

Safety of Probiotics to Reduce Risk and Prevent or Treat Disease

Executive Summary

Introduction

The Agency for Healthcare Research and Quality (AHRQ) commissioned the Southern California Evidence-based Practice Center based at RAND to carry out a systematic review on the safety of probiotics used in research to reduce the risk of, prevent, or treat disease. The evidence report was jointly sponsored by the National Institutes of Health (NIH) Office of Dietary Supplements, the NIH National Center for Complementary and Alternative Medicine, and the Food and Drug Administration Center for Food Safety and Applied Nutrition.

Probiotics (literally, “for life”) are bacteria or yeasts considered to confer a health benefit on the host organism. The review objective was to catalog what is known about the safety of interventions containing organisms from six different genera used as probiotic agents (*Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *Enterococcus*, and *Bacillus*), alone or in combination, used to reduce the risk of, prevent, or treat disease in research studies.

This evidence report has a broad scope and was not restricted to specific interventions, specific patient groups, or specific clinical outcomes. The large number of included studies allowed unique analyses to explore adverse events reported to date in research on probiotics.

Evidence-based Practice Program

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

The full report and this summary are available at www.ahrq.gov/clinic/epcix.htm.



Methods

We searched 12 electronic databases (DARE, Cochrane Database of Systematic Reviews, CENTRAL, PubMed, Embase, CINAHL, AMED, MANTIS, TOXLINE, ToxFile, NTIS, and AGRICOLA) and scanned the references of included studies and pertinent reviews for studies addressing the safety of interventions using products containing microorganisms purported to have probiotic properties (henceforth called “probiotics”) from database inception to August 2010 without language restriction.

We systematically identified studies monitoring the presence or absence of participants’ adverse health outcomes, without restriction due to study design, participant, or clinical field. Any studies that assessed the effect of microorganisms used as probiotic agents and reported on an adverse health outcome (its presence or absence) were included. Two reviewers independently screened studies for inclusion, extracted data, and assessed their quality. We differentiated studies that addressed a specific adverse event from those with nonspecific safety statements.

We investigated the quantity of adverse events (number of participants with adverse events per treatment group, number of adverse event incidences per treatment group), the quality of the adverse events (all adverse events, serious adverse events), and the nature of adverse events (e.g., gastrointestinal events, infections). The review aims to answer a large number of questions pertaining to product and participant factors. Studies reporting direct comparisons (e.g., between two different probiotic organisms) were primarily sought; in addition, indirect evidence was analyzed in stratified analyses and meta-regressions.

Results

The review demonstrates that there is a large volume of literature on probiotics. However, the literature provided only limited evidence to address the questions the review set out to answer.

The literature search identified 11,981 publications, of which 2,189 were ordered as full-text publications after title and abstract screening and 622 studies were included in the review. Of these, 235 studies made only nonspecific safety statements (e.g., “the intervention was well tolerated”) without indicating what kind of adverse events were monitored. The remaining 387 studies reported the presence

or absence of one or more specific adverse events; these studies were abstracted in detail and used to answer the Key Questions. Across all included studies and treatment arms, 24,615 participants used a probiotic product.

The review considered reports without study design restrictions and included a large number of randomized controlled trials (RCTs); however, the majority were not designed to address safety. The quality of included studies varied greatly within study design categories. Adverse events were poorly documented, and the parameters that were monitored were often not stated. Interventions were poorly documented, lacking detail, for example, on the specific probiotic strain administered. Very few of the identified studies investigated *Saccharomyces* or *Streptococcus*, and even fewer *Enterococcus* or *Bacillus*; the majority of identified studies used *Lactobacillus*, alone or in combination with other genera, most often *Bifidobacterium*.

To estimate the proportion of existing studies of probiotic organisms found in the literature that are included in this safety review, we noted all RCTs of probiotics that were found in our searches that reported on patient outcomes. Of this pool of potentially relevant RCTs, 58 percent met inclusion criteria for the review (i.e., made a nonspecific safety statement or reported the presence or absence of a specific adverse event). The remaining RCTs did not address the safety of probiotics as defined in this evidence review.

Key Questions

Key Question 1: What is the evidence that the active and lyophilized forms of probiotics (*Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *Enterococcus*, and *Bacillus*) as single ingredients or in combination with other probiotics or prebiotics in all delivery vehicles (and formulations) when used to cure, treat, mitigate, or prevent a disease or reduce disease risk are safe in the short term? In the long term?

Case studies indicated that fungemia, bacteremia, sepsis, and other infections may be associated with administered probiotic organisms; the ability to reliably determine whether administered strains match the clinical isolate is now possible through DNA-based methods.

None of the identified case series, controlled clinical trials, or parallel and crossover RCTs reported an infection caused by the administered probiotic organisms. However, studies

seldom reported that they monitored for infections of the types identified in case reports. In fact, most did not state what adverse events were monitored and did not systematically address the safety of the probiotic products.

Across parallel RCTs there was no indication that the quantity of reported adverse events was increased in short-term probiotic intervention arms compared to control groups, based on the relative risk (RR) of the number of participants with adverse events (RR 0.98; 95% CI: 0.93, 1.04, $p=0.537$; 121 RCTs) as well as the number of adverse event incidences reported in each treatment group (RR 1.00; 95% CI: 0.93, 1.07, $p=0.999$; 208 RCTs). The current available evidence does not suggest a widespread risk of adverse events associated with probiotics, but future studies that explicitly monitor for the issues of concern are needed to quantify the actual risk of specific adverse events in intervention studies.

Key Question 2: What are characteristics and associations of the reported harms in Question 1?

Across all included studies, the most commonly reported adverse events were gastrointestinal in nature. This was followed by reported infections and infestations. The third most common category was the “other” category for symptoms that could not be assigned to a specific organ system or type of adverse event.

Across identified RCTs, there was no indication that participants using probiotic organisms experienced statistically significantly more gastrointestinal (RR 1.03; 95% CI: 0.89, 1.18, $p=0.693$; 126 RCTs), infections (RR 1.00; 95% CI: 0.87, 1.16, $p=0.967$; 65 RCTs), or other adverse events (RR 1.01; 95% CI: 0.91, 1.12, $p=0.923$, 131 RCTs) compared to control group participants.

Studies rarely reported efforts to monitor adverse events specific to probiotic products. Hence, safety evaluations may change with future, more targeted assessment of adverse events in intervention studies.

Key Question 3: What is the evidence that harms of *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *Enterococcus*, and *Bacillus* differ by product and delivery characteristics?

The lack of detail in the description of administered probiotic organisms in most studies hindered evaluations of the safety. Many studies did not specify which probiotic strains were investigated, nor was there indication that intervention preparations were tested for identity of the included organisms, quantity, viability, or contaminants.

Stratified analyses by probiotic genus showed no increased risk of adverse events among the probiotic group compared to a control group in RCTs using interventions reported to contain exclusively *Lactobacillus* (RR 0.98; 95% CI: 0.87, 1.11; $p=0.785$), *Bifidobacterium* (RR 0.92; 95% CI: 0.82, 1.03; $p=0.141$), *Saccharomyces* (RR 1.00; 95% CI: 0.46, 2.18; $p=0.993$), *Streptococcus* (0.99; 95% CI: 0.78, 1.25; $p=0.907$), *Enterococcus* (RR 0.85; 95% CI: 0.47, 1.54; $p=0.588$), or *Bacillus* (0.99; 95% CI: 0.44, 2.22; $p=0.973$) strains. A meta-regression comparing the relative risk ratio associated with the genera indicated a statistically significantly higher risk for *Streptococcus* strains compared with the other genera; however this indirect comparison is based on a small number of studies that investigated *Streptococcus*, *Enterococcus*, or *Bacillus* interventions. Direct (head-to-head) comparisons of genera, species, strains, or delivery vehicles are largely absent in the literature.

There was some indication across studies that safety findings may differ by delivery vehicle. Intervention participants in studies in which yogurt or other dairy products were administered were more likely to experience adverse events compared with control group participants (RR 1.37; 95% CI: 1.05, 1.79; $p=0.022$) based on the number of adverse event incidences reported across groups in a subgroup analysis; however, studies directly comparing delivery vehicles are missing.

We did not find conclusive evidence in the existing literature that interventions with a mixture of different organisms reported more adverse events than studies using one probiotic strain only or evidence that synbiotics (mixtures of prebiotics and probiotics) differ from probiotics; however, there is a lack of direct comparisons.

Key Question 4: How do the harms of *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *Enterococcus*, and *Bacillus* vary based on (a) dose; (b) timing; (c) mode of administration; (d) age, gender, ethnicity, disease or immunologic status; (e) relationship to efficacy?

Very few studies overall explored the effect of intervention or participant characteristics on safety. To summarize, in the few studies that reported on the time of onset of gastrointestinal effects, most effects were observed in the first 3 days of treatment. The onset of infections tended to occur 1 week to several weeks after initiation of probiotics use; however, this information is primarily derived from case studies and was not systematically reported.

In indirect comparisons across studies, we found no evidence that a particular mechanism or route of administration of probiotic organisms was associated with an increased risk of an adverse event in intervention participants relative to control group participants. Stratified analyses and meta-regressions showed no increased risk of adverse events for children (RR 0.96; 95% CI: 0.88, 1.04; p=0.296, 35 RCTs), adults (RR 0.97; 95% CI: 0.79, 1.19; p=0.745, 40 RCTs), or elderly (RR 0.94; 95% CI: 0.82, 1.08; p=0.367, 4 RCTs) participants compared with adverse events observed in corresponding control groups; however, it has to be noted that only very few studies were identified that reported on elderly participants.

There was some indication that health status is associated with the experience of an adverse event when using probiotics. Case studies reporting serious adverse events described health-compromised, not generally healthy participants who contracted (most often) a serious infection potentially caused by probiotic organisms. However, subgroup analyses of RCTs in medium health-compromised participants (RR 1.03; 95% CI: 0.94, 1.13; p=0.491) and critically ill patients (RR 0.79; 95% CI: 0.51, 1.22; p=0.286) did not show a statistically significantly increased risk of experiencing adverse events for intervention participants compared with control group participants with similar patient characteristics.

Key Question 5: How often does harm associated with *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *Enterococcus*, and *Bacillus* lead to hospital admission or lengthened hospitalization?

While several case studies reported hospitalizations associated with the consumption of a product including *Saccharomyces*, *Lactobacillus*, or *Bacillus* strains, none of the case series or controlled trials reported that a probiotics intervention led to a hospitalization in the intervention participants. However, the number of hospitalizations due to adverse events was only explicitly reported on in a few of the included studies, and older publications may not have associated a hospitalization with probiotics intake.

RCTs reporting on the presence or absence of serious adverse events showed that differences across probiotic and control group participants were not statistically significant (RR 1.06; 95% CI: 0.97, 1.16; p=0.201, 66 RCTs). However, this result is primarily based on *Lactobacillus* interventions, and a few studies investigating *Saccharomyces*

and *Bifidobacterium*; there was a lack of studies reporting on the presence or absence of serious adverse events for other genera.

Key Question 6: How does harm associated with *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *Enterococcus*, and *Bacillus* relate to use of concomitant antibiotics, confounding diet therapies, corticosteroid use, immune suppressants, or other potential confounders?

We did not identify studies that addressed possible interactions or confounders of probiotics interventions. Although the risk of adverse events in general might be higher in individuals taking multiple medications, subgroup analyses of studies in which the intervention participants as well as the control group participants received antibiotics (RR 1.07; 95% CI: 0.94, 1.23; p=0.271); or corticosteroids (RR 1.04; 95% CI: 0.88, 1.22; p=0.650) found no statistically significant increased risk of adverse effects among intervention participants. There were too few studies to explore interactions with concomitant diet therapies and studies in participants using immune suppressants were also largely absent from the existing literature.

Future Research

Future studies need to characterize the intervention preparations in more detail. As identification methods progress, the reporting should include verification with DNA-based methods to identify the individual strains included in preparation, their potency and viability, and any potential confounders. The majority of existing studies report on *Lactobacillus*, alone or in combination with other genera, most commonly *Bifidobacterium* strains, and more studies are needed to explore potential adverse events associated with interventions that include the genera *Enterococcus* and *Bacillus*, in addition to studies on *Streptococcus* species selected for their probiotic properties, as well as studies on the use of *Saccharomyces* in some patient groups.

Studies should describe which adverse events were monitored to allow a clearer understanding of the presence and absence of adverse events in probiotics intervention studies. The reporting of adverse events should follow reporting guidelines such as the extension of the CONSORT statement for harms. In addition, there are comprehensive systems for cataloging adverse events, such as the Common

Terminology Criteria for Adverse Events system. Monitored harms should include infections with probiotics organisms as well as treatment failures in order to be able to quantify the risk for participants in intervention studies. Critical outcomes, such as all-cause mortality, should be assessed and reported in primary studies, and reviews should consider all studies measuring the outcome regardless of whether the study was conducted to evaluate the efficacy of the intervention or the occurrence of adverse events.

Long-term effects of probiotic interventions are largely unknown and there is a need to evaluate long-term interventions. In addition, large cohort studies following self-selected use of probiotic organisms are needed to fully understand the efficacy and safety of probiotics among representative populations.

Currently, few studies address complex questions about probiotic safety, such as interactions of participant or intervention characteristics with the use of probiotic products. The effect of product, intervention, or participant characteristics should be addressed with appropriate multivariate analyses. There is also indication that participants with compromised health should be monitored closely for potential adverse events associated with the use of probiotic products. Studies evaluating effects on elderly participants are largely absent from the literature, and the effects of delivery vehicles should be investigated systematically.

Conclusions

There is a lack of assessment and systematic reporting of adverse events in probiotic intervention studies, and interventions are poorly documented. RCTs and case studies diverge in the outcomes they report. The available evidence in RCTs does not indicate an increased risk; however, rare adverse events are difficult to assess, and despite the substantial number of publications, the current literature is not well equipped to answer specific questions on the safety of probiotic interventions with confidence.

Full Report

The executive summary is part of the following document: Hempel S, Newberry S, Ruelaz A, Wang Z, Miles JNV, Suttorp MJ, Johnsen B, Shanman R, Slusser W, Fu N, Smith A, Roth E, Polak J, Motala A, Perry T, Shekelle PG. Safety of Probiotics to Reduce Risk and Prevent or Treat Disease. Evidence Report/Technology Assessment No. 200. (Prepared by the Southern California Evidence-based Practice Center under Contract No. 290-2007-10062-I.) AHRQ Publication No. 11-E007. Rockville, MD. Agency for Healthcare Research and Quality. April 2011. Available at www.ahrq.gov/clinic/tp/probiotictp.htm.

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