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IBS-D: The Role of Pathophysiology in Assessment & Treatment

Announcer:
This is CME on ReachMD. This activity, titled *IBS-D: The Role of Pathophysiology in Assessment and Treatment*, is jointly provided by TOPEC and MedEdCom and is supported by an educational grant from Salix Pharmaceuticals.
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Here's Dr. Jeffrey B. Danzig, gastroenterologist at the Summit Medical Group in Ridgewood, New Jersey.

Dr. Danzig:
Hello, my name is Dr. Jeffrey Danzig. I'm a practicing gastroenterologist in New Jersey. I have a large experience in managing patients with irritable bowel syndrome as well as in creating policies surrounding irritable bowel syndrome.
The case I'm going to present is a patient named Debra who was very frustrated with her symptoms.

She is a 37-year-old, white woman who has had diarrhea, urgency and lower abdominal pain for 3 years. She complains that she has had 4 to 5 loose bowel movements per day, 5 of 7 days. On the other days, she has 0 to 2 bowel movements a day, but they are also loose. She occasionally has what she describes as accidents when she can't reach the bathroom on time. These are both frustrating and annoying to her. She has intermittent, severe, bilateral lower abdominal pain, which appears to improve after having a bowel movement.

Debra saw a gastroenterologist 8 months ago. At that time, blood tests, stool tests and a colonoscopy were performed, all of which she reports as having been normal. The gastroenterologist told her that her symptoms were anxiety-related and recommended a fiber supplement. She took the fiber supplement for a few days but then stopped it because it didn't seem to be working. Since that time, she has tried a variety of over-the-counter remedies. She has used 3 different probiotics: Florastor, Align and VSL3 without any improvement. She went on a different fiber supplement, Metamucil, and stopped that because it caused bloating. She has used loperamide for diarrhea, which seems to help, but it does not help her other symptoms. She went online and learned about a low-FODMAP diet. This seemed to help her bloating but did not help her abdominal pain or her diarrhea.

She has a long history of lactose intolerance where dairy products seem to bring on bloating, cramps and diarrhea. She denies having had fever, chills, sweats, gross GI bleeding or significant weight loss. She admits to feeling anxious most of the time. She believes that her anxiety is secondary to her GI symptoms rather than the other way around.

Her past medical history is remarkable for hypertension and 1 pregnancy, which resulted in a normal vaginal delivery 5 years ago. Her medications are irbesartan for hypertension, and she still does use Imodium as-needed intermittently.
Debra smokes 4 to 5 cigarettes per day for 5 years. She denies alcohol or substance abuse. She works as an administrative assistant in a law office and finds it difficult to work there because of her GI symptoms.

Her family history is remarkable for a younger brother having digestive tract symptoms, though she doesn't know the details of this. Her parents are alive and well with hypertension, and her 5-year-old daughter is alive and well.

Debra has frequent headaches. She also complains of back and extremity pain, fairly frequent urinary urgency, as well as chronic fatigue.

Her physical exam shows her to be 5'4" tall with a weight of 160 pounds. Her abdomen is soft. There is mild diffuse tenderness, no rebound, no guarding. There are no masses or hepatosplenomegaly noted. Bowel sounds are normal. Her rectal exam is normal. Her stool is negative for occult blood. Given the history and physical findings, the diagnosis of diarrhea-predominant irritable bowel syndrome was made.

Irritable bowel syndrome is a very common disorder. However, IBS-D is often undiagnosed, and up to 70% of patients do not actively seek treatment for their symptoms. Multiple studies have shown that IBS has a major negative effect on quality of life, work productivity and daily activities. 60% of patients with irritable bowel syndrome have diarrhea as a component of their irritable bowel syndrome.

The diagnosis of irritable bowel syndrome is based on clinical criteria that are known as the Rome criteria. The Rome criteria requires that a patient have recurrent abdominal pain for 1 or more days per week over the past 3 months associated with 2 or more of the following: 1) Their abdominal pain is related to defecation either in that it is improved with bowel movements or made worse by bowel movements, 2) There is an associated change in stool frequency, and/or 3) There is associated change in stool form. And these symptoms have to have been present for at least 6 months. There is a requirement for IBS-D for the patient to both have diarrhea and abdominal pain.

Our patient Debra meets all the Rome IV criteria for having IBS-D.

The next step is to search for alarm features. These are features that suggest a more pernicious cause of the patient's symptoms other than irritable bowel syndrome. After age 50 an onset of symptoms should prompt one to consider other diagnoses. Other alarm features include unexplained weight loss, progressive symptoms, gross GI bleeding or nocturnal symptoms. If a patient has alarm features, that necessitates a more aggressive approach to a diagnostic workup.

Once patients meet the criteria for IBS-D and have no alarm features, what diagnostic tests should be done? It's clear that a screening colonoscopy that's age-appropriate should be done. Selective testing has been recommended with sedimentation rate, C-reactive protein and CBC to look for signs and markers of inflammation. If the white blood cell count, sedimentation rate or CRP are elevated, then this suggests an inflammatory cause of the patient's symptoms rather than irritable bowel syndrome. Likewise, a fecal calprotectin test is fairly specific for bowel inflammation, and if that is positive, that suggests inflammatory disease of the bowel. Celiac serologies are appropriate for patients to screen for celiac disease. The anti-vinculin and anti-cytolethal distending toxin B antibody tests are fairly specific tests for the diagnoses of postinfectious and irritable bowel syndrome.

A positive anti-vinculin and anti-CdtB antibody of moderate to high titers suggests that a patient's IBS-D was either caused by a previous bout of gastroenteritis or that a previous bout of gastroenteritis unveiled a latent IBS-D.

We used to think of irritable bowel syndrome as a condition of altered gut motility fueled by stress and tension. We now know that the pathophysiology is much more complex and multifactorial. Altered gut motility is still a significant part of the pathophysiology. Studies have shown increased frequency and irregularity of muscle contractions in patients with IBS as well as abnormal sensitivity to a variety of stimulants, such as ingestion of a meal or installation of cholecystokinin.

Visceral hypersensitivity is an important component of the pathophysiology of IBS. In patients with irritable bowel syndrome, a balloon distended in the bowel will cause pain at a lower balloon volume threshold than in normal controls. That this is not a generalized lower pain threshold in these patients is supported by the fact that these patients subjected to somatic painful stimuli demonstrate a normal or higher pain threshold than controls. So the lower pain threshold in IBS patients is specific for bowel-induced pain, and that shows some degree of visceral hypersensitivity.

There is mounting evidence to suggest that an altered microbiome in the gut of patients with IBS-D plays a significant role in the pathophysiology of IBS. Some studies have shown that there are differences in fecal microbiotic composition in patients with IBS-D versus healthy adults. Other studies have shown that fecal and small bowel cultures showed distinct differences in not only quality of bacteria but quantity of bacteria, so it appears that many patients with IBS-D have an altered composition of bacteria in their intestine. It's theorized that this alteration in bacteria may lead to a variety of factors which contribute to IBS-D symptoms. This includes the fact that gut bacteria can increase the production of intestinal gas and short-chain fatty acids. Increased levels of short-chain fatty acids have been implicated for many years in the causation of diarrhea from conditions such as bile acid malabsorption, so an increased production of short-chain fatty acids by an altered microbiota in the gut may be a contributing factor to diarrhea in patients with IBS-D. Additionally, altered bacterial components, altered bacterial products and altered bacterial counts in the gut can lead to alteration in serotonin metabolism, can stimulate mucosal inflammation and stimulate the mucosal immune response. These phenomena can affect the gut in many ways, not the least of which may be a loosening of tight junctions, and therefore an increased gut permeability, which has been implicated in causing a variety of GI symptoms.

The brain gut interaction and psychosocial factors remain a significant contributor to the pathophysiology of patients with IBS-D. Patients

with IBS exhibit increased somatization, anxiety, depression and phobias compared with normal controls. In addition, patients with IBS seem to be more sensitive to bowel stimulation with corticotropin-releasing factor. Corticotropin-releasing factor is a factor that everyone secretes in excess when under stress. The fact that patients with IBS have more sensitivity in the bowel to corticotropin-releasing factor might suggest that that plays the role in explaining why patients with irritable bowel syndrome have more symptoms when under stress and why more stressful patients seem to have more symptoms. There are many instances of familial cases of irritable bowel syndrome, but these may not be genetic in origin, and at most, there is a modest genetic effect in irritable bowel syndrome. It's not really clear to what extent that actually plays a role.

So, the summary of the integrated model of IBS pathophysiology is complex. There is a complicated interaction of dysbiosis with an altered microbiome in the gut, which leads to changes in bacteria, changes in bacterial products, potentially increased permeability of the gut, the stimulation of an immune response and the release of cytokines. This can lead to GI symptoms. Stress can increase GI symptoms in these patients, perhaps through the release of corticotropin-releasing factor. This exerts itself through the enteric nervous system and on to the motility of the gut creating a complex interaction of all of these factors. The creation of increased symptoms leads to increased stress, which then leads to increased corticotropin-releasing factor, and the cycle goes on.

Most patients end up self-medicating, often with limited success. Lifestyle changes can help the symptoms of irritable bowel syndrome, and it's reasonable to decrease fructose, alcohol and caffeine intake, decrease the intake of artificial sweeteners with sorbitol and, of course, to decrease trigger foods. There is good data to show that a low-FODMAP diet, which is Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols, can reduce IBS symptoms.

IBS-D therapies that reduce power propulsions and improve altered motility include antispasmodics, tricyclic antidepressants, SSRIs, HT3 serotonin receptor antagonists such as alosetron and eluxadoline. Eluxadoline is a locally active, mixed mu opioid receptor agonist and delta opioid receptor antagonist, the sum of which ends up creating decrease in diarrhea and some decrease in abdominal pain. The use of some of these agents are limited by side effects. The use of alosetron is limited by the causation of ischemic colitis.

An alternate way to attack IBS-D is to attack the alteration in the microbiome. Rifaximin, an oral, nonsystemic antibiotic that works to modulate microbiota in the gut, is thought to alter bacterial levels primarily in the gut by inhibiting bacterial growth and reducing bacterial products that may contribute to IBS-D symptoms. It's the only FDA-approved treatment to do so. It has a potential lack of effect on gut motility, which may contribute to its low risk of constipation despite its improvement in diarrhea. Patients may, after a 2-week course, have prolonged remission of their symptoms. Another approach is to use serum-derived bovine immunoglobulin. This may improve IBS-D symptoms by binding microbial products, but the data regarding this is much less robust than that for rifaximin.

The fact that IBS remains undiagnosed in a majority of patients and that many people with IBS symptoms do not seek medical care for these symptoms points to a need for clinicians to initiate a dialogue with their patients about potential IBS-D symptoms. Many patients are reluctant to discuss some of them, so it is important to query the patient regarding the potential presence of these symptoms.

Patients with IBS and providers have a different perspective on the provider-patient relationship. Patients feel that healthcare providers don't often believe them. They feel that their healthcare provider is not supportive and think that their symptoms are solely stress-related. Many patients with IBS identify their condition as a life-threatening condition and use it synonymously with the term colitis. Healthcare providers generally underestimate the impact of IBS on the quality of life of the patient. They perceive that a psychological role exists to a greater extent than patients do. They consider IBS symptoms to be less important or less serious than the patients do, and they perceive that the patients' requests for medication, other treatments and diagnostic tests are also less reasonable than the patient does.

With this chronic, intermittent, unpredictable illness, patients need to understand that it may take time before their symptoms improve. The clinician should set realistic goals as well as expectations, how and when a medication will work and what symptoms it will treat. Providing information to patients about proposed mechanisms of pathophysiology of IBS can set the basis for therapeutic interactions. Noting that IBS does not threaten the patient's health may decrease their stress related to this significantly. It's also reasonable for the provider to acknowledge that stress may play a role in irritable bowel syndrome. A strong provider-patient communication also will result in improved outcomes for patients with IBS.

The treatment options for IBS were discussed with Debra, as was the pathophysiology of the disorder. She decided to follow a low-FODMAP diet approach in order to improve her dietary influences of IBS-D. She also decided to try treatment that alters the microbiome and chose rifaximin, firstly because there was more data behind it than serum-derived bovine immunoglobulin, and because she liked the idea that a 2-week course of treatment could potentially lead to long-term symptom remission.

In summary, IBS-D is a very common disorder. It is hallmarked by abdominal pain and diarrhea, and the symptoms can vary over time and can negatively affect the quality of life. The pathophysiology is multifactorial and includes altered gut motility, visceral hypersensitivity, as well as an altered microbiome in the gut. Over-the-counter medications and changes in diet most of the time do not

provide adequate relief of all symptoms. Considering the underlying pathophysiology of IBS-D can aid in selecting appropriate treatment, and effective communication and fortification of the provider-patient relationship can help improve outcomes in IBS-D.

Thank you for your attention.

Announcer:
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