cyclase activators to treat global IBS-C symptoms. Strong recommendation; high quality of evidence.
18	We suggest that the 5-HT_4 agonist tegaserod be used to treat IBS-C symptoms in women younger than 65 years with ≤1 cardiovascular risk factors who have not adequately responded to secretagogues. Strong/conditional recommendation; low quality of evidence
19	We do not suggest the use of bile acid sequestrants to treat global IBS-D symptoms. Conditional recommendation; very low quality of evidence.
20	We recommend the use of rifaximin to treat global IBS-D symptoms. Strong recommendation; moderate quality of evidence.
21	We recommend that alosetron be used to relieve global IBS-D symptoms in women with severe symptoms who have failed conventional therapy. Conditional recommendation; low quality of evidence.
22	We suggest that mixed opioid agonists/antagonists be used to treat global IBS-D symptoms. Conditional recommendation; moderate quality of evidence.
23	We recommend that tricyclic antidepressants be used to treat global symptoms of IBS. Strong recommendation; moderate quality of evidence.
24	We suggest that gut-directed psychotherapies be used to treat global IBS symptoms. Conditional recommendations; very low quality of evidence.
25	Using currently available evidence, we recommend against the use of fecal transplant for the treatment of global IBS symptoms. Strong recommendation; very low quality of evidence.

5-HT_4, serotonin type-4 receptor; FOADMAP, fermentable oligosaccharides, disacchardies, monosaccharides, polyols; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; IBS, irritable bowel syndrome; IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; PEG, polyethylene glycol.

conducted in North America, and these did not identify a difference in the odds of positive serological testing (1.05, 95% CI 0.21–5.15) or biopsy-proven CD (0.93, 95% CI 0.13–6.63) among patients with IBS symptoms vs controls. The increased likelihood of CD among patients with IBS symptoms was greater in studies conducted in secondary or tertiary care and less apparent in population-based studies. The meta-analysis by Irvine et al. (19) also reported the prevalence of CD in different IBS subgroups. The highest prevalence of CD was reported in IBS with diarrhea (IBS-D) (EMA or tTG 5.7%, 95% CI 3.0%–9.1%), followed by IBS with mixed or alternating bowel habits (IBS-M) (3.4%, 95% CI

© 2020 by The American College of Gastroenterology

Copyright © 2020 by The American College of Gastroenterology. Unauthorized reproduction of this article is prohibited.

Table 3. Population, intervention, comparator, and outcome statements evaluated in the IBS guideline[a]

Informal question	Population	Intervention	Comparator	Outcome	Method[b]
Should patients with IBS and diarrhea symptoms be checked for celiac disease?	Adult patients with IBS and diarrhea	Serologic tests for celiac disease	Adult patients without celiac disease	Prevalence of patients with IBS and celiac disease	1. Cohort studies 2. Case-control studies 3. Systematic review 4. Meta-analyses
Can fecal calprotectin, fecal lactoferrin, and/or CRP be used to rule out IBD in patients with IBS and diarrhea symptoms?	Adults patients with IBS and diarrhea	Evaluation of CRP, fecal calprotectin, and fecal lactoferrin	Patients with IBD; healthy controls	Clinical utility of testing to detect IBD in IBS patients (sensitivity, specificity, and positive and negative predictive value)	1. Cohort studies 2. Systematic review 3. Meta-analyses
Should IBS patients be routinely checked for stool pathogens?	Adult patients with IBS and diarrhea	Tests for stool pathogens	Healthy controls; patients with known Giardia infection	Prevalence of enteric pathogens in patients with IBS	1. Population studies 2. Cohort studies 3. Meta-analyses
Should patients younger than 45 years routinely undergo colonoscopy for IBS symptoms?	Adult patients with IBS	Colonoscopy	Adults undergoing screening colonoscopy	Prevalence of abnormal colonoscopic findings in patients with IBS	1. Prospective trials 2. RCT 3. Meta-analysis
Is it more cost-effective to approach patients with suspected IBS using a positive diagnostic strategy as opposed to one of exclusion?	Adult patients with IBS symptoms	Cost analysis	Patients with organic disease; patients without IBS	Costs of evaluation	1. Descriptive studies 2. Health claims analysis 3. Prospective RCT
Should a low FODMAP diet be used in patients with IBS?	Adult patients with IBS	Low FODMAP diet	Low FODMAP diet or standard diet	Improvement in global IBS symptoms	1. RCT 2. Systematic reviews 3. Meta-analyses
Should fiber be used to treat global IBS symptoms?	Adult patients with IBS	Soluble or insoluble fiber	Fiber vs placebo	Improvement in global IBS symptoms	1. RCT 2. Systematic reviews 3. Meta-analyses
Should antispasmodics be used to treat global IBS symptoms?	Adult patients with IBS	Antispasmodics	Antispasmodic vs placebo	Improvement in global IBS symptoms	1. RCT 2. Systematic reviews 3. Meta-analyses
Does peppermint improve global IBS symptoms?	Adult patients with IBS	Peppermint oil (different forms)	Peppermint oil vs placebo	Improvement in global IBS symptoms	1. RCT 2. Systematic reviews 3. Meta-analyses
Should probiotics be used to treat global IBS symptoms?	Adult patients with IBS	Probiotics (various formulations)	Probiotic vs placebo	Improvement in global IBS symptoms	1. RCT 2. Systematic reviews 3. Meta-analyses

Copyright © 2020 by The American College of Gastroenterology. Unauthorized reproduction of this article is prohibited.

Table 3. (*continued*)

Informal question	Population	Intervention	Comparator	Outcome	Method[b]
Should polyethylene glycol products be used to treat IBS-C symptoms?	Adult patients with IBS	PEG	PEG vs placebo, lactulose or tegaserod	Improvement in IBS-C symptoms	1. RCT 2. Systematic reviews
Should chloride channel activators be used to treat IBS-C symptoms?	Adult patients with IBS	Lubiprostone	Lubiprostone vs placebo	Improvement in IBS-C symptoms	1. RCT 2. Systematic reviews 3. Meta-analyses
Should GC-C agonists be used to treat IBS-C symptoms?	Adult patients with IBS	Linaclotide; plecanatide	Linaclotide or plecanatide vs placebo	Improvement in IBS-C symptoms	1. RCT 2. Systematic reviews 3. Meta-analyses
Should 5-HT_4 agonists be used in women younger than 65 years to treat IBS-C symptoms?	Women with IBS	Tegaserod	Tegaserod vs placebo	Improvement in IBS-C symptoms	1. RCT 2. Systematic review 3. Meta-analyses
Should bile acid sequestrants be used to treat IBS-D symptoms?	Adult patients with IBS	Colestipol and colesevelam	Open-label trials; no placebo-controlled studies	Improvement in IBS-D symptoms	1. Open-label trials 2. Reviews
Should rifaximin be used to treat global IBS-D symptoms?	Adult patients with IBS-D	Rifaximin	Rifaximin vs placebo	Improvement in global IBS-D symptoms	1. RCT 2. Systematic reviews 3. Meta-analyses
Should alosetron be used in women with IBS-D and severe symptoms?	Women with IBS and diarrhea	Alosetron	Alosetron vs placebo	Improvement in IBS-D symptoms	1. RCT 2. Systematic reviews 3. Meta-analyses
Should opioid agonists/mixed antagonists be used to treat IBS-D symptoms?	Adult patients with IBS	Eluxadoline	Eluxadoline vs placebo	Improvement in IBS-D symptoms	1. RCT 2. Systematic reviews 3. Meta-analyses
Should tricyclic antidepressants be used to treat global IBS symptoms?	Adult patients with IBS	Various TCAs	TCA vs placebo	Improvement in global IBS symptoms	1. RCT 2. Systematic reviews 3. Meta-analyses
Can psychotherapy be used to treat global IBS symptoms?	Adult patients with IBS	Various gut-directed psychotherapy (cognitive-behavior therapy, mindfulness, and hypnosis)	Psychotherapy vs standard care or education or medical therapy	Improvement in global IBS symptoms	1. RCT 2. Systematic reviews 3. Meta-analyses

© 2020 by The American College of Gastroenterology

Copyright © 2020 by The American College of Gastroenterology. Unauthorized reproduction of this article is prohibited.

Table 3. (*continued*)

Informal question	Population	Intervention	Comparator	Outcome	Method[b]
Should fecal transplant be performed to treat IBS symptoms?	Adult patients with IBS	Fecal transplant	Donor vs patient stool; different methods of transplant	Improvement in global IBS symptoms	1. RCT 2. Systematic review 3. Meta-analyses

5-HT$_4$, serotonin type-4 receptor; CRP, C-reactive protein; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, polyols; GC-C, guanylate cyclase-C; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; IBS, irritable bowel syndrome; IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; PEG, polyethylene glycol; RCT, randomized controlled trial; TCA, tricyclic antidepressant.
[a]Limited to questions evaluable by GRADE methodology.
[b]For each population, intervention, comparator, and outcome, the study providing the highest possible level of data was used for GRADE analysis (meta-analysis, RCT > observational data).

1.4%–6.2%); the lowest prevalence was reported in IBS with constipation (IBS-C) (2.1%, 95% CI 0.9%–3.8%).

In summary, it is recommended that patients who fulfill symptom-based criteria for IBS with diarrhea symptoms be screened for CD, given available evidence supports increased odds of CD among patients with IBS symptoms; the significant potential consequences of missing the diagnosis of CD; the availability of highly effective treatment; and the apparent cost-effectiveness of an early diagnosis (22,23). The limited data from North America are recognized. Based on the available data, the greatest yield of screening would be expected in patients with IBS-D (24). The ACG clinical guideline on CD recommends serological screening with immunoglobulin A (IgA) tissue transglutaminase and a quantitative IgA level. If upper endoscopy is performed, 6 biopsies from the duodenum, including the duodenal bulb, should be obtained for histological review (15).

Recommendation

We suggest that either fecal calprotectin[1] or fecal lactoferrin[2] and C-reactive protein[1] be checked in patients without alarm features and with suspected IBS and diarrhea symptoms to rule out inflmammatory bowel disease.

[1]Strong recommendation; moderate quality of evidence (CRP, fecal calprotectin).

[2]Strong recommendation; very low quality of evidence (fecal lactoferrin).

A major shortfall in making the diagnosis of IBS is the absence of biomarkers (25). It can be difficult to distinguish IBS-D from inflammatory bowel disease (IBD); symptoms alone cannot always accurately distinguish the 2 disorders (26). The pretest probability of IBD in IBS is reported to be <0.5%–1.2% (27,28). In the absence of alarm symptoms, the prevalence of IBD in patients with IBS is low; however, after 5 years of symptoms, the incidence is 2.6–5 times higher than in controls (21,29).

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are the 2 serologic tests most commonly used to exclude IBD in patients with IBS-D, although both are nonspecific (30–32). A comprehensive meta-analysis evaluated serologic markers in 2,145 subjects identified as IBD, IBS, or healthy controls and found that an elevated ESR could not discriminate between patient groups, although a CRP ≤0.5 mg/dL yielded a 1% probability of IBD with good accuracy (33). The rapid turnaround time for CRP makes it appealing because fecal inflammatory testing is often not widely available.

Two fecal-derived markers of intestinal inflammation, fecal lactoferrin (FL) (34,35) and fecal calprotectin (fCal) (33,36–39), are both diagnostically useful and perhaps superior to serologic tests (e.g., ESR and CRP) based on their diagnostic accuracy in discriminating IBD from IBS (40–43) (see Supplemental Table 1, Supplementary Digital Content, http://links.lww.com/AJG/B755). At all cutoffs for fCal, the negative predictive value (NPV) as a screening tool is superior to CRP and ESR (38). One meta-analysis comparing fCal with endoscopy showed a sensitivity and specificity of fCal for IBD of 93% (CI 85%–97%) and 96% (79%–99%), respectively (36). FL enzyme-linked immunosorbent assay has a lower sensitivity but higher specificity for active IBD vs IBS of 67%–86% and 96%–100%, respectively, with a positive predictive value and an NPV of 92%–100% and 80%–87%, respectively (35). A meta-analysis of 7 eligible small studies in adults and pediatric patients who underwent FL testing showed a pooled accuracy of

Copyright © 2020 by The American College of Gastroenterology. Unauthorized reproduction of this article is prohibited.

Table 4. Summary of quality of evidence

Recommendation	Quality of evidence
Strong: The strength of recommendation is given as strong if most patients should receive the recommended course of action	High—the estimate of effect is unlikely to change with new data
Conditional: The strength of recommendation is given as conditional if many patients should have this recommended course of action, but different choices may be appropriate for some patients	Moderate; low; very low—estimate of effect is very uncertain

88% (standard error = 0.01), sensitivity of 78%, and specificity of 94% for differentiating IBD (active and inactive) from IBS (43). At all cutoffs for fCal, the NPV as a screening tool is superior to CRP and ESR (38). Fecal rapid tests are available for both FL and fCal. Rapid testing may be even more accurate than enzyme-linked immunosorbent assay for both fecal tests, although they are not widely available (44). Importantly, significant heterogeneity is seen between cutoff values for both FL and fCal with higher levels of FL being more predictive of IBS and thus less helpful in distinguishing between the 2 diseases as compared to fCal (33).

In summary, fCal and FL are safe, noninvasive, generally available, and can identify IBD with good accuracy (45). Of the serologic testing available, CRP has the highest utility for distinguishing IBD from IBS. Although not directly tested, the combination of CRP with fecal testing—preferably fCal—may provide even greater discrimination. Although these tests are often used clinically to rule out IBD in patients with IBS, it is important to note that neither are biomarkers for ruling in IBS.

Recommendation

We recommend against routine stool testing for enteric pathogens in all patients with IBS.

Conditional recommendation; low quality of evidence.

IBS can arise within months following a variety of GI infections, including bacterial (*Campylobacter jejuni* and *Salmonella*), viral (Norwalk), and parasitic (*Cryptosporidium* spp. or Giardia [*Giardia duodenalis* or *Giardia lamblia*]) infections with an OR of 3.51 (95% CI 2.05–6.00) (46–48). The estimated pooled prevalence of postinfection IBS is 11% (95% CI 8.2–15.8), 4.2 times higher in individuals exposed to any of these pathogens as compared to nonexposed individuals. It is worth noting that this prevalence rate seems higher than recently published data (5) because of differences in how patients were defined and categorized. Postinfection IBS is more commonly seen in women, those exposed to antibiotics, and when there is a history of anxiety or depression (49). Although bacterial and viral gastroenteritides are acute and associated with alarm symptoms, parasitic infections range from asymptomatic to self-limited to chronic symptoms of bloating, diarrhea, and abdominal pain–similar to IBS. Of patients with a parasitic cause of enteritis, 41.9% develop IBS vs 13.8% of patients who had a bacterial infection (49). Giardia infection (Giardiasis) is the most common such pathogen in the United States; there are approximately 20,000 reported cases per year, although rates have been decreasing since 2012 (5.8 per 100,000 population) (50). The relative risk of developing IBS, using Rome III criteria, after Giardiasis is 3.4 (95% CI 2.9–3.9), with several studies reporting a prevalence of any parasitic infection in IBS as low as <2% (48,51,52). Based on a longitudinal cohort study using health insurance data, the 1-year incidence of IBS is higher in persons with Giardiasis (incidence ratio = 37.7/1,000 person-years) vs those without a previous Giardia infection (4.4/1,000 person-years) (53).

Animal studies show a cause-and-effect relationship among IBS symptoms and the development of visceral hypersensitivity (demonstrated by luminal balloon distension of the jejunum and rectum), activation of nociceptive signaling pathways, increased intraepithelial lymphocytes and mast cells within the jejunum, and disruption of the intestinal barrier after Giardiasis (54). Exposure to Giardia is also associated with the development of food intolerances up to 3 years after infection (55). Giardiasis is reportable to the Centers for Disease Control and Prevention which recommends screening for patients with acute diarrhea lasting >3 days (56).

Since testing for stool ova and parasites in general is widely available and inexpensive, community gastroenterologists and primary care physicians commonly order them as compared to IBS experts, despite lack of evidence demonstrating a change in diagnosis or outcome (57). However, in patients with risk factors for Giardiasis (Table 5), testing is indicated and should be performed through fecal immunoassays or polymerase chain reaction, tests which have sensitivities of 82%–100% and

Table 5. Centers for Disease Control and Prevention listing of risk factors for development of Giardia infection

Risk factors for Giardiasis
Children in childcare settings, in particular, diaper-aged children
Close contacts of people with Giardiasis (for example, people living in the same household) or people who care for those sick with Giardiasis
People who drink water or use ice made from places where *Giardia* may live (for example, untreated or improperly treated water from lakes, streams, or wells)
Backpackers, hikers, and campers who drink unsafe water or who do not practice good hygiene (for example, proper handwashing)
People who swallow water while swimming and playing in recreational water
People exposed to human feces through sexual contact
International travelers where *Giardia* may live, especially in lakes, rivers, springs, ponds, and streams

Modified from Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Foodborne, Waterborne, and Environmental Diseases (DFWED). 2015 [Public Domain].

© 2020 by The American College of Gastroenterology

Copyright © 2020 by The American College of Gastroenterology. Unauthorized reproduction of this article is prohibited.

specificities of 91.5%–100% (40,58). Since Giardiasis has the highest prevalence in developing countries, it is reasonable to perform testing in these areas. In addition, in the appropriate clinical setting (e.g., travel to endemic areas, poor water quality, camping, and daycare exposure), testing is warranted. As testing for bacterial and viral infections with subsequent treatment does not prevent development of IBS, and in fact antibiotic exposure may be a risk factor for postinfection IBS, we do not recommend routinely testing for these agents in patients with chronic IBS symptoms (49). In summary, given a lack of clear evidence from the existing literature, we do not recommend routine testing for enteric pathogens, including Giardia, in all patients with IBS, except those with a high pretest probability and definite risk factors for Giardia exposure.

Recommendation

We recommend against routine colonoscopy in patients with IBS symptoms younger than 45 years without warning signs.

Conditional recommendation; low quality of evidence.

The high prevalence of IBS greatly influences IBS patient care. An important aspect is the health and economic burden of unnecessary testing. Colonoscopy is a common test used to confirm the absence of pathology that might be responsible for a patient's intestinal symptoms, such as IBD, microscopic colitis, or colon cancer. This test imposes a significant burden to the patient because of lost work hours, morbidity from the preparation, sedation-related effects, and direct financial costs. This impact is further heightened because many primary care providers directly request a colonoscopy before GI consultation. Colonoscopy is thus one of the most frequent and most expensive tests used during the evaluation of IBS symptoms. However, the evidence to support performing a colonoscopy in younger patients without warning signs, as described below, is poor.

First, it is important to consider key patient features in the decision to conduct a colonoscopy—these are referred to as "alarm features" and include hematochezia, melena, unintentional weight loss, older age of onset of symptoms, family history of IBD, colon cancer, or other significant GI disease. When present, there is a greater sense of concern about identifying a pathologic process that could account for the patients' symptoms (59). However, alarm features in patients with IBS have a low predictive value (60).

Second, colon cancer screening is a special consideration in patients with IBS. It is important that patients are up-to-date with colon cancer screening independent from their presenting IBS complaints. In other words, if a patient believed to have IBS presents to clinic with symptoms of IBS-D at the age of 52 years having never had a colonoscopy for colon cancer screening, the colonoscopy should be based on the age of the person and considered independent of IBS symptoms. Not uncommonly, the colonoscopy is normal. In a large US study, the rate of colon polyps was lower in patients with IBS compared with healthy controls (61). The reason for this is unclear but was independent of age.

Third, colonoscopy has been recommended in patients with IBS symptoms and without warning signs because it has been suggested that pain during colonoscopy could be an adjunct to the diagnosis of IBS (62). This stems from the theory that IBS symptoms represent visceral hyperalgesia (63), a concept supported by higher levels of reported pain in patients with IBS compared with non-IBS subjects during balloon inflation of the rectosigmoid colon (64). One study found that subjects with IBS exhibited pain during colonoscopy that replicated their IBS pain (62). This was confirmed by others (65) and led investigators to suggest that pain during colonoscopy could be an "adjunct" to the diagnosis of IBS (62,65). However, this has never been proven in large scale, and controlled trials and the presence of multiple confounders (variation in sedation protocols, quality of prep, skill of endoscopist, and use of CO_2 or not) (66) make this theory untenable.

Fourth, clinicians express concern about missing important pathology in patients with IBS symptoms. Several studies have investigated this issue. Chey et al. determined that the most common lesions identified in patients with IBS during colonoscopy were hemorrhoids, diverticulosis, and polyps (61). However, polyps were found in only 7.7% of cases in patients with IBS compared with 26.1% in non-IBS patients ($P < 0.0001$). This remained significant even after controlling for age and other factors. In a more recent study of 559 subjects who met Rome III IBS criteria, alarm features had a higher rate of discoverable disease, and yet, even among the 136 subjects with no alarm features, Crohn's disease was found in 7.4% of subjects and celiac in 2.9% (59). This second study may speak to both the poor specificity of the Rome criteria, which has a positive likelihood ratio of only 3.35 (40), and the geographic prevalence of diseases such as IBD and CD when studies are conducted in northern populations. Finally, in the largest study to date from Japan of 4,528 subjects undergoing colonoscopy, 5 colonic neoplasms were identified in the 203 Rome positive IBS subjects (67). However, all were detected in subjects older than 50 years. None were seen in the subjects with IBS younger than 49 years.

Finally, 1 common indication that is used to justify colonoscopy in a patient suspected of having IBS-D is to "rule out microscopic colitis." This may be a special case among women older than 60 years where there is a higher risk of new-onset microscopic colitis. However, there are limited data here. Making things more complicated, a recent meta-analysis identified limitations of the Rome criteria since 32.5% of patients with microscopic colitis would meet Rome criteria for IBS-D while others would meet Rome criteria for functional diarrhea (67,68).

In summary, based on current evidence, in the absence of alarm features, there seems to be no justification for routine colonoscopy in subjects with IBS younger than 45 years (although beyond the scope of this manuscript, the change in screening to age 45 is controversial, and the reader is referred to recent society guidelines and publications for a comprehensive review of this topic). In patients older than 45 years, a recent negative colonoscopy for colon cancer screening or for other investigative purposes should mitigate the need for another colonoscopy for IBS symptoms in the absence of new alarm features. In patients considered to be at high risk of microscopic colitis (older age [>60], female gender, and more intense diarrhea), there may be mounting evidence to support the use of colonoscopy.

Recommendation

We suggest a positive diagnostic strategy as compared to a diagnostic strategy of exclusion for patients with symptoms of IBS to improve time to initiate appropriate therapy.

Consensus recommendation; unable to assess using GRADE methodology.

Copyright © 2020 by The American College of Gastroenterology. Unauthorized reproduction of this article is prohibited.

The role of a careful clinical history, focused on key symptoms of abdominal pain and altered bowel habits in the absence of alarm features, and their duration (>6 months), coupled with a physical examination and minimal diagnostic testing, is sufficient to confidently diagnose a patient with IBS (1,3,4). Providers are often uncomfortable, however, with a positive diagnostic strategy or a symptom-based diagnosis of IBS. Although a validated definition does not exist, a positive diagnostic strategy involves a careful history, physical examination, and the use of a standard definition to make a diagnosis, with limited diagnostic tests.

Justification for a positive diagnosis of IBS, as compared to a diagnosis of exclusion, is based on consensus and data from existing studies (described below) which show a low diagnostic yield of additional workup in suspected IBS without alarm features, and a minimal impact on patient outcomes or satisfaction. Indeed, extensive testing is unlikely to uncover new information and, despite best intentions, does not actually reassure a patient of their IBS diagnosis. In a retrospective evaluation of nearly 500 patients with IBS aged between 18 and 49 years undergoing a "peace of mind" colonoscopy, the procedure had no impact on patient reassurance, quality of life, or psychological symptoms (69).

A systematic review and meta-analysis of more than 1,000 patients compared a range of diagnostic approaches including the symptom-based Rome III criteria to diagnose IBS and noted that the symptom-based Rome criteria performed quite modestly (69.6% sensitivity and 82.0% specificity). Minor clinical enhancements to the criteria increased its overall specificity—high somatization, no nocturnal passage of stool plus high level of somatization, hospital anxiety and depression score >8 plus normal hemoglobin and CRP. Overall, the accuracy of the Rome III criteria plus clinical and laboratory enhancements increased to 95% specificity among patients referred for endoscopy for lower GI symptoms (70).

In another study, 300 primary care patients believed by their doctors to have IBS and no alarm signs were randomized to either a diagnostic strategy of exclusion, which included invasive testing such as sigmoidoscopy with biopsies, stool cultures, and simple laboratory studies (complete blood count and CRP) or to a positive diagnostic strategy which included only a complete blood count and CRP. Regardless of randomization, none of the patients meeting Rome III criteria at baseline were reclassified at 1 year with IBD, colorectal cancer, or CD. Both diagnostic approaches performed similarly in terms of symptoms, quality of life, and patient satisfaction. A positive diagnostic strategy was determined to be noninferior to a diagnosis of exclusion (71).

Not only is a positive diagnostic strategy noninferior to a diagnosis of exclusion, it can substantially shorten time to appropriate therapy. A physician who provides a confident, positive diagnosis of IBS made with minimal investigation is more likely to reduce time to initiation of therapy by engaging patients in shared decision-making. Furthermore, if a primary care physician is able to provide a confident, positive diagnosis without referring a patient to a gastroenterologist, health care costs, and potentially time to initiation of therapy could also be reduced (72). In a large study of positively diagnosed vs undiagnosed IBS-D patients, positively diagnosed patients were much more likely to have already encountered evidence-based therapies and were more likely to have received an effective prescription medication (vs dietary modifications or over-the-counter antidiarrheal agents). Many had also received a referral for brain-gut psychotherapy (73). Although not studied, the same is likely true for the other IBS subtypes.

Finally, a positive diagnosis could lead to improved patient education and reassurance, including knowledge around the multifactorial nature of IBS, thereby increasing patient acceptance of the diagnosis and early adoption of effective therapies. Despite relatively low quality of evidence supporting the specific outcome of improved time to appropriate treatment, we recommend delaying diagnostic workup when possible and treating patients with IBS empirically, as this can often apprise health care providers to the next steps in care while minimizing unnecessary testing.

Recommendation

We recommend a positive diagnostic strategy as compared to a diagnostic strategy of exclusion for patients with symptoms of IBS to improve cost-effectiveness.

Strong recommendation; high quality of evidence.

Justification for a positive diagnosis of IBS as opposed to a diagnosis of exclusion is based on consensus and data from studies (discussed below) which show a low diagnostic yield of additional diagnostic studies in patients with IBS symptoms without alarm features and a minimal impact on patient outcomes or satisfaction. Unfortunately, in a large survey of community and academic gastroenterologists, more than 70% of community-based providers believed IBS to be a diagnosis of exclusion. These providers ordered nearly twice the number tests per patient and consumed $400 more per patient than those who used a positive diagnostic strategy. Although this difference may not initially seem significant, in a highly prevalent condition such as IBS, the cost difference is substantial (57).

In an elegant Australian language analysis study of provider notes, it was determined that providing IBS patients with a clear, confident, positive diagnosis translated into less demand for additional diagnostic workup. Use of qualifying "exclusion" language around diagnosis, such as "may be suffering from" or "it's possible that," "fits the picture of…," or "working impression is…," when compared with clear, positive diagnostic language such as "she has," "she is suffering from," "she is diagnosed with," or "I have diagnosed her with" led to more studies, endoscopies, and repeat consultations, driving up the cost of care. Similarly, patients who were diagnosed in the medical record with IBS were unaware of their diagnosis, in contrast to patients with "organic" diseases (74).

In a retrospective employer-based health care claims study of patients with IBS-D, which considered the cost of care within the first 2 years after diagnosis, nearly 80% of health care costs were associated with a diagnosis of exclusion approach, including diagnostic testing, laboratory and radiology services, hospitalizations, and emergency department visits. Only about 20% of patient costs could be related to treatment specifically, including office visits and prescription medications (75). The same was previously shown in patients with IBS-C (76). Both studies show the high costs associated with considering IBS as a diagnosis of exclusion, rather than leveraging symptom-based criteria, particularly in patients younger than 50 years without alarm features. In a large national database study of patients with IBS, colonoscopy was the most frequently conducted test with half of all patients younger than 50 years undergoing at least one (12).

High quality evidence for a positive diagnostic approach comes from a study that conducted a head-to-head, randomized comparison of a positive diagnostic strategy vs an exclusion strategy in >300 patients seen in a primary care setting (71). Patients were followed over 1 year with the primary outcome of quality of life. Not only was noninferiority of the positive strategy

© 2020 by The American College of Gastroenterology

Copyright © 2020 by The American College of Gastroenterology. Unauthorized reproduction of this article is prohibited.

demonstrated, overall health care costs were almost 40% lower in the positive diagnostic group ($5,075 vs $3,160 annually), with no differences between groups in terms of GI symptoms or patient satisfaction. There were no cases of IBD, CD, or cancer discovered through either diagnostic strategy, further underscoring the cost-effectiveness of a positive one (71).

A variety of factors may predispose certain patients to excessive diagnostic testing, as shown in a large US claims database of more than 200,000 patients with IBS in which patients who were older than 50 years, female, with multiple comorbidities, and had more office visits, emergency department visits, and hospitalizations. Patients who had 3 or more diagnostic tests/procedures comprised 40% of the overall sample, with patients with IBS-C driving the most costs (77). Similar variability in diagnostic practices is seen regionally, and across health settings and provider types, high variability is associated with unnecessary costs to the US health system (12).

In summary, a positive diagnostic strategy should be used in an effort to minimize unnecessary testing and reduce health care costs.

Recommendation

We suggest that categorizing patients based on an accurate IBS subtype improves patient therapy.

Consensus recommendation; unable to assess using GRADE methodology.

Although the primary symptom of IBS is recurrent abdominal pain, identification of the patients' predominant stool form on days in which stools are perceived to be abnormal is critical to the proper selection of diagnostic studies and treatments. Current pharmacological therapies usually target diarrhea and constipation subtypes, although IBS is characterized by 4 distinct subtypes: IBS-D, IBS-C, IBS-M, and those without a significant pattern of abnormal stool (IBS-U). More than half of patients with IBS change predominant subtype over a 1-year period; therefore, clarification of subtype should be performed routinely (78). Diarrhea-predominant IBS patients are more likely to report pain and urgency with each bowel movement, whereas constipation-predominant patients report substantially more symptoms and impaired functioning in between bowel movements; thus, treatment of abdominal pain symptoms may also differ between patient subtypes (79).

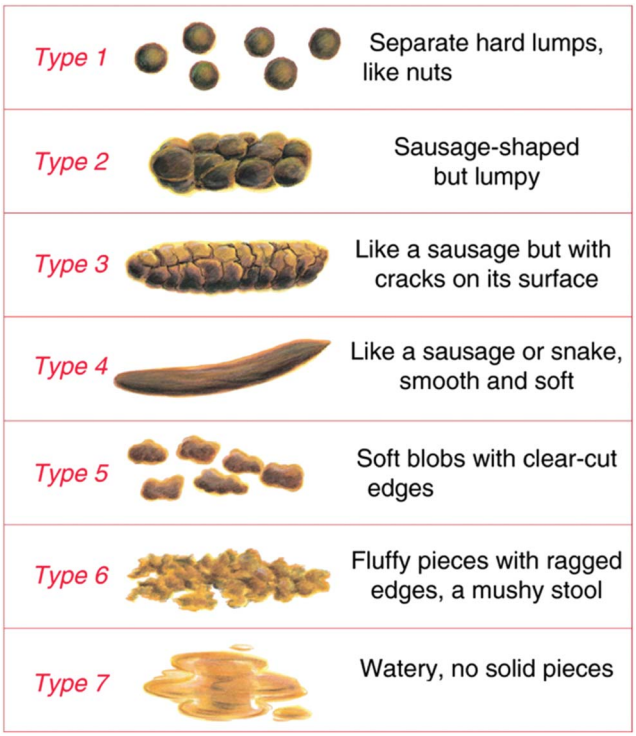

Figure 1. Bristol Stool Form Scale (English for the United States). Reprinted with permission from the Rome Foundation. ©2000 Rome Foundation. All Rights Reserved.

To accurately categorize a patient with IBS by subtype, we recommend the following:

1. Predominant stool consistency can be determined based on the Bristol Stool Form Scale (BSFS) (80) (Figure 1).
2. Determine patient's primary stool consistency only on the days s/he reports abnormal bowel movements. This determination should be made when patient is off of therapy(ies) that could affect bowel pattern. Daily diaries should be performed for 2 weeks for the most accurate assessment.
3. Once the pattern of stool consistency is determined, subtype decisions can be made according to the Rome IV criteria (4):
   a. IBS-C: >25% of bowel movements associated with BSFS 1 or 2 with BSFS 6 or 7 occurring less than 25%.
   b. IBS-D: >25% of bowel movements associated with BSFS 6 or 7 with less than 25% of bowel movements with BSFS 1 or 2.
   c. IBS-M: >25% of bowel movements associated with BSFS 1 or 2 and >25% of bowel movements associated with BSFS 6 or 7.
   d. IBS-U: cannot be determined.

In summary, most therapeutic agents used to treat IBS symptoms were developed with an emphasis on 1 specific IBS subtype; therefore, although not studied prospectively, assigning the wrong subtype to a patient could result in a treatment approach that actually worsens symptoms. Currently, there are no approved medications for the treatment of IBS-M or IBS-U; this is an important gap to be addressed in future research.

Recommendation

We do not recommend testing for food allergies and food sensitivities in all patients with IBS unless there are reproducible symptoms concerning for a food allergy.

Consensus recommendation; unable to assess using GRADE methodology.

Up to 20% of the population report adverse reactions to food (81,82). Reported symptoms are nonspecific and include abdominal pain, nausea, bloating, and diarrhea. Interestingly, when rechallenged with the offending food, only 2%–3% develop recurrent symptoms (81,83). Patients with IBS are more likely than the general population to report adverse reactions to food, with prevalence rates as high as 50% (84–86). Although the default interpretation of reactions to foods is that of an allergic reaction, this is unlikely in IBS. Food allergies are an immune-mediated event and are classified as an IgE response, a non-IgE response, or a mixed (IgE and non-IgE) response (87). Symptoms of a food allergy occur reproducibly and rapidly (usually within

Copyright © 2020 by The American College of Gastroenterology. Unauthorized reproduction of this article is prohibited.

Table 6. Clinical symptoms, rectal examination findings, and anorectal physiologic testing suggestive of a pelvic floor disorder[a]

Testing	Findings
Rectal examination findings on inspection	Dermatitis/perianal erythema Rectal prolapse Gaping anus Hemorrhoids Fistula or fissure Rectal scar Anorectal mass
Digital rectal examination findings suggesting dyssynergic defecation	Impaired sensory perception of stool (perineal sensation testing) Rectal distension and stool impaction Contraction of the diaphragm, abdomen, and rectum during push maneuvers (abdominal pressure and rectal examination must be performed simultaneously) Abnormal relaxation of external anal sphincter and puborectalis muscles (or no relaxation with Valsalva maneuver)
Anorectal physiology findings suggesting pelvic floor disorders	Uncoordinated abdominal, rectoanal, and pelvic floor muscles Rectal hyposensitivity Paradoxical increase in sphincter pressure/puborectalis muscle pressure during relaxation or simulated evacuation Prolonged balloon expulsion time Inadequate anal relaxation during push maneuvers Inadequate abdominorectal propulsive forces

[a]Many of these symptoms and examination findings are seen in all subtypes of irritable bowel syndrome and are not specific to pelvic floor dyssynergia.

minutes) on exposure to a given food and are absent during avoidance (87). For IgE-mediated food allergies, sensitization with development of specific IgE antibodies to a food allergen needs to occur (e.g., peanuts). Non-IgE food allergies are mediated by T cells, usually confined to childhood, and include food protein–induced enterocolitis syndrome and food protein–induced enterocolitis. Mixed IgE– and non-IgE–mediated food allergies include cow's milk protein allergy, eosinophilic esophagitis, and eosinophilic gastroenteritis.

Food allergies are uncommon and occur in only 1%–3% of adults (88,89). They are more likely to occur in atopic individuals, but are not more likely to occur in patients with IBS (90,91). The most common food allergies in adults, based on IgE testing (with estimated prevalence rates), are shellfish (2%), peanuts (0.6%), tree nuts (0.6%), fish (0.4%), wheat (0.4%), cow's milk (0.3%), eggs (0.2%), and sesame (0.1%) (87,92). The diagnosis of a food allergy is based on a history of a reproducible reaction to a food (e.g., itching of the palate and lips, angioedema, rhinorrhea, periorbital edema, dysphagia, laryngospasm, bronchospasm, nausea, vomiting, abdominal pain, diarrhea, urticaria, hypotension, and anaphylaxis) in conjunction with testing. A skin prick test is positive only 50% of the time in patients with true food allergies (87). Serum IgE levels correlate with the likelihood of a clinically relevant reaction to food, although levels do not correlate with the intensity of the reaction (92). The sensitivity of serum IgE levels is low; up to 25% of clinically significant reactions, including anaphylaxis, may be missed (93).

Most adverse reactions to foods represent a food intolerance or food sensitivity (81,82,86). Food intolerances are defined as an undesirable reaction to a food that is not immune mediated. These reactions may develop for a variety of reasons, including pharmacologic effects of foods (e.g., salicylates, vasoactive amines, caffeine, glutamate, serotonin, tyramine, and capsaicin), enzyme defects (e.g., lactase and sucrase-isomaltase), transport defects (e.g., fructose, glut-2, and glut-5), functional disorders (e.g., dyspepsia), or psychological factors (e.g., anorexia and orthorexia). Sensitivity to gluten is one of the most commonly reported reactions to food by patients with IBS; in many affected IBS patients, it is believed to be a nonimmunologically mediated event and possibly even an adverse reaction to the nondigestible, nonabsorbable carbohydrate, fructan (94).

Multiple tests are marketed to diagnose food intolerances; however, none have been validated, and most have not been subjected to rigorous, blinded trials. Serum IgG panels have not been validated and cannot be recommended at present (95). Results of a leukocyte activation test are intriguing but need to be confirmed (96).

In summary, the low specificity of food allergy tests means that indiscriminate testing for food allergens using a battery of tests will yield many false positives. The low prevalence of food allergies in adults, the finding that patients with IBS are not more likely to develop food allergies, and poor diagnostic test characteristics (e.g., serum IgE levels and the skin prick test), make it neither efficient nor cost-effective to test patients with IBS for food allergies.

Recommendation

We suggest that anorectal physiology testing be performed in patients with IBS and symptoms suggestive of a pelvic floor disorder and/or refractory constipation not responsive to standard medical therapy.

Consensus recommendation; unable to assess using GRADE methodology

Although the true prevalence of anorectal dysfunction in IBS is unknown, it occurs in all subtypes of IBS (IBS-D, IBS-C, and IBS-M) with prevalence rates estimated to be as high as 40% in tertiary care practices (97–100). Routine diagnostic testing with anorectal manometry (ARM) and/or balloon expulsion test (BET) is not performed in most patients because of limited availability and the absence of definitive guidelines. In symptomatic patients, a thorough rectal examination that does not identify obvious structural anorectal abnormalities increases the possibility of a pelvic floor disorder with high sensitivity (75%), specificity (87%), and NPV of 91% (101) (Table 6). See Figure 2 which illustrates normal and abnormal defecation (102).

IBS is a multifactorial disorder and symptoms alone cannot accurately distinguish IBS from dyssynergic defecation (DD) because both patient groups often have difficulty with stool evacuation and straining (97,98,103,104). The accurate diagnosis of DD requires physiologic testing with abnormalities of a defecation disorder identified in 2 of 3 tests (e.g., ARM, BET, and/or impaired evacuation by imaging) (105). A recent retrospective

© 2020 by The American College of Gastroenterology

Copyright © 2020 by The American College of Gastroenterology. Unauthorized reproduction of this article is prohibited.

Table 7. Tricyclic antidepressants

Name	Subtype	Recommended daily doses (mg)	Most common side effects
Amitriptyline: available in 10-, 25-, 50-, 75-, and 100-mg tablets	Tertiary amine	50–100	Dry mouth, urinary retention, sedation, cardiac arrhythmias, sexual dysfunction, constipation, weight gain, and blurry vision
Imipramine: available in 10-, 25-, 50-, 75-, and 100-mg tablets	Tertiary amine	50–100	Dry mouth, urinary retention, sedation, cardiac arrhythmias, sexual dysfunction, constipation, weight gain, and blurry vision
Desipramine: available in 10-, 25-, 50-, 75-, and 100-mg tablets	Secondary amine	25–100	Dry mouth, blurry vision, urinary retention, cardiac arrhythmias, weight gain, dizziness, nausea, and headache
Nortriptyline: available in 10-, 25-, 50-, and 75-mg tablets	Secondary amine	25–75	Dry mouth, blurry vision, urinary retention, cardiac arrhythmias, weight gain, dizziness, nausea, and headache

Tricyclic antidepressants should not be used in patients with known bundle branch block or Qt prolongation.
Mechanism of action of tricyclic antidepressants primarily involves inhibition of serotonin and noradrenergic receptors. Blockade of muscarinic and adrenergic receptors also occurs, but to a lesser degree.
Secondary amines generally have less antihistaminic and anticholinergic effects and are thus less likely to cause sedation or constipation.
Tertiary amines (amitriptyline and imipramine) are more likely to have antihistaminic and anticholinergic side effects.

study of female subjects with IBS-C using the 20-Item Pelvic Floor Distress Inventory showed that 44% of patients with IBS-C have prolonged BET, suggesting a DD pattern. In 1 study of 66 patients with IBS, DD was more frequent in all subgroups (41%) of IBS ($P < 0.01$) and both genders as compared to healthy controls (99). Although lower pain thresholds are observed in IBS-D and IBS-M, other manometric parameters such as paradoxical anal contraction, impaired sphincter relaxation, and symptoms of straining and incomplete evacuation do not differentiate the IBS subtypes.

In addition to DD, higher rates of obstructive defecation—painful evacuation and digital disimpaction—are seen in IBS-C (106). IBS is an independent risk factor for obstructive defecation with OR 1.78 (95% CI 1.21–2.60) and is associated with higher obstructive defecation scores ($P < 0.001$), altered pelvic mobility, and decreased perineal decent which predisposes patients to overflow diarrhea (97). As a result, patients without IBS-D with symptoms of digital disimpaction, anal pain, and longer duration of symptoms benefit most from testing with ARM and BET (98). Finally, anxiety and depression scores correlate with reduced perineal descent ($P = 0.03$ and $P = 0.01$, respectively), further highlighting the need for testing to identify possibly treatable pelvic floor disorders (98).

Perhaps, the most important reason to rule out DD in subjects with suspected pelvic floor dysfunction is the positive response of both pain and bowel symptoms to biofeedback therapy (107–109). One prospective study of biofeedback therapy in patients with DD found similar improvement in those with and without IBS ($P < 0.05$) (107). Higher rectal sensory thresholds, constipation severity scores, and delayed colonic transit pretreatment were indicators of poor treatment outcome. Abdominal pain and bloating scores were only improved in those patients with IBS with an improved defecation index and improved BET after biofeedback therapy ($P < 0.05$). Others have similarly reported that in IBS patients with DD, all domains of the Patient Assessment of Constipation Symptoms scores improved by 48% after biofeedback therapy ($P < 0.001$, all), even abdominal pain and bloating (109).

In summary, although anorectal physiology testing alone may not differentiate DD from IBS, it identifies distinct abnormalities that may respond favorably to biofeedback therapy. Given the high estimated prevalence of pelvic floor disorders in all IBS subtypes, we propose first using standard therapies for IBS targeting both abdominal pain and the predominant bowel habit. In patients with abnormal rectal examinations concerning for dyssynergia or those refractory to conventional treatments and with pelvic floor symptoms, we suggest anorectal physiology testing with ARM and BET and/or defecography to identify patients who could be treated with biofeedback therapy. The positive response seen in abdominal pain and bloating in patients with IBS to biofeedback therapy further supports this recommendation.

Recommendation

We recommend a limited trial of a low FODMAP diet in patients with IBS to improve global symptoms.

Conditional recommendation; very low quality of evidence.

The elimination of dietary fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) has quickly gained popularity as a treatment for patients with IBS (110). FODMAPs lead to increased GI water secretion and increased fermentation in the colon, thus producing short-chain fatty acids and gases which can lead to luminal distension and the triggering of meal-related symptoms in patients with IBS.

A recent meta-analysis identified 7 randomized controlled trials (RCTs), which included 397 patients with IBS, evaluating the low FODMAP diet vs several different comparators (110). Two trials in 71 patients with IBS compared the low FODMAP diet with a usual diet (111,112). Three trials including 271 patients with IBS compared a low FODMAP diet to another active diet intervention (113–115). One study compared the low FODMAP diet with a high FODMAP diet, and 1 provided IBS patients with a low FODMAP diet followed by a placebo-controlled FODMAP

Copyright © 2020 by The American College of Gastroenterology. Unauthorized reproduction of this article is prohibited.

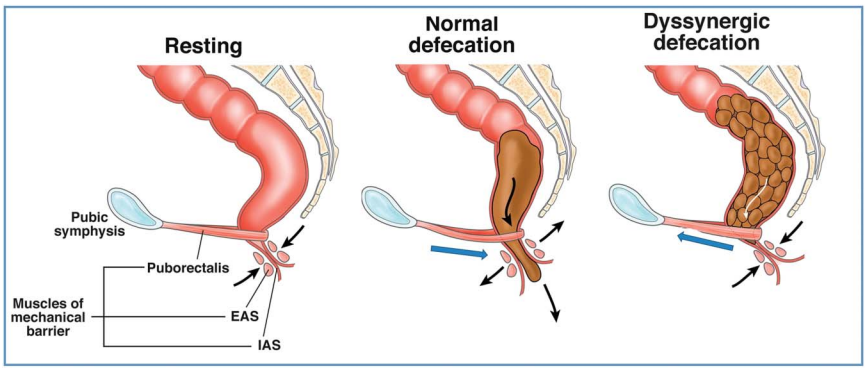

Figure 2. Pelvic floor anatomy. Adapted with permission from Advances in diagnostic assessment of fecal incontinence and dyssynergic defecation. *Clin Gastroenterol Hepatol* 2010;8:910–9. ©2010 with permission from Elsevier.

rechallenge (116,117). All published trials were deemed high risk of bias (118). The low FODMAP diet was associated with a significant reduction in global IBS symptoms compared with the different comparators (risk ratio 0.69; 95% CI 0.54–0.88, $I^2 = 25\%$; 118–120). The 3 trials that compared the low FODMAP diet with an alternative diet showed a nonsignificant trend favoring the low FODMAP diet (RR 0.82; 95% CI 0.66–1.02) (85,113,114). Interestingly, 2 studies, which compared a dietitian-led low FODMAP diet and a dietitian-led standardized dietary advice program from the United Kingdom, found nonsignificant differences in the proportions of patients reporting adequate relief of their overall IBS symptoms (119,120). That said, these trials are more difficult to interpret as they were not placebo-controlled, but rather, comparative effectiveness trials assessing 2 active interventions. Most of the trials also reported benefits of the low FODMAP diet for individual IBS symptoms, particularly abdominal pain and bloating (114). One trial failed to find a significant improvement in general quality of life while another reported a significant improvement in disease specific quality of life (113,121). Overall, the low FODMAP diet seems safe without serious adverse events (AEs), although long-term over-restriction of FODMAPs may lead to micronutrient deficiencies (119,120).

Although the current evidence is supportive, many questions about the low FODMAP diet remain unanswered. There is a need for high-quality long-term data which addresses efficacy, adherence, and harms, including any unintended effects on the gut microbiota. It is critically important for providers using the low FODMAP diet to properly instruct their patients on all 3 phases of the plan (the first stage is substitution of foods with low FODMAP choices; the second stage is a gradual reintroduction of foods into the diet while assessing symptoms; the third stage is personalization of the diet to avoid foods that trigger symptoms). Almost all the available research has focused on FODMAP restriction. However, responders to restriction of FODMAPs can be identified in 2–6 weeks. In the second phase, responders should undergo a gradual reintroduction of foods containing individual FODMAPs to determine their sensitivities. In the third phase, this information is used to personalize and liberalize the diet for extended use.

In summary, this guideline committee believes that the complexity of the low FODMAP diet, combined with the potential for nutritional deficiencies, and the time and resources required to provide proper counseling on the 3 phases of the plan, requires the services of a properly trained GI dietician. This, however, is not evidence-based but certainly warrants future study. If a trained GI dietician is not available or if a patient cannot afford to see a dietician, it is important for providers to distribute high-quality teaching materials which can allow an IBS patient to implement the diet in a medically responsible manner.

Recommendation

We suggest that soluble, but not insoluble, fiber be used to treat global IBS symptoms.

Strong recommendation; moderate quality of evidence.

A widely accepted definition describes dietary fiber as all carbohydrates that are neither digested nor absorbed in the small intestine and have a degree of polymerization of 3 or more monomeric units (122). Fiber offers a range of general health benefits, and for this reason, most experts recommend 25–35 g of total fiber intake per day (123).

Dietary fiber has diverse and incompletely understood effects in the GI tract involving the gut microbiome, metabolism, transit time, stool consistency, and bile acid absorption. Dietary fiber is frequently recommended to improve symptoms in patients with IBS, particularly when constipation is the predominant complaint. In general, different types of fiber can be distinguished on the basis of their solubility, viscosity, and ability to resist fermentation in the colon. Soluble fiber is found in psyllium, oat bran, barley, and beans. Insoluble fiber is found in wheat bran, whole grains, and some vegetables. Fibers that exert laxative effects tend to increase stool water content and resist colonic fermentation. Conversely, fibers that ferment in the colon will lose their water-holding capacity and produce gas that could aggravate symptoms of bloating and flatulence.

A recent systematic review and meta-analysis on fiber in IBS (124) identified 15 RCTs (125–139) involving 946 patients. Six trials provided information regarding IBS subtypes (133,135–139), of which 2 trials recruited only patients with IBS-C (135,136). Most trials used a "clinical diagnosis" of IBS or symptom-based criteria supplemented by negative investigations to identify study participants. Study endpoints were highly variable and did not adhere to modern regulatory guidance. Fiber led to a statistically significant benefit for IBS symptoms compared with placebo (RR of IBS not improving = 0.87; 95% CI 0.80–0.94). There was no significant heterogeneity ($I^2 = 0\%$) or funnel plot asymmetry (Egger test = −0.20 (95% CI −1.14 to 0.74, $P = 0.66$), suggesting no evidence of publication bias. Six studies including 411 patients with IBS evaluated the insoluble, nonviscous, poorly fermentable fiber, bran (125,126,131,132,136,137), 7 studies

Copyright © 2020 by The American College of Gastroenterology. Unauthorized reproduction of this article is prohibited.

including 499 patients evaluated the soluble, viscous, poorly fermentable fiber, ispaghula husk (127–130,133,134,137), and 3 studies evaluated "concentrated fiber" (135), linseeds (138), or rice bran (139). Bran provided no significant benefit for IBS symptoms (RR of IBS not improving = 0.90; 95% CI 0.79–1.03), while ispaghula did benefit IBS symptoms (RR of IBS not improving = 0.83; 95% CI 0.73–0.94, number needed to treat [NNT] 7 [95% CI 4–25]).

AE data were provided by 7 trials (130,131,133,135,137–139). Thirty-six percent of 355 patients receiving fiber reported an AE, compared with 25.1% of 251 receiving placebo (RR 1.06; 95% CI 0.92–1.22). Data were insufficient to assess AEs according to type of fiber.

In summary, soluble, viscous, poorly fermentable fiber may provide benefits in IBS. The apparent lack of significant side effects makes fiber a reasonable first line therapy for IBS patients with symptoms. The ability to improve stool viscosity and frequency logically argues for the use of fiber in patients with IBS-C, although the evidence base to support this contention is weak.

Recommendation

We recommend against the use of antispasmodics currently available in the United States to treat global IBS symptoms.

Conditional recommendation; low quality of evidence.

Antispasmodics remain one of the most frequently used treatments for IBS. Assessing their efficacy on global IBS symptoms is difficult because the class includes multiple agents with different mechanisms of action. Broadly, antispasmodics relax intestinal smooth muscle thereby reducing GI motility (140). A myriad of different formulations are available, including direct smooth muscle relaxants, calcium antagonists, scopolamine derivatives, and combination agents. Historical recommendations supporting antispasmodics for treating global IBS symptoms have been predicated on systematic reviews and meta-analyses inclusive of all agents (141). However, in an era of precision medicine, it is important to evaluate and recommend therapies based on individual, rather than group, analyses. For this guideline, we have focused on medications approved for use in the United States, conceding there are more robust data supporting the use of alternative antispasmodics available internationally. Three antispasmodics are commercially accessible—dicyclomine, hyoscyamine, and hyoscine—with a paucity of data supporting their efficacy.

Dicyclomine has been assessed in 2 small, older trials (142,143). One double-blinded study randomized patients (n = 97) to 40 mg of dicyclomine (2–4 times' standard dosing) or placebo 2–4 times daily for 2 weeks. Neither a standard definition of IBS nor a single primary endpoint was established. Overall, 84% of individuals receiving dicyclomine reported symptom improvement compared with 54% of those taking placebo (P = 0.006). Sixty-nine percent and 16% of dicyclomine and placebo-treated patients, respectively, reported adverse effects (142). A second study enrolled 96 patients; a standardized definition of IBS was not included. Individuals received 20 mg of dicyclomine or placebo 3 times daily for 10 days with subsequent crossover without a washout period, which increases the likelihood of a carryover effect. Dicyclomine was associated with subjective improvements compared with placebo. No statistical analyses were undertaken. Thirty-three percent of dicyclomine and 4% of placebo-treated patients developed side effects during the 10-day treatment period (143).

Hyoscyamine, available in multiple formulations (short or long acting, oral or sublingual), was assessed in a single clinical study from Sweden performed more than 3 decades ago (144). In this trial, 25 individuals were randomized to 0.2 mg of hyoscyamine or placebo for 2 weeks. The definition of IBS was not standardized. Hyoscyamine responses were comparable with placebo; however, AE rates were significantly higher (87% vs 7%, respectively, $P < 0.001$).

Hyoscine (scopolamine), primarily used for motion sickness, has been evaluated in 3 IBS trials, all performed outside the United States. The first 2 had similar trial designs (127,130). Neither used a standard definition for IBS. One study combined hyoscine, lorazepam, soluble fiber (ispaghula husk), and placebo in 8 permutable blocks with 12 subjects per block (127). Hyoscine fared no better than placebo over a 12-week period. The second combined hyoscine, amitriptyline with chlordiazepoxide, ispaghula, and placebo in 8 randomized blocks of 21 patients (130). At 12 weeks, individuals receiving only active hyoscine fared significantly better than those receiving placebo ($P < 0.02$). However, these findings must be interpreted with caution because none of the patients in the placebo group experienced improvement at this time point. The most recent analysis, completed 30 years ago, randomized 712 individuals to hyoscine, hyoscine plus paracetamol, paracetamol alone, or placebo for 4 weeks (145). A "response" was achieved by 76% and 64% of individuals receiving hyoscine and placebo, respectively ($P < 0.05$). Interestingly, the difference in response between hyoscine and paracetamol was only 4%. The most common AEs were dry mouth and blurred vision.

In summary, there are limited data supporting the use of antispasmodics available in the United States. The data are decades-old and of poor quality. Published studies are methodologically limited because of small sample size, lack of standardized enrollment criteria, different trial designs, and different endpoints. Side effects are common, particularly in the elderly, although anecdotal data suggest that these agents are relatively safe.

Recommendation

We suggest the use of peppermint to provide relief of global IBS symptoms.

Conditional recommendation; low quality of evidence.

Peppermint (*Mentha piperita*) is a popular natural/herbal remedy for IBS. Although the clinical benefits of peppermint oil for patients with IBS have most often been attributed to L-menthol's blockade of calcium channels and attendant smooth muscle relaxation, several other potential explanations are worthy of consideration including modulation of transient receptor potential voltage channels with effects on visceral sensation, direct antimicrobial and anti-inflammatory effects, and modulation of psychosocial distress. Translational studies have found that peppermint oil exerts effects on esophageal, gastric, small bowel, gallbladder, and colonic function (146).

The most recent meta-analysis evaluating the efficacy of peppermint oil or placebo for IBS identified 12 RCTs including 835 patients (147). Studies came from Asia, Europe, and North America. All were relatively small (n = 18–178 patients with IBS) and of short duration (2–12 weeks). The included studies did not allow for a meaningful analysis by the IBS subgroup (e.g., IBS-D, IBS-C, and IBS-M). All the included studies evaluated continuous

Copyright © 2020 by The American College of Gastroenterology. Unauthorized reproduction of this article is prohibited.

dosing regimens. None of the studies evaluated the impact of peppermint oil used on an as needed basis. For overall IBS symptom improvement, the RR from 7 RCTs for peppermint oil (n = 253) vs placebo (n = 254) was 2.39 (95% CI 1.93–2.97; $P < 0.00001$). For abdominal pain, 6 RCTs yielded an RR of 1.78 (95% CI 1.43–2.20; $P < 0.00001$) favoring peppermint oil vs placebo. The NNT to prevent 1 patient from having persistent symptoms with peppermint oil was 3 for overall IBS symptoms and 4 for abdominal pain. A recently published randomized controlled trial which was not included in this meta-analysis is worthy of mention (148). One hundred ninety patients with IBS (Rome IV) from the Netherlands were randomized to 182 mg of peppermint oil released in the small bowel, 182 mg released in the ileocolonic region, or placebo for 8 weeks. There was no difference in the primary endpoint of proportion with a >30% reduction in weekly average of worst daily pain scores compared with baseline between groups at week 4 (small bowel release 46.8% [$P = 0.170$], ileocolonic release 41.3% [$P = 0.385$], and placebo 34.4%). However, compared with placebo, small bowel release peppermint oil led to significant improvements in secondary outcomes including abdominal pain score ($P = 0.016$), discomfort ($P = 0.020$), and IBS severity ($P = 0.020$).

In 8 RCTs, AEs were similar between peppermint oil and placebo (9.3% vs 6.1%, respectively; RR 1.40; 95% CI 0.87–2.26; $P = 0.16$) (147). Despite these encouraging AE results, peppermint oil's effects on esophageal and lower esophageal sphincter function can lead to the development of heartburn in some treated patients (149). Enteric-coated formulations of peppermint oil may offer benefits in this regard.

In summary, peppermint oil may offer benefit for overall symptoms and abdominal pain in patients with IBS. For the most part, peppermint oil has been well-tolerated in the available trials. That said, only a small number of commercially available peppermint oil supplements have undergone rigorous testing of efficacy and safety (150). Further large, methodologically rigorous trials to determine the optimal formulation, relative benefits in different IBS subgroups, and comparative effectiveness are encouraged.

Recommendation

We suggest against probiotics for the treatment of global IBS symptoms.

Conditional recommendation; very low level of evidence.

The use of probiotics as a potential treatment of IBS has increased in the past decade. Much of the enthusiasm is based on the growing literature supporting a role of the microbiome in this condition. However, assessing the merits of probiotics in the treatment of IBS is challenging for a number of reasons. For one, there are a myriad of probiotics each of which claim specific advantages over others. Furthermore, studies examining probiotics in IBS have included single or multiorganism cocktails and nearly universally these studies are small, single center, and do not follow the rigorous endpoint standards set out by the US FDA for the approval of pharmacologic therapies.

A recent meta-analysis summarized the effect of probiotics in the treatment of IBS (151). Thirty-seven trials were eligible for analysis (21 involved probiotic combinations) totaling 4,403 subjects (16–391 subjects per study). Combination probiotics demonstrated a significant pooled effect (RR 0.79, CI 0.68–0.91) for symptom improvement, but there was evidence of significant heterogeneity ($I^2 = 72\%$) and publication bias by the Egger test. The combination group also benefitted from a larger number of studies to pool.

Single species studies were less impactful in the treatment of IBS in this meta-analysis (151). Each of *Lactobacillus* spp., *Bifidobacterium* spp., and *Saccharomyces* spp. did not seem to have a significant pooled benefit. *Escherichia* spp. and *Streptococcus* spp. demonstrated significant benefit in pooled analysis (CI 0.79–0.93 and 0.53–0.99, respectively), but they were based on only 2 studies for *Escherichia* spp. and 1 for *Streptococcus faecium*, with the latter containing only 39 subjects for analysis.

The meta-analysis further examined the pooled effect on individual symptoms of IBS. A similar pattern was seen whereby combination probiotics seemed to have a modest effect on abdominal pain. However, in the case of bloating, no category of probiotic demonstrated benefits in pooled analysis. This is interesting because one of the largest blinded probiotic studies (although not an IBS trial) demonstrated that a probiotic containing *Lactobacillus acidophilus* and *Bifidobacterium bifidis* produced bloating in the treatment group (152).

Several large studies in patients with IBS reported benefits from specific strains of probiotics. For example, in 1 study, more than 300 subjects were randomized to 1 of 3 doses of *Bifidobacterium infantis* 35,624 (10^6, 10^8, and 10^{10} cfu/mL) or placebo (153). Symptom improvement was reported in the group receiving 10^8 cfu/mL, but not the other 2 groups. This finding was confusing because the lack of dose response was challenging to explain.

A study by Spiller et al., which examined *Saccharomyces cerevisiae* I-3856, was important given the study's large sample size and a rigorous outcome measure of >50% of weeks with improvement, which approximates US FDA recommended outcome measures (154). At the conclusion of the trial, 32.2% of subjects receiving *S. cerevisiae* and 26.9% of placebo-treated subjects were considered responders, although this was not statistically significant ($P > 0.05$). There was no difference in abdominal pain between the 2 groups.

In summary, the use of probiotics in the treatment of IBS is an important area of research, given the importance of the intestinal microbiome in this condition. However, interpreting the existing literature is problematic because of small studies, the multiple types and strains of probiotics, the inconsistent benefits on individual symptoms, and the lack of rigorous trials based on US FDA endpoints. These challenges make meta-analysis difficult to perform and hard to interpret. Future trials incorporating yet unidentified gut microbiome biomarkers or metabolomic markers may improve probiotic efficacy.

Recommendation

We suggest against the use of PEG products to relieve global IBS symptoms in those with IBS-C.

Conditional recommendation; low quality of evidence

Polyethylene glycol (PEG) is a relatively inexpensive, widely available, nonprescription osmotic laxative that is US FDA-approved for occasional constipation based on several RCT studies (155,156). Four trials in chronic idiopathic constipation (N = 573) have yielded an NNT of 3 for PEG (95% CI 2–4) for improvement in stool frequency and stool consistency (3). However, its efficacy for IBS-C has not been supported because RCTs have failed to show that PEG improves either overall symptoms or pain in patients with IBS-C (3,141,157,158).

© 2020 by The American College of Gastroenterology

Copyright © 2020 by The American College of Gastroenterology. Unauthorized reproduction of this article is prohibited.

Two RCTs have evaluated the benefits of PEG in patients with IBS-C with noted heterogeneity in trial design and endpoints (157,158). In the first study, a small RCT (n = 42) of patients with IBS-C treated with PEG (3.45 g t.i.d.) vs placebo underwent rectal barostat testing to measure rectal sensitivity and preprandial and postprandial rectoanal tone as the primary endpoint (157). Neither rectal tone nor rectal sensitivity thresholds such as urge to defecate, or pain, were improved by PEG, although PEG improved stool consistency ($P = 0.047$). The largest (n = 139) multicenter, RCT of PEG in IBS-C failed to include abdominal pain as a component of their primary endpoint using instead mean number of spontaneous bowel movements (SBMs) in the last 7 days of the trial. Varying doses of PEG (13.8–41.1 g) were allowed; bisacodyl (5–10 mg) could be used as a rescue medication (158). A secondary endpoint of the study was abdominal pain. A responder was defined as a 10% reduction in abdominal discomfort/pain compared with run-in mean values (which is a much lower threshold compared with the 30% endpoint set by the US FDA). Although the mean weekly number of SBMs improved significantly compared with placebo ($P < 0.0001$), the secondary endpoint of abdominal pain was not met because both groups reported improvement in pain frequency (61.9% in PEG vs 47.6% in the placebo group), with no significant difference between the groups. *Post hoc* analyses based on the full responder definition (>3 SBM per week, an increase of ≥1 SBM per week, and >30% reduction in pain) showed an improvement in 33.3% vs 21%, respectively ($P > 0.01$). Finally, a small unblinded study of PEG in adolescent IBS-C patients meeting ROME II criteria for IBS confirmed improvements in bowel symptoms but not abdominal pain (159).

Treatment-related AEs were more frequent in patients treated with PEG compared with placebo (16.4% vs 8.6%, respectively) (157). The most commonly reported side effects were abdominal pain (4.5%), diarrhea (4.5%), nausea, and flatulence; these occurred in a dose-dependent manner (155,158,160). The long-term safety of PEG up to 6 months has been demonstrated in elderly patients (>70 years of age) with chronic constipation without nutritional deficiencies or biochemical abnormalities being identified (161).

In summary, despite the long-term safety and efficacy of PEG for the treatment of chronic constipation in even the most vulnerable subjects (elderly and children), there is no evidence that PEG alleviates abdominal pain and thus global symptoms in patients with IBS-C. We therefore recommend against use of PEG alone for the treatment of global IBS-C symptoms, although we recognize that clinicians may use PEG as first-line treatment of constipation in IBS, given its low cost and availability.

Recommendation

We recommend the use of chloride channel activators to treat global IBS-C symptoms.

Strong recommendation; moderate quality of evidence.

Lubiprostone is a locally acting prostaglandin E1 analog with high affinity for type-2 chloride channels located in the apical membranes of intestinal epithelial cells (162). Activation of these receptors increases intestinal secretion and peristalsis (162). Lubiprostone is classified as a secretagogue. Animal studies have suggested that lubiprostone may restore barrier function in individuals with increased intestinal permeability (163,164). Lubiprostone is US FDA-approved for the treatment of adult women with IBS-C at a dosage of 8 μg twice daily (165).

Lubiprostone has been evaluated in 3 RCTs and a high-quality systematic review/meta-analysis (3,166,167). In the latter, lubiprostone was found to be more effective than placebo for overall IBS-C symptoms with a relative risk of symptom persistence of 0.91 (95% CI 0.87–0.95) and an NNT of 12.5. The most robust data imputed into that analysis originated from 2 identically designed phase III studies involving 1,171 patients meeting Rome II criteria for IBS-C who were randomized to receive 8 μg of lubiprostone or placebo twice daily with meals for 12 weeks. The primary endpoint—a rigorous overall responder analysis—was achieved by 17.9% of individuals receiving lubiprostone compared with 10.1% for those who received placebo ($P = 0.0001$). Separation between groups did not reach statistical significance until month 2 but was maintained throughout month 3. A subsequent open-label extension with 476 of the original participants was performed for an additional 36 weeks (168). Using the same responder definition, response rates to lubiprostone were maintained or increased over time. Secondary analyses within these phase III studies also identified significant improvements in abdominal pain/discomfort, bloating, straining, stool frequency, and consistency. Monthly analyses detected variability in statistical significance for each symptom over the 3-month trial period, with exception of improvements in stool consistency. Similar findings were also identified during the open-label extension period (167,168). Based on a 2012 updated guidance document redefining global responder status in IBS-C studies, a *post hoc* analysis of 515 of the original phase III trial participants was performed, and a significantly greater percentage of individuals who received lubiprostone achieved this new endpoint (23.8% vs 12.6%, respectively, $P = 0.012$) (169).

In regard to safety and tolerability, diarrhea (6%–14%) and nausea (8%–19%) were the most frequently reported events (11% for both AEs). In a recent analysis of nausea across all IBS-C studies, the overall incidence rate of treatment-emergent nausea in RCTs was significantly greater in patients receiving lubiprostone than placebo (10.9% vs 6.4%, respectively; $P < 0.01$). Nausea rated as moderately severe was more likely to occur in lubiprostone-treated individuals ($P < 0.05$). Overall discontinuation rates were low (1.2%) and comparable with placebo (0.7%). Aggregation of long-term open-label data yielded similar results (170). Anecdotal experience has shown that nausea may be mitigated by the concurrent consumption of food.

In summary, 8 μg of lubiprostone twice daily seems effective for relieving global and individual symptoms in patients with IBS-C. Although there may be a delay in initial response, improvement in global symptoms is maintained or increases over time. Lubiprostone exhibits an appropriate safety profile with the most common AEs being GI in nature. Nausea is dose-dependent, but may be reduced by consuming lubiprostone with meals.

Recommendation

We recommend the use of guanylate cyclase activators to treat global IBS-C symptoms.

Strong recommendation; high quality of evidence.

Guanylate cyclase-C (GC-C) agonists target GC-C receptors residing in the apical membranes of intestinal epithelial cells.

Copyright © 2020 by The American College of Gastroenterology. Unauthorized reproduction of this article is prohibited.

There are currently 2 US FDA-approved agents for the treatment of IBS-C—linaclotide 290 μg and plecanatide 3 mg. Both activate GC-C receptors, increasing intestinal fluid secretion and peristalsis, with preclinical trials identifying reduced activation of visceral nociceptive neurons (171,172). These agents are classified as secretagogues. These effects explain the global improvements experienced with linaclotide or plecanatide. Recent comparative analyses suggest that both are comparably effective, safe, and well-tolerated (173).

Linaclotide has been studied in 3 North American phase IIb/III trials and evaluated in several systematic reviews/meta-analyses (173–177). Individually, each trial has demonstrated that linaclotide is more effective than placebo for improving overall IBS symptoms. Using current IBS-C US FDA guidance endpoints (178), meta-analyses yield relative risks of symptom persistence in individuals consuming 290 μg of linaclotide once daily compared with placebo of 0.80 (95% CI 0.76–0.85; NNT = 6) (3,177) and an OR of response of 2.43 (95% CI 1.48–3.98; NNT = 6) (173). Overall, 34% of 802 enrollees in 2 phase III North American studies receiving 290 μg of linaclotide met the US FDA endpoint (175–178). Significant separation from placebo occurred by the end of week 1 in both trials and was maintained throughout the double-blinded periods (175,176). Noteworthy is the fact that 1 phase III study was performed for 6 months, which is uncommon in IBS studies (175). After 12 weeks of therapy, approximately two-thirds of the 802 individuals receiving linaclotide endorsed at least some subjective improvement in abdominal pain, stool frequency, and global IBS symptoms (179). Furthermore, significant improvements were noted across a spectrum of predefined primary and secondary abdominal and stool endpoints as well as overall adequate relief of symptoms ($P < 0.03$ compared with placebo across all endpoints) (176). Overall, both studies met predefined primary endpoints and all secondary endpoints.

The safety and efficacy of plecanatide has been evaluated in 3 individual phase IIb/III studies (180,181) and 1 subsequent systematic review/meta-analysis (173). The 3-mg plecanatide daily dose achieved a relative risk of symptom persistence of 0.88 (95% CI 0.82–0.94; NNT = 10) (141) and an OR of response to treatment of 1.87 (95% CI 1.47–2.38; NNT = 9) compared with placebo using the US FDA responder endpoint (173). Overall, approximately 26% of 728 individuals randomized across phase III trials met this endpoint, and similar to linaclotide, improvements were identified across a spectrum of individual symptoms. Significant separation from placebo was observed by the end of the first treatment week and maintained throughout the 12-week blinded trial periods. Overall treatment satisfaction was also significantly improved at the completion of both studies ($P < 0.001$) (181).

The most common treatment-emergent AE, diarrhea, was experienced by approximately 20% of individuals receiving linaclotide compared with 3% receiving placebo ($P < 0.0001$). Severe diarrhea was recorded in 2% of this population, and 5% of individuals in this cohort withdrew from the trials because this AE (175,176). Diarrhea, severe diarrhea, and withdrawal due to diarrhea were reported by 4.3%, 0%, and 1.2% of individuals, respectively, in the plecanatide studies with no significant differences identified between the placebo and plecanatide cohorts (181). Recent ORs for the development of diarrhea have been calculated for both GC-C agonists, and although each exhibited increased odds compared with placebo (linaclotide 290 μg OR 8.02 95% CI 5.20–12.37; plecanatide 3 mg OR 5.55 95% CI 1.62–19.00), there were no significant differences noted between the two (173). Both exhibit high tolerability profiles presumably related to their underlying mechanism of action.

In summary, once-daily linaclotide (290 μg) and plecanatide (3 mg) seem effective for relieving overall and individual symptoms of IBS-C. Responses develop quickly and are maintained over time. Diarrhea is the most common AE experienced, but discontinuation rates due to diarrhea are low and both are well-tolerated.

Recommendation

We suggest that the 5-HT_4 agonist tegaserod be used to treat IBS-C symptoms in women younger than 65 years with ≤1 cardiovascular risk factors who have not adequately responded to secretagogues.

Conditional recommendation; low quality of evidence.

Serotonin (5-HT) is a vital neurotransmitter that modulates GI motor and sensory function. Stimulation of the serotonin type-4 receptor (5-HT_4) initiates the peristaltic reflex and accelerates GI transit (182,183). Reductions in visceral hypersensitivity have been identified in animal models, healthy volunteers (184–186), and individuals with IBS (187).

Eleven randomized, placebo-controlled trials have evaluated the efficacy of tegaserod for IBS-C; 2 of the 3 pivotal studies that led to US FDA approval are reviewed here. The first was a multinational, double-blind, placebo-controlled 12-week trial, during which 881 patients (Rome I criteria, 83% female) were treated with either tegaserod (2 or 6 mg b.i.d.) or placebo (188). The primary endpoint, a subject global assessment of relief (SGA), was met by 46.4% and 50% of patients receiving 2 and 6 mg b.i.d. of tegaserod, respectively, compared with 36.6% of those receiving placebo ($P < 0.05$). At 12 weeks, patients randomized to the 6 mg, but not the 2 mg, dose were more likely to report an improvement in individual symptoms of pain or discomfort. Stool consistency and stool frequency also improved.

A second large (all female, Rome I criteria) multinational trial compared tegaserod (6 mg b.i.d.) with placebo over 12 weeks (189). The SGA primary endpoint was met by 43.5% of tegaserod, compared with 38.8%, of placebo-treated patients ($P < 0.033$). Improvements in secondary endpoints, including abdominal pain ($P < 0.003$), stool consistency ($P < 0.0001$), stool frequency ($P < 0.05$), and bloating ($P < 0.05$), were also more likely to be achieved by patients randomized to tegaserod.

A systematic review and meta-analysis of these 11 trials was performed by Ford et al. (190). In brief, 9,242 patients with IBS were evaluated; the Rome I criteria were used in 6 trials, while 5 used Rome II criteria. Nine trials used the currently approved dose of tegaserod, 6 mg b.i.d. Overall, patients treated with tegaserod were less likely to have persistent IBS-C symptoms compared with those treated with placebo (RR 0.85; 95% CI 0.80–0.90). A recent meta-analysis updated this analysis in the context of therapies for IBS-C (191).

In clinical trials, the most common AE was diarrhea, occurring in 6% of patients treated with tegaserod compared with 2% for those treated with placebo (190). In terms of serious AEs, it was approved for the treatment of IBS-C in women in 2002, but voluntarily withdrawn from the market 5 years later because of concerns over a small excess of cardiovascular (CV) events. Two separate external adjudications of a large clinical trial database of patients with IBS, chronic constipation, and dyspepsia were

© 2020 by The American College of Gastroenterology

Copyright © 2020 by The American College of Gastroenterology. Unauthorized reproduction of this article is prohibited.

recently performed to identify and evaluate potential CV events. Ischemic events were categorized as cardiac, vascular, or cerebrovascular in nature (manuscript submitted). Approximately 18,645 patients were evaluated; 11,614 received tegaserod, and 7,031 received placebo. In the first adjudication, 13 (0.11%) patients in the tegaserod group and 1 (0.01%) patient in the placebo group had confirmed CV ischemic events. All 14 patients had at least 1 CV risk factor, and 11 had a minimum of 2 risk factors. There were 7 (0.06%) major CV events (MACEs); 4 in women younger than 65 years and 1 in a man older than 65 years. In the second adjudication, there were 7 (0.06%) confirmed CV ischemic events ($P = 0.3$) and 4 (0.03%) MACE ($P = 0.3$) in the tegaserod group vs none in the placebo group. In women younger than 65 years without a history of CV ischemic disease and ≤1 CV risk factor, only 1 (0.01%) CV ischemic event and no MACE were reported in the tegaserod group vs none in the placebo group. Additional analyses found no evidence of increased proarrhythmic risk or platelet aggregation within these studies. In 2019, based on this evaluation, tegaserod was approved again for treatment of IBS-C.

In summary, tegaserod is the only US FDA-approved 5-HT_4 receptor agonist for the treatment of adult women younger than 65 years with IBS-C. It is contraindicated in patients with more than 1 CV risk factors (see Supplemental Table 2, Supplementary Digital Content, http://links.lww.com/AJG/B755). Future studies should include large, prospective, head-to-head comparisons with other US FDA-approved therapies to provide clinically important information on efficacy and safety.

Recommendation

We do not suggest the use of bile acid sequestrants to treat global IBS-D symptoms.

Conditional recommendation; very low level of evidence.

Bile acid malabsorption (BAM) is a condition characterized by an inability to reabsorb sufficient bile acids in the terminal ileum. Excessive bile acids in the colon are exposed to colonic flora leading to production of secondary bile acids which can increase colonic secretion of fluid, thereby resulting in diarrhea. This has led to investigations into the possibility of bile acid diarrhea contributing to symptoms in a subset of individuals with IBS-D.

There are 3 potential mechanisms for bile acids to reach the colon (192). The first is the iatrogenic loss of the distal small bowel reducing the absorbing capacity of bile excreted by the biliary system during digestion. Another mechanism is cholecystectomy leading to a change in timing of bile delivery to the small intestine. This may be an important cause of worsening of IBS symptoms because there is an increased risk of cholecystectomy in patients with IBS (OR 2.09, CI 1.89–2.31) (193). Finally, an idiopathic form possibly related to the differential potential for reabsorption of bile acids in given individuals has been identified.

Testing for BAM is challenging. The most common test is the SeHCAT test. This test is available in some European countries. A recent meta-analysis has examined the prevalence of BAM in subjects with IBS-D (194). Based on pooled data from 6 studies using SeHCAT testing, 28.1% (CI 22.6%–34%) of patients with IBS-D met the predefined threshold for BAM on SeHCAT in the random effects model. However, there was significant heterogeneity ($I^2 = 72.1\%$). Recent studies have suggested stool testing may be effective as well. Data from newer stool studies measuring bile acids were predictive of higher stool wet weight in a study comparing healthy subjects with those with IBS-D and IBS-C (195). In addition, 2 serum markers may help identify BAM subjects as well. Serum testing supports that a low fibroblast growth factor 19 (FGF-19) and high C4 may be suggestive of BAM (196). Serum C4 also seems higher in IBS-D compared with IBS-C and healthy subjects with correlations to stool bile acids as well (197). Serum C4 testing is now available at some institutions.

Based on these findings, bile acid sequestrants have been suggested as a treatment for IBS-D. One open-label study examined the presence of BAM (through SeHCAT, FGF-19, and C4), and responses to treatment with colestipol in a cohort of individuals with IBS-D (198). In this open-label study, 27 subjects with IBS-D noted a significant improvement in IBS severity scores and 15/27 (55.5%) were considered responders based on study definitions. In a recent single-center trial, open-label colesevelam, at a dose of 1,875 mg daily, increased bile acid retrieval from the stool with a modest reduction in the Bristol Stool Score ($P = 0.043$) among the 12 subjects treated (199).

In summary, there seems to be a subset of IBS-D subjects with evidence of BAM. There is a need for methodologically rigorous, adequately powered trials of bile acid sequestrants in patients with IBS-D. Testing for BAM in the United States remains limited and incompletely validated. No study has evaluated the utility of testing and compared it with empiric therapy using a bile acid sequestrant, which is a reasonable course of action if BAM is suspected. In the absence of widely accessible, reliable testing, and given the lack of controlled trials of bile acid sequestrants in patients with IBS-D, the use of these therapies should be at the discretion of the clinician.

Recommendation

We recommend the use of rifaximin to treat global IBS-D symptoms.

Strong recommendation; moderate level of evidence.

Rifaximin is a nonabsorbed antibiotic which is US FDA-approved for the treatment of patients with IBS-D. Rifaximin treatment is based on the hypothesis that a portion of patients with IBS-D have an abnormal microbiome. The use of this drug is supported by multiple clinical trials.

In 2 identically designed, large-scale double-blind studies, rifaximin resulted in a significant benefit over placebo using an interim US FDA endpoint. In the month after a short (2-week) course of rifaximin, 40.8% of subjects had an improvement in both abdominal pain and stool consistency compared with 31.7% with placebo ($P < 0.001$) when both trial results were pooled in the follow-up month (200).

In a third trial, the efficacy of rifaximin retreatment was assessed (201). In this trial, all subjects initially received open-label rifaximin. After this initial treatment, 44% of subjects responded to rifaximin. Subjects were then followed for 18 weeks to assess for symptom relapse. Of the initial responders to rifaximin, 36% did not relapse. The remaining 64% eventually relapsed and were then randomized to receive rifaximin or placebo for 2 weeks. After retreatment, rifaximin was superior to placebo at improving IBS-D symptoms. This study supported approval for rifaximin for treatment with up to 2 additional treatments for symptom recurrence (201).

Copyright © 2020 by The American College of Gastroenterology. Unauthorized reproduction of this article is prohibited.

Results from other studies support the efficacy and safety of rifaximin. A recent meta-analysis summarized 5 controlled trials using rifaximin in patients with IBS-D (151). These demonstrate a significant benefit of rifaximin over placebo with an NNT of 9. In another summary of IBS treatments, rifaximin had the most favorable safety profile with a number needed to harm (NNH) of 8,971 (202). This contrasts to an NNH of 18.3 for tricyclic antidepressants (TCAs). Safety was further tested with respect to the development of bacterial resistance. Even after 3 treatments with rifaximin, no stable resistance was seen in the microbiome (203). Furthermore, there was no significant disruption in the microbiome (204) and development of *C. difficile* colitis was rare (151,205).

There remains speculation as to the predominant mechanism of action of rifaximin in patients with IBS. A new study derived from the rifaximin retreatment trial (201) has provided some clarity (203). In this trial, breath testing was conducted in a subset of patients. A positive breath test was associated with higher rates of response (56%) to the US FDA endpoint, while a negative breath test meant a lower response rate to rifaximin of 25% (206). Although this was a small subset of the total study, these data support that baseline microbiome abnormalities may be a predictor of rifaximin response.

In summary, rifaximin is an effective, safe treatment choice for patients with IBS-D symptoms.

Recommendation

We recommend that alosetron be used to relieve global IBS-D symptoms in women with severe symptoms who have failed conventional therapy.

Conditional recommendation; low quality of evidence.

Serotonin (5-hydroxytryptamine; 5-HT) plays an important role in modulating visceral sensation and motility (207). Alosetron is a 5-HT_3 antagonist, and as such, the primary mechanism of action in the treatment of IBS-D is the slowing of intestinal transit.

Two recent meta-analyses have confirmed the efficacy of alosetron for IBS-D. The first yielded a relative risk of symptom persistence of 0.79 (95% CI 0.69–0.90; NNT = 7.5) based on 8 RCTs (190) and the second an overall symptom improvement RR 1.58 (95% CI 1.42–1.75) based on 3 RCTs (208). Significant heterogeneity was identified in the first meta-analysis ($I^2 = 85\%$; $P < 0.001$) but not the latter ($I^2 = 0\%$); this discrepancy was believed to be attributable to the more-inclusive nature of the former. An in-depth analysis of the literature yielded only 3 trials assessing global symptom improvement—each limiting enrollment to women with severe IBS-D (209–211). Two studies (both double-blinded, randomized, controlled trials) assessed the efficacy of varying dosages of alosetron ranging from 0.5 to 1.0 mg b.i.d. Overall global improvement ranged from 12.2% to 32% compared with placebo ($P \leq 0.02$ for all comparisons). The third, a dose-titration (0.5–1.0 mg b.i.d.), real-world, open-label, prospective observational analysis, used the US FDA's current IBS-D clinical trial composite endpoint and identified an overall response rate of 45%.

The safety profile of alosetron has been of concern since it was voluntarily withdrawn on November 28, 2000, given postmarketing reports of increased rates of ischemic colitis, complicated constipation (obstruction or perforation), and death (212). Subsequent safety analyses yielded pooled RRs of any AE of 1.16 (95% CI 1.08–1.25); constipation was the AE most likely to occur with an RR of 4.55 (95% CI 3.30–6.28) (208). A follow-up meta-analysis of 8 trials (4,987 patients) yielded an overall NNH of 10 (141).

Alosetron was reintroduced under a risk evaluation and mitigation strategy (REMS) in June 2002, limiting use to women experiencing chronic (>6 months), severe IBS-D symptoms who previously lacked response to traditional therapies (212). The term "traditional therapies" has not been further defined, and multiple agents have been US FDA-approved for IBS-D in the years since the REMS protocol was established. Initial safety concerns have been tempered by follow-up data revealing low, stable adjudicated incidence rates of ischemic colitis and reduced rates of complicated constipation (1.03 cases and 0.25 cases/1,000 patient-years of exposure, respectively), likely attributable to restricted prescribing dosages of 0.5–1.0 mg b.i.d. established by the REMS.

Alosetron's benefits for IBS-D symptoms resulted in studies of other agents in this class. Ondansetron, another 5-HT_3 agonist, is US FDA-approved for the treatment of chemotherapy, radiation, or postoperative nausea or vomiting (213). Two small crossover studies have assessed the merits of ondansetron for IBS-D—both reporting improvements in bowel symptoms (i.e., frequency and consistency), but not abdominal pain or discomfort (214,215). AEs were recorded in 1 trial, and only constipation occurred at a higher rate in the ondansetron cohort compared with placebo (9% vs 2%). No cases of severe constipation or ischemic colitis were identified. A large international phase III study, the "TRITON" trial, is currently ongoing to further evaluate the safety and efficacy of this agent in patients with IBS-D (216).

In summary, the current evidence supports using alosetron to relieve global symptoms in women with severe IBS-D when other interventions have failed. Within a small therapeutic window (0.5–1 mg b.i.d.), it seems safe and with low risk of the development of severe constipation or ischemic colitis.

Recommendation

We suggest that mixed opioid agonists/antagonists be used to treat global IBS-D symptoms.

Conditional recommendation; moderate quality of evidence.

Eluxadoline is a peripherally acting, mixed mu- and kappa-opioid receptor agonist/delta-opioid receptor antagonist approved for the treatment of men and women with IBS-D (217,218). The recommended dose is 100 mg p.o., although a lower dose (75 mg) is recommended for some patients (218). Two large, phase 3, randomized, double-blind, placebo-controlled studies have evaluated the efficacy and safety of eluxadoline for adults meeting Rome III criteria for IBS-D (219). The primary endpoint of these studies, defined *a priori* to meet US FDA guidelines, was a decrease from baseline of ≥30% in the daily average score for worst abdominal pain on ≥ 50% days evaluated, and on the same days, a daily stool consistency score of <5 using the Bristol Stool Form Scale. Efficacy results were pooled from a 26-week study and the first 26 weeks of a separate 52-week study. In these 2 studies, the primary efficacy endpoint was more likely to be met by patients treated with eluxadoline 75 mg (n = 806) or 100 mg (n = 809) twice daily compared with those treated with placebo (n = 808)

© 2020 by The American College of Gastroenterology

Copyright © 2020 by The American College of Gastroenterology. Unauthorized reproduction of this article is prohibited.

during both the first 12 weeks (26.2% and 27.0%, vs 16.7%, respectively) ($P < 0.001$, vs placebo) and the first 26 weeks of the 2 trials (26.7% and 31.0%, vs 19.5%; $P < 0.001$, vs placebo). The NNT for symptom improvement was 10 and 14 for the 75-mg dose (weeks 1–12 and weeks 1–26, respectively), while the NNT for the 100-mg dose was 10 and 9 (for weeks 1–12 and weeks 1–26), respectively.

The most common reported AE with eluxadoline use (n = 1,666) was constipation (8% vs 2.5% for placebo). This tended to occur within the first 3 months of treatment. Nausea was reported by 7.7% of patients (vs 5% for placebo); cardiac events were few and not different between drug and placebo. A pooled safety analysis (n = 807 for 75 mg b.i.d.; n = 1,032 for 100 mg b.i.d.; placebo = 975) identified sphincter of Oddi spasm in 0.5% of patients; all occurred in those without a gallbladder (220,221). Pancreatitis occurred in 0.4% of patients; lipase normalization generally occurred within days after stopping eluxadoline (221). Eluxadoline is now contraindicated in patients with a history of pancreatitis, those without a gallbladder, patients with a history of alcoholism, alcohol abuse, or addiction, and in those who consume more than 3 alcohol-containing beverages per day (222). The 75-mg dose of eluxadoline should be used in patients with mild to moderate hepatic impairment; it should not be used in adults with severe hepatic impairment (Child-Pugh class C) (223). The NNH values for eluxadoline 75 mg and 100 mg were 25 and 23, respectively, based on AEs prompting discontinuation.

In summary, eluxadoline improves global IBS-D symptoms in men and women (219). A randomized, prospective study and a retrospective analysis have also shown that eluxadoline improves symptoms in patients with IBS-D who have failed previous trials of loperamide (224,225). Loperamide is not recommended as first-line therapy for treating IBS-D symptoms because it may improve diarrhea but not improve global IBS symptoms (141). Eluxadoline is contraindicated in some patients because of concerns over pancreatitis and sphincter of Oddi dysfunction (219,221,224,226).

Recommendation

We recommend that TCAs be used to treat global symptoms of IBS.
Strong recommendation; moderate quality of evidence.

IBS is characterized by the presence of abdominal pain in association with abnormal bowel habits of constipation, diarrhea, or both (4,141). Patients frequently report other bothersome symptoms including bloating and urgency (4, 141). TCAs are a class of agents, now commonly referred to as neuromodulators, which include amitriptyline, nortriptyline, imipramine, and desipramine. These agents improve painful conditions such as fibromyalgia, chronic headaches, and diabetic neuropathy (227–229). TCAs are believed to improve visceral pain and central pain by acting on norepinephrine, and dopaminergic receptors, thus making them attractive candidates for the treatment of IBS-related abdominal pain (230). TCAs may also improve abdominal pain because of their anticholinergic effects and, at higher doses, can also slow GI transit, thereby improving symptoms of diarrhea in some patients (230–232). Coexisting psychological distress may also improve because of the effects on dopaminergic and norepinephrine receptors (Table 7).

Twelve RCTs evaluated the efficacy and safety of TCAs for the treatment of patients with IBS (141,233–243). A total of 787 patients were evaluated; 436 received active therapy, whereas 224 received placebo. Six different TCAs were studied (2 studies each for desipramine, trimipramine, amitriptyline, and doxepin; 3 studies involved imipramine; 1 study evaluated doxepin or nortriptyline). One study enrolled only patients with IBS-D (239); 1 study involved all IBS subtypes (237); the other 10 studies did not describe the proportion of IBS subtypes enrolled in the study. The proportion of female patients ranged from 42% to 100%. Three studies were considered at low risk of bias (241–243). No statistically significant heterogeneity was detected between the studies ($I^2 = 34\%$, $P = 0.12$).

Patients with IBS randomized to a TCA were more likely to note improvement in global IBS symptoms compared with those randomized to placebo. Of patients who received active therapy, 42.7% did not improve compared with 63.8% of those randomized to placebo who did not improve. The relative risk of IBS symptoms not improving with TCA therapy was calculated at 0.65 (95% CI 0.55–0.77). The NNT with TCAs was 4.5 (95% CI 3.5–7). A recent systematic review and meta-analysis evaluated 7 RCTs that evaluated the effect of antidepressant therapy on abdominal pain (141). Antidepressants were more likely to improve symptoms of abdominal pain than placebo; however, the beneficial effects were due to TCA therapy, not SSRIs. A separate systematic review and meta-analysis (n = 5 studies; n = 428 patients) showed that TCAs improved global symptoms in patients with IBS relative to placebo (relative risk 1.36; 95% CI 1.07–1.71) (244).

The safety profile of TCAs for the treatment of IBS has been reviewed in several publications (3,141,226,232,245). A meta-analysis of 6 clinical studies found that AEs occurred at a significantly greater rate with TCAs than placebo (RR 1.59; 95% CI 1.23–2.06), with AEs of drowsiness and dry mouth occurring most commonly (3,232). In a pooled analysis of 5 studies of IBS-D (1 study did not report AEs in the placebo group), the incidence of dry mouth (36% vs 15%), insomnia (24% vs 13%), constipation (23% vs 6%), flushing (23% vs 5%), palpitations (9% vs 2%), and decreased appetite (8% vs 1%) was significantly greater with TCAs relative to placebo (202). The NNH for TCAs ranged between 9 (n = 7 studies), based on patients experiencing an AE, and 18 (n = 6 studies), based on AEs prompting discontinuation (3,202).

In summary, TCAs may improve global IBS symptoms. Data from large head-to-head trials comparing different TCAs for the treatment of patients with IBS are not available to provide recommendations on a specific TCA. We recommend that clinicians become familiar with the different types of TCAs to appreciate the differences in efficacy and adverse effects. Patients should be started on a low dose (e.g., 10-mg amitriptyline or 10 mg of desipramine) with gradual dose titration upward to achieve therapeutic relief of symptoms while minimizing side effects (230). Anecdotally, patients with IBS-D may respond better because of the anticholinergic properties of TCAs which may improve symptoms of urgency and diarrhea. However, caution should be directed toward potential side effects including dry mouth, dry eyes, urinary retention, constipation, and cardiac arrhythmias.

Recommendation

We suggest that gut-directed psychotherapies be used to treat global IBS symptoms.
Conditional recommendations; very low quality of evidence.

Copyright © 2020 by The American College of Gastroenterology. Unauthorized reproduction of this article is prohibited.

Advances in our understanding of the brain-gut-microbiome axis, and the growth of the disciplines of cognitive neurosciences and behavioral intervention science have shown that psychotherapies effective in the treatment of depression, anxiety, and chronic pain can be adapted to manage core symptoms of IBS, including abdominal pain, altered bowel habits, and IBS-specific health-related quality of life.

The pathophysiology of IBS is multifactorial, and personalized approaches based on IBS severity, most bothersome symptom(s), and factors that drive symptom experience are critical to effective care. Gut-directed psychotherapies (GDPs), which as a class include cognitive-behavior therapy (CBT)-GI and gut-directed hypnotherapy (GDH), improve IBS symptom severity by targeting the cognitive and affective factors known to drive symptom experience. Cognitive and affective states are driven by the emotional centers of the brain and determine how input from the gut is perceived, interpreted, and regulated. Examples of cognitive-affective factors that negatively impact IBS are fear of symptoms, pain catastrophizing, attentional bias/hypervigilance, somatization, and stress sensitivity. GDPs are less effective in patients with comorbid mental health conditions; these patients should be referred to non-GI mental health professionals for care.

GDPs involve a wide range of skills-based techniques, including relaxation training, cognitive reframing of unhelpful thoughts, decreasing helplessness, exposure, and behavioral experimentation around avoidance of symptoms or settings in which they occur. They can also include techniques that alter pain perception by activating brain centers that downregulate sensations from the gut and increase psychological flexibility, acceptance, and self-efficacy (245,246).

GDPs have been well-tested as adjunctive to medical therapies in moderate to severe IBS against a range of active and inactive control groups (247). For example, level 1 evidence for GDPs in the management of IBS shows efficacy and durability (232,248,249) with a slight advantage of CBT, which has the most RCTs. The largest RCTs are of CBT (250–255). RCTs for GDH trials are smaller and fewer but show similar outcomes to CBT (256,257). Finally, a recent RCT of hypnotherapy vs low FODMAPs suggested equivalence (258).

The pivotal RCTs of GDPs have not excluded patients on pharmacotherapy for IBS, and no studies have rigorously compared stand-alone GDPs against pharmacotherapy. Furthermore, there are no comparative effectiveness data to support the use of 1 GDP over another; a qualified provider will likely base this decision on patient preference, cost, ease of use, presence of contraindications, and clinical judgment. In clinical practice, techniques are often combined to enhance personalization of therapy.

The very flexibility in the delivery of GDPs with respect to the type or technique (hypnosis, cognitive therapy, CBT, mindfulness, and mindfulness-based stress reduction) and dose (# and length of sessions) is in direct contrast to IBS clinical drug trials which choose a single drug, a single, double-blinded placebo group, a single outcome measure, and a single patient population/IBS subtype. Most clinical drug trials do not allow patients to be on other medications, further enhancing rigor. IBS behavioral trials, most of which are conducted by behavior intervention scientists who are held to different (but rigorous) quality standards, are not always best evaluated with GRADE methodology. Rather, quality metrics for behavioral trials include measures of treatment fidelity (did all therapists provide the same intervention according to blind raters), blinding to hypothesis (participants and therapists know they received/provided psychotherapy but not knowing which treatment is experimental), and control for time, attention, and the therapist-patient relationship. Given the time intensity of psychotherapy, sample sizes in behavioral intervention trials are commonly 25% that of what can be collected in a medication trial. Comparison of behavioral clinical trials as a class of treatment, not a single treatment (hypnosis, CBT, and mindfulness) to single-drug trials with more clearly defined standards (sample size, placebo, and blinding) has returned a GRADE report of low quality evidence. That said, behavioral interventions, offered in conjunction with effective medical and dietary therapies, are relatively low risk, and despite low quality evidence, their NNT collectively remains 4 when the validated IBS symptom severity scale (IBS-SSS) is used as a primary outcome measure.

In summary, we suggest the use of GDPs in conjunction with other IBS therapies for patients who are emotionally stable but who exhibit cognitive-affective drivers of IBS symptoms because (i) GDPs are low risk when used by qualified health professionals—no studies to date have reported serious AEs or negative outcomes; (ii) there are long-term benefits of these therapies even after they are discontinued; and (iii) GDPs are IBS-subtype agnostic and can address the large group of patients with IBS-M or IBS-U for whom fewer pharmacological treatments are available.

Recommendation

We recommend against the use of fecal transplant for the treatment of global IBS symptoms.

Strong recommendation; very low quality of evidence.

Several lines of evidence support the concept that alterations in the gut microbiome play a role in symptom generation in some patients with IBS (4,117,259–263). Fecal microbiota transplant (FMT), a technique in which an individual's own colonic microbiome is augmented with that of a donor, is an effective treatment for recurrent *C. difficile* colitis (264). The success of FMT at treating *C. difficile* colitis has spurred researchers to determine whether the FMT could successfully treat IBS symptoms. The following section highlights data recently summarized in 2 systematic reviews and a meta-analysis on the efficacy and safety of FMT for IBS (265,266).

A comprehensive literature review by Xu et al. identified 4 studies that used Rome III criteria for the diagnosis of IBS; only 2 had been released in full manuscript form at the time of publication (265,267,268). In the intention-to-treat analysis of these 4 studies, a total of 254 patients were included (152 received FMT, and 102 received placebo). At 12-week follow-up, patients who received donor FMT reported a 49.3% response rate compared with a 51% response rate in those who received placebo FMT. No significant difference was noted in global IBS symptoms in patients who received FMT compared with placebo (RR 0.93; 95% CI 0.48–1.79, $P = 0.83$). However, when the studies using nasojejunal and colonoscopy administration were combined and compared with the 2 studies performing FMT using capsules, those who received

© 2020 by The American College of Gastroenterology

Copyright © 2020 by The American College of Gastroenterology. Unauthorized reproduction of this article is prohibited.

single-dose FMT through a nasojejunal tube or colonoscopy were more likely to report global symptom improvement. AEs were reported in only 3 of the 4 studies (267–270). FMT seemed to be generally well-tolerated, although in the studies using capsule delivery, FMT patients were more likely to report diarrhea.

In the systematic review and meta-analysis by Ianiro et al., 5 RCTs were eligible for inclusion (n = 267 patients) (266). This meta-analysis included the 2 published articles noted above in addition to 3 studies still in abstract form. The authors found that donor stool delivered during colonoscopy was superior to autologous stool in 2 RCTs, while placebo capsules were superior to capsules containing donor stool in 2 RCTs. One study showed a trend toward improvement in IBS symptoms using donor stool through a nasojejunal tube.

In summary, alterations in the gut microbiome may lead to the development of IBS symptoms in some patients. Changing the gut microbiome to improve IBS symptoms through FMT has innate appeal. However, evidence to support FMT for the treatment of IBS is limited and of very low quality and thus cannot be recommended at present. Large, multicenter, double-blind, placebo-controlled studies with endpoints similar to large pharmaceutical studies are required to determine the potential role of FMT for the treatment of IBS. In addition, research is needed to determine which is the most effective donor for FMT (e.g., fresh vs frozen; random donor vs universal donor) and which is the best technique for FMT (e.g., nasojejunal vs colonoscopy vs capsule).

SUMMARY

This ACG Clinical Guideline was written with the goal of identifying, and answering, key diagnostic and clinical questions relevant to the field of IBS. This first-ever IBS Clinical Guideline used trained GRADE methodologists to analyze the published literature relevant to these 25 key questions to assess the quality of evidence and provide the strength of each recommendation. We believe that the information provided in this Guideline will help guide both practitioners and researchers for years to come. However, as this extensive project evolved, we recognized that there are still significant gaps in our knowledge. Future research is needed to better understand the role of the gut microbiome in patients with IBS and to understand the genesis of visceral pain. Identification of biomarkers to predict treatment response is also essential. Large head-to-head trials comparing different therapeutic modalities are also need to better provide individualized care. Undoubtedly, information obtained from these studies will influence new guidelines, assist in pharmaceutical and diet development, direct changes in study design, and inform regulatory agencies.

ACKNOWLEDGMENTS

This guideline was produced in collaboration with the Practice Parameters Committee of the American College of Gastroenterology. The Committee gives special thanks to Shanti L. Eswaran, MD, who served as guideline monitor for this document and Katarina B. Greer, MD, MS Epi, who assisted with the GRADE methodologic process.

CONFLICTS OF INTEREST

Guarantor of the article: Brian E. Lacy, PhD, MD, FACG.
Specific author contributions: All authors contributed equally to researching, writing, and editing this manuscript.
Financial support: None to report.
Potential competing interests: B.E.L.—consulting/scientific advisory boards (Alpha Sigma, Arena Pharmaceuticals, Ironwood, Salix, Viver); Rome Board of Directors; and Board of Trustees, American College of Gastroenterology. M.P. has equity in Gemelli Biotech and Synthetic Biologics and is a consultant for Synthetic Biologics and Bausch Health as well as a grant from Bausch Health. Cedars-Sinai has a licensing agreement with Bausch Health, Synthetic Biologics, and Gemelli Biotech. D.M.B.—consulting/scientific advisory boards (Allergan, Alnylam, Ironwood, Salix, Takeda, Bayer, Alpha Sigma Alpha, and Arena Pharmaceuticals); Speaker (Allergan, Ironwood, Salix, and Takeda); unrestricted gift from IDP Foundation to support research. W.D.C.—consultant: Allergan, Alnylam, Bayer, Biomerica, IM Health, Ironwood, QOL Medical, Ritter, Salix/Valeant, Takeda, Urovant, and Vibrant; research grants: Biomerica, Commonwealth Diagnostics International, Ironwood, QOL Medical, Salix, Urovant, Vibrant, and Zespri; stock options: Ritter; Rome Board of Directors; and Board of Trustees American College of Gastroenterology. L.A.K.—Rome Board of Directors, consulting with Pfizer, AbbVie, AND Takeda/Shire; shareholder in metaMe Health and Trellus Health (cofounder). M.D.L.—consultant: AbbVie, Takeda, Pfizer, Janssen, UCB, Target PharmaSolutions, Salix, Valeant, and Prometheus. B.M.—consultant: Salix Pharmaceuticals, QOL Medical, Alfasigma, and Nestle; grant support: Allergan, Urovant, Takeda, Medtronic, and Ironwood; advisory board: Alnylam, Takeda, and Ironwood.

REFERENCES

1. Ford AC, Lacy BE, Talley NJ. Irritable bowel syndrome. N Eng J Med 2017;376:2566–78.
2. Drossman DA, Hasler WL. Rome IV-functional GI disorders: Disorders of gut-brain interaction. Gastroenterology 2016;150:1257–61.
3. Ford AC, Moayyedi P, Lacy BE, et al. American College of Gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. Am J Gastroenterol 2014;109(Suppl 1):S2–26.
4. Lacy BE, Mearin F, Chang L, et al. Bowel disorders. Gastroenterology 2016;150:1393–407.
5. Palsson OS, Whitehead W, Tornblom H, et al. Prevalence of Rome IV functional bowel disorders among adults in the United States, Canada and United Kingdom. Gastroenterology 2020;158:1262–73.
6. Creed F, Ratcliffe J, Fernandez L, et al. Health-related quality of life and health care costs in severe, refractory irritable bowel syndrome. Ann Intern Med 2001;134:860–8.
7. Dean BB, Aguilar D, Barghout V, et al. Impairment in work productivity and health-related quality of life in patients with IBS. Am J Manag Care 2005;11:S17–26.
8. Drossman DA, Morris CB, Schneck S, et al. International survey of patients with IBS: Symptom features and their severity, health status, treatments, and risk Taking to achieve clinical benefit. J Clin Gastroenterol 2009;43(6):541–50.
9. Lacy BE, Everhart KE, Weiser KT, et al. Medication risk taking behavior in IBS patients. Am J Gastroenterol 2012;107:804–9.
10. Canavan C, West J, Card T. Review article: The economic impact of the irritable bowel syndrome. Aliment Pharmacol Ther 2014;40: 1023–34.
11. Ladabaum U, Boyd E, Zhao WK, et al. Diagnosis, comorbidities, and management of irritable bowel syndrome in patients in a large health maintenance organization. Clin Gastroenterol Hepatol 2012;10: 37–45.
12. Lacy BE, Patel H, Guerin A, et al. Variation in care for patients with irritable bowel syndrome in the United States. PLoS One 2016;11: e0154258.
13. Guyatt GH, Oxman AD, Kunz R, et al. Rating quality of evidence and strength of recommendations: What is "quality of evidence" and why is it important to clinicians? BMJ 2008;336:995–8.

Copyright © 2020 by The American College of Gastroenterology. Unauthorized reproduction of this article is prohibited.

14. Guyatt GH, Oxman AD, Kunz R, et al. Rating quality of evidence and strength of recommendations: Going from evidence to recommendations. BMJ 2008;336:1049–51.
15. Rubio-Tapia A, Hill I, Kelly CP, et al. ACG Clinical Guideline: Diagnosis and management of celiac disease. Am J Gastroenterol 2013;100:656–76.
16. Mooney PD, Hadjivassiliou M, Sanders DS. Coeliac disease. BMJ 2014; 348:g1561.
17. Singh P, Arora A, Strand TA, et al. Global prevalence of celiac disease: Systematic review and meta-analysis. Clin Gastroenterol Hepatol 2018; 16:823–36.
18. Sanders DS, Carter MJ, Hurlstone DP, et al. Association of adult coeliac disease with irritable bowel syndrome: A case-control study in patients fulfilling ROME II criteria referred to secondary care. Lancet 2001;358: 1504–8.
19. Irvine AJ, Chey WD, Ford AC. Screening for celiac disease in irritable bowel syndrome: An updated systematic review and meta-analysis. Am J Gastroenterol 2017;112:65–76.
20. Cash BD, Rubenstein JH, Young PE, et al. The prevalence of celiac disease among patients with nonconstipated irritable bowel syndrome is similar to controls. Gastroenterology 2011;141:1187–93.
21. Canavan C, Card T, West J. The incidence of other gastroenterological disease following diagnosis of irritable bowel syndrome in the UK: A cohort study. PLoS One 2014;9:e106478.
22. Mein SM, Ladabaum U. Serological testing for coeliac disease in patients with symptoms of irritable bowel syndrome: A cost-effectiveness analysis. Aliment Pharmacol Ther 2004;19:1199–210.
23. Spiegel BM, DeRosa VP, Gralnek IM, et al. Testing for celiac sprue in irritable bowel syndrome with predominant diarrhea: A cost-effectiveness analysis. Gastroenterology 2004;126:1721–32.
24. Mohseninejad L, Feenstra T, van der Horst HE, et al. Targeted screening for coeliac disease among irritable bowel syndrome patients: Analysis of cost-effectiveness and value of information. Eur J Health Econ 2013;14: 947–57.
25. Shin A, Lembo A. IBS in America: Survey Report. American Gastroenterological Association: Bethesda, MD, 2015.
26. Bercik P, Verdue EF, Collins SM. Is Irritable bowel syndrome a low grade inflammatory bowel disease? Gastroenterol Clin North Am 2005;34: 235–45.
27. Cash BD, Schoenfeld P, Chey WD. The utility of diagnostic tests in irritable bowel syndrome patients: A systematic review. Am J Gastroenterol 2002;97:2812–9.
28. Whitehead WE, Palsson OS, Feld AD, et al. Utility of red flag symptom exclusions in the diagnosis of irritable bowel syndrome. Aliment Pharmacol Ther 2006;24:137–46.
29. Porter CK, Cash BD, Pimentel M, et al. Risk of inflammatory bowel disease following a diagnosis of irritable bowel syndrome. BMC Gastroenterol 2012;12:3–10.
30. Bitton A, Peppercorn M, Antonioli D, et al. Clinical, biological, and histologic parameters as predictors of relapse in ulcerative colitis. Gastroenterology 2001;120:13–20.
31. Mazlam MZ, Hodgson HJ. Peripheral blood monocyte cytokine production and acute phase response in inflammatory bowel disease. Gut 1992;3:773–8.
32. Henricksen M, Jahnsen J, Lygren I, et al. C reactive protein: A predictive factor and marker of inflammation in inflammatory bowel disease. Results from a prospective population-based study. Gut 2008;57: 1518–23.
33. Menees SB, Powel C, Kurlander J, et al. A meta-analysis of the utility of C-reactive protein, erythrocyte sedimentation rate, fecal calprotectin, and fecal lactoferrin to exclude inflammatory bowel disease in adults with IBS. Am J Gastroenterol 2015;110:444–54.
34. Kane SV, Sandborn WJ, Rufo PA, et al. Fecal lactoferrin is a sensitive and specific marker in identifying intestinal inflammation. Am J Gastroenterol 2003;98:1309–14.
35. Sidhu R, Wilson P, Wright A, et al. Faecal lactoferrin: A novel test to differentiate between the irritable and inflamed bowel? Aliment Pharmacol Ther 2010;31:1365–70.
36. Van Rheenen PF, Van de Vijver E, Fidler V. Faecal calprotectin for screening of patients with suspected inflammatory bowel disease: Diagnostic meta-analysis. BMJ 2010;341:c3369.
37. Sood R, Gracie DJ, Law GR, et al. Systematic review with meta-analysis: The accuracy of diagnosing irritable bowel syndrome with symptoms, biomarkers and/or psychological markers. Aliment Pharmacol Ther 2015;42:491–503.
38. Guerrant RL, Araujo V, Soares E, et al. Measurement of fecal lactoferrin as a marker of fecal leukocytes. J Clin Microbiol 1992;30:1238–42.
39. Schoepfer AM, Trummler M, Seeholzer P, et al. Discriminating IBD from IBS: Comparison of the test performance of fecal markers, blood leukocytes, CRP, and IBD antibodies. Inflam Bowel Dis 2008;14:32–9.
40. Carrasco-Labra A, Lytvyn L, Falck-Ytter Y, et al. AGA technical review on the evaluation of functional diarrhea and diarrhea-predominant irritable bowel syndrome in adults (IBS-D). Gastroenterology 2019;157: 859–80.
41. Langhorst J, Elsenbruch S, Koelzer J, et al. Noninvasive markers in the assessment of intestinal inflammation in inflammatory bowel diseases: Performance of fecal lactoferrin, calprotectin, and PMN-elastase, CRP, and clinical indices. Am J Gastroenterol 2008;103:162–9.
42. Tibble JA, Sighthorsson G, Foster R, et al. Use of surrogate markers of inflammation and Rome criteria to distinguish organic from nonorganic intestinal disease. Gastroenterology 2002;123:450–60.
43. Zhou X, Xu W, Tang X, et al. Fecal lactoferrin in discriminating inflammatory bowel disease from irritable bowel syndrome: A diagnostic meta-analysis. BMC Gastroenterol 2014;14:121.
44. Otten CM, Kok L, Witteman BJ, et al. Diagnostic performance of rapid tests for detection of fecal calprotectin and lactoferrin and their ability to discriminate inflammatory from irritable bowel syndrome. Clin Chem Lab Med 2008;46:1275–80. [Erratum appears in *Clin Chem Lab Med* 2008;46:1798].
45. Mindermark M, Larsson A. Ruling out IBD: Estimation of the possible economic effects of pre-endoscopic screening with F-calprotectin. Clin Biochem 2010;45:552–5.
46. Futagami S, Itoh T, Sakamoto C, et al. Systematic review with meta-analysis: Post-infectious functional dyspepsia. Aliment Pharmacol Ther 2015;41:177–88.
47. Zanini B, Ricci C, Bandera F, et al. Incidence of post-infectious irritable bowel syndrome and functional intestinal disorders following a water-borne viral gastroenteritis outbreak. Am J Gastroenterol 2012;107: 891–9.
48. Havevik K, Dizdar V, Langeland N, et al. Development of functional gastrointestinal disorders after Giardia lamblia infection. BMC Gastroenterol 2009;9:27.
49. Klem F, Wadhwa A, Prokop LJ, et al. Prevalence, risk factors, and outcomes of irritable bowel syndrome after infectious enteritis: A systematic review and meta-analysis. Gastroenterology 2017;152: 1042–54.
50. Painter JE, Gargano JW, Collier SA, et al. Giardiasis surveillance—United States, 2011-2012. MMWR Morb Mortal Wkly Rep 2015;64:15–25.
51. Hanevik K, Wensaas KA, Rortveit G, et al. Irritable bowel syndrome and chronic fatigue 6 years after giardia infection: A controlled prospective cohort study. Clin Infect Dis 2014;59:1394–400.
52. Hamm LR, Sorrells SC, Hardin JP, et al. Additional investigations fail to alter the diagnosis of irritable bowel syndrome in subjects fulfilling the Rome Criteria. Am J Gastroenterol 1999;94:1279–82.
53. Nakao JH, Collier SA, Gargano JW. Giardiasis and subsequent irritable bowel syndrome: A longitudinal cohort study using health insurance data. J Infect Dis 2017;215:798–805.
54. Halliez MC, Motta JP, Feener TD, et al. Giardia duodenalis induces paracellular bacterial translocation and causes postinfectious visceral hypersensitivity. Am J Physiol Gastrointest Liver Physiol 2016;310: G574–85.
55. Litleskare S, Wensaas KA , Eide GE, et al. Perceived food intolerance and irritable bowel syndrome in a population 3 years after giardiasis-outbreak: A historical cohort study. BMC Gastroenterol 2015;15:164.
56. Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Foodborne, Waterborne, and Environmental Diseases (DFWED). Parasites-Giardia. (https://www.cdc.gov/parasites/giardia/index.html). Updated July 22, 2015. Accessed November 24, 2020.
57. Spiegel BM, Farid M, Esrailian E, et al. Is irritable bowel syndrome a diagnosis of exclusion?: A survey of primary care providers, gastroenterologists, and IBS experts. Am J Gastroenterol 2010;105: 848–58.
58. McHardy IH, WU M, Shcimizu-Cohen, et al. Detection of intestinal protozoa in the clinical laboratory. J Clin Microbiol 2014;52:712–20.
59. Patel P, Bercik P, Morgan DG, et al. Prevalence of organic disease at colonoscopy in patients with symptoms compatible with irritable bowel

© 2020 by The American College of Gastroenterology

Copyright © 2020 by The American College of Gastroenterology. Unauthorized reproduction of this article is prohibited.

syndrome: Cross-sectional survey. Scand J Gastroenterol 2015;50: 816–23.
60. Black TP, Manolakis CS, DiPalma JA. "Red flag" evaluation yield in irritable bowel syndrome. J Gastrointestin Liver Dis 2012;21:153–6.
61. Chey WD, Nojkov B, Rubenstein JH, et al. The yield of colonoscopy in patients with non-constipated irritable bowel syndrome: Results from a prospective, controlled US trial. Am J Gastroenterol 2010;105:859–65.
62. Cullingford GL, Coffey JF, Carr-Locke DL. Irritable bowel syndrome: Can the patient's response to colonoscopy help with diagnosis? Digestion 1992;52:209–13.
63. Mayer EA, Gebhart GF. Basic and clinical aspects of visceral hyperalgesia. Gastroenterology 1994;107:271–93.
64. Mertz H, Naliboff B, Munakata J, et al. Altered rectal perception is a biological marker of patients with irritable bowel syndrome. Gastroenterology 1995;109:40–52.
65. Kim ES, Cheon JH, Park JJ, et al. Colonoscopy as an adjunctive method for the diagnosis of irritable bowel syndrome: Focus on pain perception. J Gastroenterol Hepatol 2010;25:1232–8.
66. Imai A, Kato M, Ono S, et al. Efficacy of carbon dioxide-insufflating colonoscopy in patients with irritable bowel syndrome: A randomized double-blind study. J Gastroenterol Hepatol 2012;27:1623–8.
67. Ishihara S, Yashima K, Kushiyama Y, et al. Prevalence of organic colonic lesions in patients meeting Rome III criteria for diagnosis of IBS; a prospective multicenter study utilizing colonoscopy. J Gastroenterol 2012;47:1084–90.
68. Guagnozzi D, Arias A, Lucendo AJ. Systematic review with meta-analysis: Diagnostic overlap of microscopic colitis and functional bowel disorders. Aliment Pharmacol Ther 2016;43:851–62.
69. Spiegel BM, Gralnek IM, Bolus R, et al. Is a negative colonoscopy associated with reassurance or improved health-related quality of life in irritable bowel syndrome? Gastrointest Endosc 2005;62:892–9.
70. Sood R, Camilleri M, Gracie DJ, et al. Enhancing diagnostic performance of symptom-based criteria for irritable bowel syndrome by additional history and limited diagnostic evaluation. Am J Gastroenterol 2016;111: 1446–54.
71. Begtrup LM, Engsbro AL, Kjeldsen J, et al. A positive diagnostic strategy is noninferior to a strategy of exclusion for patients with irritable bowel syndrome. Clin Gastroenterol Hepatol 2013;11:956–62.e1.
72. Flik CE, Laan W, Smout AJ, et al. Comparison of medical costs generated by IBS patients in primary and secondary care in the Netherlands. BMC Gastroenterol 2015;15:168.
73. Sayuk GS, Wolf R, Chang L. Comparison of symptoms, healthcare utilization, and treatment in diagnosed and undiagnosed individuals with diarrhea-predominant Irritable Bowel Syndrome. Am J Gastroenterol 2017;112:892–9.
74. Linedale EC, Chur-Hansen A, Mikocka-Walus A, et al. Uncertain diagnostic language affects further studies, endoscopies, and repeat consultations for patients with functional gastrointestinal disorders. Clin Gastroenterol Hepatol 2016;14:1735–41.e1.
75. Buono JL, Mathur K, Averitt AJ, et al. Economic burden of irritable bowel syndrome with diarrhea: Retrospective analysis of a U.S. commercially insured population. J Manag Care Spec Pharm 2017;23: 453–60.
76. Doshi JA, Cai Q, Buono JL, et al. Economic burden of irritable bowel syndrome with constipation: A retrospective analysis of health care costs in a commercially insured population. J Manag Care Spec Pharm 2014; 20:382–90.
77. Lacy BE, Ayyagari R, Guerin A, et al. Factors associated with more frequent diagnostic tests and procedures in patients with irritable bowel syndrome. Therap Adv Gastroenterol 2019;12:1756284818818326.
78. Palsson OS, Baggish JS, Turner MJ, et al. IBS patients show frequent fluctuations between loose/watery and hard/lumpy stools: Implications for treatment. Am J Gastroenterol 2012;107:286–95.
79. Shah ED, Almario CV, Spiegel BM, et al. Presentation and characteristics of abdominal pain vary by Irritable Bowel Syndrome subtype: Results of a nationwide population-based study. Am J Gastroenterol 2020;115: 294–301.
80. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol 1997;32:920–4.
81. Young E, Stoneham MD, Petruckevitch A, et al. A population study of food intolerance. Lancet 1994;343:1127–31.
82. Pereira B, Venter C, Grundy J, et al. Prevalence of sensitization to food allergens, reported adverse reactions to foods, food avoidance, and food hypersensitivity among teenagers. J Allergy Clin Immunol 2005;116: 884–92.
83. Zuberbier T, Edenharter G, Worm M, et al. Prevalence of adverse reactions to food in Germany: A population study. Allergy 2004;59: 338–45.
84. Lacy BE, Weiser K, Noddin L, et al. Irritable bowel syndrome: Patients' attitudes, concerns, and level of knowledge. Aliment Pharmacol Ther 2007;25:1329–241.
85. Bohn L, Storsrud S, Tornblom H, et al. Self-reported food-related gastrointestinal symptoms in IBS are common and associated with more severe symptoms and reduced quality of life. Am J Gastroenterol 2013; 108:634–41.
86. Monsbakken K, Vandvik P, Farup P. Perceived food intolerance in subjects with irritable bowel syndrome: Etiology, prevalence and consequences. Eur J Clin Nutr 2006;60:667–72.
87. Sischerer SH, Sampson HA. Food allergy. J Allergy Clin Immunol 2010; 125: S116–125.
88. Rona RJ, Keil T, Summers C, et al. The prevalence of food allergy: A meta-analysis. J Allergy Clin Immunol 2007;120:638–46.
89. Liu AH, Jaramillo R, Sicherer SH, et al. National prevalence and risk factors for food allergy and relationship to asthma: Results from the National Health and Nutrition Examination Survey 2005–2006. J Allergy Clin Immunol 2010;126:798–806.
90. Zar S, Kumar D, Benson MJ. Food hypersensitivity and irritable bowel syndrome. Aliment Pharmacol Ther 2001;15:439–49.
91. Lea R, Whorwell PJ. The role of food intolerance in irritable bowel syndrome. Gastroenterol Clin North Am 2005;34:247–55.
92. Turnbull JL, Adams HN, Gorard DA. Review article: The diagnosis and management of food allergy and food intolerances. Aliment Pharmacol Ther 2015;41:3–25.
93. Roberts G, Lack G. Diagnosing peanut allergy with skin prick and specific IgE testing. J Allergy Clin Immunol 2005;115:1291–6.
94. Skodje GI, Sarna VK, Minelle IH, et al. Fructan, rather than gluten, induced symptoms in patients with self-reported non-celiac gluten sensitivity. Gastroenterology 2018;154:529–39.
95. Atkinson W, Sheldon TA, Shaath N, et al. Food elimination based on IgG antibodies in irritable bowel syndrome: A randomized controlled trial. Gut 2004;53:1459–64.
96. Ali A, Weiss TR, McKee D, et al. Efficacy of individualized diets in patients with irritable bowel syndrome: A randomized controlled trial. BMJ Open Gastroenterol 2017;4:e000164.
97. Suttor VP, Prott GM, Hansen RD, et al. Evidence for pelvic floor dyssynergia in patient with irritable bowel syndrome. Dis Colon Rectum 2010;53:156–60.
98. Prott G, Shim L, Hanson R, et al. Relationships between pelvic floor symptoms and function in irritable bowel syndrome. Neurogastroenterol Motil 2010;22:764–9.
99. Mulak A, Paradowski L. Anorectal function and dyssynergic defecation in different subgroups of patient with irritable bowel syndrome. Int J Colorectal Dis 2010;25:1011–6.
100. Singh P, Seo Y, Ballou S, et al. Pelvic floor symptom related distress in chronic constipation correlates with a diagnosis of irritable bowel syndrome with constipation and constipation severity but not pelvic floor dyssynergia. J Neurogastroenterol Motil 2019;25:129–36.
101. Tantiphlachiva K, Rao P, Attaluri A, et al. Digital rectal examination is a useful tool for identifying patients with dyssynergia. Clin Gastro Hepatol 2010;8:955–60.
102. Rao SS. Advances in diagnostic assessment of fecal incontinence and dyssynergic defecation. Clin Gastroenterol Hepatol 2010;8:910–9.
103. Whitehead WE, Palsson OS, Simren M. Biomarkers to distinguish functional constipation from irritable bowel syndrome with constipation. Neurogastroenterol Motil 2016;28:783–92.
104. Prior A, Maxton DG, Whorwell PJ. Anorectal manometry in irritable bowel syndrome: Differences between diarrhea and constipation predominant subjects. Gut 1990;31:458–62.
105. Rao SS, Bharucha AE, Chiarioni G, et al. Anorectal disorders. Gastroenterology 2016;150:1430–42.
106. Cavallaro PM, Staller K, Savitt LR, et al. The contributions of internal intussusception, irritable bowel syndrome, and pelvic floor dyssynergia to obstructed defecation syndrome. Dis Colon Rectum 2019;62:56–62.
107. Patcharatrakul T, Gonlachanvit S. Outcome of biofeedback therapy in dyssynergic defecation patients with and without irritable bowel syndrome. J Clin Gastroenterol 2011;45:593–8.

Copyright © 2020 by The American College of Gastroenterology. Unauthorized reproduction of this article is prohibited.

108. Baker J, Eswaran S, Saad R, et al. Abdominal symptoms are common and benefit from biofeedback therapy in patients with dyssynergic defecation. Clin Transl Gastroenterol 2015;6:e105.
109. Chiarioni G, Whitehead WE, Pezza V, et al. Biofeedback is superior to laxatives for normal transit constipation due to pelvic floor dyssynergia. Gastroenterology 2006;130:657–64.
110. Dionne J, Ford AC, Yuan Y, et al. A systematic review and meta-analysis evaluating the efficacy of a gluten free diet and a low FODMAP diet in treating symptoms of IBS. Am J Gastroenterol 2018;113:1290–300.
111. Halmos EP, Power VA, Shepherd SJ, et al. A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. Gastroenterology 2014; 146:67–75.
112. Staudacher HM, Lomer MCE, Anderson JL, et al. Fermentable carbohydrate restriction reduces luminal bifidobacteria and gastrointestinal symptoms in patients with irritable bowel syndrome. J Nutr 2012;142:1510–8.
113. Staudacher HM, Lomer MCE, Farquharson FM, et al. A diet low in FODMAPs reduces symptoms in patients with irritable bowel syndrome and a probiotic restores Bifidobacterium species: A randomized controlled trial. Gastroenterology 2017;153:936–47.
114. Eswaran SL, Chey WD, Han-Markey T, et al. A randomized controlled trial comparing the low FODMAP diet vs. modified NICE guidelines in US with IBS-D. Am J Gastroenterol 2016;111:1824–32.
115. Bohn L, Storsrud S, Liljebo T, et al. Diet low in FODMAPs reduces symptoms of irritable bowel syndrome as well as traditional dietary advice: A randomized controlled trial. Gastroenterology 2015;149: 1399–407.
116. McIntosh K, Reed DE, Schneider T, et al. FODMAPs alter symptoms and the metabolome of patients with IBS: A randomized controlled trial. Gut 2017;66:1241–51.
117. Hustoft TN, Hausken T, Ystad SO, et al. Effects of varying dietary content of fermentable short-chain carbohydrates on symptoms, fecal microenvironment, and cytokine profiles in patients with irritable bowel syndrome. Neurogastroenterol Motil 2017;29:e12969.
118. Krogsgaard LR, Lyngesen M, Bytzer P. Systematic review: Quality of trials on the symptomatic effects of the low FODMAP diet for irritable bowel syndrome. Aliment Pharmacol Ther 2017;45:1506–13.
119. Eswaran S, Dolan RD, Ball SC, et al. The impact of a 4-week low FODMAP and mNICE diet on nutrient intake in a sample of US adults with IBS and diarrhea. J Acad Nutr Diet 2020;120:641–9.
120. Staudacher HM, Ralph FSE, Irving PM, et al. Nutrient intake, diet quality, and diet diversity in IBS and the impact of the low FODMAP diet. J Acad Nutr Diet 2020;120:535–47.
121. Eswaran S, Chey WD, Jackson K, et al. A low FODMAP diet improves quality of life, reduces activity impairment, and improves sleep quality in patients with irritable bowel syndrome and diarrhea: Results from a US randomized controlled trial. Clin Gastroenterol Hepatol 2017;15: 1890–9.
122. Food & Drug Administration. Fed Regist 2016;81:33581–4240.
123. Reynolds A, Mann J, Cummings J, et al. Carbohydrate quality and human health: A series of systematic reviews and meta-analyses. Lancet 2019;393:434–45.
124. Moayyedi P, Quigley EM, Lacy BE, et al. The effect of fiber supplementation on irritable bowel syndrome: A systematic review and meta-analysis. Am J Gastroenterol 2014;109:1367–74.
125. Soltoft J, Gudmand-Hoyer E, Krag B, et al. A double-blind trial of the effect of wheat bran on symptoms of irritable bowel syndrome. Lancet 1977;8034:270–2.
126. Manning AP, Heaton KW, Harvey RF, et al. Wheat fibre and irritable bowel syndrome. Lancet 1977;8035:417–8.
127. Ritchie JA, Truelove SC. Treatment of irritable bowel syndrome with lorazepam, hyoscine butylbromide, and ispaghula husk. Br Med J 1979;1: 376–8.
128. Longstreth GF, Fox DD, Youkeles L, et al. Psyllium therapy in the irritable bowel syndrome. Ann Intern Med 1981;95:53–6.
129. Arthurs Y, Fielding JF. Double blind trial of ispaghula/poloxamer in the irritable bowel syndrome. Irish Med J 1983;76:253.
130. Nigam P, Kapoor KK, Rastog CK, et al. Different therapeutic regimens in irritable bowel syndrome. J Assoc Physicians India 1984;32:1041–4.
131. Kruis W, Weinzierl P, Schussler P, et al. Comparison of the therapeutic effects of wheat bran and placebo in patients with the irritable bowel syndrome. Digestion 1986;34:196–201.
132. Lucey MR, Clark ML, Lowndes JO, et al. Is bran efficacious in irritable bowel syndrome? A double blind placebo controlled crossover study. Gut 1987;28:221–5.
133. Prior A, Whorwell PJ. Double blind study of ispaghula in irritable bowel syndrome. Gut 1987;28:1510–3.
134. Jalihal A, Kurian G. Ispaghula therapy in irritable bowel syndrome: Improvement in overall well-being is related to reduction in bowel dissatisfaction. J Gastroenterol Hepatol 1990;5:507–13.
135. Fowlie S, Eastwood MA, Prescott R. Irritable bowel syndrome: Assessment of psychological disturbance and its influence on the response to fibre supplementation. J Psychosomatic Res 1992;36:175–80.
136. Rees G, Davies J, Thompson R, et al. Randomised-controlled trial of a fibre supplement on the symptoms of irritable bowel syndrome. J R Soc Promot Health 2005;125:30–4.
137. Bijkerk CJ, de Wit NJ, Muris JW, et al. Soluble or insoluble fibre in irritable bowel syndrome in primary care? Randomised placebo controlled trial. Br Med J 2009;339:b3154.
138. Cockerell KM, Watkins AS, Reeves LB, et al. Effects of linseeds on the symptoms of irritable bowel syndrome: A pilot randomised controlled trial. J Hum Nutr Diet 2012;25:435–43.
139. Kamiya T, Shikano M, Tanaka M, et al. Therapeutic effects of biobran, modified arabinoxylan rice bran, in improving symptoms of diarrhea predominant or mixed type irritable bowel syndrome: A pilot, randomized controlled trial. Evid Based Complement Alternat Med 2014;2014:828137.
140. Camilleri M, Ford AC. Pharmacotherapy for irritable bowel syndrome. J Clin Med 2017;6:E101.
141. Ford AC, Moayeddi P, Chey WD, et al. American College of Gastroenterology monograph on management of irritable bowel syndrome. Am J Gastroenterol 2018;113:1–18.
142. Page JG, Dirnberger GM. Treatment of irritable bowel syndrome with Bentyl (dicyclomine hydrochloride). J Clin Gastroenterol 1981;3:153–6.
143. Matts SGF. An assessment of dicyclomine hydrochloride ('Merbentyl') in irritable colon syndrome. Br J Clin Pract 1967;21:549–51.
144. Carling L, Svedberg LE, Hulten S. Short term treatment of irritable bowel syndrome: A placebo-controlled trial of peppermint oil against hyoscyamine. OPMEAR 1989;34:55–7.
145. Schafer VE, Ewe K. The treatment of irritable colon. Efficacy and tolerance of buscopan plus, buscopan, paracetamol and placebo in ambulatory patients with irritable colon. Fortschr Med 1990;108: 488–92.
146. Chumpitazi BP, Kearns GL, Shulman RJ. Review: The physiological effects and safety of peppermint oil and its efficacy in IBS and other functional disorders. Aliment Pharmacol Ther 2018;47:738–52.
147. Alammar N, Wang L, Saberi B, et al. The impact of peppermint oil on the irritable bowel syndrome: A meta-analysis of the pooled clinical data. BMC Compliment Altern Med 2019;19:21.
148. Weerts ZZ, Masclee AAM, Witteman BJM, et al. Efficacy and safety of peppermint oil in a randomized, double-blink trial of patients with IBS. Gastroenterol 2020;158:123–36.
149. Khanna R, MacDonald JK, Levesque BG. Peppermint oil for the treatment of irritable bowel syndrome: A systematic review and meta-analysis. J Clin Gastroenterol 2014;48:505–12.
150. Cash BD, Epstein MS, Shah SM. A novel delivery system of peppermint oil is an effective therapy for irritable bowel syndrome symptoms. Dig Dis Sci 2016;61:560–71.
151. Ford AC, Harris LA, Lacy BE, et al. Systematic review with meta-analysis: The efficacy of prebiotics, probiotics, synbiotics and antibiotics in irritable bowel syndrome. Aliment Pharmacol Ther 2018;48:1044–60.
152. Allen SJ, Wareham K, Wang D, et al. Lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhea and *Clostridium difficile*: A randomised, double-blind, placebo-controlled multicenter trial. Lancet 2013;382:1249–57.
153. Whorwell PJ, Alringer L, Morel J, et al. Efficacy of an encapsulated probiotic *Bifidobacterium infantis* 35624 in women with irritable bowel syndrome. Am J Gastroenterol 2006;101:1581–90.
154. Spiller R, Pelerin F, Cayzeele Decherf A, et al. Randomized double blind placebo-controlled trial of *Saccharomcyces cerevisiae* CNCM I-3856 in irritable bowel syndrome: Improvement in abdominal pain and bloating in those with predominant constipation. United Eur Gastroenterol J 2016;4:353–62.
155. DiPalma JA, Cleveland M, McGowan J, et al. A randomized, multicenter, placebo-controlled trial of polyethelene glycol laxative for chronic treatment of constipation. Am J Gastroenterol 2007;102:1436–41.

© 2020 by The American College of Gastroenterology

Copyright © 2020 by The American College of Gastroenterology. Unauthorized reproduction of this article is prohibited.

156. Di Palma, Cleveland MV, McGowan J, et al. A randomized, multicenter comparison of polyethylene glycol laxative and tegaserod in treatments of patients with chronic constipation. Am J Gastroenterol 2007;102: 1964–71.
157. Awad RA, Camacho S. A randomized, double-blind, placebo-controlled trial of polyethylene glycol effects on fasting and postprandial rectal sensitivity and symptoms in hypersensitive constipation-predominant irritable bowel syndrome. Colorectal Dis 2010;12:1131–8.
158. Chapman RW, Stanghellini V, Geraint M, et al. Randomized clinical trial: macrogol/PEG 3350 plus electrolytes for treatment of patients with constipation associated with irritable bowel syndrome. Am J Gastroenterol 2013;108:1508–15.
159. Khoshoo V, Armstead C, Landry L. Effect of a laxative with and without tegaserod in adolescents with constipation predominant irritable bowel syndrome. Aliment Pharmacol Ther 2006;23:191–6.
160. Chaussade S, Minic M. Comparison of efficacy and safety of two doses of two different polyethylene glycol-based laxatives in the treatment of constipation. Aliment Pharmacol Ther 2003;17:165–72.
161. Chassagne P, Ducrotte P, Garnier P, et al. Tolerance and long-term efficacy of polyethylene glycol 4000 (Forlax) compared to lactulose in elderly patients with chronic constipation. J Nutr Health Aging 2017;21: 429–39.
162. Lacy BE, Campbell LL. Lubiprostone: A chloride channel activator. J Clin Gastroenterol 2007;41:345–51.
163. Cuppoletti J, Malinowska DH, Tewari KP, et al. SPI-0211 activates T84 cell chloride transport and recombinant human ClC-2 chloride currents. Am J Physiol Cell Physiol 2004;287:C1178–1183.
164. Moeser AJ, Nighot PK, Engelke KJ, et al. Recovery of mucosal barrier function in ischemic porcine ileum and colon is stimulated by a novel agonist of the ClC-2 chloride channel, lubiprostone. Am J Physiol Gastrointest Liver Physiol 2007;292:G647–656.
165. FDA approves lubiprostone (Amitiza) for women with IBS with constipation. Medpage Today. (https://www.drugtopics.com/view/fda-approves-lubiprostone-amitiza-ibs-constipation) (2008). Accessed September 30, 2019.
166. Johanson JF, Drossman DA, Panas R, et al. Clinical trial: Phase 2 study of lubiprostone for irritable bowel syndrome with constipation. Aliment Pharmacol Ther 2008;27:685–96.
167. Drossman DA, Chey WD, Johanson JF, et al. Clinical trial: Lubiprostone in patients with constipation-associated irritable bowel syndrome-results of two randomized, placebo-controlled studies: Aliment Pharmacol Ther 2009;29:329–41.
168. Chey WD, Drossman DA, Johanson JF, et al. Safety and patient outcomes with lubiprostone for up to 52 weeks in patients with irritable bowel syndrome with constipation. Aliment Pharmacol Ther 2012;35: 587–99.
169. Chang L, Chey WD, Drossman DA, et al. Effects of baseline abdominal pain and bloating on response to lubiprostone in patients with irritable bowel syndrome with constipation. Aliment Pharmacol Ther 2016;44: 1114–22.
170. Cryer B, Drossman DA, Chey WD, et al. Analysis of nausea in clinical studies of lubiprostone for the treatment of constipation disorders. Dig Dis Sci 2017;62:3568–78.
171. Currie MG, Folk KF, Kato J, et al. Guanylin: An endogenous activator of intestinal guanylate cyclase. Proc Natl Acad Sci USA 1992;89:947–51.
172. Forte LR Jr. Uroguanylin and guanylin peptides: Pharmacology and experimental therapeutics. Pharmacol Ther 2004;104:137–62.
173. Shah ED, Kim HM, Schoenfeld P. Efficacy and tolerability of guanylate cyclase-c agonists for irritable bowel syndrome with constipation and chronic idiopathic constipation: A systematic review and meta-analysis. Am J Gastroenterol 2018;113:329–38.
174. Johnston JM, Kurtz CB, MacDougall JE, et al. Linaclotide improves abdominal pain and bowel habits in a phase IIb study of patients with irritable bowel syndrome with constipation. Gastroenterology 2010;139: 1877–86.
175. Chey WD, Lembo AJ, Lavins BJ, et al. Linaclotide for irritable bowel syndrome with constipation: A 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. Am J Gastroenterol 2012;107:1702–12.
176. Rao S, Lembo AJ, Shiff S, et al. A 12-week randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. Am J Gastroenterol 2012;107:1714–24.
177. Atluri DK, Chandar AK, Bharucha A, et al. Effect of linaclotide in irritable bowel syndrome with constipation (IBS-C)L a systematic review and meta-analysis. Neurogastroenterol Motil 2014;26:499–509.
178. U.S. Department of Health and Human Services Food and Drug Administration. Guidance for Industry Irritable Bowel Syndrome—Clinical Evaluation of Drugs for Treatment. FDA: Silver Spring, MD, 2012:1–14.
179. Lacy BE, Lembo AJ, MacDougall JE, et al. Responders vs clinical response: A critical analysis of data from linaclotide phase 3 clinical trials in IBS-C. Neurogastroenterol Motil 2014;26:326–33.
180. Miner PB, DeLuca R, LaPortilla MD, et al. Plecanatide, a novel uroguanylin analog: A 12-week, randomized, double-blind, placebo-controlled, dose-ranging trial to evaluate efficacy and safety in patients with irritable bowel syndrome with constipation (IBS-C). Am J Gastroenterol 2014;109:S541.
181. Brenner DM, Fogel R, Dorn SD, et al. Efficacy, safety, and tolerability of plecanatide in patients with irritable bowel syndrome with constipation: Results of two phase 3 randomized clinical trials. Am J Gastroenterol 2018;113:735–45.
182. Grider J, Foxx-Orenstein AE, Jin JG. 5-Hydroxytryptamine-4 receptor agonists initiate the peristaltic reflex in human, rat, and Guinea pig intestine. Gastroenterology 1998;115:370–80.
183. Prather C, Camilleri M, Zinsmeister AR, et al. Tegaserod accelerates orocecal transit in patients with constipation-predominant irritable bowel syndrome. Gastroenterology 2000;118:463–8.
184. Sun YN, Luo JY. Effects of tegaserod on Fos, substance P and calcitonin gene-related peptide expression induced by colon inflammation in lumbarsacral spinal cord. World J Gastroenterol 2004;10:1830–83.
185. Jiao HM, Xie PY. Tegaserod inhibits noxious rectal distention induced responses and limbic system c-Fos expression in rats with visceral hypersensitivity. World J Gastroenterol 2004;10:2836–41.
186. Coffin B, Farmachidi JP, Rueegg P, et al. Tegaserod, a 5-HT4 receptor partial agonist, decreases sensitivity to rectal distension in healthy subjects. Aliment Pharmacol Ther 2003;17:577–85.
187. Langaker KJ, Morris D, Pruitt R, et al. The partial 5-HT4 agonist (HTF 919) improves symptoms in constipation-predominant irritable bowel syndrome (C-IBS). Digestion 1998;59(Suppl 3):20.
188. Muller-Lissner SA, Fumagalli I, Bardhan KD, et al. Tegaserod, a 5-HT4 partial agonist, relieves symptoms in irritable bowel syndrome patients with abdominal pain, bloating and constipation. Aliment Pharmacol Ther 2001;15:1655–66.
189. Novick J, Miner P, Krause R, et al. A randomized, double-blind, placebo-controlled trial of tegaserod in female patients suffering from irritable bowel syndrome with constipation. Aliment Pharmacol Ther 2002;16: 1877–88.
190. Ford AC, Brandt LJ, Young C, et al. Efficacy of 5-HT3 antagonists and 5-HT4 agonists in irritable bowel syndrome: Systematic review and meta-analysis. Am J Gastroenterol 2009;104:1831–43.
191. Black CJ, Burr NE, Ford AC. Relative efficacy of tegaserod in a systematic review and network meta-analysis of licensed therapies for irritable bowel syndrome with constipation. Clin Gastroenterol Hepatol 2020;18: 1238–9.
192. Camilleri M, Vijayvargiya P. The role of bile acids in chronic diarrhea. Am J Gastroenterol 2020;115:1596–603.
193. Longstreth GF, Yao JF. Irritable bowel syndrome and surgery: A multivariable analysis. Gastroenterology 2004;126:1665–73.
194. Slattery SA, Niaz O, Aziz Q, et al. Systematic review with meta-analysis: The prevalence of bile acid malabsorption in the irritable bowel syndrome with diarrhoea. Aliment Pharmacol Ther 2015;42:3–11.
195. Vijayvargiya P, Camilleri M, Burton D, et al. Bile and fat excretion are biomarkers of clinically significant diarrhoea and constipation in irritable bowel syndrome. Aliment Pharmacol Ther 2019;49:744–58.
196. Walters JRF, Tasleem AM, Omer OS, et al. A new mechanism for bile acid diarrhea: Defective feedback inhibition of bile acid biosynthesis. Clin Gastroneterol Hepatol 2009;7:1189–94.
197. Wong BS, Camilleri M, Carlson P, et al. Increased bile acid biosynthesis is associated with irritable bowel syndrome with diarrhea. Clin Gastroenterol Hepatol 2012;10:1009–15.
198. Bajor A, Tornblum H, Rudling M, et al. Increased colonic bile acid exposure: A relevant factor for symptoms and treatment in IBS. Gut 2015;64:84–92.
199. Camilleri M, Acosta A, Busciglio I, et al. Effect of colesevelam on fecal bile acids and bowel functions in diarrhoea-predominant irritable bowel syndrome. Aliment Pharmacol Ther 2015;41:438–48.

Copyright © 2020 by The American College of Gastroenterology. Unauthorized reproduction of this article is prohibited.

200. Pimentel M, Lembo A, Chey WD, et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. N Engl J Med 2011; 364:22–32.
201. Lembo A, Pimentel M, Rao SS, et al. Repeat treatment with rifaximin is safe and effective in patients with diarrhea predominant irritable bowel syndrome. Gastroenterol 2016;151:1113–21.
202. Shah E, Kim S, Chong K, et al. Evaluation of harm in the pharmacotherapy of irritable bowel syndrome. Am J Med 2012;125: 381–93.
203. Fodor AA, Pimentel M, Chey WD, et al. Rifaximin is associated with modest, transient decreases in multiple taxa in the gut microbiota of patients with diarrhoea-predominant irritable bowel syndrome. Gut Microbes 2019;10:22–33.
204. Pimentel M, Cash BD, Lembo A, et al. Repeat rifaximin for irritable bowel syndrome: No clinically significant changes in stool microbial antibiotic sensitivity. Dig Dis Sci 2017;6:2455–63.
205. Schoenfeld P, Pimentel M, Chang L, et al. Safety and tolerability of rifaximin for the treatment of irritable bowel syndrome without constipation: A pooled analysis of randomised double-blind, placebo-controlled trials. Aliment Pharmacol Ther 2014;39:1161–8.
206. Rezaie A, Heimanson Z, McCallum R, et al. Lactulose breath testing as a predictor of response to rifaximin in patient with irritable bowel syndrome with diarrhea. Am J Gastroenterol 2019;114:1886–93.
207. Mawe GM, Coates MD, Moses PL. Review article: Intestinal serotonin signaling in irritable bowel syndrome. Aliment Pharmacol Ther 2006;23: 1067–76.
208. Zheng Y, Yu T, Tang Y, et al. Efficacy and safety of 5-hydroxytryptamine 3 receptor antagonists in irritable bowel syndrome: A systematic review and meta-analysis of randomized controlled trials. PLoS One 2017;12: e0172846.
209. Lembo T, Wright RA, Bagby B, et al. Alosetron controls bowel urgency and provides global symptom improvement in women with diarrhea-predominant irritable bowel syndrome. Am J Gastroenterol 2001;96: 2662–70.
210. Krause R, Ameen V, Gordon SH, et al. A randomized, double-blind, placebo-controlled study to assess efficacy and safety of 0.5 and 1 mg alosetron in women with severe diarrhea-predominant IBS. Am J Gastroenterol 2007;102:1709–19.
211. Lacy BE, Nicandro JP, Chuang E, et al. Alosetron use in clinical practice: Significant improvement in irritable bowel syndrome symptoms using the US Food and Drug Administration composite endpoint. Therap Adv Gastroenterol 2018;8:1756284818771674.
212. US FDA. Lotronex (alosetron hydrochloride) Information. (https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/lotronex-alosetron-hydrochloride-information) (https://www.fda.gov/cder/drug/infopage/lotronex/lotronex.htm). Updated January 6, 2016. Accessed November 23, 2020.
213. (https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/ondansetron-marketed-zofran-information).
214. Maxton DG, Morris J, Whorwell PJ. Selective 5-hydroxytryptamine antagonism: A role in irritable bowel syndrome and functional dyspepsia? Aliment Pharmacol Ther 1996;10:595–9.
215. Garsed K, Chernova J, Hastings M, et al. A randomized trial of ondansetron for the treatment of irritable bowel syndrome with diarrhea. Gut 2014;63:1617–25.
216. Gunn D, Fried R, Lalani R, et al. Treatment of irritable bowel syndrome with diarrhea using titrated ondansetron (TRITON): Study protocol for a randomized controlled trial. Trials 2019;20:517–28.
217. Wade PR, Palmer JM, KcKenney S, et al. Modulation of gastrointestinal function by MuDelta, a mixed mu opioid receptor agonist/delta opioid receptor antagonist. Br J Pharmacol 2012;167:1111–25.
218. (https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206940s000lbl.pdf). Accessed May 1, 2019.
219. Lembo AJ, Lacy BE, Zuckerman MJ, et al. Eluxadoline for irritable bowel syndrome with diarrhea. N Engl J Med 2016;374:242–53.
220. Dove LS, Lembo A, Randall CW, et al. Eluxadoline benefits patients with irritable bowel syndrome with diarrhea in a phase 2 study. Gastroenterology 2013;145:329–38.
221. Cash BD, Lacy BE, Schoenfeld PS, et al. Safety of eluxadoline in patients with irritable bowel syndrome with diarrhea. Am J Gastroenterol 2017; 112:365–74.
222. (https://www.fda.gov/Drugs/DrugSafety/ucm546154.htm). Accessed May 1, 2019.
223. Marbury TC, Berg JK, Dove LS, et al. Effect of hepatic impairment on eluxadoline pharmacokinetics. J Clin Pharmacol 2017;57:1454–9.
224. Lacy BE, Chey WD, Cash BD, et al. Eluxadoline efficacy in patients with irritable bowel syndrome with diarrhea who experience inadequate symptom control with loperamide. Am J Gastroenterol 2017;112: 924–32.
225. Brenner DM, Sayuk GS, Gutman CR, etal. Efficacy and safety of eluxadoline in patients with irritable bowel syndrome with diarrhea who report inadequate symptom control with loperamide: RELIEF phase 4 study. Am J Gastroenterol 2019;114:1502–11.
226. Lacy BE. Review article: An analysis of safety profiles of treatments for diarrhea-predominant irritable bowel syndrome. Aliment Pharmacol Ther 2018;48:817–30.
227. Moore RA, Derry S, Aldington D, et al. Amitriptyline for fibromyalgia in adults. Cochrane Database Syst Rev 2015;7:CD008242.
228. Jackson JL, Shimeall W, Sessums L, et al. Tricyclic antidepressants and headaches: Systematic review and meta-analysis. BMJ 2010;341:c5222.
229. Griebeler ML, Morey-Vargas OL, Brito JP, et al. Pharmacologic interventions for painful diabetic neuropathy: An umbrella systematic review and comparative effectiveness network meta-analysis. Ann Intern Med 2014;161:639–49.
230. Drossman DA, Tack J, Ford AC, et al. Neuromodulators for functional gastrointestinal disorders (disorders of gut-brain interaction): A Rome Foundation Working team report. Gastroenterology 2018;154: 1140–71.e1.
231. Gorard DA, Libby GW, Farthing MJ. Influence of antidepressants on whole gut orocaecal transit times in health and irritable bowel syndrome. Aliment Pharmacol Ther 1994;8:159–66.
232. Ford AC, Lacy BE, Harris L, et al. Effect of antidepressants and psychological therapies in irritable bowel syndrome: An updated systematic review and meta-analysis. Am J Gastroenterol 2019;114: 21–39.
233. Talley NJ, Kellow JE, Boyce P, et al. Antidepressant therapy (imipramine and citalopram) for irritable bowel syndrome: A double-blind, randomized, placebo-controlled trial. Dig Dis Sci 2008;53:108–15.
234. Heefner JD, Wilder RM, Wilson ID. Irritable colon and depression. Psychosomatics 1978;19:540–7.
235. Myren J, Groth H, Larssen SE, et al. The effect of trimipramine in patients with the irritable bowel syndrome: A double-blind study. Scand J Gastroenterol 1982;17:871–5.
236. Boerner D, Eberhardt R, Metz K, et al. Wirksamkeit und vertraglichkeit eines antidepressivuns beim colon irritabile. Therapiewoche 1988;38: 201–8.
237. Vij JC, Jiloha RC, Kumar N, et al. Effect of antidepressant drug (doxepin) on irritable bowel syndrome patients. Indian J Psychiatry 1991;33:243–6.
238. Bergmann M, Heddergott A, Schlosser T. [Die therapie des colon irritabile mit trimipramin (Herphonal): Eine kontrollierte studie]. Z Klin Med 1991;46:1621–8.
239. Vahedi H, Merat S, Momtahen S, et al. Clinical trial: The effect of amitriptyline in patients with diarrhea-predominant irritable bowel syndrome. Aliment Pharmacol Ther 2008;27:678–84.
240. Abdul-Baki H, El Hajj II, ElZahabi L, et al. A randomized controlled trial of imipramine in patients with irritable bowel syndrome. World J Gastroenterol 2009;15:3636–42.
241. Ghadir MR, Habibinejad H, Heidari A, et al. Doxepin is more effective than nortriptyline and placebo for the treatment of diarrhea-predominant irritable bowel syndrome: A randomized triple-blind placebo-controlled trial. Tehran Univ Med J 2011;69:352–8.
242. Agger JL, Schroder A, Gormsen LK, et al. Imipramine versus placebo for multiple functional somatic syndromes (STreSS-3): A double-blind, randomised study. Lancet Psychiatry 2017;4:378–88.
243. Drossman DA, Toner BB, Whitehead WE, et al. Cognitive-behavioral therapy versus education and desipramine versus placebo for moderate to severe functional bowel disorders. Gastroenterology 2003;125:19–31.
244. Xie C, Tang Y, Wang Y, et al. Efficacy and safety of antidepressants for the treatment of irritable bowel syndrome: A meta-analysis. PLoS One 2015;10:e0127815.
245. Ford AC, Quigley EM, Lacy BE, et al. Effect of antidepressants and psychological therapies, including hypnotherapy, in irritable bowel syndrome: Systematic review and meta-analysis. Am J Gastroenterol 2014;109:1350–65.
246. Black CJ, Thakur ER, Houghton LA, et al. Efficacy of psychological therapies for irritable bowel syndrome: Systematic review and network meta-analysis. Gut 2020;69:1441–51.

© 2020 by The American College of Gastroenterology

Copyright © 2020 by The American College of Gastroenterology. Unauthorized reproduction of this article is prohibited.

247. Van Oudenhove L, Levy RL, Crowell MD, et al. Biopsychosocial aspects of functional gastrointestinal disorders. Gastroenterology 2016;150: 1355–67.
248. Laird KT, Tanner-Smith EE, Russell AC, et al. Comparative efficacy of psychological therapies for improving mental health and daily functioning in irritable bowel syndrome: A systematic review and meta-analysis. Clin Psychol Rev 2017;51:142–52.
249. Laird KT, Tanner-Smith EE, Russell AC, et al. Short-term and long-term efficacy of psychological therapies for irritable bowel syndrome: A systematic review and meta-analysis. Clin Gastroenterol Hepatol 2016; 14:937–47 e934.
250. Lackner JM, Jaccard J, Radziwon CD, et al. Durability and decay of treatment benefit of cognitive behavioral therapy for irritable bowel syndrome: 12-month follow-up. Am J Gastroenterol 2019;114:330–8.
251. Lackner JM, Jaccard J, Keefer L, et al. Improvement in gastrointestinal symptoms after cognitive behavior therapy for refractory irritable bowel syndrome. Gastroenterology 2018;155:47–57.
252. Everitt HA, Landau S, O'Reilly G, et al. Cognitive behavioural therapy for irritable bowel syndrome: 24-month follow-up of participants in the ACTIB randomised trial. Lancet Gastroenterol Hepatol 2019;4:863–72.
253. Everitt H, Landau S, Little P, et al. Therapist telephone-delivered CBT and web-based CBT compared with treatment as usual in refractory irritable bowel syndrome: The ACTIB three-arm RCT. Health Technol Assess 2019;23:1–154.
254. Blanchard EB, Lackner JM, Sanders K, et al. A controlled evaluation of group cognitive therapy in the treatment of irritable bowel syndrome. Behav Res Ther 2007;45:633–48.
255. Craske MG, Wolitzky-Taylor KB, Labus J, et al. A cognitive-behavioral treatment for irritable bowel syndrome using interoceptive exposure to visceral sensations. Behav Res Ther 2011;49:413–21.
256. Whorwell PJ, Prior A, Faragher EB. Controlled trial of hypnotherapy in the treatment of severe refractory irritable-bowel syndrome. Lancet 1984;2:1232–4.
257. Flik CE, Laan W, Zuithoff NPA, et al. Efficacy of individual and group hypnotherapy in irritable bowel syndrome (IMAGINE): A multicentre randomised controlled trial. Lancet Gastroenterol Hepatol 2019;4: 20–31.
258. Peters SL, Yao CK, Philpott H, et al. Randomised clinical trial: The efficacy of gut-directed hypnotherapy is similar to that of the low FODMAP diet for the treatment of irritable bowel syndrome. Aliment Pharmacol Ther 2016;44:447–59.
259. Boeckxstaens GE, Camilleri M, Sifrim D, et al. Fundamentals of neurogastroenterology: Physiology/motility-sensation. Gastroenterology 2016;150:1292–304.
260. Barbara G, Feinle-Bisset C, Ghoshal UC, et al. The intestinal microenvironment and functional gastrointestinal disorders. Gastroenterology 2016;150:1305–18.
261. Kassinen A, Krogius-Kurrika L, Makivuokko H, et al. The fecal microbiota of irritable bowel syndrome patients differs significantly from that of healthy subjects. Gastroenterology 2007;133:24–33.
262. Liu HN, Wu H, Chen YZ, et al. Altered molecular signature of intestinal microbiota in irritable bowel syndrome patients compared with healthy controls: A systematic review and meta-analysis. Dig Liver Dis 2017;49: 331–7.
263. Spiller R, Lam C. An update on post-infectious irritable bowel syndrome: Role of genetics, immune activation, serotonin and altered microbiome. J Neurogastroenterol Motil 2012;18:258–68.
264. Quraishi MN, Widlak M, Bhala N, et al. Systematic review with meta-analysis: The efficacy of faecal microbiota transplantation for the treatment of recurrent and refractory *Clostridium difficile* infection. Aliment Pharmacol Ther 2017;46:479–93.
265. Xu D, Chen VL, Steiner CA, et al. Efficacy of fecal microbiota transplantation in irritable bowel syndrome: A systematic review and meta-analysis. Am J Gastroenterol 2019;114:1043–50.
266. Ianiro G, Eusebi LH, Black CJ, et al. Systematic review with meta-analysis: Efficacy of faecal microbiota transplantation for the treatment of irritable bowel syndrome. Aliment Pharmacol Ther 2019;50:240–8.
267. Johnsen PH, Hilpusch F, Pauline J, et al. Faecal microbiota transplantation versus placebo for moderate-to-severe irritable bowel syndrome: A double-blind, randomized, placebo-controlled, parallel-group, single-centre trial. Lancet Gastroenterol Hepatol 2018;3:17–24.
268. Halkjaer SI, Christensen AH, Lo BZS, et al. Faecal microbiota transplantation alters gut microbiota in patients with irritable bowel syndrome: Results from a randomized, double-blind, placebo-controlled study. Gut 2018;67:2107–15.
269. Holvoet T, Joossens M, Jerina B, et al. Fecal microbiota transplantation in irritable bowel syndrome with predominant abdominal bloating: Results from a double-blind, placebo-controlled clinical trial. Gastroenterology 2018;154:S130.
270. Aroniadis OC, Brandt LJ, Oneto C, et al. A double-blind, randomized, placebo-controlled trial of fecal microbiota transplantation capsules (FMTC) for the treatment of diarrhea-predominant irritable bowel syndrome (IBS-D). Gastroenterology 2018;154:S154–155.

Copyright © 2020 by The American College of Gastroenterology. Unauthorized reproduction of this article is prohibited.