ADVANCES IN IBS

Current Developments in the Treatment of Irritable Bowel Syndrome

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The Brain-Gut-Microbiome Axis and Irritable Bowel Syndrome

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

PB Communication between the brain and the gut occurs along various pathways within the body. The enteric nervous system, which is sometimes called the second brain, is responsible for managing digestion and gut motility, with inputs from the autonomic nervous system that include sympathetic and parasympathetic nerves, such as the vagus nerve. The sensory signals arising from the gut are processed in the brain, with the insular cortex playing an important role. Other brain regions, such as the hippocampus and amygdala, are also important, as they are involved in the regulation of anxiety and depression, which are the 2 main psychiatric comorbidities of irritable bowel syndrome (IBS). The gut-brain communication is bidirectional, and there is evidence that a disruption in either of these pathways can contribute to symptoms of IBS, such as abdominal pain and altered bowel habits (constipation or diarrhea), or to psychiatric comorbidities.

G&H What is the role of the gut microbiome in the pathogenesis of IBS?

PB IBS is a disorder of gut-brain communication, and accumulating data suggest that the gut microbiome plays a key role in its pathogenesis. There are several lines of evidence to support this concept. One of the highest risk factors for developing IBS is infectious gastroenteritis, whether caused by pathogenic bacteria, viruses, or parasitic infections. Research suggests that approximately 10% of people who have bacterial gastroenteritis develop postinfectious IBS. Antibiotics, which are sometimes prescribed for nongastrointestinal causes to fight infections, can trigger an imbalance of gut bacteria, making IBS more likely in some individuals. However, antibiotics have been also shown to be beneficial in some patients with IBS, mainly in those with diarrhea or abnormal gut microbiota in the small intestine.

Multiple studies have demonstrated differences in the composition and function of the gut microbiome within a subset of patients with IBS compared to healthy controls. In vitro and animal studies have also reported that individual strains of bacteria can directly influence functions of the gut, such as motility, permeability, and visceral sensation.

Finally, there is a proof of concept that microbiota from patients with IBS can induce gut dysfunction. My colleagues and I performed a study several years ago in which we collected stool samples from patients with diarrhea-predominant IBS as well as from healthy controls, which we then used to colonize germ-free mice. We found that the mice who received fecal microbiota from the patients with IBS developed abnormalities that are also seen in patients, such as faster intestinal transit, increased gut permeability, and low-grade inflammation; some even

exhibited signs of anxiety. These results demonstrate the potential of the gut microbiota to contribute to both intestinal and behavioral manifestations of IBS.

G&H What is the relationship between gut microbiota and psychiatric disorders such as depression and anxiety?

PB Several studies show that patients with major depression or generalized anxiety disorder have different microbiota profiles compared to healthy controls. Translational research, such as the aforementioned study that my colleagues and I performed, suggests that anxiety-like behaviors and changes in brain chemistry can be triggered by transplanting fecal microbiota from patients with depression and anxiety. However, clinicians should be cautious in interpreting the results from clinical studies on microbiome profiles. It is known that medication can change the microbiota composition, and most patients with major depression, anxiety, or schizophrenia take at least 1 psychotropic medication. Furthermore, many of these patients with psychiatric disorders have altered dietary habits, and it has been established that long-term diet is one of the main determinants of microbiome composition and activity. Therefore, we need more studies, both clinical and translational, to clearly establish the role of gut microbiota in psychiatric abnormalities.

G&H How common are psychiatric comorbidities in patients with IBS?

PB Data show that a significant proportion of patients with IBS have psychiatric comorbidities. Studies performed in primary care centers found that approximately half of patients with IBS have at least 1 psychiatric comorbidity, while data from tertiary centers suggest that up to 90% of patients have a psychiatric comorbidity. Anxiety and, to a lesser extent, depression are the most common psychiatric comorbidities in patients with IBS.

G&H Are there data to support a correlation between oxidative stress and IBS?

PB Clinical data on this topic are lacking, although it is well established that low-grade inflammation, which has been documented in a subset of patients with IBS, can lead to an increased level of oxidative stress. Data in animal models also suggest this trend. In the aforementioned study our group conducted, mice who were colonized with fecal microbiota from patients with IBS displayed low-grade inflammation, and, when analyzing in detail which genes were involved, we found that one of the pathways that was activated was the reactive oxygen species. Thus, at least in mice colonized with IBS microbiota, there is evidence of oxidative stress. However, more high-quality studies are needed in this area.

G&H What have studies shown regarding the association between the microbiome and neurologic disorders?

PB Numerous animal studies investigating neurologic disorders (eg, Alzheimer disease and Parkinson disease) suggest that gut microbiota are an important modifier of disease. Clinical studies have reported different microbiome profiles between patients with neurologic disorders and healthy controls, suggesting that microbiota can play an important role. Patients with neurologic disorders are usually taking multiple medications, which, as stated earlier, are known to affect microbiome profiles.

From the mechanistic point of view, some neuropsychiatric disorders have an immune component, and it is known that the gut microbiome shapes the immune system and can induce low-grade inflammation. Gut bacteria can produce neurotransmitters (eg, dopamine, norepinephrine, serotonin) and other neuroactive metabolites and alter host production of neurotransmitters, which is another pathway through which the gut microbiome could affect neuropsychiatric diseases.

G&H What have animal studies shown regarding the effect of probiotics on symptoms of IBS? Are clinical data available?

PB A large number of animal studies have shown that certain strains of probiotics have beneficial effects on the immune system, gut motility and permeability, and visceral sensitivity, and have identified specific pathways through which probiotic bacteria signal to the host. Evidence in humans is rather limited, but I would like to highlight 1 study that demonstrates that probiotics can affect multiple pathways. A mechanistic study from a group in the Netherlands randomized healthy volunteers in a crossover design to 3 different probiotics (all *Lactobacillus* species) in drink form, and biopsies from the duodenum were taken 6 hours later. The authors found that the probiotics had different effects on gene expression: while one affected immune response pathways and hormonal signaling, another altered genes involved in the Th1/Th2 balance, and the third affected wound healing and angiogenesis.

Many clinical trials have shown that certain probiotics are beneficial for patients with IBS; however, these studies tend to be smaller and have slightly different outcomes. Some of these studies suggest that probiotics reduce visceral hypersensitivity or exert anti-inflammatory effects,

whereas other probiotics improve intestinal motility, bloating, and flatulence. My colleagues and I performed a clinical study in patients with IBS and comorbid depression and found that administration of *Bifidobacterium longum* NCC3001 improved not only IBS symptoms but also decreased depression scores and altered brain activation patterns, as assessed by magnetic resonance imaging. Thus, while many small studies suggested that probiotics may work in IBS, most of these were not reproduced, and some studies showed no benefit. Overall, strong clinical evidence is lacking to recommend specific probiotics to treat patients with IBS. In this regard, the American Gastroenterological Association recently published new guidelines on the use of probiotics in chronic gastrointestinal diseases, including IBS.

G&H What other microbiota manipulation strategies are available for IBS management?

PB Antibiotics, as mentioned earlier, have a role in IBS treatment. In the United States and Canada, rifaximin (Xifaxan, Salix) is used quite frequently and can be beneficial in a proportion of patients. Fecal microbiota transplantation (FMT) is a highly debated strategy for IBS management. Several previous randomized, placebo-controlled trials yielded controversial results, but a recently published study from a group in Norway showed that FMT can be highly beneficial in patients with IBS. Diet has been shown in both animal and human studies to be a key modifier or determinant of microbiota profile and function. Diet is a complex topic, and more research is needed to better understand the microbiota diet–host interaction in order to recommend specific diets to individual patients. Prebiotics, which are nondigestible substances that serve as food for the gut microbiota, can preferentially promote certain beneficial bacteria.

G&H Are any other types of microbiome-based therapeutic options being explored?

PB One approach is ecobiotherapy using defined microbial communities, which could replace FMT in the future. While FMT uses whole microbiota from a healthy donor, ecobiotherapy utilizes a selected group of bacteria based on their functional properties. Several research groups and companies are exploring this option. An important aspect that differs between the 2 approaches is safety; with FMT, there is a theoretical possibility of transferring pathogens (bacterial or viral) from donors to recipients. Now in the era of COVID-19, this notion may affect the way both patients and clinicians perceive FMT. Another approach is bacteriophage therapy, which uses specific viruses to target bacteria that can be detrimental to patients. However, more research is needed to identify the bacteria involved in IBS pathogenesis to allow for targeted therapy.

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

PB The main priority is to identify the specific mechanism and bacteria underlying this disorder. IBS is a heterogeneous disorder with likely multiple pathways involved, and it can be assumed that multiple microbiome-based mechanisms are responsible. Both clinical and translational studies are needed to understand what is happening in patients and to learn the detailed mechanisms in animal models, including humanized mice. Combining these 2 approaches will allow clinicians to better understand the microbiome-host interactions.

Dr Bercik has no relevant conflicts of interest to disclose.

Suggested Reading

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