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Probiotics: Mechanisms of Action and Clinical Applications

Vijaya K Gogineni[1], Lee E Morrow[2]* and Mark A Malesker[3]

[1]Pulmonary and Critical Care Fellow, Division of Pulmonary, Critical Care and Sleep Medicine, Creighton University Medical Center, USA
[2]Associate Professor of Medicine and Pharmacy Practice, Nebraska and Western Iowa Veteran's Affairs Hospital, Division of Pulmonary, Critical Care and Sleep Medicine, Creighton University Medical Center, USA
[3]Professor of Pharmacy and Pharmacy Practice, Creighton University School of Pharmacy and Health Professions, USA

Abstract

Probiotics are living microorganisms which when taken in adequate amount provides benefit to the host. While this beneficial effect was originally thought to stem from improvements in the intestinal microbial balance, there is now substantial evidence that probiotics can also provide benefits by modulating immune functions. Extrapolation of immunomodulatory effects found in the laboratory and in animal studies with outcomes in human trials presents a difficult challenge. Not all probiotics are created equal and the benefits are strain and dose specific. With newer strain-specific clinical trials and meta-analysis of the clinical trials, the beneficial role of probiotics in certain diseases has been evolving. Some uncertainity still exists with probiotics in other diseases with regard to the therapeutic role, strain-specificity, dosage and duration. Identification of clinical characteristics of effective probiotic strains, their mechanisms of action and testing of probiotic-based treatment may provide the true beneficial effect of probiotics in various disorders.

Keywords: Probiotics; Bacteriocins; Microcins; Antibiotic-associated diarrhea; *Clostridium difficile* infection; Acute pancreatitis; Necrotizing enterocolitis; Ventilator-associated pneumonia, Multi-organ dysfunction syndrome

Introduction

Recent research has revealed a potential therapeutic role for the manipulation of the microbiota in the maintenance of human health and treatment of various mucosal disorders. Probiotic microorganisms can shape the immune system both at the local and systemic level which will allow future probiotics as treatments for many diseases. The benefits include either a shortened duration of infections or decreased susceptibility to pathogens [1].

The word 'probiotic', derived from the Greek language, means 'for life' was first used by Kollath [2]. Lilly and Stillwell [3] defined probiotics as substances produced by microorganisms which promoted the growth of other microorganisms. According to the currently adopted definition by FAO/WHO [4], probiotics are: "Live microorganisms which when administered in adequate amounts confer a health benefit on the host". Prebiotics are indigestible food ingredients that selectively promote the growth or activity of beneficial bacteria, thereby benefiting the host [5]. Synbiotics are combinations of probiotics and prebiotics designed to improve the survival of ingested microorganisms and their colonization of the intestinal tract [5]. Commonly used bacterial probiotics include *Lactobacillus* species, *Bifidobacterium* species, *Escherichia coli*, *Streptococcus* species, *Lactococcus lactis* and some *Enterococcus* species. Currently, the only probiotic yeast used is the nonpathogenic *Saccharomyces boulardii*.

Mechanisms of Probiotic Function

Probiotics do not always colonize the intestinal tract to exert their effects. For example, some probiotics like *Bifidobacterium longum* become part of the human intestinal microflora, whereas others like *Lactobacillus casei* indirectly exert their effects in a transient manner as they pass through by remodeling or influencing the existing microbial community [6]. The following are the major mechanisms of action of probiotics on the host (Table 1).

Barrier function

Probiotics are capable of influencing many of the components of epithelial barrier function either by decreasing apoptosis of intestinal cells or increased mucin production. *Lactobacillus rhamnosus* GG was able to prevent cytokine-induced apoptosis in intestinal epithelial cell models by inhibiting tumor necrosis factor (TNF) [7]. *Lactobacillus* species have been shown to increase mucin expression *in vitro* in human intestinal epithelial cells, thus blocking pathogenic *E. coli* invasion and adherence [8,9]. *Lactobacillus rhamnosus* GG has shown to prevent inflammation and programmed cell death of the lining intestinal epithelial cells [10] and shown to exert mitogenic effects and enhancing mucosal regeneration [11].

Production of antimicrobial substances

Probiotics either by inducing host cells to produce peptides or by directly releasing peptides interfere with pathogens, and prevent epithelial invasion. Defensins (hBD protein) and cathelicidins are the antimicrobial peptides expressed constitutively by the intestinal epithelial cells and display antimicrobial activity against a wide variety of bacteria, fungi and some viruses [12]. Certain probiotic strains like *E. coli* strain DSM 17252 G2 (one of the three Symbioflor 2 genotype strains) and several *Lactobacilli* species have shown to express certain defensins [13]. Healthy volunteers who received probiotics had increased fecal hBD protein and remained elevated for 9 weeks after completion of 3 weeks of probiotic treatment [13,14]. Probiotics have been shown to suppress pathogen growth through the release of a variety of antimicrobial factors like defensins, bacteriocins,

***Corresponding author:** Lee E. Morrow, Associate Professor of Medicine and Pharmacy Practice, Nebraska and Western Iowa Veteran's Affairs Hospital, Division of Pulmonary, Critical Care and Sleep Medicine, Creighton University Medical Center, USA, Tel: 402-449-4486; E-mail: leemorrow@creighton.edu

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Mode	Process	Mechanism	Examples
Barrier Function	Decreased apoptosis of epithelial cells	Decreased TNF-α production	*Lactobacillus rhamnosus* GG
	Increasing mucin production	Increased expression of MUC 2	*Lactobacillus* sp
Host cell Antimicrobial Peptides	Defensins (hBD protein)	Increased up regulation of Defensin	*E coli strain* DSM 17252S2
	Cathelcidins	By butyrate production	
Probiotic Antimicrobial Factors	Lowering the luminal pH	By secretion of SCFA's	Most of the probiotics bacteria
	Bacteriocin production	By Gram positive probiotics	
	Microcin production	By Gram negative probiotics	
Epithelial Adherence	By competing with pathogens	Directly or indirectly by producing protein that block adherence	
Immune Modulation	Blocking pro Inflammatory molecules	By attenuating IL-8 secretion or blocking the degradation of the counter-regulatory factor IκB	*Salmonella tyhimurium* VSL#3 probiotics
	Increasing mucosal immunity	Increasing IgA Production	*L. casei*
Interference with Quorum Sensing Signaling	Blocks the communication between pathogenic bacteria	By secreting molecules which blocks quorum sensing signaling	*L. acidophilus*

Table 1: Various mechanisms of probiotics action on human intestine cells.
Abbreviations: TNF-α: Tumor necrosis factor alpha; MUC 2: Mucin 2, hBD: Hemoglobin subunit delta; SCFA: Short chain fatty acids; IL-8: Interleukin 8; and IκB: Inhibitor of kappa B.

hydrogen peroxide, nitric oxide, and short chain fatty acids (SCFA), such as lactic and acetic acids, which reduce the pH of the lumen [15]. SCFA can disrupt the outer membranes of gram-negative pathogens causing inhibition of pathogen growth [16]. Bacteriocins can either permeabilize the inner membrane of gram-negative bacteria, leading to disruption and formation of pores [17]. Microcins (produced by gram negative bacteria), on the other hand, can target the inner membrane, enzymes that are involved in DNA or RNA structure and synthesis, or protein synthesis enzymes [18].

Competition for adherence

Probiotic bacteria compete with invading pathogens for binding sites to epithelial cells and the overlying mucus layer in a strain-specific manner. Surface layer proteins purified from *L. helveticus* R0052 inhibited enterohemorrhagic *Escherichia coli* O157:H7 adherence and the subsequent rise in permeability, without altering the growth of the pathogen [19]. *S. boulardii* secretes a heat-labile factor which has shown to be responsible for the decreased bacterial adherence [20].

Immune modulation

L. casei have been shown to augment total and pathogen-specific secretory IgA levels upon infection in mice by stimulating B cell class switching to IgA [21]. Specific antibodies against *L. casei* were not produced, indicating the non-responsiveness of the gut immune system to this beneficial bacterium. In infant rabbits pretreated with *L. casei*, morbidity of subsequent EHEC (Entero-Hemorrhagic *E. coli*) infection was reduced due to increased mucosal levels of anti-EHEC and anti-Shiga toxin IgA antibodies compared with controls [22]. *L. casei* down-regulated the transcription of a number of genes encoding pro-inflammatory effectors such as cytokines and chemokines and adherence molecules induced by invasive *S. flexneri*. This resulted in an anti-inflammatory effect that appeared mediated by the inhibition of the NF-κB pathway, particularly through stabilization of I-κBα [23].

Interference with quorum sensing signaling

Bacteria communicate with each other as well as with their surrounding environment through chemical signalling molecules called auto-inducers. This phenomenon is called quorum sensing [24]. The use of this cell-to-cell signaling mechanism facilitates the regulation of important traits of enteric microbes that allow them to successfully colonize and/or start infection in their host [25]. Medellin-Pena et al. [26] demonstrated that *Lactobacillus acidophilus* secretes a molecule that inhibits the quorum sensing signalling or directly interact with bacterial transcription of *E. coli* O157 gene, involved in colonization and thus, bacterial toxicity is opposed.

Role of Probiotics in Various Diseases

Probiotic research is moving forward on two stages: laboratory studies and clinical trials to evaluate the safety and efficacy of probiotics in treatment and prevention of various medical conditions. In this article, we will review the evidence of probiotics in various diseases by reviewing the clinical trials and meta-analysis of the clinical trials (Table 2).

Antibiotic-associated Diarrhea

The incidence of antibiotic-associated diarrhea (AAD) ranges between 5% and 30% [27]. The risk is greatest with aminopenicillin therapies (Ampicillin or Amoxicillin), aminopenicillin combined with clavulanic acid, cephalosporins, and clindamycin [27]. Probiotics given in conjunction with antibiotics have been extensively studied for the prevention of AAD in both adults and children. The major changes in the microbiota of the gut with antibiotics are decrease in total number and species diversity of *Bacteroides* and *Bifiobacteria* associated with decreased amylolytic activity with increase in facultative anaerobes such as *Fusobacteria, Clostridia*, and *Eubacteria* species [28]. Decreased short chain fatty acid production and increased proteolytic activity was also noted in elderly patients treated with antibiotics [29].

Several clinical trials have been conducted using *Saccharomyces boulardii* for the prevention of AAD [30-36]. All but one concluded that *S. boulardii* was an effective agent for prevention of AAD [34]. With increasing number of trials over the last several years on the role of probiotics in preventing AAD, new single-strain meta-analysis are now being published. A meta-analysis of several randomized controlled trials testing the efficacy of *S. boulardii* in preventing AAD in adults showed *S. boulardii* was significantly protective for AAD with an overall pooled relative risk of 0.47 (95% Confidence Interval=0.35, 0.63; p<0.001) [37]. The number needed to prevent one case of AAD was 10.2. A meta-analysis of five randomized controlled trials by Szajewska and Mrukowicz [38] involving 1076 subjects showed a significantly protective effect of *S. boulardii* was found (pooled RR=0.43, 95% CI: 0.23-0.78).

In addition, several randomized controlled trials have shown efficacy for *Lactobacillus rhamnosus* GG (LGG) in prevention of AAD

[39-42]. Two of these trials focused on children only [40,41]. All but one showed a benefit over placebo or no treatment [42].

Saccharomyces boulardii alone is available as a probiotic in the market and sold as Florastor capsules. It contains 5 billion colony forming units. *Lactobacillus rhamnosus* GG (LGG) alone is available in market as Culturelle capsules and it contains 10 billion CFU's in each capsule (Table 3).

Probiotics and *Clostridium difficile* Infections

Clostridium difficile is a spore-forming, anaerobic, Gram-positive bacterium that causes gastrointestinal infection with diarrhea and colitis. There has been a marked increase in the incidence and severity of *Clostridium difficile* infection (CDI) during the past decade. The clinical outcomes of CDI range from asymptomatic carriage to mild diarrhea to fulminant, often fatal, pseudomembranous colitis. Recurrent CDI is one of the most challenging aspects of the disease. Approximately 25% of patients treated for CDI with metronidazole or vancomycin experience recurrent symptoms, typically within 4 weeks of completing antibiotic therapy. Owing to increasing incidence, rising death rates, and frequent recurrences, there is a substantial need for more effective approaches to CDI prevention and therapy.

Castagliuolo et al. [43] found a 54 kDa serine protease produced by *S. boulardii* which directly degrades *C. difficile* toxin A and B and also produces a protease capable of degrading the colonic receptor site for *C. difficile*. *S. boulardii* may cause an increase in anti-toxin secretory IgA levels in the intestine [44]. Probiotics have been studied in prevention, and treatment of *Clostridium difficile* infections (CDI) and recurrent CDI.

Several randomized-controlled trials used *Lactobacillus* spp, *Saccharomyces boulardii* or a combination with *C. difficile* toxin acquisition and/or CDI as a primary or secondary outcome [45-52]. The trials had a small number of cases and short follow-up, the longest being 7 weeks by McFarland et al. [45]. Hickson et al. [52] showed a statistically significant decrease in CDI with use of a combination probiotic milkshake. No patients in the probiotic group acquired CDI, whereas 9 out of 53 (17%) in the placebo group developed CDI (P=0.001). None of the remaining trials demonstrated a statistically significant decrease in CDI or *C. difficile* toxin acquisition with the use of probiotic therapy [45-51]. The above trials lacked adequate statistical power to determine the efficacy of probiotics. Few studies of probiotics have been performed but none has shown a consistent evidence of efficacy in prevention or treatment of CDI.

In another randomized, controlled trial, patients with recurrent CDI were prescribed either one of two doses of vancomycin (2 g/d or 500 mg/d) or metronidazole (1 g/d) then randomized to either *S. boulardii* or placebo (1 g/d for 4 weeks). Patients treated with the high dose vancomycin and the probiotic had significantly decreased recurrence rates (16.7%) compared to vancomycin and placebo (50%) [53]. The probiotic given with the low dose vancomycin or metronidazole was not significantly protective of CDI. *S. boulardii* was shown to be effective in recurrent CDI.

Saccharomyces boulardii alone is available in the market as Florastor capsules. *Lactobacillus* spp alone are available as Lactinex, Fem-Dophilus, and Culturelle capsules. *Lactobacillus* spp are available in combination with *Bifidiobacterium* spp as Align capsules, Attune nutrition bars, Adult Formula CP-1 capsules, and OWP probiotics capsules. There has been increase in the practice of using probiotics along with vancomycin or metronidazole for recurrent CDI.

Probiotics and *Helicobacter pylori* Infections

Helicobacter pylori, a small curved to spiral rod shaped bacterium, is strongly associated with duodenal peptic ulceration and it is the main etiologic agent of chronic gastritis and gastric cancer and other gastric malignancies. Today the therapy to eradicate this bacterium is based on a combination of antibiotics and proton pump inhibitors. Probiotics seem to have a direct antimicrobial effect, as shown through *in vitro*

Disease	Probiotic Strain	Comments
Prevention of antibiotic associated diarrhea (AAD)	*S. boulardi* [37,38]	Number needed to treat (NNT) is 10.2 to prevent one case of AAD.
	Lactobacillus rhamnosus GG (LGG) [39-41]	Effective on adults and children in RCT's.
Prevention of Clostridium difficile Infection (CDI)	*S. boulardii*, LGG, or both [52]	Study results are not statistically significant.
Prevention of recurrence after first CDI	*S. boulardii* [53]	Reduction of recurrence of CDI by half.
Helicobacter pylori eradication	*Lactobacillus rhamnosus* GG (LGG), *S. boulardii*, *L acidophilus* [55]	Moderate evidence for improving eradication but good evidence of reduction in side effects leading to improved compliance.
Ulcerative Colitis	*E coli* Nissle 1917 [68]	Promising role in maintenance of remission.
	*VSL#*3 [70]	Role in induction and maintenance of remission of UC.
Crohn's Disease	*Lactobacillus rhamnosus* GG (LGG) [71,72], *Lactobacillus johnsonii LA1*[73]	No role in induction or prolonging of remission of CD.
Irritable Bowel Syndrome	*Bifidobacterium infantis* 35624 [80], VSL#3 [81]	Significant improvements in IBS symptoms.
Acute Pancreatitis	*Lactobacillus plantarum* 299 [88]	But PROPATRIA trial showed an increased incidence of infection, MODS and bowel ischemia.
Necrotizing Enterocolitis (NEC)	*Bifidusbacterium* spp and *Lactobacillus acidophilus* [148]	Prophylactic probiotics reduced NEC and mortality. Increased infection is noted among VLBW (<750 g).
Multi-Organ Dysfunction Syndrome (MODS)	*VSL#*3 [118]	Increased systemic IgA and IgG concentrations are noted but MODS scores were not significantly affected by probiotic treatment.
Allergy and Immune Response	*Lactobacillus rhamnosus* GG (LGG) [125-127]	Alone when given to mothers during pregnancy did decrease the risk of atopic dermatitis but similar results were not seen when given with other probiotic strains.
Ventilator Associated Pneumonia (VAP)	*Lactobacillus rhamnosus* GG (LGG) [142]	Number needed to treat (NNT) is 5 to prevent one case of VAP.

Table 2: List of different probiotic strains studied in treatment and/or prevention of various diseases.

studies, through competition with *H. pylori*, inhibition of adherence and production of metabolites and antimicrobial molecules.

In a randomized, double blind, placebo-controlled trial, 60 participants were treated with triple antibiotic therapy on days 1-7 and *Lactobacillus GG* on days 1-14 [54]. Probiotics significantly improved symptoms, including nausea, taste disturbance, and diarrhea; however, epigastric pain did not significantly improve during eradication treatment. Eradication rates did not differ significantly between the groups (83.3% vs 80%).

In another randomized, double blind, placebo-controlled trial, 85 *H. pylori* positive asymptomatic patients were randomized to receive *Lactobacillus GG* (group I), *Saccharomyces boulardii* (group II), *Lactobacillus acidophilus* and *Bifidobacterium lactis* (group III), or placebo (group IV) on days 1-14, with *H. pylori* treatment on days 1-7 [55]. Probiotics significantly improved symptoms, including taste disturbance and diarrhea; however, nausea and epigastric pain did not significantly improve during *H. pylori* treatment. All of the differences were noted between the probiotics and placebo. None of the probiotics was superior to another. Eradication rates were not significantly different among the 4 groups receiving probiotics.

Myllyluoma et al. [56] did a randomized double-blind, placebo-control trial on 47 patients using a milk based fruit drink containing *Lactobacillus GG*, *Propionibacterium*, *Bifidobacterium*, or placebo on days 1-28 and triple antibiotic therapy days 1-7. Probiotics did not significantly improve symptoms including nausea, taste disturbance, diarrhea, and epigastric pain. Eradication rates did not significantly differ between the groups (91% vs 79%; p=0.42).

A meta-analysis recently published illustrated that supplementation with *S. boulardii* significantly increased the eradication rate and reduced the risk of overall *H. pylori* therapy-related adverse effects especially diarrhea [57].Unfortunately, the products used in these studies are not typically sold in the US, which makes selecting a probiotic supported by evidence difficult. Even though a specific strain of *Lactobacillus* supported by evidence may not be available in the US, it may not be reasonable to extrapolate the effects of that strain to other types of *Lactobacillus* when product selections are limited.

Probiotics and Inflammatory Bowel Diseases (IBD)

Inflammatory bowel disease (IBD) is a chronic, relapsing, inflammatory disorder of the gastrointestinal tract that includes two entities, namely Crohn's disease (CD) and ulcerativ*E. coli*tis (UC). Up to one-third of patients with IBD are intolerant of [58] and a further 10% are unresponsive to thiopurine [59]. The role of probiotics in the treatment or relapse prevention in patients with inflammatory bowel diseases (IBD) is more complex and still remains controversial. Anti-tumour necrosis factor (anti-TNF) drugs have proven to be effective in patients with Crohn's disease (CD) [60] and ulcerativ*E. coli*tis (UC) [61], only approximately one-fifth of all initially treated CD and UC patients are in remission at 1 year. There is still a large gap in the therapeutic armamentarium of both conditions.

Studies using a 16S rRNA technique have shown reductions in *bifidobacteria* [62,63] and *lactobacilli* in patients with UC [64]. *Lactobacillus paracasei* significantly decreased the plasma and lymphocyte content of proinflammatory cytokines in patients with UC [65]. VSL#3 induces IL-10 and downregulates IL-12p40 production by lamina propria DC in patients with UC [66]; similar cytokine changes were seen in patients who were treated with corticosteroids [67]. *E. coli Nissle* 1917 seems to have efficacy comparable to that of the antiinflammatory mesalamine for maintenance of remission in ulcerativ*E. coli*tis patients [68]. In a randomized double-bind trial on patients with active ulcerativ*E. coli*tis, E.coli *Nissile* 1917 did not differ in rate and time to remission compared to placebo [69]. In an open-label trial, VSL#3 did induce remission in 53% and response in 24% over 6 weeks of therapy in patients with active ulcerativ*E. coli*tis when given along with other treatments [70].

In randomized double-blind, placebo-control trials, *Lactobacillus rhamnosus* GG did not show any superiority over placebo in patients

Trade Name	Manufacturer	Comments
Yo-Plus yogurt	Yoplait Inc	Contains *B. animalis* lacis Bb-12 in addition to *S. thermophilus* abd *L. bulgaricus* per serving.
DanActive Cultured milk	Dannon Inc	Contains *S. thermophilus* and *L. bulgaricus* in addition to *L. casei* DN-114 001. Each serving contains 10 billion CFUs.
VSL#3 packets	Sigma-Tau Pharmaceuticals	Contains *B. breve*, *B. infantis*, *B. longum*, *L. acidophilus*, *L. bulgaricus*, *L. casei*, *L. plantarum* and *Streptococcus thermophiles*. Each packet contains 450 billion CFUs. Lemon flavored and is consumed by mixing in atleast 4 oz of cold water.
Philips Colon Health capsules	Proctor & Gamble	Includes *Lactobacillus gasseri* KS-13, *Bifidobacterium bifidum* G9-1 and *Bifidobacterium longum* MM-2. Each capsule contains 1.5 billions cells.
Florastor capsules	Biocodax, inc	Contains *Saccharomyces boulardii*. Each 250 mg capsule contains 5 billion CFUs.
Florastor Kids	Biocodex Inc	Contains *Saccharomyces boulardii*. Available as powder.
Attune nutrition bars	Attune Foods	Contains Koshar *Lactobacillus acidophilus* NCFM, *L. casei* Lc-11 and *Bifidobacterium lactis* HN019. Contains 3g fiber. Each serving contains 6.1 billion CFUs.
Align capsules	Proctor & Gamble	Contains *Bifidobacterium infantis* 35624 in a vegetarian capsule shell. Each capsule contains 1 billion bacteria.
Sustenex	Schiff Nutrition International	Contains Bacillus coagulans GBI-30, 6086 (BC30). Available as capsules, chewies and gummies.
Lactinex	Becton, Dickinson, and Co	Contains *Lactobacillus acidophilus* and *Lactobacillus helveticus* (*bulgaricus*). Available as capsules and packets.
Fem-Dophilus	Jarrow formulas	Contains *Lactobacillus reuteri* RC-14, *Lactobacillus rhamnosus* GR-1. Available as capsules.
Culturelle Digestive	Amerifit Nutrition, Inc	Contains *L. rhamnosus* GG. Each capsule contains 10 billion CFUs.
Adult Formula CP-1	Custom Probiotics Inc	Contains five probiotic strains: *L. Acidophilus*, *L. Rhamnosus*, *L. Plantarum*, *B. Lactis* and *B. Bifidum*. Each capsule has 50 billion CFUs.
OWP probiotics	One Wellness Place	Contains *B. longum*, *B. breves*, *B. infantis*, *L. plantarum*, *L. rhamnosus*, and *L. acidophilus*. Each capsule has 15 billion CFUs.
Good Belly fruit drink	NextFoods	Contains *L. plantarum* 299v. Each serving contains 20 billion CFUs.

Table 3: List of selected commercially available probiotics in United States.

with active Crohn's disease [71] and patients with Crohn's disease who are in remission with medical therapy [72]. In randomized double-blind, placebo-control trial, *Lactobacillus johnsonii* LA1 did show statistically non-significant decrease in endoscopic recurrence at 6 months when compared with placebo (49% vs 64%) [73].

Routine use of probiotics for IBD may be premature at this stage as we need stronger evidence in the form of large randomized double blinded and placebo control studies and meta-analysis of single probiotic strains to support it.

Probiotics and Irritable Bowel Syndrome (IBS)

Epidemiological, physiological and clinical studies have suggested the role of intestinal bacteria in the pathogenesis of IBS. Many previous studies indicate that gastroenteritis is a trigger for IBS. In Canada following an outbreak of gastroenteritis, a cohort analysis revealed an increased odd of IBS within 2 years (OR 4.8) [74] and continued for 8 years [75]. In another study, incidence of gastroenteritis in the previous 2 years was associated with almost a four-fold increase in the risk of developing IBS [76]. Physiological studies on animals and humans showed a profound effect of alterations in the composition of the intestinal microbiota (dysbiosis) on the intestinal physiological functions and IBS [77]. A review of several case-control studies revealed abnormal breath test results in patients with IBS following a sugar challenge when compared with controls [78]. The increased risk of developing IBS following gastroenteritis, dysbiosis, and elevated luminal gas production and immune activation, indicate that the gastrointestinal microbiota may be a therapeutic target in IBS.

Though numerous RCTs have evaluated the efficacy of probiotics in IBS patients, most suffer from serious methodological flaws [79]. In a recent systematic review, Brenner and colleagues reported that of 16 RCTs evaluating probiotics in the treatment of IBS, *Bifidobacterium infantis* 35624 was the only probiotic which provided significant improvements in IBS symptoms [80]. In randomized cross-over trials in 59 children with IBS, VSL#3 demonstrated a greater improvement in global symptoms, abdominal pain and abdominal bloating in the probiotic group [81]. Some meta-analysis indicated a more beneficial impact of probiotics on global symptoms than on abdominal pain and flatulence [82-84].

Bifidiobacterium infantis alone is available in the market as Align capsules or in combination with other probiotic organisms as OWP probiotic capsules, and VSL#3 packets. More evidence is needed before using probiotics for symptom control in IBS.

Probiotics and Acute Pancreatitis

Probiotics have been shown to be effective in preventing complications in experimental acute pancreatitis by reducing bacterial translocation [85-87]. A clinical trial conducted by Oláh et al. [88] on patients with acute pancreatitis with *L. plantarum* 299 dose of 1×10^9 along with oat fiber significantly reduced infected pancreatic necrosis and the number of surgical interventions. Subsequently, several studies reported similarly positive effects of probiotics with or without prebiotics [89-93]. Besselink et al. [94] (PROPATRIA trial) conducted a large multi-center, randomized double-blinded controlled trial involving 296 patients in 15 hospitals, and compared the use of a multi-species probiotics preparation with a placebo. This study showed that infectious complications occurred in 30% of the patients in the probiotics group and in 28% of the placebo group. Nine patients developed bowel ischemia (8 died) in the probiotics group, whereas none developed this complication in the placebo group. Multiple organ failure occurred in 22% of the patients in the probiotics group and in 10% in the placebo group. In all, 16% patients in the probiotics group and 6% in the placebo group died. Further analyses suggested that higher rates of bowel ischemia in the probiotic patients (6% vs. 0%) may have accounted for the between-group disparity in mortality. This study has been criticized for its design, approval and conduct [95]. The patients in the Besselink group received a higher number and more strains of probiotic organisms (six strains of probiotics vs. 1-4 strains of probiotics in other studies) and some of the patients were receiving pressors. Randomized controlled trials and meta-analysis have not demonstrated significant benefits of prophylactic antibiotics on patients with necrotizing acute pancreatitis [96-98]. Further large-scale, high-quality, placebo-controlled, double-blind trials are needed.

Probiotics and Necrotizing Enterocolitis (NEC)

Necrotizing enterocolitis is a potentially devastating disease, characterized by severe intestinal inflammation and necrosis, which occurs primarily in preterm infants. The risk of developing NEC is inversely related to gestational age and birth weight. Neonates younger than 28 weeks gestation and of extremely low birth weight (<1000 g) are particularly susceptible. An exaggerated inflammatory response of the immature intestine occurs during a complex interplay between bacterial colonization, initiation of enteral nutrition, and hypoxic-related intestinal injury [99].

Evidence suggests that bacterial colonization patterns are important in the pathogenesis of NEC. Studies have shown that preterm infants of mothers receiving broad-spectrum antibiotics prenatally or preterm infants receiving antibiotics directly postnatally are at higher risk for NEC [100,101] Isolated studies have demonstrated associations with organisms including *Enterobacteriaceae* [102,103], delta toxin positive methicillin resistant *Staphylococcus aureus* [104], and *Clostridium spp* [105,106]. There are 4 meta-analyses on this subject [107-110]. Two more RCTs have been published since the meta-analyses were completed [111,112]. Each meta-analysis, as well as the 2 recent RCTs, documented reduced rates of NEC and mortality with the use of prophylactic probiotics with an overall reduction in the relative risk (RR) of NEC (Bell ≥ 2) to 0.35 (95 % CI 0.23-0.55) and of mortality to 0.41 (0.28-0.60) [113]. Best results appear to be achieved with probiotics based on 2 or more probiotic species and/or with a combination of *Bifidusbacterium* spp. and *Lactobacillus acidophilus*.

There was an increased risk of sepsis in neonates receiving orally administered probiotics in the randomized, controlled clinical trial by Lin et al. [111], especially in the most vulnerable neonates with birth weights <750 g. However, none of the positive blood cultures grew *Lactobacillus* or *Bifidobacterium* spp.

Our review of studies found that the use of probiotics reduces the occurrence of NEC and death in premature infants born less than 1500 grams. There is insufficient data with regard to the benefits and potential adverse effects in the most at risk infants less than 750 grams at birth.

Probiotics and Multi-Organ Dysfunction Syndrome (MODS)

Impaired intestinal barrier function has been assumed to play a role in the development of sepsis and multiple organ failure (MOF) in patients with decreased gut perfusion following major surgery, trauma or shock [114,115]. Feeding probiotics (VSL#3) to experimental animals resulted in a normalization of colonic physiologic function

and barrier integrity in conjunction with a reduction in mucosal levels of proinflammatory cytokines [116]. In a prospective study of 25 patients who developed severe SIRS following ICU admission had significantly lower anaerobes in their gut flora and higher counts of pathogenic *Pseudomonas aeruginosa* and *Staphylococcus* spp. in the gut than healthy volunteers [117]. A double-blind, placebo-controlled, randomized design by Alberda et al. [118] to determine the effects of viable probiotics and probiotic sonicates on the development of MODS in critically ill, enterally fed patients showed a significantly larger increase in systemic IgA and IgG concentrations in patients who received viable probiotics than in the patients who received placebo or sonicates ($P<0.05$). MODS scores were not significantly affected by probiotic treatment. Most of the patients in this study showed a reduction in CRP concentrations over the treatment period, those patients who received viable probiotics had a lesser decline in CRP concentrations than did those patients who received either placebo or bacterial sonicates. Spindler-Vesel et al. [119] also demonstrated reduced infection rates in trauma patients treated with a combination of probiotics and prebiotics.

There are insufficient data to make a recommendation on the use of prebiotics/probiotics/synbiotics in critically ill patients.

Probiotics and Allergy and Immune Response

Recent research in mucosal immunology demonstrated interactions between microbes and host at an early age even when mucosal barrier and immune system are still immature [120]. Probiotics have been found to enhance the innate immunity and modulate pathogen induced inflammation via toll-like receptor-regulated signaling pathways [121]. The mode of delivery has a great impact on the acquisition of the intestinal bacteria, also beyond the immediate neonatal period. Vaginally born infants and infants born by cesarean section show major differences in cultural microbiota up to 6 months of age [122]. Infants harboring *Bacteroides fragilis* and *Bifidobacterium* species had more circulating immunoglobulin (Ig) A-secreting and IgM-secreting cells. Bacteria in breast milk and microbes potentially present in the amniotic fluid may affect the composition of gut microbiota [123]. Gut microbiota stimulates the TH1, TH3, and T regulatory cells, which can balance the IL-4, IL-5, and IL-13 secreted by TH2 cells in atopic diseases like allergic rhinoconjunctivitis, asthma and atopic eczema [124].

In a randomized double blind placebo-controlled studies of probiotic use, *Lactobacillus GG* or placebo when given to pregnant mothers with a strong family history of eczema, allergic rhinitis or asthma, and to their infants for the first six months after delivery. The frequency of developing atopic dermatitis in the offspring's of pregnant mothers who received *Lactobacillus GG* was significantly reduced by 2, 4, and 7 years, by 50%, 44%, and 36% respectively [125-127]. *Lactobacillus acidophilus* strain was not able to produce same result in a different study suggesting the strain specificity [128]. *Lactobacillus GG* in combination with *B. lactis* during pregnancy and breastfeeding reduced the risk of atopic eczema and allergic sensitization in child [129], whereas a mixture of probiotics (*Lactobacillus GG*, L. *rhamnosus* LC705, *B. breve*, and *Propionibacterium freudenreichii* ssp. *Shermanii* JS) failed to reduce the risk atopic eczema [130], indicates the strain differences and interactions.

Lactobacillus GG also shown to increase protective hemagglutinin inhibition titers against the virus with no side effects when treated for 28 days after administration of live-attenuated influenza vaccine in a randomized, double-blind, placebo-controlled pilot study. This suggests the role of probiotics as a potential adjuvant to improve influenza vaccine [131]. A pilot study involving healthy adults showed higher levels of antityphoid antibodies when *Lactobacillus GG* was given for 10 days before vaccination than those who received placebo [132].

We suggest not using prebiotics, probiotics, or synbiotics for the prevention of any allergic conditions as bibliographical data do not enable any clear conclusion regarding its beneficial effects on the prevention or treatment of allergy. Initial meta-analyses suggest a benefit of probiotics in reducing the development of eczema, but not any other allergic outcome.

Probiotics and Ventilator Associated Pneumonia (VAP)

Ventilator-associated pneumonia (VAP), defined as pneumonia occurring more than 48 hours after endotracheal intubation, is a leading hospital-acquired infection in the US [133]. Importantly, VAP prolongs the duration of mechanical ventilation, length of stay in the intensive care unit (ICU) and possible recovery of the lung function [134]. Furthermore, patients with VAP may have a 2 to 10 fold higher risk of death compared to mechanically ventilated patients without pneumonia, with crude mortality rates ranging from 24% to 76% [135,136]. The pathogenesis of VAP is complex but typically involves colonization of the aerodigestive tract with pathogenic bacteria, formation of biofilms, and microaspiration of contaminated secretions [137,138]. Rising antibiotic resistance rates have prompted a transition in research efforts from treatment to prevention [135].

In a clinical trial, Forestier et al. [139] using *Lactobacillus casei rhamnosus* strain 35 (Lcr35) demonstrated a decrease in VAP incidence in probiotic group compared to placebo group (2.9% vs 7.5%) along with decreased new gastric colonization by *Pseudomonas aeruginosa* (3% vs 6%) and new *P. aeruginosa* respiratory colonization (5% vs 12%). Knight et al. [140] performed a prospective, randomized, double-blind, placebo controlled trial by randomized patients to receive either Synbiotic 2000 FORTE (n=130) or placebo (n=129) twice a day. The primary endpoint, VAP incidence, was similar between groups (9% of patients in the synbiotic group and 13% of patients in the placebo group; $p=0.42$). Secondary endpoints, including ventilator days, VAP rates per 1000 ventilator days, ICU length of stay, ICU mortality, and hospital mortality did not differ significantly between groups. The only meta-analysis of randomized, controlled clinical trials using probiotics to prevent ventilator-associated pneumonia (VAP) found significant reductions in the incidence of VAP and length of ICU stay [141]. Five studies were included for analysis, including 2 studies described above [139,140]. Mortality, however, was not affected. Morrow et al. [142] recently reported the results of a single-center, double-blind, clinical trial including 146 mechanically ventilated patients, randomized to receive standard care or enteral probiotics (*Lactobacillus rhamnosus*) twice a day. VAP incidence was decreased from 40 to 19% in patients treated with prophylactic probiotic therapy and standard care, respectively ($P=0.007$) which was associated with an estimated number needed to treat to prevent 1 case of VAP as approximately 5 patients. Additionally, a decrease in infections due to *Clostridium difficile* (18.6 vs. 5.8%; $P=0.02$) was reported. Other measures, such as VAP antibiotic days, duration of mechanical ventilation, ICU stay, hospital stay, and total charges, were similar between groups.

In conclusion, we don't have enough data to firmly support the use of probiotic bacteria in the setting of intensive care units. Well-designed multi-center clinical studies with defined mixtures of probiotics and defined endpoints are warranted in this field.

Probiotics as Commercial Products

Probiotic research and industry have continued to grow from these early observations, and the global market for probiotic ingredients, supplements, and foods amounted to $21.6 billion in 2010 and are expected to reach $31.1 billion by 2015 [143]. Probiotics are available in the market under different trade names and varies in different doses and different combinations. Following are the list of some of the commercial probiotics available in the market (Table 3). The list is to give the readers a sense of what is commercially available, not provide recommendations for probiotic strain use. Administration of bacteria-derived probiotics should be separated from antibiotics by at least 2 hours.

Not all probiotics are created equal and the benefits are strain and dose specific. Some formulations also have prebiotics. The choice of probiotic depends upon the health benefit for which it is required. The number of bacteria per serving (CFUs) matter since the administered probiotic is going to be a tiny and transient part of trillions of bacteria already in your gut. The beneficial effects of probiotics cease in 2-4 weeks after stopping adminstration. This is because the probiotic bacteria stay in our gut only transiently and do not establish permanent residence.

All yogurts sold in the United States are made with the yogurt starter bacteria (*S. thermophilus* and *L. bulgaricus*). Yogurts frequently do not include the levels of bacteria present in the final product on their labels, so the only way to know if a yogurt carries enough of the right type of probiotics to be beneficial is to contact the manufacturer.

We recommend consumers to check with their health care provider before taking probiotics.

Safety

In the US, probiotics are classified as dietary supplements by the Food and Drug Administration (FDA), thus having less stringent requirements in their demonstration of safety, efficacy, and purity. Specific strains of probiotics fall into the FDA status of generally regarded as safe, while others do not [144]. Generally regarded as safe status only evaluates safety; clinical efficacy is not assessed during this process.

Probiotics are viable organisms with the potential to induce systemic infection in the host. A review of literature by McFarland found 12 cases of *Lactobacillus* probiotic, mostly in children (9 cases) [145]. There are 24 cases of fungemia in patients associated with the probiotic *S. boulardii* [146]. The major risk factors identified were prematurity in infants, chronic disease, immunodeficiency, and/or debilitation. Munoz et al documented 3 patients with *Saccharomyces cerevisiae* fungemia in an ICU associated with *S. boulardii* therapy [147]. Health care providers should change gloves after handling *S. boulardi* powder. Some experts recommend avoiding *S. boulardi* in patients with central venous catheters [148]. Thirty-nine case reports of infection due to *Lactobacillus rhamnosus* GG were reported between 1950 and 2003 by Cannon et al. [149]. In the clinical trials, no reports of bacteremia or fungemia have been associated with probiotic use. All cases of probiotic bacteremia or fungemia have occurred in patients with underlying immune compromise, chronic disease, or debilitation, and no reports have described sepsis related to probiotic use in otherwise healthy persons. Many case reports of probiotic sepsis describe persons with preexisting intestinal pathology, including diarrhea and short intestine. These may be common indications for probiotic use, but would also be expected to increase the risk of probiotic translocation through the intestinal mucosa.

Secondly, probiotics have the theoretical risk of transfer of antibiotic-resistance genes to pathogenic bacteria. Many *Lactobacillus* strains are naturally resistant to vancomycin, which raises concerns regarding the possible transfer of such resistance to more pathogenic organisms, particularly enterococci and *Staphylococcus aureus*. However, the vancomycin-resistant genes of *Lactobacillus* spp. are chromosomal and, therefore, not readily transferable to other species [150]. The PROPATRIA trial has been discussed in the probiotics and acute pancreatitis section above.

Challenges

Extrapolation of immunomodulatory effects found in the laboratory and in animal studies with outcomes in human trials presents a difficult challenge. Immunomodulatory effects conferred by *L. plantarum* WCFS1 *in vitro* [151], in animal models [151,152] as well as in humans [153,154] highlight the difficulties of comparing similar effects by a single strain in different contexts. Generally, the discrepancies between *in vitro* and *in vivo* results observed in published trials can be partly explained by the host contribution (genetic factors, different baseline immune functions between individuals, microbiome diversity, differences in the body sites targeted, intra-person variation) as well as environmental factors (diet, stress, etc.) partially controlled by each individual.

Several properties that are thought to be important for the probiotic effect as they can (at least) modify the survival capacity of the strain *in vivo* clearly differ between strains of different or similar species. They include tolerance to acid, bile, and pancreatin; adherence to mucus or to epithelial cells; enzymatic activity; and antibiotic resistance or production of antimicrobial compounds. Several studies have also shown differences in the immunomodulating properties of various probiotics between strains within the same species. For example, Medina et al. [155] showed that different strains of *Bifidobacterium longum* varied greatly in their capacity to induce cytokine production (IL-10, IFN-γ and TNFα) by peripheral blood mononuclear cells and could even drive the immune responses in different directions. Head-to-head comparisons of different strains in human studies are rare. The implications of this strain-specificity are that for commercial products, documentation of health effects must be conducted on the specific strain being sold, one should avoid any extrapolation of positive or negative effects between probiotic strains or products and meta-analysis of the effect of probiotics with different active molecules should also be avoided.

Conclusion

Probiotics seem to have promising role in shortening duration of infections or decreasing susceptibility to the pathogens. Use of the different strains, dosage, duration of treatment and smaller size of the trials makes interpretation of the available data more difficult. Current evidence also indicates that probiotic effects are strain-specific, they do not act through the same mechanisms nor are all probiotics indicated for the same health conditions. It is currently unknown whether there are optimal probiotic species, doses, and/or formulations. Although the data with probiotics are still far too weak to convince clinicians, the concept is fascinating, and further studies would be more than welcome.

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