# ADVANCES IN IBS

Current Developments in the Treatment of Irritable Bowel Syndrome

Section Editor: William D. Chey, MD

## Insights Into the Role of the Microbiome in Irritable Bowel Syndrome

Madhu Grover, MBBS
Associate Professor of Medicine & Physiology
Division of Gastroenterology and Hepatology
Department of Internal Medicine
Mayo Clinic
Rochester, Minnesota

### G&H What microbiota changes may influence the development of irritable bowel syndrome?

**MG** Most of the studies on irritable bowel syndrome (IBS)-related microbiota have been cross-sectional in nature. The idea of the development of IBS has been relatively underaddressed. One of the areas where researchers have been studying IBS development is postinfection IBS. This is where individuals have an episode of gastroenteritis, which is extremely common in the community, and about 10% to 15% of those patients may develop IBS 6 to 9 months later. Many of those patients stay on with that phenotype several years after the infection. Studies have tried to understand microbiome differences in those who develop IBS vs those who do not. Some of the taxa that are of interest include the Rikenellaceae family, particularly bacteria in the *Alistipes* genus. Researchers have been trying to understand not only how the absence of that bacteria may play into IBS development, but also how that may influence the mechanisms underlying IBS development, particularly the regulation of proteases in the gut. From studies performed by my colleagues and I at Mayo and others, we now know that proteases play a significant role in pathophysiology of IBS.

### G&H What are the challenges associated with understanding microbiota changes in IBS?

**MG** There are several challenges to highlight. First, IBS is known to be quite heterogeneous. It has multiple mechanisms and manifestations. It also overlaps with other disorders of gut-brain interaction, such as dyspepsia, as well as with nongastrointestinal disorders, such as fibromyalgia and migraine. Patients with IBS are often on several medications that treat a variety of these conditions and that are known to influence microbiota. The heterogeneity of the disease itself and the heterogeneity that comes from overlap between other gastrointestinal conditions and nongastrointestinal conditions create challenges in performing and interpreting microbiome data. Second, diet influences microbiota, and many IBS patients follow dietary restrictions on a doctor's advice or self-imposed restrictions based on symptoms they experience. This can certainly influence gastrointestinal microbiota. Third, the microbiome changes over time; diversity of gut bacteria may increase or decrease over the course of the day and with the seasons. Even disease severity can influence the microbiome. Furthermore, the phenotype of IBS can change over time. Patients who had constipation can later develop diarrhea. Intrinsic properties of the gut such as transit changes can influence the microbiome. It is known that IBS patients often have slow or rapid motility in the intestinal tract, and motility in the intestinal tract is one of the key determinants of microbiota. These are just a few of the factors that can influence the microbiome and thus pose unique challenges when studying IBS.

### G&H What are the key drivers of the differences in the microbiota seen in IBS?

**MG** IBS phenotype (diarrhea vs constipation and associated transit variation in the gut) is likely one of the most

prominent drivers of microbiota changes, followed by diet-mediated changes. Other factors include psychosocial stress, comorbidities, and medications. Although it is not comprehensively studied, plausibly the mechanisms underlying IBS can also have distinct effects (eg, postinfection IBS vs general IBS, IBS associated with bile acid diarrhea).

### **G&H** How does intestinal barrier dysfunction relate to IBS symptomatology?

**MG** When thinking about the peripheral pathophysiology of IBS, there are 3 main aspects to consider. These are transit, which is essentially gut motility; sensation, which is how the gut perceives a signal from the lumen; and barrier, which is how the gut responds to allowing or inhibiting the passage of noxious substances that are coming into the lumen. The lumen of the gastrointestinal tract has the largest interface with one's external environment. The gut is constantly challenged through dietary and infectious stimuli. Thankfully, the gut has evolved with a barrier, which inhibits passage of not-so-friendly substances from the lumen into the submucosal space.

Studies have shown that about 35% to 40% of IBS patients have impaired barrier function. Some studies have observed this in the small bowel and others in the colon. Barrier disruption is associated with, for example, severity of abdominal pain in IBS. Patients who have a disrupted barrier tend to have more abdominal pain, and there are some plausible mechanisms for that. Luminal mediators like proteases can disrupt the intestinal barrier and excite the visceral nerves, innervating the gut, and hence can cause pain.

More research is needed in this area. However, an association between barrier disruptions and clinical symptomatology has been reported, again, particularly with abdominal pain, and this happens more so in IBS with diarrhea. My colleagues and I performed a study of IBS with constipation, and we did not see the barrier changes that are seen, for example, in diarrhea-predominant IBS. This again reflects the heterogeneity of IBS.

### **G&H** To what degree are barrier changes associated with psychological comorbidities and quality of life?

**MG** First, it should be noted that psychosocial stress, such as anxiety, depression, and somatization, has been shown to disrupt the gut barrier. In an interesting study performed in Europe, researchers took jejunal biopsies from healthy volunteers, then immersed the volunteers' hands in extremely cold water for several minutes. Afterward, the jejunal biopsies were repeated. This brief stress was enough to cause gene expression and protein changes in the jejunal biopsies, indicating that a physical stress can alter gut barrier properties. The impact of stress induced by public speaking was measured in another study in which students were evaluated before and after they gave a public speech. This stress also induced barrier loss along with an increase in the levels of the stress hormones. These findings suggest that the hypothalamic-pituitary-adrenal axis and the stress hormones released downstream of that likely weaken the gastrointestinal barrier.

This influence of stress is also manifested in postinfection IBS because individuals who have increased stress during infection or in the months preceding infection are at higher risk for developing IBS. This begs the question, what is the interplay between stress coming from the central nervous system and the barrier, as well as neuronal properties? Basic science work has been done in this area comparing animals exposed to infections with animals exposed to infections plus a psychological stress. When stress is added on the top of an infection, the odds of developing visceral hypersensitivity are much higher. To summarize, both association and mechanistic studies have linked stress to a disrupted barrier and to development of postinfection IBS. Again, there are still questions that need to be resolved (eg, how is stress really influencing the barrier and if that then affects IBS development).

### **G&H** What is the metabolome and why might it be important to IBS?

**MG** At the beginning of the journey with IBS and the microbiome, investigators were curious about which microbes are changed. As the field has evolved, these changes have been largely realized to be dependent on the context of the host, their diet, and environment. The broader idea of dysbiosis has been challenged, as the normal microbiome is poorly understood and based on the interactions with the host (ie, an abnormal microbiome for one host may not be abnormal for another host). This realization has opened the paradigm for trying to move away from understanding who is there, to what is their functionality, and how is this microbiome change affecting that host and its functioning.

Thus, researchers started unraveling the substances that microbiota produce, either directly or in conjunction with the host. Directly, these are enzymes, proteins, and other metabolites that bacteria intrinsically produce, and then there are metabolites that bacteria produce such as short-chain fatty acids. Alternatively, microbiota can influence proteins and metabolites produced by the host. When it comes to effects on the host function, researchers are appreciating how microbial metabolites not only affect the peripheral function in the gut but also affect

brain function. Over the years, research has been moving into a renaissance where the metabolome (as well as the proteome, or the metaproteome of the microbiota) is becoming highly relevant and increasingly more appreciated for its influence on the functioning of the host.

### G&H What are the key treatment strategies targeting the microbiota in patients with IBS?

**MG** Although there is interest, obviously, in microbiota-based therapies, there has been little progress in this area. The marketing of some products has, in fact, gone way ahead of the available scientific rationale. When it comes to hard evidence, there are data for only a few therapies. One robust placebo-controlled clinical trial suggested that *Bifidobacterium infantis* 35624 may be helpful for treating IBS, particularly bloating and diarrhea symptoms. Other studies have looked at either single bacteria or a simplified consortium, and many have not shown a signal for efficacy. Providers must be careful when thinking about microbiota supplementation, as both the type and doses can have undesired effects.

One robust placebo-controlled clinical trial suggested that *Bifidobacterium infantis* 35624 may be helpful for treating IBS, particularly bloating and diarrhea symptoms.

Another way of supplementing microbiota is through fecal microbiota transplantation (FMT), which has been in existence for *Clostridioides difficile* infection and is of great interest to both patients with IBS and investigators. However, studies on FMT have shown heterogeneity in the results. There have been some trials in which the fecal material from a very well-defined donor, or super-donor, was transplanted into patients, and investigators found a very good response that lasted upwards of 2 to 3 years after the single FMT treatment. However, the effects have also varied based on the route of administration.

More progress is likely to come in both areas, with probiotics and prebiotics as well as with complex community such as with FMT. Treatment response will likely remain context-dependent; for example, maybe not all IBS patients are suitable for the same treatment, and maybe there are subsets within IBS who can benefit from these replacements. Potentially, providers must be more careful in who to use as a donor and whether the donor has the right kind of bacteria that can be helpful for the patients. Currently, the answer is complex. The hope is that some of the ongoing mechanistic studies in the field (again, in the areas of metabolomics and host-bacterial interactions, where the effort is to try to understand how the presence or absence of a particular microbe affects host function) will yield future microbiome-treatment strategies.

### G&H What are some key considerations for future studies examining the role of the microbiome in IBS?

**MG** Researchers in the field must be more careful about the various challenges and factors that can influence microbiota. Studies need to be larger and ideally should take multiple samples from the same patient. More care should be given to capturing the dietary intake of IBS patients (this way, any potential confounding effects of diet can be used in the analysis). Efforts to help standardize how microbiota samples are collected and processed would be welcome improvements in microbiota assessment for patients.

***Disclosures***

*Dr Grover receives funding from the National Institutes of Health for his work on microbiota in IBS.*

## Suggested Reading

Berumen A, Edwinson AL, Grover M. Post-infection irritable bowel syndrome. *Gastroenterol Clin North Am.* 2021;50(2):445-461.

Edwinson AL, Yang L, Peters S, et al. Gut microbial β-glucuronidases regulate host luminal proteases and are depleted in irritable bowel syndrome. *Nat Microbiol.* 2022;7(5):680-694.

Hanning N, Edwinson AL, Ceuleers H, et al. Intestinal barrier dysfunction in irritable bowel syndrome: a systematic review. *Therap Adv Gastroenterol.* 2021;14:1756284821993586.

Peters SA, Edogawa S, Sundt WJ, et al. Constipation-predominant irritable bowel syndrome females have normal colonic barrier and secretory function. *Am J Gastroenterol.* 2017;112(6):913-923.

Ringel-Kulka T, McRorie J, Ringel Y. Multi-center, double-blind, randomized, placebo-controlled, parallel-group study to evaluate the benefit of the probiotic *Bifidobacterium infantis* 35624 in non-patients with symptoms of abdominal discomfort and bloating. *Am J Gastroenterol.* 2017;112(1):145-151.