

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Diseases

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Probiotic Therapies for IBD

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G&H How do orally administered probiotics affect the gastrointestinal tract?

RF In the last decade, researchers have gained a much more detailed understanding of the specific physiologic actions of probiotics within the gastrointestinal tract and the body's mucosal and systemic immune system, which distinguishes them from general nutrition. When a meal is eaten, it imparts general health and nutrition, as does any food. When probiotics are ingested, it has historically been taught that similar general health benefits were accrued. However, it is now becoming clear that the health benefits attained from probiotics can be very specific, specific enough that they hover or cross over into drug-like effects.

It appears that these specific health benefits are mediated by unique physiologic effects of probiotics on the body. Some probiotics, we know, are available to attach themselves to the epithelial cells lining the gastrointestinal tract and prevent bacteria and viruses from crossing the lumina into the bloodstream. Probiotics are also able to secrete antimicrobial products that destroy pathogenic bacteria in the lumina of the intestine. Some probiotics can reduce secretions or diarrhea. They can also change the way the body's mucosal immune system functions, making it less inflammatory by changing the various cytokines and altering T-cell function. Recently, gastroenterologists have demonstrated that probiotics are able to downregulate the immune system by sequestering T-cells in the mesenteric lymph nodes. One of the most impor-

tant discoveries regarding probiotic mechanisms is their ability to affect the dendritic cells of the innate immune system. These are cells in the lamina propria that sense and react to the luminal microflora.

Thus, probiotics appear to have the capacity to change the body in ways beyond general health and nutrition, and these physiologic effects of probiotics may translate into disease treatment and prevention. For example, in preventing pathogenic bacteria from migrating from the lumina to the lamina propria, probiotics prevent an important mechanism in rotavirus or *Clostridium difficile*-associated diarrhea infections. Probiotics' ability to induce changes in the mucosal and systemic immune systems and downregulate inflammatory response is most likely important in their role in inflammatory bowel disease (IBD). As science uncovers these and additional mechanism of action of various probiotics, it is very likely that we will be able to match a probiotic to treatment of individual gastrointestinal diseases.

G&H What probiotics have proven useful in the setting of IBD?

RF The best data available in the setting of IBD are in pouchitis, where three separate randomized, controlled trials have provided Level 1 evidence demonstrating probiotics' ability to prevent pouchitis reactivation. If patients with pouchitis can achieve remission with antibiotic therapies, they can then be administered a probiotic to prevent the pouchitis from returning. Further, in patients with a newly constructed pouch given probiotics, pouchitis appears to be prevented, or delayed, from occurring. However, in patients with active pouchitis, probiotics do not seem to be useful until the disease is controlled with antibiotics. The probiotic VSL#3 (VSL Pharmaceuticals) is the probiotic most studied in pouchitis. VSL#3 is a combination product, containing eight different probiotics.

In ulcerative colitis (UC), for induction of remission, there is Level 2 evidence utilizing the probiotic *Escherichia coli* nissle. Three randomized controlled trials have demonstrated this. For maintenance of remission, there are three randomized controlled trials demonstrating Level 1 evidence with *E. coli* nissle achieving efficacy levels similar

to mesalamine. Smaller open-label trials of other probiotics have not demonstrated the same level of efficacy to that found with *E. coli* nissle. However, there are ongoing large randomized, controlled trials examining induction of remission in UC with several probiotics formulations.

In Crohn's disease, the only data are from small pilot studies ranging anywhere from 4 to 25 patients. Results have been positive, but these open-label trials are difficult to use as evidence. To date, there have been no large, randomized controlled trials in this setting.

Most of the IBD studies have been conducted in the mild-to-moderate disease population, rather than in patients with severe/fulminant disease. This is most likely the population where probiotics will have a role as a primary therapy.

G&H Are probiotics generally administered in combination with other therapies?

RF In many of the probiotic trials that have been conducted, they have been added to existing therapy. For example, in the ulcerative colitis trials, probiotics were added to existing therapy regimens (eg, 5-aminosalicylates, steroids, immune modulators).

Another cotherapy possibility is the addition of a prebiotic. Probiotics are bacteria, which require food in the form of carbohydrates to grow. Prebiotics are essentially food for probiotics that can be administered simultaneously so that the probiotics grow faster and bigger and reproduce more rapidly. The probiotics that may grow with prebiotic administration could be endogenous within the gastrointestinal tract or could be administered with the prebiotic, in a symbiotic manner.

G&H Are there challenges in the administration of probiotics that differ from those for other medical therapies?

RF The technology for capturing and growing these bacteria and putting them into capsules certainly exists, and these capsules can be taken like any other pill. The main concern with probiotics is one of regulation. In a recent sampling of 15 over-the-counter probiotics, 11 were formulated as advertised; 4 were either not formulated at the advertised dose or contained dead bacteria. If these products are going to be utilized as drugs to treat specific diseases, they need to be regulated like drugs. The US Food and Drug Administration (FDA) will need to devise policies and enforce the same level of consistent quality

in manufacturing that they would for any other medical therapy. Currently, probiotics are classified as food supplements or natural health products. Manufacturing regulations for food and health products are not the same as those for drugs. Currently, anyone with the means can manufacture a probiotic, put it in a capsule, and sell it, and there are few regulations to manage the health claims or the quality of the product.

If probiotics are working in randomized controlled trials and then are not working when patients take them, lack of regulation may be the reason. The patient could be taking a completely invalid formulation found on the Internet or at the local health food store. Further, not all probiotics are the same. Although VSL#3 has been shown to be effective in pouchitis, this evidence cannot be extended to every probiotic on the market. In the research community, we know that different probiotics create different physiologic responses. Thus, not all probiotics will be effective in all disorders. Our regulatory agencies need to catch up with the science.

G&H What are the next steps in the research of probiotics?

RF Future research needs to focus on the individual mechanisms of action for the different probiotics, and these mechanisms need to be specifically linked to the disease states that would most benefit from them and then tested in appropriately designed randomized clinical trials. For example, if a patient has an infected finger, he or she should not receive an antihypertensive medication. They would need an antibiotic. Probiotics need to be considered in the same way. Define the mechanisms of action, and then prescribe based upon the disease where efficacy has been documented. I believe this is where we need more research. Mechanisms need to be identified for the various probiotics and clinical trials designed accordingly.

Suggested Reading

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