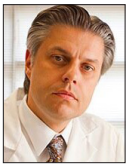
CLINICAL UPDATE

Advances in Irritable Bowel Syndrome

Update on Irritable Bowel Syndrome Diagnostics and Therapeutics



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G&H How common is irritable bowel syndrome in the general population of the United States?

MP According to recent estimates, there are 45 million people with irritable bowel syndrome (IBS) in the United States. This includes all 3 types of IBS: mixed IBS (IBS-M), which comprises approximately 30% of IBS patients; IBS with constipation (IBS-C), which also comprises approximately 30% of IBS patients; and IBS with diarrhea (IBS-D), which comprises approximately 40% of IBS patients. Thus, IBS affects a very large population, which is why the condition is so expensive in terms of health economics; there is a very large number of patients undergoing numerous procedures and expensive testing.

G&H What is the current understanding of the pathophysiology of IBS?

MP We have entered the era of the microbiome. There is now enough evidence to suggest that the microbiome is part of the picture and at least helps contribute to a significant portion of IBS. In addition, in the past, stress was thought to cause IBS, but we now know that there is no level 1 evidence to support this hypothesis; it appears that stress is only a factor in the degree of the presenting symptoms of IBS. What we know for sure is that acute gastroenteritis can cause IBS. By now, more than a dozen prospective studies have shown that acute gastroenteritis causes a subset of IBS.

G&H What are the current diagnostic criteria for IBS? What were the most important updates from Rome IV?

MP The new Rome IV criteria for IBS (and other functional gastrointestinal disorders) were released just this past May. The Rome III criteria had defined IBS as having both abdominal pain and discomfort. One of the biggest updates with the Rome IV criteria was the removal of the word *discomfort* from the IBS criteria. There were also other subtle changes to the criteria. Essentially, IBS is now defined as abdominal pain in the setting of altered bowel patterns, whether involving constipation, diarrhea, or a mixture of both.

G&H Which specific conditions should be excluded when examining patients with possible IBS?

MP The entire premise of the Rome criteria is that other conditions have been ruled out first and then the criteria are applied. Therefore, these patients end up undergoing many different tests, including colonoscopies, blood tests (eg, to obtain erythrocyte sedimentation rates and C-reactive protein levels), and stool tests, so that the clinician can rule out organic disorders. Specific conditions that have to be ruled out in these patients include Crohn's disease, celiac disease, and microscopic colitis, depending on the patient population. Clinicians also need to take into account any red flag symptoms/risk factors, such as blood in stool, age over 50 years, and family history of colon cancer, to decide whether a patient needs a colonoscopy or other diagnostic tests to be certain that no conditions are overlooked.

G&H How, specifically, is a diagnosis of IBS currently established?

MP Previously, the approach was to rule out organic findings with testing, and if the findings were negative, to apply the Rome criteria. However, as of last year, a test is available to diagnose IBS. Recent research has shown that food poisoning, particularly involving the cytolethal distending toxin B (CdtB), may be triggering autoimmunity leading to IBS. Based on this research, I helped develop the first blood test to diagnose IBS (IBS*chek*, Commonwealth Laboratories), which has been on the market for approximately 1 year. The test is based on the detection of antibodies to CdtB and the resulting autoantibody, antivinculin. Data were presented at the 2016 Digestive Disease Week (DDW) meeting validating the test beyond the United States in a Mexican population and in a tertiary care population, and also comparing its use in IBS-M, -C, and -D. Based on these new data, the test works well to diagnose IBS-D and -M.

G&H What is the sensitivity and specificity of this test?

MP Based on a validation study of almost 3000 patients that was published this year, the test is over 90% specific and approximately 40% sensitive. The test was created this way so that if it is positive, the patient has IBS and if it is negative, the patient may not.

G&H How exactly does the test work?

MP It is an enzyme-linked immunosorbent assay that searches for antibodies to CdtB, a toxin from food poisoning such as *Escherichia coli* or *Campylobacter jejuni*. The presence of circulating anti-CdtB can diagnose IBS-D or -M. This reaction also generates antibodies to a human cell migration and adherence protein called vinculin. Measurement of antivinculin antibodies further refines the test.

G&H What are the advantages of this blood test?

MP This test prevents the need for multiple investigations, which have inherent risks, and prevents the wasting of time and health resources to diagnose IBS. Doctors often order multiple and different procedures because they do not feel comfortable with the diagnosis of IBS. Having a single test that says whether or not a patient has the condition helps the doctor and patient feel confident about the diagnosis. A study showed that it takes an average of more than 6 years (of seeing physicians and undergoing tests) to reach a definitive diagnosis of IBS from the onset of symptoms. In contrast, this blood test takes only a few days to establish a diagnosis.

G&H What are the disadvantages or limitations of this test?

MP The test is not perfect, but it is a good start to at least identify a subset of patients with IBS. Although it is helpful for identifying patients with IBS-D and -M, it is not useful in the setting of IBS-C. There is also some criticism about the low sensitivity of the test. However, it should be noted that the test was designed to diagnose specifically the subgroup of IBS that is derived from gastroenteritis, not every subgroup of IBS.

G&H Is cost/insurance reimbursement an issue?

MP Thus far, insurance companies have been paying for the test. The highest copay I have seen was around $30.

As for overall health costs, a cost-effectiveness analysis that was recently released online ahead of print publication suggested that the test may result in significant health care cost savings by avoiding unnecessary tests and allowing patients to receive treatment earlier.

G&H Are there any other diagnostic blood tests for IBS currently available or under development?

MP Currently, there are no other blood tests for diagnosing IBS.

G&H Are there any other recent advances involving the diagnosis of IBS?

MP The 2 most significant recent diagnostic advances are the Rome IV criteria and the new blood test. There has also been some interesting recent research showing the importance of methane on breath testing specifically for IBS-C. Methane slows down the gut by 60%, so reversing methane might treat constipation. My colleagues and I were involved in a double-blind study of the first nonantibiotic drug being targeted for IBS-C that inhibits methanogens from producing methane; the drug was found to improve constipation in IBS-C patients.

G&H What pharmacologic therapies have traditionally been used for the different types of IBS?

MP A number of therapies for IBS have been approved by the US Food and Drug Administration (FDA). For IBS-D, the 2 most commonly used FDA-approved drugs are rifaximin (Xifaxan, Salix), which is a nonabsorbed antibiotic, and eluxadoline (Viberzi, Allergan), which is an opioid agonist. Both drugs have been fairly effective at

treating IBS-D patients. For IBS-C, linaclotide (Linzess, Allergan and Ironwood Pharmaceuticals) and lubiprostone (Amitiza, Sucampo) are commonly used, effective, and approved by the FDA.

In terms of safety, rifaximin has fairly significant long-term data, as it has been used for treating conditions in humans for over 20 years. The other drugs have been on the market for only 1 to 3 years, so there is not as much experience with them, but they appear to be safe thus far.

G&H Are any new data being expected on the current treatment options, and are any new IBS drugs currently under development?

MP For the current treatment options, no new data are expected within the next 3 to 6 months. The only other drug currently in the pipeline for FDA approval is the uroguanylin analog plecanatide (Synergy), which might be approved in the first quarter of 2017.

G&H Why was a new FDA endpoint recently established for IBS drugs?

MP The new FDA endpoint is quite complicated. Initially, there was some concern about the endpoint because it was thought to be difficult to meet. The old endpoint asked whether the patient felt better this week, which is a subjective, global method of assessing how the patient felt in the previous week. The new endpoint is more objective. It is a combination of 3 factors: a reduction in abdominal pain, a shift in stool consistency (firmer for IBS-D and softer for IBS-C), and the occurrence of both in the same week. In addition, patients with IBS-D are expected to have less diarrhea, and patients with IBS-C are expected to have less constipation.

G&H What is the current understanding of the role of nonpharmacologic interventions for IBS?

MP Based on emerging microbial concepts, new diets have emerged for IBS. The most common of these is a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs). Essentially, a low-FODMAP diet is an extreme diet that eliminates as many fermentable food products as possible. This reduction in fermentable foods often causes patients with IBS to experience less gas and other symptoms caused by fermentation.

In addition to diet, psychological therapies have shown some benefit for IBS. For example, studies have shown that cognitive behavioral therapy can help patients with IBS.

G&H Are prebiotics and probiotics useful in IBS patients?

MP Prebiotics are food items, often fermentable, that are administered to increase certain types of bacteria in the gut. This is almost the opposite of the concept of a low-FODMAP diet. For prebiotics, good randomized controlled data are not available. On the other hand, there are numerous studies examining probiotics as a treatment for IBS. However, most of these trials are unsuccessful. Nevertheless, despite the poor evidence for probiotic use, these items are frequently used by IBS patients.

G&H What is the current understanding of relapse in IBS, and how significant of an issue is it?

MP Relapse is a challenging issue. One of the premises in IBS is that the condition, at least a segment of it, is due to alterations in the microbiome. The concept of relapse emerges from that philosophy. For example, when rifaximin is used to treat IBS-D for 2 weeks, patients feel better, some for up to 6 months, but then they relapse, in which case they have to be re-treated. The FDA has allowed a retreatment pathway in the label of rifaximin for up to 2 retreatments. In the case of the other IBS drugs, it is expected that when the patient is on the drug, the patient is better, but when the patient stops the drug, his or her symptoms return.

G&H What research is currently being conducted involving the role of the microbiome in IBS?

MP There is a tremendous amount of research going on in this area. A number of groups are looking at stool microbiome and small intestinal microbiome, and much of that data will likely emerge at next year's DDW. The effects of bile acid on the intestine and mechanisms of functional bowel disorder are also being studied.

G&H What are the most important remaining research needs in terms of IBS diagnostics and therapeutics?

MP One of the biggest recent advances has been definitively identifying IBS based on pathophysiology. Now, new therapies should be built around the cause of the condition, rather than just treating the symptoms.

Dr Pimentel has been instrumental in the development of rifaximin for IBS. Cedars-Sinai has a licensing agreement with Salix Pharmaceuticals, the manufacturer of rifaximin. Dr Pimentel also receives honoraria for commercial lecturing and consulting fees. In addition, he has equity in Synthetic Biologics. Finally, Cedars-Sinai has additional licensing agreements with Commonwealth Laboratories, for which Dr Pimentel is a consultant.

Suggested Reading

Chey WD, Kurlander J, Eswaran S. Irritable bowel syndrome: a clinical review. *JAMA*. 2015;313(9):949-958.

Ford AC, Quigley EM, Lacy BE, et al. Efficacy of prebiotics, probiotics, and synbiotics in irritable bowel syndrome and chronic idiopathic constipation: systematic review and meta-analysis. *Am J Gastroenterol*. 2014;109(10):1547-1561; quiz 1546, 1562.

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(9):1367-1374.

Pimentel M, Chang C, Chua KS, et al. Antibiotic treatment of constipation-predominant irritable bowel syndrome. *Dig Dis Sci*. 2014;59(6):1278-1285.

Pimentel M, Morales W, Rezaie A, et al. Development and validation of a biomarker for diarrhea-predominant irritable bowel syndrome in human subjects. *PLoS One*. 2015;10(5):e0126438.

Pimentel M, Purdy C, Magar R, Rezaie A. A predictive model to estimate cost savings of a novel diagnostic blood panel for diagnosis of diarrhea-predominant irritable bowel syndrome [published online May 31, 2016]. *Clin Ther*. doi:10.1016/j.clinthera.2016.05.003.