Multiple *Lactobacillus* Infections Caused by Probiotics at Pediatric and Adult Academic Medical Centers

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ABSTRACT

Background: Probiotics are synthetic oral supplements containing live bacterial and fungal species hypothesized to help with various gastrointestinal conditions. However, they can cause infection if the organism spreads outside of the gastrointestinal tract. The aim of this study was to identify and describe patients who experienced systemic infections caused by probiotic use.

Methods: This study was a retrospective chart review of pediatric and adult patients at academic medical centers who received probiotics and subsequently developed positive cultures from a sterile site for probiotic-related species. Two individuals completed the chart reviews to determine if the probiotic was the true cause of the infection.

Results: *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces* cultures were reviewed, with a total of 71, 8, and 2 cultures isolated from sterile sites for each organism, respectively. Further review revealed 23 *Lactobacillus* cultures from 13 unique patients who were taking *Lactobacillus*-containing probiotics. Four patients without gastrointestinal tract compromise were included in the final analysis, including 1 patient whose culture was confirmed as identical to the probiotic. Types of infections included meningitis and bacteremia. Targeted antimicrobial therapy included ampicillin, ampicillin-sulbactam, and piperacillin-tazobactam, with total durations of therapy ranging from 10 to 22 days. No patients had mortality attributed to *Lactobacillus* infection.

Conclusions: Probiotics are not harmless supplements as they come with risk of serious infection as demonstrated in this review. Before use, the risks of probiotics should be considered carefully for each individual patient. Clinicians should consider avoiding probiotics in hospitalized patients, especially those with vascular or extra-ventricular access devices.

INTRODUCTION

Probiotics are synthetic oral supplements containing live microorganisms that have questionable efficacy and safety to consumers. A common species contained in probiotics is *Lactobacillus* – a gram-positive, anaerobic rod commonly found in the gastrointestinal (GI) tract of humans – in addition to *Bifidobacterium* and *Saccharomyces*.[1] Studies suggest that intestinal colonization with *Lactobacillus* may be protective against intraabdominal infections.[2,3] Numerous clinical trials have shown probiotics to be ineffective for GI tract disorders, and the American Gastroenterological Association (AGA) describes a lack of high-quality evidence to suggest efficacy of probiotics; the organization either does not provide a recommendation for probiotic use or provides a conditional recommendation for use based on low levels of evidence in the pediatric and adult populations.[4] Despite these guidelines, consumers and health care providers often think of probiotics as benign supplements. Currently, the US Food and Drug Administration (FDA) recognizes probiotics as generally safe dietary supplements or live microbial food supplements, but they are not approved by the FDA as a medication and, therefore, are not formally evaluated for safety and efficacy prior to release for consumer consumption.[5]

The organisms within probiotics have the ability to become opportunistic pathogens and cause significant infection.[6] There are several proposed mechanisms for probiotic-mediated alter ations to the GI tract that allow for increased infection risk,

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including changes to the composition of the microbiome, modification of the immune system, and adherence to the GI mucosa.[3] When *Lactobacillus* is present in the GI tract – whether from a probiotic or as a naturally occurring microorganism – there is opportunity for spread elsewhere in the body if the GI tract is leaking, inflamed, or immature.[7] As methods of probiotic administration and delivery have continued to advance to produce sustained organism survival within the GI tract, longer organism lifespans may lead to increased opportunity for infection.[8] Published literature has documented a range of probiotic-related systemic infections and other harms, including transmissible antibiotic resistance, metabolic disturbance, allergic response, bowel ischemia, and mortality.[5-6,9-12]

The objective of this single-center retrospective cohort study was to identify and describe multiple patients who experienced clinically significant systemic infections associated with the use of *Lactobacillus* probiotic products.

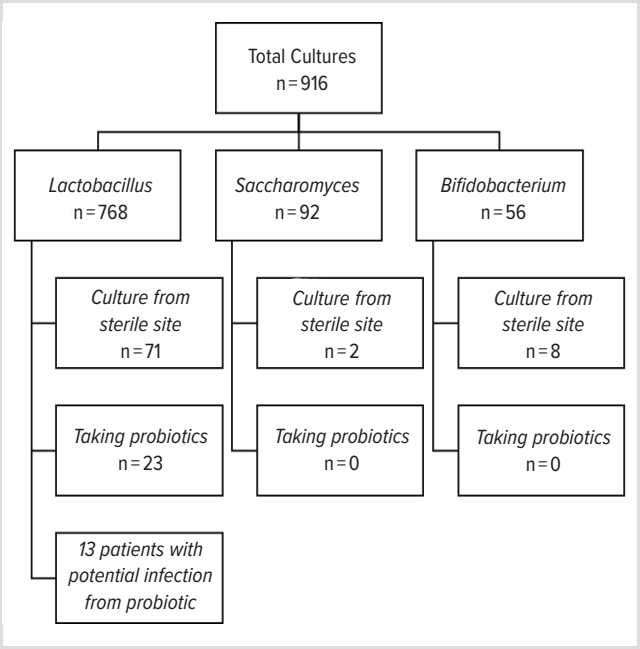
METHODS

This retrospective review is 1 part of a multidisciplinary, Institutional Review Boards-exempt quality improvement project at a health system containing 1 adult and 1 pediatric academic medical center. All adult and pediatric patients admitted to the institutions with a positive culture for *Lactobacillus*, *Bifidobacterium*, or *Saccharomyces* from a sterile site were included in the retrospective review. Patients were excluded if the culture was drawn at an outside hospital or clinic and sent to the academic medical center for laboratory processing. Sterile sites including blood, peritoneal fluid, ascites fluid, pleural fluid, and cerebral spinal fluid were reviewed. Urine cultures were not considered universally sterile and were excluded from analysis.

Positive culture results were obtained from the institution's laboratory database. All positive cultures obtained from January 1, 2019, to July 31, 2022, were eligible for inclusion. Data available from the laboratory, including patient medical record number, culture date, culture type, culture source, and organism, were automatically collected while all other data were collected by manual chart review. Additional variables collected included but are not limited to patient demographics, medical history, hospitalization information, antibiotic choice, treatment duration, mortality, and probiotic exposure. Probiotic exposure was characterized as any probiotic administration within 1 week of obtaining the positive culture, either inpatient or prior to admission. Patients were considered immunocompromised if they had a primary immunodeficiency, acquired immunodeficiency, or drug-induced immunodeficiency, which was defined as receipt of monoclonal antibodies, chemotherapy, anti-rejection medications, or steroid use equivalent to prednisone 20 milligrams per day or more for at least 2 weeks within the past month.[13]

Chart review by 2 authors (MGL and JAM) was performed on all patients with both positive cultures for probiotic-associated species and preceding probiotic exposure to determine if the infection was attributed to probiotic use. Cases were not definitively attributed to probiotic use in patients with clinical improvement in the absence of appropriate antimicrobial therapy, low suspicion for true infection by the treating medical team, or an anatomically or functionally compromised GI tract, such as perforated bowel or cirrhosis. An infection was attributed to probiotic use if the case did not meet any of the above exclusion criteria and had no other identifiable source.

Figure 1. Patient Inclusion and Exclusion Summary



Depiction of number of patients initially acquired from laboratory database from and final included patients for analysis.

Table 1. Patient Demographics

Patient	Age (Years)	Sex	Race	Ethnicity	Immune Deficient	365-Day Mortality
1	70	Female	White	Not Hispanic	No	Yes
2	1	Male	White	Not Hispanic	No	No
3	33	Male	White	Hispanic	No	No
4	33	Female	Black	Not Hispanic	No	Yes

RESULTS

A total of 768 *Lactobacillus*, 56 *Bifidobacterium*, and 92 *Saccharomyces* positive cultures were obtained during the specified time frame (Figure 1). There were 71 *Lactobacillus*, 8 *Bifidobacterium*, and 2 *Saccharomyces* positive cultures obtained from sterile sites. Of these sterile cultures, there were 39 blood cultures, 14 peritoneal fluid cultures, 7 pleural fluid cultures, 6 cerebral spinal fluid cultures, and 15 other miscellaneous sterile body fluid cultures. None of the patients with positive

Bifidobacterium or *Saccharomyces* cultures were confirmed to be taking probiotics with the associated organism. However, 23 positive *Lactobacillus* cultures were obtained from 13 unique patients who were taking probiotics. After independent chart review, 4 patients were excluded due to low suspicion for true infection by the treating medical team, and 5 patients were excluded due to presence of a compromised GI tract. Four patients were considered to have an invasive *Lactobacillus* infection from probiotic use and were included in the complete analysis.

Of the 4 patients with probiotic-mediated infections, 2 were male and 2 were female, with an average age of 34.2 years (Table 1). Patient ages ranged from 1 year to 70 years old and included only 1 pediatric patient. Primary admitting services included neurosurgery intensive care and hematology/oncology. None of the patients received probiotics prior to admission; all probiotic exposure was due to *Lactobacillus* consumption during the admission. Of note, in addition to administration of a probiotic to the pediatric patient, the mother of the patient was breastfeeding and taking a *Lactobacillus*-based probiotic as well.

Three patients had *Lactobacillus* bacteremia and 1 patient had *Lactobacillus* meningitis (Table 2). All patients received the probiotic product via opening the capsule formulation and administering the powder through a nasogastric tube (Table 3). Bacterial identification revealed *Lactobacillus rhamnosus* in all patients. Each patient received the same probiotic product from the institution's formulary containing a monomicrobial strain of *Lactobacillus rhamnosus*. Time to positivity for blood cultures ranged from 24 to 82 hours, with only 1 culture growing after 48 hours. One patient had *Lactobacillus* recovered on multiple cultures. All cultures were monomicrobial without growth of other organisms. None of the patients had a known immunodeficiency. All 3 patients with bacteremia had an indwelling peripherally inserted central catheter (PICC) line, while the patient with meningitis had an external ventriculostomy drain (EVD). Given the presence of indwelling hardware at the site of infection for all patients and probiotics being administered via opening of capsules, nosocomial transmission through contamination of indwelling lines and drains from capsule opening was the presumed cause of infection.

The institution's infectious diseases team was consulted for 3 of the 4 patients to assist with management of the infections. Definitive antimicrobial therapy included ampicillin, ampicillin-sulbactam, or piperacillin-tazobactam (Table 3). Of note, ceftriaxone, cefepime, and vancomycin were not considered appropriate targeted therapy based on lack of expected activity against the isolated organism. Duration of therapy ranged from 10 to 22 days, which included all days of antibacterial treatment regardless of expected activity against *Lactobacillus*. The average length of hospital stay was 43.0 days, with a range of 18 to 74 days. One patient required intensive care unit (ICU) admission related to hemodynamic instability, which may have been attributed to sepsis from *Lactobacillus*. All-cause mortality was 50% within 1 year of infection, including 25% within 30 days. No patients had mortality attributed directly to the *Lactobacillus* infection, although the possibility of infection as a contributing factor cannot be excluded.

The case of *Lactobacillus rhamnosus* meningitis warrants special consideration given the persistent growth on cerebrospinal fluid samples despite targeted antibiotic therapy. The patient was

Table 2. Infection Description

Patient	Infection	Culture Source	Species	No. of Positive Cultures	Time to Positivity (Hours)	Hardware or Central Access
1	Meningitis	Ventricular fluid	*Lactobacillus rhamnosus*	6	Not specified	Yes
2	Bacteremia	Upper extremity, left	*Lactobacillus rhamnosus*	1	23.7	Yes
3	Bacteremia	Forearm, right	*Lactobacillus rhamnosus*	1	37.0	Yes
4	Bacteremia	Foot, right	*Lactobacillus rhamnosus*	1	81.8	Yes

Table 3. Description of Probiotic and Antibiotic Use

Patient	Indication for Probiotic Use[a]	Duration of Probiotic Use (Days)	Dose, Route, Frequency of Probiotic Administration	Infection Type Associated With Probiotic Use	Antibiotic Treatment for Probiotic Infection[b]	Duration of Antibiotic Therapy (Days)[c]
1	Prevention of AAD	33	1 capsule, nasogastric tube, 2x/daily	Meningitis	Ampicillin	22
2	AAD	7	1 capsule, nasogastric tube, 1x/daily	Bacteremia	Ampicillin	12
3	Prevention of AAD	10	1 capsule, nasogastric tube, 2x/daily	Bacteremia	Ampicillin-sulbactam	10
4	Prevention of AAD	14	1 capsule, nasogastric tube, 2x/daily	Bacteremia	Piperacillin-tazobactam	11

Abbreviations: AAD, antibiotic-associated diarrhea.

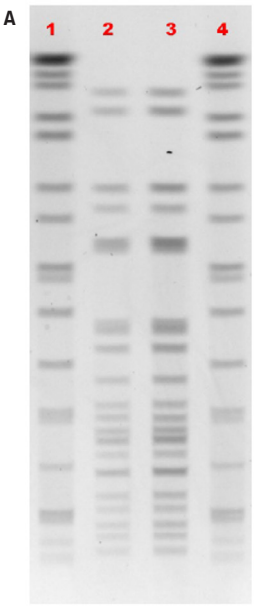
[a]The 3 patients with the probiotic indication of "prevention of AAD" were initiated on probiotics because the probiotic was automatically ordered on admission as part of the admission order sets.

[b]Definitive treatment for completion of antibiotic course after narrowing to targeted therapy for treatment of *Lactobacillus*.

[c]Total duration of antibiotic therapy including all days of antibacterial treatment regardless of expected activity against *Lactobacillus*.

a 70-year-old female admitted following subarachnoid hemorrhage status-post decompression with EVD placement. The cerebrospinal fluid grew *Lactobacillus rhamnosus* on 6 separate days. No probiotics were taken prior to admission, but she was exposed to a *Lactobacillus*-containing probiotic during the hospitalization–including during the first 4 days of positive cultures–before discontinuation due to concern for contamination of the EVD from opening the capsules prior to administration via nasogastric tube. Pulsed field gel electrophoresis confirmed the infecting *Lactobacillus rhamnosus* strain and the administered probiotic as indistinguishable (Figure 2). She remained hospitalized for 62 days, including 2 days requiring continued ICU-level care for hemodynamic instability and an additional 20 days receiving intravenous antimicrobials. She was treated with a variety of antibiotics prior to consolidating to ampicillin monotherapy after speciation and initial clinical improvement. The EVD was exchanged on day 6 of infection with 1 subsequent positive culture prior to clearing. Final duration of antimicrobial therapy was 22 days with no subsequent recurrence of *Lactobacillus* infection. Unfortunately, the patient died within 1 year of admission related to a brain abscess caused by a different infectious organism.

Figure 2. Pulsed Field Gel Electrophoresis Summary



A) Pulsed field gel electrophoresis image. Lanes 1 and 4 are Salmonella enterica ser. Braenderup H9812 Standard controls, Lane 2 is the cerebrospinal fluid sample, and Lane 3 is the probiotic capsule.[a]

B) Pulsed field gel electrophoresis dendrogram.

[a]Results of the pulsed field gel electrophoresis indicated that the patient isolate and probiotic capsule were indistinguishable using the Tenover criteria for pattern interpretation. The Tenover criteria defines "indistinguishable" as patterns that were identical; "closely related" as 1-3 band(s) different between patterns, which could be achieved by a single mutation; "possibly related" as 4-6 bands different between patterns, which requires a minimum of 2 mutations; and "unrelated" as ≥7 bands different between patterns, which requires a minimum of 3 mutations.

DISCUSSION

In this retrospective review, 4 cases of serious bacterial infections with concern for probiotic use as a causative factor are described. This study adds to the existing literature regarding the risk of nosocomial probiotic use and suggests that infectious risks of probiotics may be higher in patients with an indwelling central line or EVD. Each case demonstrates the route of transmission was likely via probiotic contamination of the central line or EVD rather than through GI tract translocation given the absence of gastrointestinal pathology, although the latter cannot be excluded. Regardless, nosocomial transmission is confirmed for each patient due to lack of receipt of probiotics prior to the hospitalization. For the patients who experienced *Lactobacillus* infection in the absence of probiotic consumption, nosocomial transmission from neighboring patient rooms sharing the same clinicians cannot be excluded.

As described, these infections were not benign. All patients required initiation of broad-spectrum antimicrobials, extended durations of therapy, and increased hospital length of stay. Although none of the patients had mortality directly caused by overwhelming infection, there remained a high 1-year mortality rate amongst patients with probiotic-associated *Lactobacillus* infections, which highlights the weakened protoplasm of infected individuals and importance of reconsidering the use of probiotics–especially in the inpatient setting–to prevent morbidity. At the time these infections occurred, there were no restrictions associated with inpatient probiotic use at the institutions and clinicians did not require input from the infectious diseases team prior to initiating these products. Some order sets in the adult academic medical center included probiotics by default upon admission, which is where the probiotic orders for the 3 adult patients admitted to neurosurgery intensive care originated. Due to numerous probiotic-associated infections in the neurosurgical ICU, probiotics have since been removed from all admission order sets at the institution due to institutional safety concerns with probiotic use.

This retrospective study uniquely aimed to identify infections caused not only by *Lactobacillus*-containing probiotics but also *Bifidobacterium*- and *Saccharomyces*-containing probiotics, although there were no patients who qualified for the latter 2 infection types. However, multiple previous large studies have described infections due to bacterial species associated with such products.[14-18] Fungemia due to ingestion of *Saccharomyces*-containing probiotics is heavily documented, and *Bifidobacterium* bacteremia due to probiotic supplementation has been widely reported--most frequently in neonates.[19,20] *Lactobacillus* bacteremia and other severe infections caused by consumption of probiotics also have been published.[10] Although *Lactobacillus*

meningitis has been described previously, no previous studies have described meningitis confirmed to be caused by probiotics through techniques such as pulsed field gel electrophoresis sequencing.[15,21-24]

In patients with reduced gut integrity or weakened immune systems, probiotics pose a greater risk of infection as the organism in the probiotic can translocate and cause infection.[2,7] This risk is highest in patients who have perforated, leaky, inflamed, or immature GI tracts. The organisms also have unique hemolysis, adhesin, and enzymatic properties that can increase risk of translocation and subsequent infection, biofilm formation, and colonization within the GI tract. Moreover, the organisms in probiotics are synthetically modified and consequentially have enhanced duration of action within the GI tract.[3] Due to the unique properties and mechanism of action of probiotics to survive the normal defenses of the GI tract, probiotics can become pathogenic in a susceptible host. Multiple patients with cultures positive for *Lactobacillus* were excluded due to the presence of GI compromise resulting in inherent uncertainty of the cause of infection and the clinical significance of the isolate; however, the possibility remains that GI leakage of the consumed probiotic may have caused a clinically significant infection.

Antibiotic resistance remains a large risk with use of probiotics. A recently published study demonstrated high rates of drug resistance amongst *Lactobacillus* isolates from probiotics.[25] *Lactobacillus* in the supplements was found to be universally resistant to vancomycin, amikacin, and fluoroquinolones and occasionally resistant to tetracyclines and cephalosporins. The strains remained susceptible to penicillins, carbapenems, and linezolid. Previous studies found similar resistance patterns but identified less resistance to clindamycin.[6,15,16] Resistance to currently available broad-spectrum antibiotics is alarming and raises the possibility of high rates of treatment failure with limited treatment options, particularly if isolates have developed resistance to beta lactams. Furthermore, antibiotic resistance genes from probiotics can undergo horizontal gene transfer to other organisms naturally residing in the GI tract, which can lead to multidrug-resistant organisms.[7]

The AGA published a clinical practice guideline in 2020 summarizing its recommendations surrounding the use of probiotics for various GI conditions.[4] There is acknowledgement within the guideline that there is a lack of foundational research in this area to make any strong recommendations and, therefore, advises clinicians to consider avoiding probiotic use to prevent harm. Specifically, for patients with *Clostridioides difficile* infection, inflammatory bowel disease, and irritable bowel syndrome, the AGA advises against routine use of probiotics. Similar to other over-the-counter supplements, probiotics are not approved by the FDA and their production and marketing are not evaluated for safety and efficacy in the same manner as medications.

There are many patient and institutional costs attributed to probiotic-induced invasive infections including but not limited to the costs of the probiotic product, antimicrobial treatment, prolonged hospitalization, and additional resultant nosocomial-associated events from prolonged hospitalizations. These extensive costs are avoidable by ceasing unnecessary probiotic use. In addition, the impact of culture contamination from a probiotic-related organism also should be included as an indirect cost as each isolation of *Lactobacillus* of unclear clinical significance results in diagnostic uncertainty requiring subsequent testing, clinical burdens, and antimicrobial exposure. Probiotics must be used with caution, or avoided entirely, to minimize causing unintended patient harm and excess costs.

As all data in this review are descriptive and retrospective in nature, this study is unable to establish true causation of infection or mortality, although suspicion is high due to extensive nature of the chart review and removing as many confounding factors as possible. Confounding factors include the presence of infections at multiple sites, prolonged length of broad-spectrum antibiotic use for empiric versus targeted coverage, critically ill status of patients, timeline of probiotic use, and inability to identify the status of GI tract integrity. Attributing the infection to probiotic exposure required clinical review, which introduces the risk for bias; however, this risk was mitigated using 2 independent reviewers. A strength of this study was the detailed chart review utilized to determine the cause of infection and the description of subsequent therapies received for treatment. In addition, this is the first known publication to confirm a probiotic strain as the cause of *Lactobacillus rhamnosus* meningitis and includes the pulsed field gel electrophoresis analysis. Previously published case reports of *Lactobacillus* meningitis do not include methods to provide definitive confirmation of a probiotic causing the infection, so the inclusion of sequencing makes this study a unique, significant addition to currently existing literature.[15,21-24]

CONCLUSIONS

This retrospective study of pediatric and adult patients who developed serious infections caused by probiotic consumption demonstrates that probiotics are not benign, harmless supplements that can be used in all patients. Initiation of probiotic therapy should be considered carefully and individualized to each patient within the context of risk versus benefit analysis. Hospitalized patients appear to be an already at-risk population—especially those with vascular or extra-ventricular catheters—and clinicians should avoid probiotic use in these patients. Due to the lack of data surrounding any indication for probiotic use, patients should be advised to not consume probiotics in the inpatient or outpatient setting due to the serious, albeit rare, risk of systemic infection leading to potential morbidity and mortality.

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