

Risk and Safety of Probiotics

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Probiotics have been used safely for years. Safety outcomes are inconsistently reported in published clinical trials. In 2011, a report released by the Agency for Healthcare Research and Quality concluded that, although the existing probiotic clinical trials reveal no evidence of increased risk, “the current literature is not well equipped to answer questions on the safety of probiotics in intervention studies with confidence.” Critics point out that the preponderance of evidence, including the long history of safe probiotic use as well as data from clinical trials, and animal and in vitro studies all support the assumption that probiotics are generally safe for most populations. Theoretical risks have been described in case reports, clinical trial results and experimental models, include systemic infections, deleterious metabolic activities, excessive immune stimulation in susceptible individuals, gene transfer and gastrointestinal side effects. More research is needed to properly describe the incidence and severity of adverse events related to probiotics.

Keywords. probiotics; *Lactobacillus*; *Saccharomyces*; safety; bacteremia.

Probiotics have been used safely in foods and dairy products for over a hundred years. Recently, there has been increasing interest in their use to prevent, mitigate or treat specific diseases. A multitude of clinical trials have investigated the use of probiotics for diseases ranging from necrotizing colitis in premature infants to hypertension in adults [1, 2]. Examples of populations studied and associated adverse events seen are in Table 1. Safety outcomes are inconsistently reported in published clinical trials.

The US Food and Drug Administration (FDA) designation Generally Recognized as Safe (GRAS) has been applied to certain probiotic organisms when added to food (<http://www.fda.gov/food/IngredientpackagingLabeling/GRAS/>), although few systematic safety studies have been done, especially in vulnerable populations.

In 2011, a report was released by the Agency for Healthcare Research and Quality (AHRQ) based on research sponsored by the National Institutes of Health and the FDA and conducted by the Southern California Evidence-based Practice Center reviewing the safety of

probiotics. The report was an exhaustive review of the literature including 622 studies of organisms from 6 genera: *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *Enterococcus*, and *Bacillus*. The authors of the report concluded that, although the existing probiotic clinical trials reveal no evidence of increased risk, “the current literature is not well equipped to answer questions on the safety of probiotics in intervention studies with confidence [3].” The vast majority of the existing published studies simply have not adequately assessed and reported on safety. In a commentary on this report, Wallace and MacKay [4] point out that “to explore the question ‘are probiotics safe’ using a drug-based framework assumes that the literature will include drug-like safety and toxicology data.” Indeed, one can presume that this type of data was omitted from the majority of clinical trial reports in the literature because the researchers didn’t have any reason to think that such detailed safety assessments would be either necessary or even appropriate. Wallace and MacKay suggest that the research community should recognize that the most appropriate way to evaluate the safety of such products is based on the “totality of evidence” at least in healthy populations. This evidence includes its long history of safe use as well as data from clinical trials, and animal and in vitro studies. To make the point that the results of the AHRQ report should be used to support rather than raise doubts about the

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Table 1. Populations Studied in Clinical Trials and Toxicity Seen

Population	Strains Studied	Toxicity Seen
Children [5, 6]	<i>Enterococcus</i> T-110, <i>Clostridium butyricum</i> , <i>Bacillus mesentericus</i> , <i>Bifidobacterium longum</i>	None
Hospitalized children [7, 8]	LGG, <i>Lactobacillus acidophilus</i> , <i>Lactobacillus rhamnosum</i> , <i>Bifidobacterium longum</i> , <i>Bifidobacterium bifidum</i> , <i>Saccharomyces boulardii</i> , <i>Streptococcus thermophilus</i>	None
Hospitalized adults [9–11]	LGG, BioK+	None
Immunocompromised [12–14]	<i>Pediococcus pentosaceus</i> , <i>Leuconostoc mesenteroides</i> , <i>Lactobacillus paracasei</i> subspecies <i>paracasei</i> F19, <i>Lactobacillus plantarum</i> , LGG, <i>L. johnsonii</i> LA 1, VSL #3, <i>L. plantarum</i> 299V (liver transplant), <i>S. boulardii</i> (HIV)	One episode of invasive disease noted (LGG)
Infants [15–18]	LGG, LC705, Bb99, and <i>Propionibacterium freudenreichii</i> spp <i>shermanii</i> , Bb12, <i>L. reuteri</i>	One mechanical choking episode reported
Pregnant women [19–21]	LGG, LC705, Bb99, and <i>Propionibacterium freudenreichii</i> spp <i>shermanii</i>	None
Premature neonates [22–25]	LGG, <i>B. longum</i> BB536, <i>Bifidobacterium</i> Bb12	None
Elderly [26]	VSL#3 (<i>Streptococcus thermophilus</i> DSM 24731, <i>Bifidobacteria</i> (<i>B. longum</i> DSM 24736, <i>B. breve</i> DSM 24732, <i>B. infantis</i> DSM 24737), <i>Lactobacilli</i> (<i>L. acidophilus</i> DSM 24735, <i>L. plantarum</i> DSM 24730, <i>L. paracasei</i> DSM 24733, <i>L. delbrueckii</i> subsp. <i>bulgaricus</i> DSM 24734)	None
Inflammatory bowel disease [27, 28]	<i>Lactobacillus acidophilus</i> LA-5, <i>Lactobacillus delbrueckii</i> subsp. <i>bulgaricus</i> LBY-27, <i>Bifidobacterium animalis</i> subsp. <i>lactis</i> BB-12, <i>Streptococcus thermophilus</i> STY-31, LGG	None

Abbreviation: LGG, *Lactobacillus GG*.

safety of probiotics, they make an astute comparison to the study of apples, stating that “if the AHRQ intended to answer the question ‘are apples safe?’ it would likely come to the same conclusion, which is that the current literature is not well equipped to answer questions on the safety of apples with confidence.”

It should be noted that just as no 2 probiotic strains can be expected to have exactly the same clinical effect, each probiotic strain, including those that have not yet been developed, would be anticipated to have a different safety profile. Perhaps more importantly, the safety of a commercially available probiotic product depends not only on the probiotic organism but on the other constituents of the product, be it a food or medicinal formulation.

According to a 2002 report jointly released by the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) of the United Nations (<http://www.fda.gov/ohrms/dockets/dockets/95s0316/95s-0316-rpt0282-tab-03-ref-19-joint-faowho-vol219.pdf>), “probiotics may theoretically be responsible for four types of side effects:

1. Systemic infections.
2. Deleterious metabolic activities.
3. Excessive immune stimulation in susceptible individuals.
4. Gene transfer”.

Minor gastrointestinal symptoms have also been reported.

The WHO/FAO working group recommended that new probiotic strains be evaluated for safety by testing for antibiotic

resistance, toxin production and hemolytic potential, assessing metabolic activities such as D-lactate production and bile salt deconjugation, conducting human studies to evaluate side effects and post-market surveillance of commercial consumers, and, ideally, studying their use in immunocompromised animals to determine infectivity of the probiotic organism in this type of host. What follows is a summary of what is known about each category of potential adverse event.

SYSTEMIC INFECTIONS

A number of case reports describe episodes of infection caused by organisms consistent with probiotic strains in patients who consumed probiotics prior to symptom onset. The most commonly reported single event is fungemia, with at least 33 reports of the presence of *Saccharomyces cerevisiae* or *Saccharomyces boulardii* (these organisms are microbiologically indistinguishable) in blood cultures of patients who had consumed the probiotic *S. boulardii* [29–50]. At least eight cases of bacteremia associated with *Lactobacilli* have been reported, including *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Lactobacillus GG* [51–56].

Nine cases of overt sepsis have been reported [57–63], associated with *S. boulardii* [*cerevisiae*], *Lactobacillus GG*, *Bacillus subtilis*, *Bifidobacterium breve*, or combination probiotics.

Endocarditis events due to both *Lactobacillus* and *Streptococcus* probiotics have been reported as well [64, 65]. The

development of an abscess associated with *Lactobacillus rhamnosus* was also reported twice [66, 67].

Because some of the cases of *L. bacteremia* occurred in an intensive care setting in the presence of a central venous catheter, experts recommend the use of scrupulous hand hygiene when manipulating central venous catheters after handling probiotic preparations. In our hospital, we recommend that nurses change gloves after handling probiotic capsules and before touching vascular access catheters.

Compelling evidence in favor of the safety of *L. rhamnosus* strain GG (LGG, one of the more popular probiotic strains consumed in Finland) comes from Finnish surveillance data showing no increase in *Lactobacillus* bacteremia over the decade from 1990 to 2000 despite the increasing popularity of this specific probiotic [68]. *Lactobacilli* represented 0.02% of all positive blood cultures. There was no temporal change in this prevalence over the course of the decade. Eleven of 89 strains isolated from blood appeared identical to the probiotic strain LGG by pulse field gel electrophoresis [69]; however, in a subsequent study, the LGG-like isolates from the blood cultures were found to be phenotypically different from probiotic LGG [70] when subjected to tests that might indicate pathogenicity, including in vitro adhesion rate and induction of respiratory burst.

The absence of any change in the prevalence of *L. bacteremia*, particularly that due to *L. rhamnosus* strain GG, is remarkable given that the consumption of *Lactobacillus* GG increased from 1 L per person per year in Finland to 6 L per person per year over the time period studied.

Lactobacillus bacteremia in Sweden was also examined over a 6-year period, during which time there was increasing use of 3 commercial probiotic *Lactobacillus* strains. There was no change in the rate of lactobacillemia, and no case of *Lactobacillus* isolated from the blood stream was identified as one being related to the probiotic strains [71].

There are studies of safe use of probiotics in solid organ transplant recipients, and other immunocompromised hosts, without development of systemic infection [12–14].

DELETERIOUS METABOLIC ACTIVITIES

One clinical trial [72] caused significant concern about probiotic safety. The PROPATRIA study was a double-blind placebo-controlled randomized controlled trial that examined the ability of a multistrain probiotic to prevent infectious complications in 296 patients with severe pancreatitis. Subjects assigned to the probiotic arm of the study experienced a higher mortality which was attributed to bowel ischemia. Speculating on the cause of intestinal ischemia in critically ill patients who received this particular group of 6 probiotics, the authors postulated that perhaps the administration of probiotic bacteria increased the oxygen demand in the gut mucosa, in the setting of already reduced

blood flow. Alternatively, the probiotics may have triggered an inflammatory reaction in the small bowel with reduction of capillary blood flow. Two prior smaller-scale studies (later pooled to increase power) [73, 74] demonstrated a reduction in septic complications, surgical intervention and infected necrosis in patients with pancreatitis given a symbiotic containing lactic acid bacteria and fiber. No mention was made of intestinal ischemia. However in 2 other studies of critically ill adults [75] and children [76], nonsignificant but possible increases in infectious complications were observed in patients given probiotics.

Other metabolic concerns include the effects of D-lactate produced by probiotic strains, and deconjugation of bile salts. Five reports of D-lactic acidosis can be found in the literature [77–79], one in a patient with short bowel syndrome.

EXCESSIVE IMMUNE STIMULATION IN SUSCEPTIBLE INDIVIDUALS

Because probiotics have been shown to affect both the innate and adaptive immune systems, including effects on cytokine secretion and dendritic cell function [80–83], concern has been raised about the potential to overly stimulate the immune response in some individuals, possibly leading to autoimmune phenomena or inflammation. This theoretical concern has not been reported in any human subjects.

GENE TRANSFER

Lactic acid bacteria possess plasmids containing genes conferring resistance to tetracycline, erythromycin, chloramphenicol or lincosamide, macrolide, streptomycin, and streptogramin [84–86].

There is some evidence that leuconostoc species and pediococcus species can accept broad host range antibiotic resistance plasmids from lactococcus species [87]. Conjugation transfer from enterococci to lactobacilli and lactococci can occur in the gut of animals as well as in vitro; however, the transfer to lactobacilli is quite rare [88].

There have also been attempts at molecular identification of vancomycin resistance genes in lactobacilli. None were found. There is no evidence of Van A, B, H, X, Z, Y, or S by hybridization or polymerase chain reaction products [89, 90].

Despite the theoretical possibility of lateral gene transfer between probiotic organisms and other organisms in the gut or other site, no clinical evidence of transfer of antimicrobial resistance has ever been seen. This is particularly important to note given the common use of probiotics concomitantly with antibiotics.

GASTROINTESTINAL SIDE EFFECTS

Studies have reported minor gastrointestinal symptoms, such as abdominal cramping, nausea, soft stools, flatulence, and taste

disturbance, occurring in subjects receiving probiotics. However, in both a meta-analysis and a systematic review of the use of probiotics for prevention of *Clostridium difficile*-associated diarrhea, subjects receiving probiotics were 18%–20% less likely to experience these adverse effects than controls [91, 92].

IMPLICATIONS FOR FUTURE RESEARCH

Despite the clear need for more research on both the safety and efficacy of probiotics, at the time of this writing, only 7 US federally funded human interventional studies are being conducted in this field (http://projectreporter.nih.gov/reporter_SearchResults.cfm?icde=21874157; accessed 12 February 2015). In a 2010 draft guidance from the FDA (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM229175.pdf), probiotics were defined as live biotherapeutic products, in other words, drugs, and as such submission of an Investigational New Drug (IND) applications is required before investigators can proceed with clinical research in this area. Road blocks experienced during the probiotic IND process have included unwillingness of the probiotic manufacturer to share relevant information with the FDA, and requirement to restrict enrollment using an extensive list of exclusion criteria (personal communication with FDA, 2007–2009). As a result, many investigators have participated in discussions with regulators over the difficulty these policies create for those wishing to further scientific knowledge about the efficacy and safety of these products. Nevertheless in 2013, FDA guidance on INDs and human research studies included the statement that “if an edible product that might otherwise be a conventional food is intended for a use other than providing taste, aroma, or nutritive value, such as blocking the absorption of carbohydrates in the gut, that product becomes a drug because the primary purpose of consuming it has changed”. In other words, the product is no longer being consumed as a food—primarily for taste, aroma, or nutritive value—but used as a drug for some other physiological effect (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM229175.pdf). Populations suggested by the FDA to be potentially at risk for adverse events in probiotic clinical trials are listed in Table 2.

RECOMMENDATIONS TO RESEARCHERS

Despite the controversy over the necessity of safety data for probiotics, their increasing use to treat, prevent, or mitigate disease seems to have resulted in a call for such data from the scientific community. For this reason, we recommend that investigators who carry out clinical trials using probiotics conduct active surveillance for cases of infection associated with the probiotic and for occurrence of other adverse effects. Some patients may be at higher risk for adverse events. These include those with

Table 2. Populations Potentially at Risk According to FDA

Population	Examples
Immunosuppressed	anti-rejection medication after stem cell or solid organ transplant, injectable immunosuppressive drugs for autoimmune disease, or corticosteroids (greater than ½ mg per kg body weight or prednisone or its equivalent); chemotherapy or radiation
Structural heart disease	Valve abnormality or replacement, history of endocarditis
Inpatient	
Pregnant	
Potential for translocation of probiotic across bowel wall	Presence of an active bowel leak, acute abdomen, active intestinal disease including colitis, or significant bowel dysfunction; presence of neutropenia or anticipation of neutropenia after chemotherapy; radiation therapy

Abbreviation: FDA, Food and Drug Administration.

immune compromise, premature infants, patients with short bowel syndrome, those with central venous catheters, and patients with cardiac valve disease. If there is a case of infection that appears to be caused by a probiotic strain, it is important to confirm the identity of the organism using molecular testing at a reference laboratory.

Notes

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