

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Efficacy of Probiotics for the Management of Inflammatory Bowel Disease

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G&H What is the rationale for using probiotics as a treatment for inflammatory bowel disease?

RBS Normal gut bacteria (microbiota) have been implicated in the pathogenesis of Crohn's disease (CD) and pouchitis, and they probably contribute to ulcerative colitis (UC) as well. Probiotics are thought to work by several different mechanisms. One mechanism involves altering the composition of the intestinal microbiota by producing bacteriocins, which are products that eliminate certain bacteria, or by altering pH, which will alter the growth characteristics of certain bacteria. As a result of these changes, probiotics could decrease the concentration and perhaps composition of gut bacteria that preferentially cause inflammatory bowel disease (IBD).

A second mechanism involves altering the epithelial barrier function of the intestine. For example, some probiotics produce a metabolite called butyrate, which is a short-chain fatty acid (SCFA) that is very important for the health of colonocytes, particularly the epithelial cells in the rectum and left colon. In addition to improving the viability, health, and repair of the mucosal lining through production of SCFAs, probiotics have been shown to block attachment of pathogenic bacteria to gut epithelial cells, thereby preventing invasion by pathogenic gut bacteria.

Finally, probiotics have been shown to have important immunoregulatory activity, so certain probiotics and their products can activate regulatory T cells and regulatory pathways, leading to downregulation of inflammation. Conversely, probiotic products can directly turn off effector immune cells that cause tissue damage.

Together, these mechanisms suggest that probiotics have great therapeutic potential, at least from a theoretical standpoint; unfortunately, they have not realized this potential in clinical trials.

G&H In which patients are probiotics most effective?

RBS The efficacy of probiotics in IBD has only been well documented in 2 areas. First, a combination product called VSL#3 (VSL Pharmaceuticals) has been shown to be effective for the management of recurrent pouchitis. In a widely cited study of patients with pouchitis who were in remission following treatment with antibiotics, use of probiotics for 9 months yielded a profound difference in relapse rates: 100% relapse over 9 months in the placebo group versus 15% relapse in the group treated with probiotics.

Probiotics have also shown efficacy for preventing relapse in UC. In one study, *Escherichia coli* Nissle, which is currently available in Europe, was shown to be as effective as low-dose mesalamine for preventing relapse in UC. However, we currently lack any data showing efficacy for probiotics in CD, and there is limited evidence regarding the use of probiotics to treat active UC.

G&H What are the latest data regarding the use of probiotics in IBD?

RBS Some recently published data showed that combinations of probiotics can be effective in active UC. However, the majority of these data have come from relatively small trials. A not-yet-published study was recently conducted in Canada that evaluated probiotics for the prevention of CD recurrence following surgery, with negative results.

G&H Have any studies evaluated the use of probiotics in combination with other treatments?

RBS Yes, researchers are actively studying the possibility of using probiotics in combination with prebiotics, which are food substances that stimulate the growth of protective bacteria and the production of SCFAs such as butyrate. These combinations of a probiotic plus a prebiotic are called synbiotics.

Another combination that has not been well studied but that could have great potential is the use of antibiotics followed by probiotics. The pouchitis study mentioned above is an example of such a combination; remission was induced with an antibiotic and then was maintained with a probiotic.

Studies examining medical therapy in combination with probiotics might also be worthwhile. For example, no one has really explored the possible benefit of using an immunosuppressive agent plus a probiotic, or an immunomodulator combined with a probiotic. Personally, I would love to see a study where remission is induced with corticosteroids, biologic agents, or other medical therapies, and then a probiotic is used to sustain remission. Such an approach seems conceptually promising, but those kinds of studies have not yet been done.

G&H What factors hinder research in this area?

RBS Probiotics are considered to be food substances rather than US Food and Drug Administration (FDA)–approved medications, so companies have very little impetus to perform large, expensive, placebo-controlled trials. To have a probiotic approved as a food product, the manufacturer only needs to show that the product is safe; they do not have to show efficacy. Since probiotic manufacturers do not need to conduct rigorous trials to gain FDA approval, studies of probiotics tend to be hindered by a fairly low budget, which typically results in small sample sizes. For example, the pouchitis study mentioned above had only 20 patients in each group. In most drug studies, in contrast, data are collected from several hundred people.

G&H Which specific probiotics have the most data demonstrating efficacy?

RBS Many probiotics show promise, but only a few have been tested in rigorous clinical trials. In addition to the combination product VSL#3 and *E. coli* Nissle, which have been shown to be effective in patients with pouchitis and UC, respectively, *Lactobacillus rhamnosus* GG has been heavily studied as a possible therapeutic agent. Unfortunately, most of the literature on this probiotic consists of basic science articles; very few clinical trials of *L. rhamnosus* have been conducted. Finally, a yeast product called *Saccharomyces boulardii* has been studied for the treatment of recurrent *Clostridium difficile* infections; while not relating directly to IBD, some well-performed clinical trials have shown that *S. boulardii* can decrease the likelihood of relapse of infection in these patients.

G&H What are possible side effects of probiotics?

RBS Probiotics are generally regarded to be safe, but there are some minor side effects that can limit their use, specifically bloating and increased gas. When patients start taking a probiotic, it alters their microbiota and bacterial metabolism, and a subset of patients will experience distention and gaseousness as a result. Fortunately, these symptoms typically resolve within a couple of weeks with continued administration. While these problems are typically transient, some people do find such symptoms unsettling.

In addition, there are rare reports of sepsis due to probiotics, typically in patients who are already sick or immunosuppressed, such as patients who are hospitalized with multiorgan failure or diabetic complications. In the ambulatory gastroenterology setting, such reports are extraordinarily rare, but the potential for serious side effects still exists in immunosuppressed patients.

G&H What are your main concerns regarding available research in this area?

RBS The biggest issues with probiotic studies are the lack of research funding and the small number of patients who are enrolled in clinical studies. Another impediment has been the lack of mechanistic components in clinical studies; large numbers of in vitro studies have shown that various probiotics may have some therapeutic potential, but researchers have not yet translated these findings into human studies. Another deficit of many clinical trials is their failure to consider subsets of patients who might be particularly responsive to probiotics. For example, if a study could identify patients who have a particular alteration

in their gastrointestinal microbiota, it might find such a group to be particularly responsive to a targeted probiotic treatment. Finally, an unresolved question that needs to be answered in future clinical trials is how various foods affect the retention of probiotics and alter the growth of under-represented, protective bacteria in the gut.

Another major deficit of current research into probiotics is that I believe researchers are emphasizing the wrong group of bacteria when they consider potential probiotics. I think we ought to be emphasizing the protective bacteria that normally live in the body, rather than looking at bacteria that do not normally reside in the gut. A problem with traditional probiotics is that they disappear within 2–3 weeks after administration. Because these probiotics do not colonize the gut, they remain present only as long as the patient continues taking them. In contrast, organisms that are normally found in the body are conceptually much more attractive as probiotics because they could potentially result in permanent alterations of the gastrointestinal microbiota.

Overall, there is tremendous potential for well-designed clinical trials of probiotics, so I would encourage the research community to translate the excitement from basic science studies into clinical studies.

G&H Have clinicians considered using probiotics to prevent disease in patients who are at risk for IBD but have not yet shown symptoms?

RBS I think preventative use of probiotics has huge potential. While such studies have not yet been conducted, I think such studies are needed, particularly since researchers can now perform genetic analyses to identify patients who are at risk for IBD. However, such research will require prospective studies involving many patients who are followed over a long period of time; therefore, such studies will be extremely expensive and must be conducted over many years.

One interesting study that was conducted a few years ago examined the benefit of a particular protective organism called *Faecalibacterium prausnitzii*. In this paper, French investigators showed that the mucosal concentrations of *F. prausnitzii* at the time of surgery predicted postoperative relapse in patients with CD. Specifically, patients who had lower levels of *F. prausnitzii* had higher relapse rates during the follow-up period. These researchers also performed animal studies in which they showed that *F. prausnitzii* and its metabolites could decrease experimental colitis. In theory, if clinicians could identify those patients who have low mucosal levels of

F. prausnitzii at the time of surgery, they might be able to administer *F. prausnitzii* as a probiotic or suggest foods or prebiotics that could stimulate growth of *F. prausnitzii*, and thus protect these patients against relapse.

G&H Overall, are available data sufficient to support the use of probiotics as a treatment for IBD?

RBS I think that data supporting use of probiotics in the majority of patients are marginal. In certain situations, such as relapsing pouchitis, the evidence supporting probiotics is fairly good. Also, use of probiotics is probably safer than long-term use of antibiotics, which is the only real alternative for these patients. However, relapsing pouchitis is probably the only type of IBD in which use of probiotics is well supported. I mentioned a study that showed benefit for probiotics in preventing relapse in quiescent UC, but this study compared probiotics with a very low dose of mesalamine—far below the dose traditionally used in the United States—so I do not know whether that particular study is really clinically relevant.

Given the current data, my attitude regarding the use of probiotics in IBD is that they should be considered as adjunctive therapies. I encourage patients who want to take a probiotic to continue their pharmaceutical-based treatment regimen; they can then use probiotics as a potential adjunct, as the probiotics likely will not cause any severe side effects and could provide some benefit. Unfortunately, the most effective probiotics tend to be the most expensive ones, and most probiotics are not reimbursed by insurance companies. VSL#3 is reimbursed by some insurance companies, but other probiotics are not reimbursed at all. Thus, financial considerations may also play a role in this decision.

Suggested Reading

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