ADVANCES IN IBS

Current Developments in the Treatment of Irritable Bowel Syndrome

Section Editor: William D. Chey, MD

Highlights of the AGA Technical Review on Functional Diarrhea and Diarrhea-Predominant Irritable Bowel Syndrome

William D. Chey, MD
Nostrant Professor of Gastroenterology & Nutrition Sciences
Director, GI Physiology Laboratory
Director, GI Nutrition and Behavioral Health Program
Medical Director, Michigan Bowel Control Program
Division of Gastroenterology
Michigan Medicine
Ann Arbor, Michigan

G&H Why was this technical review on functional diarrhea and diarrhea-predominant irritable bowel syndrome conducted?

WC Gastroenterologists and primary care physicians encounter patients with functional diarrhea and diarrhea-predominant irritable bowel syndrome (IBS-D) in their clinical practices on a daily basis. These common conditions need to be differentiated from other causes, including celiac disease, chronic infection, inflammatory bowel disease, and microscopic colitis. There tends to be a lot of confusion regarding which tests are necessary for patients who present with complaints of persistent diarrhea with or without abdominal pain. In some cases, physicians undertest patients; other times, physicians overtest. The purpose of the technical review is to provide an evidence-based summary of the diagnostic tests that might offer value in this clinical setting.

G&H What was the methodology for including studies in this review?

WC Expert methodologists from McMaster University followed the rigorous guidance structure laid out by the American Gastroenterological Association to conduct a series of systematic reviews and meta-analyses. A total of 38 studies evaluating the use of diagnostic fecal and blood tests in the setting of functional diarrhea and IBS-D were included in the review. A modified version

of the Quality Assessment of Diagnostic Accuracy Studies II and the Grading of Recommendations Assessment, Development, and Evaluation approach were used to assess the risk of bias and the certainty in the evidence, respectively. The methodologists calculated the pooled sensitivity and specificity of the diagnostic tests as well as the proportion of patients with true- and false-positive and true- and false-negative results.

G&H Which diagnostic tests were evaluated in this review?

WC We were specifically interested in making recommendations on the value of serologic testing for celiac disease and tests that identify evidence of inflammation to rule out inflammatory bowel disease in patients with chronic diarrhea. Therefore, we evaluated blood-based tests, including erythrocyte sedimentation rate and C-reactive protein, which look for a systemic immune response, as well as stool tests, such as fecal lactoferrin and fecal calprotectin, which more specifically identify patients with bowel-related inflammation. Additionally, we wanted to know if there were any tests for infectious etiologies of chronic diarrhea, such as giardia infection, that were worthy of a recommendation. We evaluated the most recent literature relevant to the emerging role of bile acid diarrhea as a cause of functional diarrhea or IBS-D symptoms. Lastly, we assessed the currently available data on the first-generation tests for anticytolethal distending

toxin B (CdtB) and antivinculin antibodies, which are novel diagnostic tests that are intended to "rule in" irritable bowel syndrome (IBS) rather than to "rule out" other organic diseases. We did not include breath tests for small intestinal bacterial overgrowth in the evaluation, as they are not part of a standard diarrhea workup.

G&H What were the main findings of the serologic tests for celiac disease?

WC The population prevalence of celiac disease is 1% or less in the United States. International studies suggest that the prevalence of celiac disease is higher in patients with IBS-D symptoms than in healthy controls. Although limited data from the United States have not confirmed these results, it may be cost-effective to screen for this disease in patients with IBS-D symptoms. Perhaps more importantly, celiac disease is a very important diagnosis to establish, as a missed diagnosis can lead to a wide range of negative health consequences, have implications for family members, and make it less likely for a patient to be treated with a gluten-free diet. Based on the available evidence, we recommend screening with an immunoglobulin (Ig) A tissue transglutaminase test, which had a sensitivity range of 0.79 to 0.99 and a specificity range of 0.90 to 0.99. Because a small proportion of patients with celiac disease can be IgA-deficient, physicians should also order either a quantitative IgA or an IgG deamidated gliadin test.

G&H How effective were the blood and stool tests for inflammatory bowel disease?

WC Fecal calprotectin and fecal lactoferrin were highly effective at screening out patients with inflammatory bowel disease among individuals who had symptoms suggestive of functional diarrhea or IBS-D. In ranges of 50 to 60 µg/g and 4.0 to 7.25 µg/g, fecal calprotectin and fecal lactoferrin, respectively, had the lowest proportion of false-negative results. Fecal calprotectin had a pooled sensitivity of 0.81 (95% CI, 0.75-0.86) and a pooled specificity of 0.87 (95% CI, 0.78-0.92), whereas fecal lactoferrin had a pooled sensitivity of 0.79 (95% CI, 0.73-0.84) and a pooled specificity of 0.93 (95% CI, 0.63-0.99).

In contrast, the blood tests performed much less well. Although erythrocyte sedimentation rate and C-reactive protein were similar at discriminating organic from functional disease, with a sensitivity and specificity, respectively, between 0.54 and 0.78 and 0.46 and 0.95 for erythrocyte sedimentation rate and of 0.73 and 0.78 for C-reactive protein, erythrocyte sedimentation rate should not be used as a screening test to exclude inflammatory bowel disease in patients with symptoms suggestive of functional diarrhea or IBS-D. C-reactive protein, which

performed slightly better, is not quite as effective as a stool test. Thus, we recommend that stool tests should be used if they are available. If the stool tests either are not available or are not covered by insurance, C-reactive protein should be the blood test used to screen for inflammatory bowel disease in patients with diarrhea-related symptoms.

G&H What tests are recommended for diagnosing giardia infection?

WC The prevalence of giardia infection varies widely across the United States. If a patient with chronic diarrhea is in an area of the country in which giardia is endemic, particularly during summer months when people are swimming in streams or lakes and can become exposed, he or she should be screened for giardia. Tests that look for the giardia antigen, such as an RNA-based test or a polymerase chain reaction–based test, are ideal. The older method of screening with an ova and parasite examination on a routine basis is no longer recommended.

G&H What were the findings regarding tests for bile acid diarrhea?

WC A rapidly emerging body of literature suggests that a significant minority (≥20%) of patients with functional diarrhea or IBS-D have evidence of bile acid malabsorption on the basis of an abnormal quantitative stool test or selenium homotaurocholic acid test (SeHCAT). Data also suggest that these patients are more likely to improve with a bile acid sequestrant, such as cholestyramine or colesevelam, supporting the idea that bile acid malabsorption actually leads to patients' diarrhea. Therefore, screening for bile acid malabsorption with SeHCAT is recommended where the test is available. In the United States, where it is currently not available, quantitative bile acid stool assays and indirect, blood-based markers for bile acid malabsorption, including 7α-hydroxy-4-cholesten-3-one and serum fibroblast growth factor 19, are recommended.

G&H What is the evidence for the use of anti-CdtB and antivinculin antibodies to diagnose IBS?

WC Anti-CdtB and antivinculin antibodies are generated in response to acute gastroenteritis. For example, individuals who develop food poisoning or traveler's diarrhea develop these antibodies. In individuals who recover, anti-CdtB and antivinculin antibodies return to normal relatively quickly. In contrast, individuals who develop persistent IBS-like symptoms will have measurable, persistent increased levels of these antibodies. Therefore,

anti-CdtB and antivinculin antibodies appear to identify individuals with IBS that results from a previous infection. While the preliminary data are conceptually quite promising, we did not feel that they were robust enough to support a recommendation regarding the use of these tests in routine clinical practice. Additional research is needed to determine whether these tests might be able to identify patients with IBS generally and with postinfection IBS specifically.

G&H How can this review be applied to practicing clinicians and gastroenterologists?

WC The main takeaways of this technical review are that patients with symptoms suggestive of functional diarrhea or IBS-D should be screened for celiac disease and should undergo stool tests to exclude inflammatory bowel disease. Patients should also undergo testing to exclude giardia where this infection is a concern. We also felt that testing to exclude bile acid malabsorption should be considered in patients with chronic diarrhea, acknowledging that commercial testing remains inconsistently available in the United States. Currently, no tests are available that reliably rule in IBS, although anti-CdtB and antivinculin antibody testing deserve further evaluation in appropriately designed and powered prospective studies.

G&H What is the priority of research in this area?

WC With the exception of the anti-CdtB and antivinculin antibodies, all of the aforementioned tests are used to exclude organic conditions that can masquerade as IBS. Moving forward, it will be very important to develop diagnostic tests that rule in functional diarrhea or IBS-D and identify the underlying abnormalities in pathophysiology responsible for an individual patient's symptoms. For example, testing for bile acid diarrhea is exciting because it appears to identify the specific cause of diarrhea and leads to a targeted therapy with a high likelihood of clinical improvement. If we were able to validate antivinculin or anti-CdtB antibodies as effectively identifying patients with postinfection IBS, perhaps that might steer us toward a microbiome-based therapy, such as antibiotics, probiotics, or diet. Therefore, the main research priority is to develop and validate biomarkers that rule in functional diarrhea or IBS and identify the specific underlying cause of symptoms so that we can choose the right treatment for the right patient.

Suggested Reading

Carrasco-Labra A, Lytvyn L, Falck-Ytter Y, Surawicz CM, Chey WD. AGA Technical Review on the evaluation of functional diarrhea and diarrhea-predominant irritable bowel syndrome in adults. *Gastroenterology*. 2019;157(3):859-880.

Talley NJ, Holtmann G, Walker MM, et al. Circulating anti-cytolethal distending toxin B and anti-vinculin antibodies as biomarkers in community and healthcare populations with functional dyspepsia and irritable bowel syndrome. *Clin Transl Gastroenterol*. 2019;10(7):e00064.