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## IBS-D: A Case Study Approach to Improved Screening and Detection

Announcer:

This is CME on ReachMD. This activity, titled *IBS-D: A Case Study Approach to Improved Screening and Detection*, is jointly provided by TOPEC and MedEdCom and is supported by an educational grant from Salix Pharmaceuticals, Inc.

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Here's Dr. Anthony J. Lembo.

Dr. Lembo:

Hello, my name is Dr. Anthony Lembo, and I'm an Associate Professor of Medicine at Harvard Medical School, and I'm the Director of the GI Motility Laboratory at the Beth Israel Deaconess Medical Center in Boston, Massachusetts. today, we're going to be discussing the diagnosis of irritable bowel

syndrome with diarrhea. We'll be reviewing a case of a 45-year-old man with recurrent abdominal pain, bloating, flatulence, and intermittent stools.

Alan is a 45-year-old man with a 3-year history of recurrent, right lower-quadrant abdominal cramping, bloating, flatulence, and intermittent loose stools. His symptoms began after an acute gastrointestinal illness he developed while vacationing. His stools are described as being loose, non-bloody and without mucous. His weight has been stable. He has had no fecal incontinence but has had several close calls due to severe rectal urgency. He limits his social engagements, and when he goes out, he always looks for the nearest restroom. Alan has tried loperamide and bismuth intermittently with only limited success.

His family history is negative for inflammatory bowel disease, colorectal cancer, or a history of irritable bowel syndrome. His affect is normal, and he denies significant stress in his life or history of depression or anxiety. Physical exam is unremarkable except for mild left lower-quadrant tenderness with deep palpation. Rectal exam reveals a soft, brown, guaiac-negative stool in the vault. Tone and squeeze pressures as well as relaxation of the anal sphincter on simulated bear-down appear to be normal.

This slide reviews the epidemiology and the burden of irritable bowel syndrome. It's estimated that the prevalence of IBS is approximately 11% worldwide and slightly higher in the United States, with estimates approximately 12% among adults. It's most common between the ages of 30 and 50 years, and it affects women more commonly than men. IBS is common following an enteric infection, similar to what we saw with Alan's presentation. It has decreased work productivity and is associated with a decrease in the health-related quality of life. In fact, it is similar to those people with chronic depression and renal failure and is second only to GERD for burden of GI illness, with significant direct and indirect costs associated with IBS.

IBS is a very heterogeneous disorder with multiple potential causes — host factors, environmental factors, and luminal factors, many of which may interact with each other. If we just focus on the host-related factors, we know that patients with IBS have alteration in their GI motility; there's increase in visceral hypersensitivity that's present in approximately 50% of patients; there's even evidence now that patients, particularly those with IBS with diarrhea, have alteration in their intestinal permeability; there is significant brain-gut interactions that can occur; and there is evidence of innate immune activation that's present in patients with IBS.

We also know that environmental factors are important for the development of IBS pathophysiology. For example, psychosocial distress, such as anxiety and depression, have been associated with a number of host factors, including alteration motility, changes in hypersensitivity, permeability, and immune activation. Food is a common trigger for patients. In fact, approximately 70% to 80% of IBS

patients report that food is a major trigger for their symptoms. Antibiotics can alter the intestinal microbiome, and chronic use of antibiotics has been associated with the development of IBS. Finally, enteric infections is commonly associated with IBS. Long-term many of these patients who develop an infection can develop chronic IBS symptoms. And unlike standard IBS that may wax and wane, post-enteric infection IBS or post-infectious IBS tends to improve over time, although approximately 10% of patients will develop long-term symptoms.

And finally, there are luminal factors. Dysbiosis has recently been studied in IBS, and there have been shown to be some changes in the intestinal flora of patients with IBS. We know there are neuroendocrine mediators that are important for the development of IBS and have been shown to be altered in patients, particularly in the post-infectious IBS realm. And recently, we've seen that patients with IBS, particularly those with IBS with diarrhea, may have an increased amount of bile acids within their stool.

This slide shows the Rome IV criteria for IBS. This is the most commonly used criteria for IBS, and it defines it as recurrent abdominal pain at least 1 day per week in the last 3 months that is associated with 2 or more of the following, so that pain should be related to defecation, or the onset is associated with a change in stool frequency, or associated with a change in stool form or appearance. And the criteria should be fulfilled for the last 3 months, with a symptom onset for at least 6 months prior to the diagnosis.

The IBS subtypes are based on stool consistency during days with abnormal bowel movements. As we saw from our presentation with our patient Alan who had loose stools, he met the criteria for IBS with diarrhea, which is in the lower part of the slide, type 6 and 7 on the Bristol Stool Form Scale, and these are stools that are typically very mushy or entirely liquidy, or type 6 and 7. And to meet the criteria for IBS with diarrhea, patients should have these loose or watery stools for at least 25% of the bowel movements that are abnormal and should not have hard or lumpy stools, or type 1 or 2 on the Bristol Stool Scale, for more than 25% of the time to meet the criteria for IBS with diarrhea. And our patient Alan met the definition for this.

There are a number of other associated conditions with IBS. These include motility disorders, psychiatric disorders, and even chronic back pain or fibromyalgia, headaches, pelvic pain, and urinary symptoms as well as dysmenorrhea. When present, these symptoms tend to portend a worse prognosis for patients with IBS, and they tend to have worse health-related quality of life and to have more severe symptoms. So it's important to look for these other associated conditions in your patient with IBS.

To make a diagnosis, you need to do a detailed history and physical exam—the history, of course,

looking for presenting symptoms to determine if they meet the criteria for IBS. It's also important to establish a history timeline. Many of these patients have had symptoms for many years. There may be waxing and waning, and that can help you feel confident about the diagnosis. Of course, you should look for the presence of alarm features, which we'll talk about in the next slide. Going through a family history for organic disorders and determining if there's a history of IBS within the family is also very helpful, since IBS does tend to cluster within families. Reviewing prior tests and treatments for patients and, of course, reviewing current medications is important, as many medications can exacerbate symptoms or in some cases can mimic IBS. For example, the use of NSAIDs or even magnesium, metformin, etc., can all have significant effects on patients' bowel habits.

The examination should look for signs of systemic and local diseases. The Carnett's test is helpful to distinguish somatic from visceral abdominal pain. You should assess the anorectum and pelvic floor muscles, not only for relaxation to assess if the pelvic floor does relax appropriately, but also to look for other abnormalities in this area. And then, of course, any other relevant abnormalities on your physical exam, that is important as well.

The alarm features, or red flags, as they are sometimes known, include the onset of symptoms after the age of 50, GI bleeding or iron-deficiency anemia, nocturnal diarrhea, weight loss, or a family history of organic disease, such as colorectal cancer, inflammatory bowel disease, or celiac disease. The presence of one or more of these may suggest that you need to do further evaluation in your patient.

This slide shows the role of CRP and fecal calprotectin in excluding inflammatory bowel disease in patients with IBS symptoms. Patients presenting with IBS with diarrhea—one of the major differentials is whether or not they have inflammatory bowel disease causing their symptoms, and we can use the CRP and fecal calprotectin to help exclude inflammatory bowel disease, as shown in this meta-analysis from the University of Michigan group in 2015. They looked at the role of CRP and fecal calprotectin, both of which seem to be useful in distinguishing, as opposed to the ESR, which they showed was of no significant value. And when you use a cutoff of 0.5 for CRP and a fecal calprotectin level of less than 40 mg/g, if either one of those or both of those are present, there is a less than 1% risk of a patient having inflammatory bowel disease. So in a person that you may not otherwise want to do a colonoscopy on and they have a low CRP or fecal calprotectin, the odds of them having inflammatory bowel disease causing the symptoms is extremely low and you won't necessarily need to do the colonoscopy, at least at that point in time.

What about the role of celiac antibody testing? We know that patients with celiac disease can present with IBS-like symptoms, and there have been several studies that have looked at the prevalence of celiac disease in people presenting with IBS-related symptoms. And as you can see, overall there

seems to be a higher rate of celiac disease in patients, particularly those presenting with IBS with diarrhea. It's worth noting, though, that not all studies, and particularly the Chey study that was done in the United States, did not show a higher rate. Nevertheless, it is recommended, particularly in those patients with IBS with diarrhea, that antibody testing for celiac disease should be performed.

The role of colonoscopy is still debated in patients presenting with IBS symptoms. This was a study done by Bill Chey's group presented in 2010 in the American Journal of Gastroenterology that looked at the role of colonoscopy in patients without alarm features. And if you look on the right-hand side, you can see that the rate of diagnosing inflammatory bowel disease was extremely low, and the rate of diagnosing microscopic colitis was also very low, although it was more common in patients with IBS with diarrhea-type symptoms and that were over the age of 45. But I think the take-home message for this is that if you do not have alarm features, the rate of picking up inflammatory bowel disease and microscopic colitis is going to be relatively low.

But who should be evaluated for microscopic colitis? There are features that will favor IBS versus those that will favor microscopic colitis, and these are often important to think about before putting a patient through a colonoscopy. If they have meal-related diarrhea with intermittent symptoms or longstanding symptoms, their symptoms are worse with stress or family history of IBS, or if they are younger, they are more likely to have IBS, as opposed to having nocturnal diarrhea, persistent symptoms, relatively recent onset of symptoms, adding of a new drug in the past few months, particularly an NSAID, other autoimmune disorders, and older women — all make the odds more likely that it will be microscopic colitis. For those patients, it may be worth doing a colonoscopy, and you can often make the diagnosis with just left-sided biopsies alone, but oftentimes we'll proceed to a full colonoscopy because the right side is where you tend to see most of the microscopic colitis.

The role of breath testing to diagnose small intestinal bacterial overgrowth, or SIBO, in IBS remains controversial. Current breath tests that use either glucose or lactulose may not accurately detect SIBO. Glucose may underdetect the amount of SIBO that's present, whereas lactulose may overdetect the amount of SIBO that's present. That being said, even with glucose or lactulose breath testing, the rate of a positive SIBO breath testing is higher in IBS than it is in the general population, suggesting that at least in a subset of patients, SIBO may be an important cause of symptoms in patients with IBS.

Another area that's of interest is the role of bile acid diarrhea in IBS with diarrhea. We know from studies done in Europe that up to 40% of patients with IBS with diarrhea may have bile acid diarrhea. It's not clear whether this is due to the rapid transit or if there is an impairment of the reuptake of bile acid in these patients. We haven't been able to, at least in the United States, measure bile acid malabsorption clinically until recently, and there is a new test that's called the C4 test that's now

available in the United States, and so we may be able to more accurately diagnosis these patients and initiate treatment if appropriate in these patients. This is a serum blood test, which is now clinically available.

So the role of post-infectious antibody titers in differentiating IBS with diarrhea from inflammatory bowel disease and celiac disease has recently been introduced. I'm not entirely clear where this fits in the diagnosis of IBS. There are two antibodies, the anti-CdtB and the anti-vinculin antibodies. The CdtB antibody is an antibody you would make after a gram-negative infection—enteric infection, that is—and, as you can see from the graph on the left-hand side, in IBS they seem to have a higher amount of this antibody present than compared to these other groups. And the same may be true with anti-vinculin, using that combination of anti-CdtB and anti-vinculin, that you can have a fairly high specificity but a very low sensitivity. So when present, it may be helpful, though if they are not present, it's not going to be very helpful in making the diagnosis.

So let's summarize the workup of patients with suspected IBS with diarrhea. In patients presenting with typical IBS with diarrhea symptoms that fulfill the Rome IV criteria that include abdominal pain that's associated with alteration in bowel habits and to fulfill the diagnosis for IBS with diarrhea, they would typically have loose or watery stools for at least 25% of their days with abnormal bowel habits and not more than 25% of those days with hard or lumpy stools. So those patients with typical IBS-type symptoms, you'll evaluate them for alarm features, such as onset of symptoms after the age of 50, bleeding or iron-deficiency anemia, and nocturnal diarrhea with abnormal weight loss or family history of organic disease. If these are not present, then you would consider doing limited evaluation, including a CBC, a CRP or fecal calprotectin, a tTg to exclude celiac disease; and recently, as we discussed, the C4 has become available in the United States, which is a serum blood test for bile acid that could be considered in some patients. Some people may suggest an empiric trial with a bile acid binder. Of course, age-appropriate colorectal cancer screening is necessary. If a patient is going to have a colonoscopy or sigmoidoscopy, then you should obtain random biopsies to exclude microscopic colitis, but it would be for the more refractory patients. Patients that have any of these alarm features, you may want to do additional testing as clinically appropriate.

So, back to Alan. Based on Alan's symptoms, his history, physical exam, the following tests were performed: a tTg antibody, a CBC, CRP, and a stool calprotectin. After evaluation of these tests, all of which were negative, a diagnosis of IBS with diarrhea is made, allowing the physician to recommend appropriate and effective treatment.

Let's summarize what we've gone through today. IBS with diarrhea can be diagnosed using symptom-based criteria, a detailed physical exam, and select tests to exclude organic diseases. Tests to



consider include CBC, CRP and stool calprotectin, tTg, and stool analysis if appropriate. Assessment for bile acid malabsorption should be considered where available. And the role of breath testing remains unclear in patients with IBS.

Thank you for your attention.

Announcer:

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