Probiotics in Functional Bowel Disorders
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Growing interest in probiotics
The public’s interest in and spending on probiotics and “functional foods” that claim to provide a health benefit beyond basic nutrition have been climbing steadily. Often marketed through direct-to-consumer advertising, they are seen as natural alternatives to traditional Western medicines. Unfortunately, their purported efficacy is often not justified by unbiased studies, nor does the Food and Drug Administration generally evaluate these claims.

Is the gut microbiota important?
Over the past decade, several areas of research suggest an important role for gut flora in irritable bowel syndrome (IBS) pathogenesis. These include:
- Infectious triggers in post-infectious IBS
- Evidence of intestinal immune activation
- Links between small intestinal bacterial overgrowth and IBS
- Differences in gut microbiota in IBS versus control patients

Moreover, germ-free animal studies have shown alterations in gut motility that normalize following introduction of normal gut flora. Post-infectious animal models of IBS, including the C. jejuni rat infection model developed by our group, recapitulate several features of IBS. Unfortunately, attempts to characterize the altered gut microbiota in humans have yielded inconsistent results in the specific species that are either under-represented or over-abundant. This inconsistency likely reflects both significant disease heterogeneity in IBS and the different techniques used as well as their resolving power in these studies. Potential mechanisms to explain a probiotic effect in functional bowel disease include interactions with the gastrointestinal immune system, direct modulation of intestinal pain, effects on mucosal integrity, reductions in colonic gas made by bacteria, increased short-chain fatty acids and colonic propulsion, and reduced bile acid malabsorption.

What do the studies show?
If alterations in gut microbiota account for a large fraction of IBS, it seems reasonable that probiotics should restore a “healthy” gut microbiota and alleviate IBS symptoms. Unfortunately, the numerous controlled trials of probiotics in IBS have shown mixed results at best. These studies used a variety of probiotic species and strains, with heterogeneity of dosing regimens and clinical endpoints, reviewed by Parkes and colleagues.1

The data are strongest for Bifidobacterium and Lactobacillus strains. Bifidobacterium infantis 35624, Lactobacillus salivarius UCC4331 or placebo was given to 77 patients, and after eight weeks, the B. infantis group had a significant reduction in composite IBS symptom scores and abdominal pain scores versus placebo (P<.05).2 In addition, a decrease in the ratio of IL-10/IL-12 cytokine expression in peripheral mononuclear cells suggested an additional anti-inflammatory effect that was not characterized further. No significant benefit was noted with the Lactobacillus strain.

A larger multicenter study of 362 women with IBS randomized them to receive B. infantis (at a dose of 106, 108 or 1010 CFU daily) or placebo for four weeks followed by a two-week washout.3 Only the middle dose led to statistically significant but modest improvements in abdominal pain, bloating/distention and IBS composite scores at the end of treatment. The unexpected dose response may have reflected poor capsule dissolution and subsequent lack of bioavailability of the higher-dose probiotic following ingestion.

VSL#3 (a probiotic mixture of eight species of Bifidobacterium, Lactobacillus and Streptococcus) or placebo was given to 25 D-IBS patients for eight weeks. No difference in the primary endpoint of global symptom relief or gastrointestinal transit was seen. However, the investigators observed a significant reduction in the secondary endpoint of abdominal bloating.4 A larger follow-up study did not demonstrate a significant benefit for bloating.

Continued on page 2 (see “Probiotics”)
Evaluating Harm in Medications for IBS

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Pharmacologic treatments for irritable bowel syndrome (IBS) have been few, and this condition represents a significant unmet need. Although the pathophysiology of IBS is still being studied, a number of existing hypotheses have generated treatment possibilities. The hypothesis that IBS is derived from alterations in the brain-gut axis has inspired the use of antidepressants and drugs (i.e., alosetron) that manipulate gut transit by acting on serotonin and its receptors. Recently, a hypothesis suggested that IBS is derived from alterations in gut flora, leading to studies of rifaximin in the hopes of improving IBS symptoms by reducing bacterial overgrowth as well as studies of probiotics intended to restore a healthy gut microbiota (see related article on page 1).

As these drugs have emerged as possible IBS treatments, researchers have attempted to determine the relative efficacy of these products. One measuring stick for IBS treatments is the number needed to harm (NNH). Although drugs may have efficacy for IBS, IBS is a very common non-lethal condition, and therefore side effects should be carefully weighed against efficacy. In a recent study in the American Journal of Medicine, Cedars-Sinai researchers conducted a meta-analysis to evaluate drugs for the number needed to harm (NNH). The NNH was calculated by determining the number of subjects who stopped a study drug in excess of placebo. Alysetron and TCAs both had many side effects whose incidence was far greater than placebo. Ironically, for both of these drugs, constipation was seen in greater percentages than improvement in diarrhea.

The NNH was even more telling: approximately 20 for both. In other words, for every 20 subjects who received a drug, one subject had to stop due to a side effect. In contrast, lubiprostone and rifaximin had much lower levels of harmful side effects, with an NNH of greater than 800 for rifaximin and even better for lubiprostone. While lubiprostone produced nausea more commonly in subjects, this did not result in study withdrawal (used as our definition of harm). Interestingly, when harm was balanced with efficacy, for every three patients who benefitted from TCA or alysetron, one had to stop the drug. However, for rifaximin, more than 800 IBS subjects would benefit before one person stopped the drug.

Overall, the study of drug harm is an important exercise. Too often in medicine, we analyze and summarize efficacy. In a condition like IBS, harm is an important outcome. While it is not clear what threshold of harm IBS patients are willing to accept, presenting this information is important to the education of IBS sufferers before they decide on a course of therapy with their physician.

Reference

Disclosure: Dr. Pimentel discovered the use of rifaximin for IBS. Cedars-Sinai holds patent rights to the discovery and has a licensing agreement with Salix Pharmaceuticals Inc., which markets the drug. Dr. Pimentel is a consultant to Salix and serves on its scientific advisory board.

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Gastroesophageal reflux disease (GERD) is one of the most common gastrointestinal disorders in the United States today with a prevalence of 360 cases per 100,000 people. For the majority of patients, this is a self-limited condition that may be improved with changes in lifestyle or medical therapy. However, approximately 25 percent of patients with GERD will develop progressive disease that does not respond to simple therapy.

Laparoscopic Nissen fundoplication surgery to correct GERD has many advantages over traditional surgery, including reduced scarring, reduced recovery time and reduced risk of infection. In many cases, a patient’s total recovery time can be as little as one to two weeks, compared with four to six weeks for traditional open surgery.

Case study
A 46-year-old male with a 25-year history of GERD presented to a facility in Las Vegas with symptoms of daily heartburn, cough and intermittent regurgitation when lying flat. For many years previous, his symptoms were well controlled on proton-pump inhibitors and H2RAs for breakthrough relief. He then developed dysphagia to solid foods and subsequently underwent an upper endoscopy with biopsy. The endoscopy revealed an esophageal stricture at 37 cm from the incisors and the biopsy of the distal esophagus revealed mild chronic esophagitis and low-grade dysplasia with underlying Barrett’s esophagus. Over the next five months, the patient underwent several repeat upper endoscopies to dilate his esophageal stricture with minimal temporary relief. At this time, he was referred to Cedars-Sinai.

At Cedars-Sinai, he underwent an extensive evaluation of his reflux, peptic esophageal stricture and evidence of Barrett’s esophagus with low-grade dysplasia. High-resolution esophageal manometry revealed 100 percent peristalsis with normal amplitudes and a low resting LES pressure of 8. He was unable to tolerate an ambulatory 24-hour pH study due to vomiting out the catheter. A CT scan of the chest revealed thickening of the mid- and distal esophagus in addition to a small paraesophageal lymph node. An EUS was then performed, which showed marked narrowing of the gastroesophageal junction. A nodule was noted at 37 cm from the incisors, and a biopsy showed Barrett’s esophagus extending from 35 to 38 cm from the incisors with no evidence of dysplasia. A Seattle protocol biopsy at 36 and 38 cm was performed, which showed mild esophagitis, Barrett’s esophagus and a focus indefinite for dysplasia. A barium esophagram showed an esophageal stricture and a hiatal hernia located 38 to 41 cm from the incisors. No mediastinal lymph nodes were noted and no discrete mass was appreciated on the endoscopic ultrasound.

Once malignancy was definitively ruled out, the patient agreed to undergo surgery. A laparoscopic hiatal hernia repair, Collis gastroplasty and Nissen fundoplication were performed. A barium swallow study on postoperative day 1 showed no evidence of extravasation or leak and revealed an intact fundoplication below the level of the diaphragm with no evidence of any hiatal hernia. The patient’s diet was slowly advanced to a regular diet. Currently, the patient has no dysphagia, is eating well and has complete resolution of all his symptoms, including no further symptoms of heartburn, cough, increased sputum production or dysphagia.

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Laparoscopic Nissen Fundoplication and Collis Gastroplasty

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Figure 1: Large hiatal hernia (A). Hiatal hernia reduced, revealing large hernia sac (B). Repair of hiatal hernia (C). Completed repair of hiatal hernia (D). Complete Collis-Nissen fundoplication (E).
In recent years, gut microbes have been shown to influence systemic as well as intestinal immune responses and have been linked with a diverse list of diseases, including allergic asthma, cystic fibrosis, rheumatoid arthritis and autism. Mechanistic studies are revealing a complex relationship between intestinal microbes and the host immune system that extends to immune cell populations beyond the gut. Indeed, recent studies have revealed that the microbiota regulate the production of innate immune cells in the bone marrow, with consequences for immune function in peripheral tissues.

A recent Nature Medicine study by Swiss investigators, for instance, demonstrated that the short chain fatty acid (SCFA) propionate, which is produced upon fermentation of dietary fiber by intestinal bacteria, promotes the production of dendritic cells in the bone marrow.\(^1\) They showed that dietary fiber content influences the composition of the intestinal microbiota in mice, with high-dietary fiber favoring bacterial species that produce acetate and propionate, which can be found in the circulation as well as in the intestines. A low-fiber diet, on the other hand, reduced the diversity of intestinal bacteria, shifted the balance of bacterial species and decreased circulating SCFA levels.

The investigators also reported that circulating SCFAs influence the function of newly generated dendritic cells, reducing their ability to initiate allergic T cell responses. Consequently, in a model of allergic airway disease, mice fed a low-fiber diet exhibited more allergic inflammation than control mice, while propionate supplementation had the opposite effect.

Commensal microbes have previously been shown to limit basophil-mediated allergic inflammation due to the detection of microbial components by B cells.\(^2\) Investigators at the University of Pennsylvania reported in Nature Medicine that elevated serum IgE levels in mice lacking commensal bacteria (antibiotic-treated or germ-free) drive increased basophil production by progenitors in the bone marrow.

In another recent study, published in Cell Host and Microbe, investigators from the California Institute of Technology, Cedars-Sinai and Mount Sinai School of Medicine demonstrated that intestinal microbes promote the production of macrophages and neutrophils.\(^3\) They showed that germ-free mice have fewer macrophages and neutrophils in their bone marrow and spleens than control mice. This was due to lower production of these cells by progenitors in the bone marrow and spleen as well as defective proliferation of splenic macrophages. Oral antibiotic administration similarly reduced macrophage populations.

As a consequence of the deficiency in tissue-resident phagocytic cells, germ-free and antibiotic-treated mice exhibited increased susceptibility to Listeria monocytogenes infection. SCFA administration was not sufficient to overcome the deficiency. However, oral delivery of killed bacteria restored some of the macrophage and neutrophil populations, indicating that detection of commensal microbe components (presumably either in the intestine or by bone marrow progenitors) supports the production of these innate immune cells.

These reports highlight the broad impact of gut microbes on immune function and the potentially detrimental effects of antibiotics that target commensal as well as pathogenic bacteria. Moreover, they illustrate how mechanistic studies are already revealing possible therapeutic strategies to overcome deficiencies in commensal populations, such as administration of SCFAs or microbial components.

References