Patient-Centric Care of Diarrhea-Predominant Irritable Bowel Syndrome

Brian E. Lacy, MD, PhD, FACG

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

After reading the review article on diarrhea-predominant irritable bowel syndrome (IBS-D), participants should be able to:

- Describe the evidence indicating that irritable bowel syndrome (IBS) is both a brain-gut and a gut-brain disorder
- Describe the role of the Rome IV criteria, colonoscopy, and other tests used to diagnose IBS
- Implement strategies to facilitate provider understanding of patient concerns and disease burden
- Individualize treatment for IBS-D based on current evidence-based guidelines to address patient concerns and improve quality of life

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of irritable bowel syndrome – diarrhea predominant.

DISCLOSURES

As a continuing medical education provider accredited by the Accreditation Council for Continuing Medical Education (ACCME), Primary Care Education Consortium (PCEC) requires any individual in a position to influence educational content to disclose any financial interest or other personal relationship with any commercial interest. This includes any entity producing, marketing, re-selling or distributing health care goods or services consumed by, or used on, patients. Mechanisms are in place to identify and resolve any potential conflict of interest prior to the start of the activity. In addition, any discussion of off-label, experimental, or investigational use of drugs or devices will be disclosed by the faculty.

Dr. Lacy discloses that he serves on the advisory boards for Salix Pharmaceuticals and Allergan.

Gregory Scott, PharmD, RPh, editorial support, discloses he has no real or apparent conflicts of interest to report. Additional PCEC staff report no conflicts of interest.

SPONSORSHIP

This activity is sponsored by Primary Care Education Consortium.

ACCREDITATION

The Primary Care Education Consortium is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

CREDIT DESIGNATION

AMA PRA Category 1 – Primary Care Education Consortium designates this activity for a maximum of 1 AMA PRA Category 1 credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

CME is available October 1, 2019 to September 30, 2020.

METHOD OF PARTICIPATION

PHYSICIANS: To receive CME credit, please read the journal article and, on completion, go to www.pceconsortium.org/IBSD to complete the online post-test and receive your certificate of credit.
PHYSICIAN ASSISTANTS: AAPA accepts certificates of participation of educational activities certified for AMA PRA Category 1 Credit™ from organizations accredited by ACCME or a recognized state medical society.

FACULTY

Brian E. Lacy, MD, PhD, FACG, Co-Editor in Chief, American Journal of Gastroenterology, Senior Associate Consultant, Mayo Clinic, Jacksonville, FL

ACKNOWLEDGEMENT

Editorial support was provided by Gregory Scott, PharmD, RPh, at the Primary Care Education Consortium (PCEC).

SUPPORTER

This article is supported by an educational grant from Salix Pharmaceuticals, Inc.

"With IBS-D, there's always that sense of dread. I know it's going to happen again, but I don't really know when or where it's going to happen again. When it does, I could end up in the bathroom for a good long while doubled over in agony. And after a flare, I suffer from extreme lethargy. It leaves my body so drained that I literally can't do anything. If I'm at work, I have to go home. If I'm at home, I go straight to bed."

JO C.
IBS-D SUFFERER

PATIENT BURDEN RELATED TO IBS

The quote from Jo, a patient with irritable bowel syndrome (IBS) and diarrhea symptoms, nicely illustrates the often-overlooked fact that health-related quality of life is

diminished in patients with IBS. Patients with diarrhea-predominant irritable bowel syndrome (IBS-D) have significantly lower self-esteem compared to both healthy controls[1] and patients with constipation-predominant IBS (IBS-C).[2] Although surprising to many health care providers, patients with IBS-C, IBS-D, or IBS-mixed (IBS-M) report significantly greater symptom severity than patients with inflammatory bowel disease.[3] A survey involving 1102 people with IBS-D showed that one-third experience mild symptoms, 50% moderate symptoms, and 13% severe symptoms.[4] Approximately one-quarter experience daily or near daily symptoms, while more than one-quarter report their symptoms as very or extremely bothersome.

For patients with IBS-D, symptoms that most affect quality of life are urgency (64%), gas (41%), bloating (39%), fatigue (33%), gastroesophageal reflux disease (14%), and nausea (10%).[5] In contrast, patients with IBS-C report the most bothersome symptoms are abdominal pain/bloating (32%), sensation of incomplete evacuation (23%), straining during bowel movements (19%), sensation of anorectal obstruction/blockage (16%), and infrequent stools (10%).[6] Psychological symptoms such as depression, anxiety, and panic disorder also contribute to the diminished quality of life in patients with IBS.[7,8] The economic impact of IBS can be substantial due to work absenteeism, presenteeism (ie, working while sick, often resulting in a loss in productivity), and decreased productivity.[4]

Comorbidities

Unfortunately, patients with IBS frequently have to cope with a variety of other health conditions as well. The IBS in America 2017 survey of 1337 people with an IBS diagnosis showed that 51% also suffer from allergies, 50% from anxiety or panic disorders, 47% from being overweight or obese, 40% from gastroesophageal reflux disease (GERD), 39% from arthritis, and 22% from hypertension.[9]

Analysis of the 2013 Truven Health MarketScan research database (n=19,653 each for IBS-D and matched controls) showed that one-quarter of patients with IBS-D suffer from GERD, while one-in-five suffer from anxiety, functional/chronic pain, depression, and/or malaise/fatigue.[10]

Barriers to care

An estimated 11% of people worldwide suffer from IBS, yet the diagnosis of IBS in the United States is often delayed, with one estimate indicating it may take an average of nearly 3 years from the onset of symptoms.[11] Another survey of 1094 individuals meeting criteria for IBS-D found that 43.1% had not received a formal diagnosis of IBS.[5] One reason for this is that patients with IBS often initially ignore or self-manage their symptoms. According to the IBS in America 2017 survey, 53% tolerated the symptoms at first and went on with their life.[9] Twenty-six percent thought the symptoms were not serious enough to seek medical care, while 43% tried to treat their symptoms with over-the-counter treatments. Twenty-nine percent weren't aware that their symptoms were the result of a medical condition.

The IBS in America 2017 survey also showed that half were relieved to receive a diagnosis for their symptoms highlighting the importance of educating patients to their condition. Unfortunately, one-third felt their health care provider was dismissive of their symptoms.[9] At diagnosis, the majority of patients wish they had received education about: (1) how IBS relates to diet (71%); (2) symptoms of IBS (69%); (3) the effect of IBS on lifestyle (63%); (4) the impact of IBS on mental health (62%); and (5) different types of medication options and how they work (60%).

Additional barriers to care include patient misconceptions regarding normal bowel function and difficulty communicating with health care providers, including being afraid to misspeak, not using the right language, and embarrassment. Patients often have limited understanding of treatment goals and options, particularly related to treatment safety. Being able to afford treatment is also a common barrier, resulting in suboptimal adherence.

Half of the patients responding to the IBS in America 2017 survey were upset that there is no cure for IBS and nearly two-thirds were frustrated that they might never find a way to manage their symptoms. While nearly one-quarter of patients were satisfied with self-management of symptoms, nearly half were not satisfied with the care they receive from their health care provider.

Providers may not always inquire about bowel function and habits, and when they do, competing care agendas may result in less attention to the patient's gastrointestinal (GI) symptoms. Consequently, providers often underestimate the disease burden imposed on patients by IBS.[12] A recent analysis of over 200,000 patients with IBS found that there are wide geographic variations in IBS care.[13]

These barriers to care can be ameliorated through patient-provider communication and building a mutually respectful therapeutic relationship. A good patient-provider relationship fosters mutual understanding and helps the patient with IBS make sense of their symptoms, leading to an improved ability to self-manage IBS and maintain a better quality of life.[14] Patients want more information about their condition so that they can understand and apply self-management techniques to treat their IBS symptoms.[12] Educational points that have been found to benefit most patients with IBS are listed in **TABLE 1**.[12] An empathetic approach is invaluable as well.

One approach to improve patient-provider communication and strengthen the therapeutic relationship is the technique of shared decision-making. The SHARE approach, recommended by the Agency for Healthcare Research and Quality, is a five-step process that includes exploring and comparing the benefits, harms, and risks of each option through meaningful dialogue about what matters most to the patient. A variety of tools and guides to implement the SHARE approach are available at: https://www.ahrq.gov/professionals/education/curriculum-tools/shareddecisionmaking/tools/index.html.

PATHOPHYSIOLOGY

The precise etiology of IBS remains unclear, but a combination of psychological factors and GI dysfunction appears to be central to its pathophysiology. These include changes in the gut microbiota, low-grade mucosal inflammation, epithelial dysfunction, genetic polymorphisms, and environmental factors such as diet and enteric infections.[15] Identification of these factors and their interaction with the brain has resulted in the current concept that IBS is a disorder of gut-brain interactions.[16]

Increasing evidence implicates the GI microbiota as a key factor in the pathogenesis of IBS.[17,18] Various studies have compared the gut microbiota in patients with IBS to healthy volunteers. No consistent alteration in specific microbes has been identified, likely due to the heterogeneous nature of IBS. A recent systematic review showed a decrease in *Clostridium*, *Faecalibacterium*, and *Bifidobacterium* species and an increase in *Enterobacteriaceae*, *Lactobacillus*, and *Bacteroides* species.[19] Notably, the diversity of the gut microbiota was either decreased or not different in patients with IBS compared with controls.

Additional evidence supporting the importance of the gut microbiota in IBS symptoms is that a prior acute infectious gastroenteritis is the strongest risk factor for IBS. The prevalence of postinfectious IBS among those who experience infectious enteritis is thought to range from 4% to 36%,[20-22] although some experts believe it may be higher.[15] Postinfectious IBS is thought to arise due to an interaction between central and peripheral factors; it is unknown if there are unique pathophysiologic mechanisms contributing to postinfectious IBS.[15] The main risk factors include female sex, younger age, psychological factors (eg, anxiety, depression, somatization, neuroticism, negative illness beliefs) before or during the acute gastroenteritis, and severity of the acute episode. Evidence suggests that postinfectious IBS symptoms decrease over time and the prognosis may be better than for patients with IBS who do not have a preceding infection.[15]

The role of infectious gastroenteritis as a risk factor for IBS suggests that systemic inflammation in concert with an altered gut microbiome may lead to a cycle of chronic, low-grade, subclinical inflammation. In addition to mucosal inflammation, neuroinflammation may be involved via the gut-brain axis leading to altered neuroendocrine pathways and glucocorticoid receptor genes, resulting in an overall proinflammatory phenotype and dysregulated hypothalamic-pituitary-adrenal axis and serotonergic functioning.[23]

TABLE 1 Educational points that benefit most patients with IBS

• IBS is a real GI condition; it is not 'in your head'.
• IBS can significantly affect one's quality of life.
• IBS is a chronic medical condition for most patients, although the symptoms can fluctuate over time.
• IBS does not cause cancer, colitis, or any other problems. It does not shorten your life.
• There are many things we can do to help you better manage your IBS symptoms.
• There is no 'magic pill' that can cure all IBS symptoms.
• For some people with IBS, stress can trigger symptoms or make them worse.
• We need to work together to help you manage your IBS.

Abbreviations: GI, gastrointestinal; IBS, irritable bowel syndrome.

PATIENT MANAGEMENT

Recently, Lacy et al proposed 7 pillars of quality care for patients with IBS that align with quality indicators described by The National Academy of Medicine (**TABLE 2**).[24] Noting that IBS is a highly prevalent, chronic disorder, they suggest that implementation of these quality metrics will help to ensure that all patients are evaluated fairly and similarly and provided with an adequate level of care. Moreover, they note the importance of quality metrics in determining reimbursement.

Diagnosis

The diagnosis of IBS can be confidently made based on a thoughtful history, physical examination, limited laboratory testing, and the use of the Rome IV criteria.[17,24] Abdominal bloating and distension are often present, but neither is required for the diagnosis of IBS. Patients should be asked about their most troublesome symptom and possible warning signs or 'red flags', such as presence of overt GI bleeding, nocturnal passage of stool, unintentional weight loss, age >45 years without prior colon cancer screening, and family history of IBD or colorectal cancer. If a red flag symptom is identified, further assessment is appropriate.

In the absence of red flags, limited testing is recom-

mended to include: (1) complete blood count to ensure the absence of anemia; (2) C-reactive protein and/or fecal calprotectin to lower the suspicion for IBD and to prevent indiscriminate use of colonoscopy; and (3) serologic testing to rule out celiac disease.[17,25] In those without red flag symptoms, further testing does not increase the sensitivity of the diagnosis.[26,27] A colonoscopy should be limited to patients with persistent diarrhea with suspected IBD, those who have failed empiric therapy, or age-appropriate patients with worrisome changes in bowel habits.[24] Consideration should be given to additional conditions that mimic IBS, such as lactose or fructose intolerance, small intestine bacterial overgrowth, microscopic colitis, and functional constipation or diarrhea.[28,29] Stool studies are not routinely recommended; these should be performed based on the patient's history of travel, antibiotic use, and possible exposure. The presence of comorbidities that increase the likelihood of a functional GI disorder should be investigated as well. Examples include fibromyalgia, temporomandibular joint syndrome, migraine headaches, and interstitial cystitis.

Utilization of the Rome IV criteria (https://theromefoundation.org/rome-iv/whats-new-for-rome-iv/) is encouraged to facilitate making a positive diagnosis as opposed to a diagnosis of exclusion. Rome IV criteria require recurrent abdominal pain at least 1 day/week (on average) in the last 3 months associated with at least 2 of the following: (1) related to defecation; (2) associated with a change in stool frequency; and (3) associated with a change in form of stool. Symptom onset should be at least 6 months prior to diagnosis. A key feature of the Rome IV criteria is that IBS subtype is based on the proportion of days per month with symptomatic bowel movements rather than measuring all days.

The Rome IV criteria are also useful to categorize IBS sub-type, ie, IBS-C, IBS-D, or IBS-M, based on the predominant symptom.[25] The estimated proportion of patients with IBS-D, IBS-C, and IBS-M is 40%, 35%, and 23%, respectively.[30] Women with IBS are more likely to experience abdominal pain and constipation-related symptoms, while men with IBS are more likely to experience diarrhea-related symptoms.[31]

Treatment

The treatment of patients with IBS-D can be approached based on symptom severity (**FIGURE**).[17] For patients with severe IBS-D symptoms, the goal is to improve function and quality of life, rather than completely eliminating all symptoms. Nonpharmacologic therapy plays a role at all severity stages, while the importance of pharmacologic therapy increases with severity. A key principle of treatment is to focus on the IBS subtype and predominant symptom (**TABLE 2**).[24]

In 2018, the American College of Gastroenterology (ACG) updated their 2014 guidelines providing evidence-based recommendations regarding the nonpharmacologic and pharmacologic management of patients with IBS.[32] For IBS-D, the 2018 review recommends several nonpharmacologic options for overall symptom improvement. These include exercise, soluble fiber, a low fermentable oligo-, di-, mono-saccharides

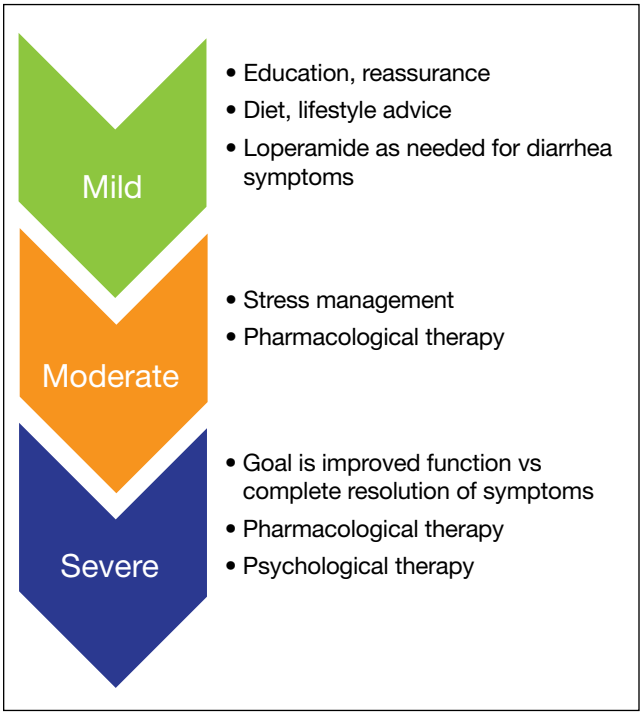
TABLE 2 Seven pillars of quality care in IBS

Positive diagnosis	• Make a positive diagnosis as soon as possible • Use Rome IV criteria to accurately categorize each patient based on bowel symptoms (IBS-C, IBS-D, IBS-M)
Limited testing	• Perform limited diagnostic testing at the first visit • CBC, CRP, and fecal calprotectin and celiac serologies, if clinically indicated
Limited colonoscopy	• Not required in all patients with suspected IBS symptoms • Perform in patients with suspected IBD, those with persistent symptoms of diarrhea who have failed standard therapy, and age-appropriate patients with a change in bowel habits or who require colorectal cancer screening
Patient education	• Counsel on the diagnosis of IBS; review treatment options and expectations; discuss fears and concerns about diagnosis and management
Treatment	• Initiate treatment at the initial visit or follow-up visit after limited diagnostic testing, based on guidelines, consensus statements, and large RCTs • Focus on the predominant symptom
Dietary consultation	• Request in those with persistent symptoms thought to be related, in part, to diet who have failed empiric therapy
Referral as needed	• Refer patients with persistent psychological distress, eg, anxiety, depression, somatization, catastrophization, affecting quality of life for appropriate evaluation and treatment

Abbreviations: CBC, complete blood count; CRP, C-reactive protein; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IBS-C, constipation-predominant irritable bowel syndrome; IBS-D, diarrhea-predominant irritable bowel syndrome; IBS-M, irritable bowel syndrome with mixed symptoms of constipation and diarrhea; RCTs, randomized clinical trials.

Source: Lacy BE, Ford AC, Talley NJ. Quality of care and the irritable bowel syndrome: Is now the time to set standards? Am J Gastroenterol. 2018;113(2):167-169; https://journals.lww.com/ajg/Citation/2018/02000/Quality_of_Care_and_the_Irritable_Bowel_Syndrome_.3.aspx.

FIGURE **Severity-based treatment of IBS-D**



Abbreviation: IBS-D, diarrhea-predominant irritable bowel syndrome.

and polyols (FODMAP) diet, and probiotics. Soluble fiber should be in the form of psyllium rather than wheat bran. Probiotics may help some patients, although the best dose and strain of probiotic are unknown. The ACG panel recommended against the use of a gluten-free or exclusion diet, as well as prebiotics and synbiotics, due to the lack of data.[32] Psychological therapies such as cognitive behavioral therapy, relaxation therapy, hypnotherapy, and multicomponent psychological therapy are also recommended for overall symptom improvement.[32]

Regarding pharmacotherapy options for IBS-D, alosetron, eluxadoline, rifaximin, some antidepressants, and antispasmodics are recommended for overall symptom improvement (**TABLE 3**).[32] Alosetron is a selective serotonin antagonist that is recommended only for women with severe IBS-D who have failed standard therapy. Its use is limited due to the possibility of severe constipation and ischemic colitis. Eluxadoline is a mixed opioid agonist-antagonist that may be particularly useful to improve stool consistency. Eluxadoline should not be used in those with prior cholecystectomy or in patients who abuse alcohol or who have a history of pancreatitis, due to an increased risk of pancreatitis. Rifaximin is a nonabsorbable antibiotic that can help global IBS-D symptoms, especially bloating in some patients. Research has shown that rifaximin may cause modest changes in the gut microbiota, although these changes are not sustained. Tricyclic antidepressants improve IBS-D symptoms through both

TABLE 3 **Therapies recommended for IBS-D**

Intervention	Relative risk of remaining symptomatic vs placebo (95% CI)	Number needed to treat (95% CI)	Strength of recommendation	Level of evidence
Alosetron	.79 (.69-.90)	7.5 (5-16)	Weak	Low
Eluxadoline	.91 (.85-.97)	12.5 (8-33)	Weak	Moderate
Rifaximin	.86 (.81-.91)	10.5 (8-16)	Weak	Moderate
Tricyclic antidepressants	.65 (.55-.77)	4 (3.5-7)	Strong	High
Selective serotonin reuptake inhibitors	.68 (.51-.91)	5 (3-16.5)	Weak	Low
Antispasmodic, eg, dicyclomine	.65 (.45-.95)	4 (2-25)	Weak	Very low
Peppermint oil	.54 (.39-.76)	4 (3-6)	Weak	Low

Abbreviations: CI, confidence interval; IBS, irritable bowel syndrome.

central and visceral effects, and while pain-modifying effects are observed, their use may be limited by adverse events, such as dry mouth. The antispasmodics dicyclomine and peppermint oil may provide short-term improvement in overall symptoms. The use of enteric coated peppermint oil may reduce the occurrence of heartburn sometimes experienced with other peppermint oil preparations.

Dietary consultation may be considered for patients who have failed empiric therapy and have persistent symptoms thought to be related, in part, to diet. Sub-specialty referral may be considered for patients with persistent psychological distress, eg, anxiety, depression, somatization, or catastrophization, that affects quality of life.[24]

SUMMARY

IBS is a common disorder that causes substantial patient morbidity; however, health care providers may underestimate the patient's disease burden. Greater understanding of the pathophysiology indicates that IBS is both a brain-gut and gut-brain disorder, with the gut microbiota playing a key role. The diagnosis of IBS is primarily based on the history and physical examination that includes fulfilment of the Rome IV criteria, supplemented by limited testing to rule out disorders that may mimic IBS. Treatment is individualized based on the patient's predominant symptom and concerns. Treatment usually begins with dietary modifications, increased exercise, and stress reduction. Evidence-based pharmacologic options for IBS-D include alosetron, eluxadoline, rifaximin, tricyclic antidepressants, diet, and smooth muscle antispasmodics, with the choice based on benefits, risks, and costs. ●

REFERENCES

1. Grodzinsky E, Walter S, Viktorsson L, Carlsson AK, Jones MP, Faresjo A. More negative self-esteem and inferior coping strategies among patients diagnosed with IBS compared with patients without IBS—a case-control study in primary care. *BMC Fam Pract.* 2015;16:6.
2. Singh P, Staller K, Barshop K, et al. Patients with irritable bowel syndrome-diarrhea have lower disease-specific quality of life than irritable bowel syndrome-constipation. *World J Gastroenterol.* 2015;21(26):8103-8109.
3. Lee AD, Spiegel BM, Hays RD, et al. Gastrointestinal symptom severity in irritable bowel syndrome, inflammatory bowel disease and the general population. *Neurogastroenterol Motil.* 2017;29(5).
4. Buono JL, Carson RT, Flores NM. Health-related quality of life, work productivity, and indirect costs among patients with irritable bowel syndrome with diarrhea. *Health Qual Life Outcomes.* 2017;15(1):35.
5. Sayuk GS, Wolf R, Chang L. Comparison of symptoms, healthcare utilization, and treatment in diagnosed and undiagnosed individuals with diarrhea-predominant irritable bowel syndrome. *Am J Gastroenterol.* 2017;112(6):892-899.
6. Tse Y, Armstrong D, Andrews CN, et al. Treatment algorithm for chronic idiopathic constipation and constipation-predominant irritable bowel syndrome derived from a Canadian national survey and needs assessment on choices of therapeutic agents. *Can J Gastroenterol Hepatol.* 2017;2017:8612189.
7. Zhu L, Huang D, Shi L, et al. Intestinal symptoms and psychological factors jointly affect quality of life of patients with irritable bowel syndrome with diarrhea. *Health Qual Life Outcomes.* 2015;13:49.
8. Ballou S, Keefer L. The impact of irritable bowel syndrome on daily functioning: Characterizing and understanding daily consequences of IBS. *Neurogastroenterol Motil.* 2017;29(4).
9. Health Union LLC. The long and dificult journey to an IBS diagnosis. https://irritablebowelsyndrome.net/infographic/long-difficult-journey-diagnosis/. Accessed April 30, 2019.
10. Buono JL, Mathur K, Averitt AJ, Andrae DA. Economic burden of irritable bowel syndrome with diarrhea: Retrospective analysis of a U.S. commercially insured population. *J Manag Care Spec Pharm.* 2017;23(4):453-460.
11. American Academy of Family Physicians. Irritable bowel syndrome evaluation and treatment in primary care pilot project. Published 2018. https://www.aafp.org/patient-care/nrn/studies/all/ibs.html. Accessed May 2, 2018.
12. Halpert A. Irritable bowel syndrome: Patient-provider interaction and patient education. *J Clin Med.* 2018;7(1).
13. 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(4):e0154258.
14. Hulme K, Chilcot J, Smith MA. Doctor-patient relationship and quality of life in Irritable Bowel Syndrome: an exploratory study of the potential mediating role of illness perceptions and acceptance. *Psychol Health Med.* 2018;23(6):674-684.
15. Barbara G, Grover M, Bercik P, et al. Rome Foundation Working Team Report on Post-Infection Irritable Bowel Syndrome. *Gastroenterology.* 2019;156(1):46-58.e47.
16. Drossman DA, Hasler WL. Rome IV-Functional GI Disorders: Disorders of Gut-Brain Interaction. *Gastroenterology.* 2016;150(6):1257-1261.
17. Ford AC, Lacy BE, Talley NJ. Irritable bowel syndrome. *N Engl J Med.* 2017;376(26):2566-2578.
18. Bhattarai Y, Muniz Pedrogo DA, Kashyap PC. Irritable bowel syndrome: a gut microbiota-related disorder? *Am J Physiol Gastrointest Liver Physiol.* 2017;312(1):G52-G62.
19. Pittayanon R, Lau JT, Yuan Y, et al. Gut microbiota in patients with irritable bowel syndrome-a systematic review. *Gastroenterology.* 2019;157(1):97-108.
20. Shah ED, Riddle MS, Chang C, Pimentel M. Estimating the contribution of acute gastroenteritis to the overall prevalence of irritable bowel syndrome. *J Neurogastroenterol Motil.* 2012;18(2):200-204.
21. Wensaas KA, Langeland N, Hanevik K, Morch K, Eide GE, Rortveit G. Irritable bowel syndrome and chronic fatigue 3 years after acute giardiasis: historic cohort study. *Gut.* 2012;61(2):214-219.
22. Marshall JK, Thabane M, Garg AX, Clark WF, Salvadori M, Collins SM. Incidence and epidemiology of irritable bowel syndrome after a large waterborne outbreak of bacterial dysentery. *Gastroenterology.* 2006;131(2):445-450; quiz 660.
23. Ng QX, Soh AYS, Loke W, Lim DY, Yeo WS. The role of inflammation in irritable bowel syndrome (IBS). *J Inflamm Res.* 2018;11:345-349.
24. Lacy BE, Ford AC, Talley NJ. Quality of care and the irritable bowel syndrome: Is now the time to set standards? *Am J Gastroenterol.* 2018;113(2):167-169.
25. Lacy BE, Mearin F, Chang L, et al. Bowel disorders. *Gastroenterology.* 2016;150:1393-1407.
26. 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(8):956-962.e951.
27. Engsbro AL, Begtrup LM, Kjeldsen J, et al. Patients suspected of irritable bowel syndrome—cross-sectional study exploring the sensitivity of Rome III criteria in primary care. *Am J Gastroenterol.* 2013;108(6):972-980.
28. Lacy BE, Patel NK. Rome criteria and a diagnostic approach to irritable bowel syndrome. *J Clin Med.* 2017;6(11).
29. Lacy BE. Diagnosis and treatment of diarrhea-predominant irritable bowel syndrome. *Int J Gen Med.* 2016;9:7-17.
30. Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. *Clin Gastroenterol Hepatol.* 2012;10(7):712-721.e714.
31. Adeyemo MA, Spiegel BM, Chang L. Meta-analysis: do irritable bowel syndrome symptoms vary between men and women? *Aliment Pharmacol Ther.* 2010;32(6):738-755.
32. Ford AC, Moayyedi P, Chey WD, et al. American College of Gastroenterology Monograph on Management of Irritable Bowel Syndrome. *Am J Gastroenterol.* 2018;113(Suppl 2):1-18.