Statement of Editorial Purpose

The Hospital Physician Infectious Diseases Board Review Manual is a study guide for fellows and practicing physicians preparing for board examinations in infectious diseases. Each manual reviews a topic essential to current practice in the subspecialty of infectious diseases.

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Probiotics: A Review

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Probiotics: A Review

Alpa Garg, MD, Nitesh Upadhyay, MD, and Varsha Moudgal, MD

INTRODUCTION

The human gastrointestinal tract is colonized with a diverse population of microbial flora that not only provide digestive function but also contribute to intestinal epithelial homeostasis and innate immunity. Alteration of the microflora has been postulated in the pathogenesis of various diseases including infectious, inflammatory, allergic, and immunological conditions. Disruption of the normal commensals occurs from use of antibiotics and immunotherapy, stress, and dietary changes, thus leading to increased susceptibility to disease processes. A fuller understanding of the importance of intestinal microflora has generated much interest around the use of probiotics to promote and maintain health.

Probiotics, as defined by a group of experts convened jointly by World Health Organization and Food and Agriculture Organization of the United Nations, are “live microorganisms which when administered in adequate amounts confer a health benefit on the host.” The history of probiotics goes back hundreds of years with their use in the regular diet in foods such as yogurt, cheese, and fermented foods. However, the health benefits of probiotics were first described a century ago by Russian Nobel Laureate Dr. Élie Metchnikoff, who postulated that the longevity of Bulgarian peasants was related to the consumption of sour milk, which contains lactic acid bacteria whose growth in the intestine displaces disease-producing organisms.

Most commonly used probiotics come from the genera *Lactobacillus* and *Bifidobacterium*. Others include *Streptococcus thermophilus*, nonpathogenic strains of *Escherichia coli*, *Enterococcus*, *Bacillus*, and yeasts such as *Saccharomyces boulardii*. However, the list of probiotics continues to grow. Dunne and colleagues outlined the following criteria that microbes must fulfill to be used as probiotics: they should be of human origin, non-pathogenic, resistant to processing, resistant to gastric acid and bile, able to attach to gut epithelial tissue, colonize the gastrointestinal tract, produce antimicrobial substances, modulate immune responses, and influence metabolic activities of the host. However, with the growing use of probiotics as topical agents, such as vaginal suppositories, colonization of the gastrointestinal tract may not be an essential requirement. Another important consideration is the need for survival of sufficient number of microbes in the probiotic throughout the shelf life of the product. This article reviews the mechanism of action, various health benefits, and adverse effects of probiotics.

MECHANISMS OF ACTION

There are various proposed mechanisms that describe how different probiotics work, and these vary depending on the particular strain of the probiotic. The effects of probiotics also depend upon the dosage and the route of administration. Thus, the mechanisms of action cannot be extrapolated
to all the probiotics. Proposed mechanisms include the following:

- Compete against the pathogenic bacteria to bind to the intestinal epithelial cells.\(^4\)
- Enhance intestinal epithelial barrier function by increasing the production of mucin,\(^5\) preventing injury of the epithelium from pathogens\(^6\) and reducing cell permeability.\(^7\) They may also enhance the mucosal barrier function by inducing expression of antimicrobial peptides like defensins.\(^8\)
- Inhibit the growth of the pathogens by secreting another class of antimicrobial peptides like bacteriocins\(^9\) and reuterin.\(^10\) Some of the probiotics, particularly lactic acid bacteria, inhibit the growth of the pathogens by creating an acidic environment through the production of organic acids.\(^11\)
- Enhance the production of serum IgA as well secretory IgA, which plays a crucial role in intestinal humoral immunity.\(^12,13\)
- Enhance phagocytosis,\(^14\) increase activity of natural killer cells,\(^15\) promote cell-mediated immunity,\(^16\) and stimulate various other nonspecific immune responses against pathogens.
- Down-regulate production of pro-inflammatory cytokines,\(^17\) prevent apoptosis,\(^18\) and suppress T-cell proliferation,\(^19\) thus preventing various inflammatory conditions.
- Produce hydrogen peroxide to suppress the pathogens associated with bacterial vaginosis.\(^20\)

In general, a wide range of immunomodulatory, anti-inflammatory, and antimicrobial properties of probiotics that are presumed to promote health and well being have been established by in vitro observations. However O’Hanlon et al underscored the fact that not all in vitro studies reflect in vivo findings, based on his observation that lactic acid, not hydrogen peroxide, produced by lactobacilli helps to suppress the bacteria associated with bacterial vaginosis in a physiological environment.\(^21\)

### ROLE IN PREVENTING/TREATING DISEASE

#### ACUTE DIARRHEAL DISEASE

There is growing evidence to support the use of probiotics in both prevention and treatment of acute diarrhea in children and adults. A meta-analysis by McFarland et al has shown that probiotics reduced the mean duration of diarrhea by 13 hours, reduced treatment failures by 38%, and were also effective in the prevention of diarrhea in children.\(^22\) A Cochrane review of 63 randomized and quasi-randomized controlled trials, of which 56 trials involved infants and children, concluded that probiotics were effective in reducing the mean duration of diarrhea and emphasized the need for more research on the use of various probiotic agents in specific groups of patients.\(^23\) A systematic review of 10 randomized, double-blind, placebo-controlled trials by Szajewska and Mrukowicz reported the efficacy of probiotics in the treatment of acute infectious diarrhea, particularly gastroenteritis due to rotavirus, in infants and children and suggested that the most consistent effect was seen with *Lactobacillus* GG.\(^24\) A systematic review and meta-analysis of 11 randomized controlled trials (RCTs) in children with acute diarrhea found that therapy with *Saccharomyces boulardii* significantly reduced the duration of acute infectious diarrhea by 24 hours.\(^25\) In addition, data from 9 RCTs involving 1128 children showed that *S. boulardii* significantly reduced the risk of diarrhea on the third day of illness, with a reduction in the frequency of watery stools by day 2 of diarrheal illness.
ANTIBIOTIC-ASSOCIATED DIARRHEA AND CLOSTRIDIUM DIFFICILE

A recent meta-analysis and systematic review of 63 RCTs by Hempel and colleagues evaluated the efficacy of probiotics for the prevention and treatment of antibiotic-associated diarrhea (AAD) and found that concomitant probiotic administration statistically significantly decreased the incidence of AAD.26 Further subgroup analysis of the pooled data suggested that the efficacy varied depending upon the strain of probiotic used. The data showed significant relative risk reduction of AAD with the use of Lactobacillus-based probiotics and S. boulardii–based probiotics in 17 and 15 RCTs, respectively. The analysis demonstrated beneficial effect of concomitant probiotics with antibiotics in both children and adults up to age 65 years. At this time, however, more clinical studies are needed to determine the relative benefits of different probiotic formulations.

Another recent meta-analysis of 16 RCTs by Pattani and colleagues evaluated the efficacy of probiotics for prevention of AAD and Clostridium difficile infection (CDI) among hospitalized patients and found significant reduction in the risk of AAD and CDI among patients concurrently receiving probiotics during therapy with antibiotics.27 Further subgroup analysis of the pooled data showed reduction in AAD and CDI associated with Lactobacillus–based probiotic formulations and S. boulardii–based probiotic formulations. The combined analyses of Lactobacillus–based formulations showed a reduction that was statistically significant. The authors noted statistically significant reductions in both AAD and CDI for short-term follow-up (ie, less than 4 weeks). However, with longer follow up periods (more than 4 weeks), only the reduction in AAD remained significant. The authors concluded that determination of need for co-administration of probiotics with antibiotics should be based on the local prevalence of AAD and CDI.

Meta-analyses by McFarland and Johnston et al have shown benefit from the use of probiotics in prevention of CDI in patients receiving antibiotics.28,29 The meta-analysis by McFarland et al included 31 studies with 3164 patients. Although S. boulardii, Lactobacillus rhamnosus GG, and probiotic mixtures were shown to be effective in the prevention of AAD, only S. boulardii was shown to have efficacy in the prevention of CDI.30 Johnson et al evaluated 11 randomized, placebo-controlled studies to evaluate the efficacy of probiotics in the prevention of CDI; 2 studies showed significantly lower CDI rates in probiotic recipients.31 A combined analysis of 7 trials using lactobacilli and S. boulardii showed lower rates of CDI in probiotic-treated patients, suggesting that primary prophylaxis of CDI with probiotics may be feasible.

In sharp contrast, the PLACIDE trial, a large randomized trial involving almost 3000 patients, evaluated the use of lactobacilli and Bifidobacterium in the prevention of AAD and C. difficile diarrhea in older inpatients and failed to show any efficacy of these agents.30

In summary, the meta-analyses support the use of probiotics in the treatment and prevention of AAD, but the results are conflicting with regards to use in prevention or treatment of CDI. However, many providers advocate the use of probiotics in the prevention and treatment of CDI along with the standard therapy based on anecdotal evidence of benefit and lack of side effects in the majority of patients.

INFLAMMATORY BOWEL DISEASE

It has been postulated that alteration of normal intestinal microflora plays an important role in the
pathogenesis of inflammatory bowel disease (IBD). Studies of the fecal microbiota in patients with IBD have demonstrated that these patients have higher total bacterial numbers but less bacterial diversity, resulting in a different overall microbiome composition in patients with IBD as compared to control patients.\(^3\,2^\) Hence, several studies evaluating the effects of microbiome manipulation on the disease course of IBD have been performed. Jonkers and colleagues conducted a systemic review to evaluate the efficacy of probiotics in the treatment of IBD in adults.\(^3\,3^\) The authors reviewed studies involving a variety of probiotic agents including \textit{Escherichia coli} Nissle, Bifido-fermented milk, and \textit{L. rhamnosus} GG. They found no overall significant effect in patients with ulcerative colitis associated with the use of Bifido-fermented milk. The meta-analysis of studies involving use of VSL #3 probiotic (a probiotic consisting of 4 strains of \textit{Lactobacillus}, 3 strains of \textit{Bifidobacterium}, and 1 strain of \textit{Streptococcus}) in active ulcerative colitis patients showed significant benefit of VSL #3 over the control group in inducing remission in active ulcerative colitis. The analysis was limited by moderate heterogeneity between the studies. The authors performed a meta-analysis of 3 RCTs evaluating the effect of the probiotic \textit{E. coli} Nissle 1917 compared to mesalazine and found equal efficacy of the agents in maintaining remission in patients with ulcerative colitis. A meta-analysis of 3 RCTs showed VSL #3 to be more effective than placebo in preventing pouchitis, but unfortunately these results could not be confirmed in an uncontrolled clinical practice setting, where 25 of 31 patients treated with this probiotic developed relapses or adverse symptoms.\(^3\,3^\)

The data on probiotic use in patients with Crohn disease is sparse. In a single study, \textit{S. boulardii} appeared to be beneficial in this patient population. This effect needs to be confirmed in larger RCTs. Smaller studies involving the use of different species of lactobacilli in patients with Crohn disease did not demonstrate significant benefit, but all studies were limited by high dropout rates.

The authors concluded that while the data for use of VSL #3 and \textit{E. coli} Nissle appeared promising in ulcerative colitis patients, larger trials are required to confirm these effects. Although VSL #3 appeared to be effective in the prevention of pouchitis in clinical trials, its efficacy will need to be demonstrated in more real life clinical settings. More data is required in Crohn disease patients before use of probiotics can be justified in this group of patients. In fact, a meta-analysis by Shen and colleagues, which included 6 RCTs with 359 patients, suggested that \textit{L. rhamnosus} GG increased the relapse rates as compared to placebo in patients with Crohn disease.\(^3\,4^\)

**IRRITABLE BOWEL SYNDROME**

The pathophysiology of irritable bowel syndrome (IBS) is not well understood; however, alteration in the intestinal flora has been postulated as one of the etiologies. There is also no cure for IBS, so the treatment is mainly focused on symptom relief and probiotics have been tried as one of the therapeutic modalities. Several different meta-analyses have assessed the use of probiotics in the treatment of IBS and they have shown promising results. A meta-analysis of 8 randomized, placebo-controlled trials suggested that probiotics may improve symptoms of IBS.\(^3\,5^\) Similarly, McFarland and Dublin in a meta-analysis of 20 RCTs also demonstrated that the use of probiotics was associated with improvement of global IBS symptoms as a primary outcome and less abdominal pain as a secondary outcome.\(^3\,6^\) A systematic review of 10 RCTs by Moayyedi et al showed that probiotics were effec-
tive in the treatment of IBS. In subgroup analysis, there was a statistically significant improvement in pain scores and flatulence in probiotic-treated patients. Though improvement was also seen in bloating, it failed to reach statistical significance and there was no statistically significant change in urgency with probiotic use.37 Another meta-analysis including 14 RCTs suggested improvement in overall symptoms after administration of probiotics. The subgroup analysis demonstrated a statistically significant improvement in abdominal pain, flatulence, and bloating using dichotomous data, but this effect was not shown to be statistically significant when continuous data was used.38

TRAVELER’S DIARRHEA

A meta-analysis of 12 RCTs by McFarland found that on the whole, several probiotics were efficacious in the prevention of traveler’s diarrhea. Of the 12 trials reviewed, 6 reported a significant difference in the prevention of traveler’s diarrhea in the probiotic-treated group. Of the remaining 6 studies, one trended towards efficacy of probiotics and the remaining 5 demonstrated no difference between the probiotic-treated and control groups.39

HELCOBACTER PYLORI INFECTION

A meta-analysis of 14 randomized trials suggested that probiotics supplementation increased the eradication rate and reduced the risk of side effects from the therapy for treatment of H. pylori.40 In contrast, Szajewska et al, in a randomized, double-blind, placebo-controlled trial in children, found no significant difference associated with Lactobacillus GG supplementation in the H. pylori eradication rate or with reduction of side effects of therapy.41 Similarly, other studies have also found no significant difference in the eradication rate of H. pylori with probiotic supplementation.42,43

INTESTINAL TRANSIT TIME

A systematic review and meta-analysis of 11 clinical trials including 464 patients showed that probiotic supplementation decreases the intestinal transit time, with greater treatment effect demonstrated in constipated or elderly adults.44 In addition, 2 probiotic strains, Bifidobacterium lactis HN019 and B. lactis DN-173 010 demonstrated greater efficacy as compared to other probiotics, although this evidence was by no means conclusive.

OTHER GASTROINTESTINAL CONDITIONS

Probiotics have also been tried with some success in the prevention of uncomplicated diverticular disease45 and diverticulitis,46 reduction of symptoms from collagenous colitis,47 treatment of functional constipation,48 prevention of necrotizing enterocolitis in preterm infants,49 and treatment of functional abdominal pain disorders in children.50 Though different strains of probiotics have been used effectively in lactose intolerance, a systematic review found that probiotics did not reduce the signs and symptoms of lactose intolerance.51 There are some promising results from studies supporting the use of probiotics alone or with prebiotics in the treatment of hepatic encephalopathy.52–54 A case report of resolution of prolonged cryptosporidiosis with probiotic treatment was intriguing.55 In vitro and animal studies have suggested that probiotics may also have a role in the prevention of colorectal cancer.56 Probiotics may also have benefits in preventing radiation- and chemotherapy-induced diarrhea.57,58 In a review, Teughels et al concluded that probiotics may have a role in promoting oral health and preventing periodontal diseases but also suggested the need for properly designed clinical studies.59

Capurso et al reviewed the literature on the effects of probiotics in acute pancreatitis and found
some benefit associated with their use. In contrast, the results of the PROPATRIA study not only showed that the combination of probiotic prophylaxis did not reduce the risk of infectious complications in acute severe pancreatitis, but in fact it was associated with an unexpected increase in mortality. Although several criticisms have been made regarding study design, including the choice of probiotics used, randomization, and increased bowel ischemia observed in the probiotic group, the study illustrates that in certain situations probiotic use is not altogether benign.

ALLERGIC CONDITIONS

The literature on use of probiotics in allergic conditions is controversial. A meta-analysis of RCTs by Elazab et al suggested that administration of probiotics in prenatal and early life showed benefit in reducing IgE levels in children and may have a protective effect against atopic sensitivity, although no effect of probiotic was noted in the reduction of asthma or wheezing. In contrast, an RCT by Kopp et al showed probiotics supplementation had no effect on the incidence or severity of atopic dermatitis in children. Instead, use of probiotics was associated with increased episodes of wheezing and bronchitis. A systematic review of RCTs suggested that probiotics may have some benefit in the treatment of allergic rhinitis and may be associated with overall clinical improvement, including reduction in severity of symptoms and decreased medication use in patients with seasonal allergic rhinitis and perennial rhinitis, although no effects were seen in the treatment of asthma. A recent meta-analysis published by Pelucchi et al reviewed 14 RCTs to evaluate the efficacy of probiotics for prevention of atopic dermatitis and IgE–associated dermatitis in infants and young children. Pooled analysis demonstrated a reduction in the incidence of atopic dermatitis and IgE–associated dermatitis by 20% in probiotics-treated patients. The authors concluded that probiotics use plays a moderate role in the prevention of atopic dermatitis and IgE-mediated dermatitis in infants.

OTHER POTENTIAL BENEFITS

Studies have also reported possible benefits of probiotics in other areas including delaying Pseudomonas colonization and infection in critically ill patients, clearing of vancomycin-resistant enterococci colonization, treatment of mastitis during lactation, and prevention of recurrent urinary tract infection in women. A recent meta-analysis by Huang et al reviewed 12 RCTs including 1304 participants and suggested that probiotic supplementation may improve the cure rate in adult bacterial vaginosis. However, the main limitation of the analysis was heterogeneity across various studies.

SIDE EFFECTS

It has been well established that the intestinal microflora plays an important role in the metabolic activity and immune system of the host, and probiotics help to promote microflora. However, it can also be argued that manipulation of the normal microflora by probiotic use may theoretically increase the risk of adverse metabolic and immunomodulatory effects. Some minor adverse effects that have been reported include thirst and constipation with S. boulardii use, bloating and flatulence with L. rhamnosus GG use, as well as nausea, vomiting, abdominal pain, rash, diarrhea and constipation. Although serious complications from use of probiotics are exceedingly rare, given that probiotics are live microorganisms, it is conceivable that they may rarely result in invasive infections.
Mackay et al reported a case of lactobacillus endocarditis with probiotic use in a patient with underlying mitral valve disease. A case of liver abscess due to *L. rhamnosus* was reported in a diabetic patient who was consuming dairy products containing *L. rhamnosus* GG. Kunz et al and Land et al reported cases of lactobacillus sepsis associated with probiotic use in children. A case of recurrent *Bacillus subtilis* septicemia has also been reported in an immunocompromised patient after the use of probiotics containing *B. subtilis*. There have also been several reported cases of *S. boulardii* fungemia associated with probiotic use. Most cases of invasive infections associated with probiotic use have occurred in patients with intravenous catheters, the elderly, and immunocompromised persons.

These anecdotal case reports of infection after probiotic use have not been confirmed in larger studies, although the results of the PROPATRIA study discussed above raise concerns with use of probiotics in certain patient groups. Salminen et al found no association of lactobacillus bacteremia with the increased use of *L. rhamnosus* GG in a study conducted in Finland. A small randomized controlled study involving 17 HIV-positive patients also demonstrated no adverse events after a 2-week course of probiotic *L. rhamnosus* GG. Similarly, the safety of the probiotics containing strains of *Lactobacillus* and *Bifidobacterium* was evaluated in infants and no adverse events were observed.

**CONCLUSION**

There is a growing interest in defining the proper use of probiotic agents because they may have beneficial effects in a large number of clinical conditions. Probiotics have been studied in a number of different conditions, as described here, but thus far there is strong evidence to support their use only in several conditions, including treatment of acute diarrheal diseases, prevention of AAD, and prevention of pouchitis. The efficacy of probiotics is strain- and dose-dependent and therefore the choice of probiotics may influence results in specific conditions. Most of the clinical trials using probiotics have been plagued by clinical and methodological differences that have rendered it impossible to conclusively assess their efficacy. There is a great need for the scientific community to conduct randomized, double-blinded, placebo-controlled trials to answer these questions about probiotics. Although probiotics appear for the most part to be safe, caution should be used in specific subgroups of patients such as the immunocompromised, the elderly, and patients with indwelling intravenous catheters.

**BOARD REVIEW QUESTIONS**

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