

ADVANCES IN IBS

Current Developments in the Treatment of Irritable Bowel Syndrome

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Microbiome-Based Treatment Strategies for Irritable Bowel Syndrome



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G&H What is the relationship between irritable bowel syndrome and the microbiome?

WC There is evidence to suggest that the microbiome is implicated in the pathogenesis of irritable bowel syndrome (IBS), at least in some patients. First, a significant proportion of IBS patients can trace their symptom onset back to some type of acute gastroenteritis, whether it is bacterial, viral, or parasitic gastroenteritis, as all have been associated with an increased risk of developing postinfection IBS. Between approximately 7% and 15% of patients with an acute gastroenteritis will develop chronic symptoms compatible with the diagnosis of IBS. Second, observational studies have suggested that children who were exposed to multiple courses of antibiotics had an increased likelihood of developing IBS later in life. Third, patients with IBS have a microbiome signature and metabolomics (the metabolic consequences of the microbiome) that differ from that of healthy controls. Fourth, microbiome-based strategies (eg, probiotics, diet, antibiotics) offer benefits to subsets of patients with IBS.

G&H How do probiotics and prebiotics interact with the microbiome?

WC Probiotics are bacteria, which, when consumed in sufficient quantities, confer a health benefit to the host. Prebiotics are foods, usually carbohydrates, that promote the growth of probiotic bacteria in the gastrointestinal (GI) tract. Synbiotics are the combination of a prebiotic and probiotic.

G&H What do guidelines recommend regarding the use of prebiotics to treat IBS symptoms?

WC There is very little evidence to support the use of prebiotics in patients with IBS. That being said, one of the challenges that clinicians currently face is the difficulty of isolating and formulating probiotics in a way that delivers the right dose, the right strain, and viable organisms to individuals who purchase a probiotic supplement at a store. Consumers and gastroenterologists should be aware of the quality and viability of the product that is bought at a drugstore or supermarket. Another popular microbiome-based strategy is the use of antibiotics. Although antibiotics work in some patients, unintended consequences are possible, particularly with repeated courses of systemically absorbed antibiotics. Therefore, a prebiotic strategy is attractive, as it is not nearly as difficult to develop a specific carbohydrate and formulate it into a product for use in patients with IBS. However, until more evidence is available, guideline recommendations are lacking.

G&H What are the possible mechanisms by which probiotics may impact IBS?

WC There are many potential mechanisms of probiotic activity that might offer benefits in patients with IBS. Mechanisms thought to be important to the pathogenesis of IBS are that probiotics alter the ability of pathogenic bacteria to access the mucosa, and that probiotics have

effects on intestinal permeability and immune activation. Probiotics may also exert effects on neuroendocrine cell function, and they can have effects on the luminal microenvironment, affecting such factors as bile acid metabolism.

G&H What has research shown regarding the safety and efficacy of probiotics in managing symptoms of IBS?

WC Numerous studies and meta-analyses have been performed on the use of various probiotic supplements in IBS. When the data are evaluated in aggregate, there appears to be a small but statistically significant benefit offered by probiotics compared to placebo in patients with IBS. However, as Dr Alexander C. Ford and colleagues addressed in a recent systematic review and meta-analysis, specific studies do not allow precise recommendations for individual probiotic supplements, making it challenging for clinicians to recommend certain probiotics to their patients. Likely the best evidence for an individual probiotic supplement is for *Bifidobacterium infantis* 35624 (Align, Procter & Gamble). Currently, there are 2 randomized, controlled trials suggesting benefit for this probiotic in patients with IBS.

G&H What should patients know about the differences between probiotic supplements, functional foods, and medications?

WC Probiotics, as defined earlier, are bacteria that offer a health benefit when consumed in sufficient quantities. Patients can purchase probiotics at drugstores and supermarkets. As such, there are issues regarding quality control and probiotic viability, as patients cannot know exactly what the product contains nor can they know whether or not what they are consuming is viable. On the other hand, probiotics have very little in the way of side effects.

Functional foods are foods or food components that can be consumed to exert a health benefit. The primary challenge with foods is that they are complex; when eating whole foods or even processed foods, patients are ingesting multiple components at once and not just the part that they are intending. Just as a functional food will have some proposed effect and potential benefit in the GI tract, the same can be said for all the other elements that are being ingested.

Medications are regulated by the US Food and Drug Administration and are pure. They contain precisely what the manufacturer says they will contain. Thus, quality control is much improved, and there are no issues of viability because they are not live organisms

but are biochemical agents that are intended to exert some effect. The downside is that no drug is completely free of side effects, and some side effects are more significant than others.

G&H What are the effects of antibiotics on the microbiome?

WC Most of the efficacy data for diarrhea-predominant IBS (IBS-D) are on rifaximin (Xifaxan, Salix), which is a poorly absorbed broad-spectrum antibiotic that acts almost exclusively within the GI tract. Because rifaximin is lumenally acting, it significantly reduces the unintended consequences in other parts of the body that are associated with taking a systemically absorbed antibiotic. Multiple randomized, controlled trials have consistently shown a statistically significantly greater likelihood of overall symptom improvement in patients with IBS-D who take rifaximin compared to placebo. Approximately 45% to 50% of patients improve on rifaximin, which is approximately 10% more than patients who take placebo.

G&H What are the safety and adverse-event profiles of rifaximin?

WC An integrated safety analysis of randomized, controlled trials on rifaximin in IBS-D patients found that the adverse-event profile related to short-term therapy (approximately 12 weeks) was very similar to that of placebo. This differs from systemically absorbed antibiotics, which are often associated with a wide range of adverse events, such as nausea, vomiting, dyspepsia, diarrhea, and *Clostridium difficile* colitis, and suggests that rifaximin is safe to use for the treatment of IBS-D.

G&H Which dietary strategies are available to manage IBS symptoms?

WC My colleagues and I conducted a survey of 1500 gastroenterologists from across the United States and found that the most commonly utilized dietary strategies in clinical practice are a lactose-reduced diet; a gluten-free diet; and the low-fermentable oligosaccharide, disaccharide, monosaccharide, and polyol (FOD-MAP) diet. Interestingly, a majority of patients will try to identify culprit foods and eliminate them from their diet using a trial-and-error method, employing a lactose-reduced diet and gluten-free diet, before meeting with their gastroenterologist. However, of the 3 diets, the one that gastroenterologists most commonly recommend is the low-FODMAP diet. Additionally, the greatest body of data supports the efficacy of the low-FODMAP diet

in patients with IBS. Several randomized, controlled trials have evaluated the low-FODMAP diet vs a range of different control diets, including placebo diets, high-FODMAP diets, and standard IBS diets, in this patient population. The weight of the data reported in a recently published meta-analysis suggests that the low-FODMAP diet offers statistically significant benefits vs comparator diets in patients with IBS. The meta-analysis also contained 2 studies that evaluated a gluten-free diet. We concluded that the evidence available does not support any benefit of a gluten-free diet in patients with IBS; however, it may be premature to make any kind of conclusive recommendation in that regard.

G&H What are the mechanisms by which the low-FODMAP diet affects IBS symptoms?

WC It is understood that the low-FODMAP diet benefits patients with IBS by reducing the consumption of short-chain carbohydrates. These carbohydrates are difficult, if not impossible, for the small intestine to break down and absorb, leading to an increase in substrates reaching the colon. The substrates are then fermented by bacteria in the colon to produce short-chain fatty acids and gases, which alter the luminal microenvironment and cause distention of the colon, both of which can trigger symptoms in patients with IBS. It is thought, but not proven, that short-chain carbohydrates and other byproducts of fermentation may lead to a cascade of other effects that could also lead to benefits in patients with IBS. For example, fermentation byproducts may exert effects (positive or negative) on the microbiome as well as on permeability and immune activation. There is much that remains to be understood that extends beyond fermentation and the production of gas and short-chain fatty acids that trigger symptoms in patients with IBS.

G&H Can the low-FODMAP diet be combined with probiotics?

WC One of the observations that has been made regarding the low-FODMAP diet is that it may reduce the production of butyrate in the colon. Because butyrate is an important energy source for colonocytes, this reduction may be a negative effect of the low-FODMAP diet. A recent study by researchers at King's College London evaluated the effects of probiotics vs the low-FODMAP diet vs probiotics and the low-FODMAP diet combined in patients with IBS. The study confirmed that the low-FODMAP diet offers benefits compared with a placebo diet, and found that giving a probiotic supplement along with the low-FODMAP diet actually reduced the impact of the low-FODMAP diet on the fecal microbiome.

G&H How effective is fecal microbiota transplantation in treating IBS symptoms?

WC The use of fecal microbiota transplantation (FMT) for the treatment of IBS is a controversial issue. Several studies have evaluated FMT in patients with IBS, with mixed results. For example, a Scandinavian study found that FMT offered benefits to overall symptoms in patients with IBS. In contrast, a study conducted in the United States did not find benefits of FMT vs sham transplantation. Thus, FMT should be considered experimental at the current time.

G&H What role will biomarker-based strategies play in treating patients with IBS?

WC This is another area that is experimental and undergoing evaluation. The microbiome offers potentially attractive targets for the development of biomarkers that could identify patients who are more or less likely to improve with microbiome-based strategies. For example, several studies have identified characteristics of the microbiome or metabolome, collected from stool samples of patients with IBS, that predict a greater likelihood of response to the low-FODMAP diet. Additionally, volatile organic compounds measured in headspace gases from stool collected in patients with IBS may also predict a greater likelihood of response to the low-FODMAP diet. This evidence, while not conclusive, points to the possibility of leveraging the microbiome in a way that allows clinicians to choose the right treatment for the right patient.

Dr Chey serves as a consultant for Allergan, Biomerica, IM HealthScience, Ironwood Pharmaceuticals, OrphoMed, Outpost Medicine, QOL Medical, Salix/Valeant, Takeda/Shire, Urovant Sciences, Ritter Pharmaceuticals, and Forcont Medical. He has received research grants from Biomerica, Commonwealth Diagnostics, QOL Medical, and Salix/Valeant.

Suggested Reading

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