

# ADVANCES IN IBS

Current Developments in the Treatment of Irritable Bowel Syndrome

Section Editor: William D. Chey, MD

## The Role of Gut-Brain Interactions in Influencing Symptoms of Irritable Bowel Syndrome



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**G&H** What is the evidence to support a role of the microbiome in the pathogenesis of irritable bowel syndrome?

**EM** Four recent studies have demonstrated that some patients with irritable bowel syndrome (IBS) have an alteration in the composition of their gut microbes based on the 16S ribosomal RNA gene sequencing technique. Two studies (one of which my colleagues and I conducted) found that there are likely subsets of IBS patients, one with an altered gut composition and one with a gut composition that is not significantly different from healthy control subjects. A third study showed that IBS patients and healthy controls were not different from each other. However, within the IBS cohort, the severity of symptoms played a role in the gut microbial composition; patients with more severe symptoms had alterations, whereas patients with mild symptoms did not. The fourth study showed no significant group differences. Because these were association studies, it is not known whether altered microbes result in IBS symptoms or if something in the IBS pathophysiology, such as regional patterns of gastrointestinal motility, causes changes in the gut microbes.

Additional papers are in preparation, some of which will be presented in abstract form at Digestive Disease Week 2018. In a cognitive behavioral intervention study led by Dr Jeffrey Lackner, we were able to show that pre-treatment microbial community structure was a predictor

of treatment outcome. A study led by Dr Kirsten Tillisch also found changes in the gut microbiome of IBS patients using a mindfulness-based stress reduction intervention.

These published and ongoing studies provide convincing evidence for alterations in the microbiome of patients with IBS. Changes in response to therapies that target the brain in the brain-gut-microbiome axis can also influence the gut microbiome.

**G&H** What are the key parts of the brain and nervous system that play a role in IBS symptoms?

**EM** There are 3 key points to consider. The first point of consideration is that IBS is a stress-sensitive disorder; epidemiologic studies have demonstrated that approximately 60% of IBS patients report the first onset or flare of their symptoms in association with psychosocial stressors. There is evidence from both animal and human studies that stress plays an important role in triggering IBS symptoms, as the brain has an increased sensitivity to perceived stressors and responds with gastrointestinal consequences. Animal studies have shown that there is a molecule within the brain called corticotropin-releasing factor, which can induce IBS-like patterns of motility upon injection into the brain. When this molecule is blocked with an antagonist, changes in gut motility and function can be prevented.

The second point of consideration is that IBS patients are characterized by visceral hypersensitivity.

Data show that the presence of chronic visceral hypersensitivity involves the central nervous system, resulting in the amplification of sensory signals that come from the gut at the brain and, possibly, at the spinal cord level.

The third point of consideration is that a significant number of patients with IBS have increased psychiatric comorbidities, particularly anxiety and, to a lesser degree, depression.

### **G&H** Are psychological symptoms more common in patients with IBS?

**EM** The majority of patients with IBS have increased nonclinical levels of anxiety and depression symptoms when evaluated with a questionnaire such as the Hospital Anxiety and Depression Scale, which assesses the presence of anxiety and depression symptoms. Additionally, IBS patients have an increased prevalence (10%-20%) of a diagnosis of an anxiety disorder according to strict psychiatric diagnostic criteria such as in the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*. A diagnosis of depression in these patients is less common compared with a diagnosis of anxiety.

### **G&H** Does the microbiome influence the brain, or does the brain influence the microbiome?

**EM** Based on animal studies, there are clearly pathways that allow communication in both directions. A study found that when chronic stress was produced in mice, their gut microbial composition was altered. However, when stool samples were transplanted from the stressed mice into nonstressed mice, the nonstressed mice developed altered emotional behavior. Thus, there is good evidence that stress causes the brain to send signals to the gut, resulting in altered gut microbial composition and function, and that changes in the composition of the microbes (either from a fecal microbiota transplant or from antibiotic treatment) result in altered microbial signals being sent to the brain.

In humans, the 2 previously mentioned unpublished studies utilizing cognitive behavioral therapy and mindfulness-based stress reduction provide evidence for communication from the brain to the gut. A study by Dr Tillisch and colleagues that was published in *Gastroenterology* had previously demonstrated that if the normal gut microbiome in healthy young women is perturbed, brain function could be changed in response to a laboratory emotion recognition test. Therefore, data exist that the influence is bidirectional, and that the involved pathways are the autonomic nervous system (going from the brain to the gut) and the vagus nerve (which communicates changes in the gut microbiome to the brain).

### **G&H** What do the data suggest regarding the role of psychological distress in the microbiome? Is there a connection between childhood trauma and IBS?

**EM** In both animal and human studies, there is evidence that early-life trauma or stress has a detrimental effect on IBS. A child may experience a range of factors (eg, chronic illness of the primary caregivers; death of a parent; marital discord of parents or caregivers; physical, verbal, or sexual abuse) that permanently bias the stress responsiveness of the brain. My colleagues and I performed a study showing that these early-life influences increased the risk for IBS, and previous studies had shown similar effects for a whole range of medical illnesses, including cardiovascular events and mental health disorders. Male patients with IBS appear to be more affected by these experiences than females. It is important to note that there are many attenuating factors in humans; an individual who undergoes early-life trauma but who has a good social support system will experience less detrimental consequences. The risk for IBS is also partially determined by genetic makeup. Childhood trauma may have a greater impact on the manifestation of IBS if there is a family history of depression or IBS.

The role of psychological stress on the gut microbiome has been investigated in animal studies. My colleagues and I conducted a study using a maternal separation model in which a whole litter of pups was removed from the mother for 3 hours a day. The separation stresses the mother, who in turn becomes less caring, which affects the pups. The pups then grow up with a high risk of anxiety-like behavior, altered gastrointestinal function, and even altered gut microbiome.

### **G&H** Can probiotics be used to alter, reverse, or otherwise manage the effects of early-life trauma on IBS?

**EM** Theoretically, it is possible that specific probiotics—or psychobiotics, a term used for the effect of certain microbes on emotional behaviors—could be beneficial in patients with early-life stress-related dysbiosis. My colleagues and I studied 2 groups of patients that differed in their gut microbiome and regional brain structure. The main factor that correlated with an altered microbiome and brain structure was a history of early adverse life events. Exposure to stress increases signaling from the brain to the gut, and we hypothesized that the gut microbiome could be influenced early in its development and that alterations in the gut microbiome would persist throughout life. If this hypothesis is correct, probiotics would be helpful in managing IBS symptoms. However, such results have not been demonstrated convincingly in humans.

## G&H How might the interaction between the microbiome, brain, and IBS be leveraged to develop new diagnostic and treatment strategies?

**EM** Several strategies are being discussed but are not yet available for use. Studies have demonstrated that there is a subset of IBS patients who have a particular gut microbial abnormality, but research is needed to determine whether it should be targeted with a probiotic that currently exists or with novel psychobiotics. Another possibility would be to identify specific metabolites that are produced by microbes (known as postbiotics) and either manipulate the microbes to produce less of the metabolite (ie, “drugging the bug”) or to provide a probiotic that stimulates production of the metabolite. In the latter case, a prebiotic would be beneficial in boosting the growth of a certain group of microbes that may be deficient in a given patient. In contrast to the current approach of empiric treatment with pre- or probiotics, in a few years we may be able to fingerprint each patient based on his or her gut microbial composition and blood or stool metabolites and tailor a particular intervention to the individual microbial fingerprint. Several companies (including Viome, uBiome, and DayTwo) are now working on such an approach.

## G&H What are the priorities of research in this field?

**EM** The main priority is to study a large number of well-characterized IBS patients in order to narrow down the subgroups of patients who have gut microbial alterations or changes in the gut microbial metabolites. Several studies are currently ongoing, and results should be available within the next couple of years.

The second priority is to determine the causality of the changes in the microbiome related to top-down influences of the brain and whether they are responsible for causing IBS symptoms. Right now, we only have information about associations between altered microbes, altered brain structure function, behavior, and symptoms. Identifying causality requires an intervention either to the

brain or to the microbes to see if the symptoms change, and this will take time.

Lastly, we need to develop diagnostic tests that will allow clinicians to make a diagnosis of IBS or an IBS subtype that would need to be treated in a particular way with a specific intervention. This goal may also take several years to achieve.

It is important to note that all of the currently available treatments and interventions are empiric and not based on a definitive pattern of the microbiome. However, science is rapidly evolving, including the use of metabolomics, shotgun metagenomics, and metatranscriptomics. Additionally, we are just beginning to characterize the virome and the fungi living in the gut, and their interactions with the microbes. Despite all the excitement about the rapidly evolving microbiome science, it is important to realize that we are only at the earliest stages of understanding of this very complex system living in our gut.

*Dr Mayer serves on the scientific advisory boards of Danone, Viome, Axial Biotherapeutics, Amare, Pharmavite, and Prolacta Bioscience, and is the author of the book The Mind-Gut Connection.*

## Suggested Reading

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