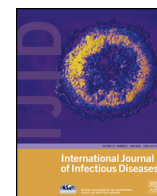Contents lists available at SciVerse ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

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INTERNATIONAL SOCIETY FOR INFECTIOUS DISEASES

Investigation of inpatient probiotic use at an academic medical center

Jacques Simkins [a,*], Anna Kaltsas [a], Brian P. Currie [a,b]

[a] Division of Infectious Diseases at Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY 10467, USA
[b] Foundation for Applied Epidemiology, Northvale, New Jersey, USA

ARTICLE INFO

SUMMARY

Objectives: Despite the widespread use of probiotics, there are limited data regarding their safety. The aims of this study were to characterize inpatient probiotic use and to determine the incidence of probiotic-related bloodstream infections due to *Lactobacillus acidophilus/Lactobacillus bulgaricus*.
Methods: This study was a two-part retrospective study conducted at a large academic medical center. The first part was the characterization of probiotic use during 2007–2008, which included the type of prescribing provider, choice of probiotic prescribed, indications for use, and presence of potential risk factors for probiotic infection among recipients; the second part was the determination of the incidence of probiotic-related bloodstream infections due to *L. acidophilus/L. bulgaricus* for September 2000–August 2008.
Results: Probiotic use was uncommon (0.4%). Ninety-six percent of patients received Lactobacillus-based compounds. Use was common in patients at theoretical risk for probiotic infection. The maximum estimated incidence of probiotic-related bacteremia due to *L. acidophilus/L. bulgaricus* during the 8-year period was 0.2%.
Conclusions: *L. acidophilus/L. bulgaricus* probiotic use at our institution appeared to be associated with a minimal risk of probiotic-related infection, even though it was used at a high frequency among inpatients who could be considered at high theoretical risk for probiotic-related bloodstream infection.

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1. Introduction

Probiotics have been defined as "…live microorganisms, which when administered in adequate amounts confer a health benefit on the host".[1] A theoretical concern for probiotic-related infection exists, given that the organisms present in the probiotic supplements are viable. Probiotics have been reported to have therapeutic applications for many medical conditions,[2] but have been regulated as food supplements by the United States Food and Drug Administration (FDA).[3,4] As such, although they have been widely commercialized as food products, they have never been subjected to the comprehensive FDA safety evaluations that pharmaceuticals receive. Subsequently, probiotic safety data are scarce. An extensive review of the literature performed by the Agency for Healthcare Research and Quality (AHRQ), found that adverse events due to probiotics were poorly documented and that monitoring for probiotic-related infections was not routinely done.[5] The acquisition of probiotic safety data is further complicated by the fact that a variety of yeast and bacterial species and strains, which may vary in risk, have been used in probiotic preparations,[6] and because manufacturing standards may even vary between commercial preparations of the same species of probiotic agent.[7] Furthermore, until the FDA established a requirement for reporting of probiotic adverse events to a central registry in 2006, there was no surveillance program for probiotic-associated infections.[8]

The AHRQ review previously referenced also noted that there was some indication that patient health status was associated with the risk of a probiotic-related adverse event, and noted that case studies reporting adverse events were described among health compromised rather than healthy individuals, and most often consisted of a serious probiotic-related infection. However, a subgroup analysis of existing randomized clinical trials did not demonstrate a statistically significant increased risk of probiotic adverse events among critically ill patients using probiotics relative to control patients with similar patient characteristics.[5]

Another review that included data from 7526 patients enrolled in 143 clinical trials who were receiving 11 different *Lactobacillus* species, five different *Bifidobacterium* species, and two streptococcal species as probiotics, identified no probiotic-related infections.[9] No increase in the incidence of Lactobacillus bacteremia was found in either Finland or Sweden after widespread use of Lactobacillus probiotics in dairy products.[10,11] However, there have been sporadic case reports of probiotic-related infections with both *Saccharomyces boulardii* and *Lactobacillus* species-based probiotic preparations.[12–18] Most have occurred in immunocompromised patients.[12,13,17] Data

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* Corresponding author.
E-mail address: jsimkins@med.miami.edu (J. Simkins).

related to probiotic safety in immunosuppressed patients have been limited to small studies investigating patients with severe neutropenia,[19] liver transplant recipients,[20] and HIV-infected patients[21,22] receiving *Lactobacillus reuteri*, *Enterococcus faecium*, or *Lactobacillus rhamnosus*-based probiotics, all of which reported no probiotic-associated infections. The presence of abnormal heart valves and impaired intestinal integrity have also been proposed as risk factors for probiotic-related infection.[13,23] Lactobacillus is a known possible cause of endocarditis, especially in the presence of abnormal heart valves,[16,24] and a case report describes Lactobacillus probiotic-associated endocarditis in a patient with underlying mitral regurgitation.[18] To our knowledge, there have been no studies to date that have investigated probiotic safety in patients with underlying abnormal heart valves. Studies looking specifically for probiotic-related infections among patients with impaired intestinal integrity are limited to a single study investigating patients with inflammatory bowel disease,[25] and even though there were no probiotic-related infections, it is known that impairment of the intestinal mucosal barrier may favor bacterial translocation.[26]

The aim of this study was to characterize inpatient prescription probiotic use at an academic medical center, with a particular focus on evaluating the use of probiotics in patients considered at theoretical high risk for probiotic-related infection. We also sought to quantify the incidence of these infections.

2. Methods

2.1. General

This study was a two-part retrospective study that was performed at the Moses and Weiler hospitals of Montefiore Medical Center, a large tertiary care medical center located in the Bronx, New York that serves as the University Hospital for the Albert Einstein College of Medicine. Both hospitals combined had 1145 beds and shared the same microbiology laboratory and electronic medical record system. All probiotics had non-formulary status during the period encompassed by this investigation (2000–2008), and could be ordered electronically via physician order entry from a non-formulary compendium, or by directly typing in the desired product. All probiotic orders required telephone contact with the pharmacy prior to dispensing, but no request was denied. This study was approved by the Montefiore Medical Center Institutional Review Board.

The statistical analysis was performed using Stata 10. Chi-square and Fisher's exact tests were used to evaluate categorical variables, and the Student's *t*-test and Wilcoxon test were used to evaluate continuous variables. Statistical significance was set at $p < 0.05$.

2.2. Characterization of probiotic use

The clinical information system was queried for any inpatient prescribed any Saccharomyces-, Lactobacillus-, or Bifidobacterium-based probiotic during the 1-year period from 2007 to 2008. In order to characterize the inpatient probiotic prescribing patterns, all patients already taking probiotics at the time of admission were excluded. A retrospective chart review was conducted to obtain information regarding: (1) type and duration of probiotics prescribed; (2) type of prescribing provider; (3) indications for probiotic prescription; and (4) patient characteristics, including immunosuppression, impaired intestinal integrity, and abnormal heart valves.

Immunosuppression was characterized as mild, moderate, or severe. Mild immunosuppression was defined as age ≥80 years, or the presence of chronic renal disease, diabetes mellitus, cirrhosis, or non-hematologic cancer. Moderate immunosuppression was defined as HIV-positive with a CD4 count >200/mm³, concurrent

systemic steroid administration, or two or more of the criteria for mild immunosuppression. Severe immunosuppression was defined as the presence of either a solid organ transplant, AIDS (CD4 count <200/mm³), neutropenia (absolute neutrophil count <1000/μl), or hematologic malignancy.

Impaired intestinal integrity was defined in any patient with abdominal imaging identifying either bowel thickening, dilatation, or diverticulitis within 2 weeks of taking a probiotic; colonoscopy identifying colitis within 2 weeks of taking a probiotic; or any bowel surgery within 4 weeks of taking a probiotic.

Heart valve abnormality was defined as a history of any heart valve replacement or repair, or any echocardiogram indicating moderate or severe valvular insufficiency or stenosis within 6 months prior to taking a probiotic.

2.3. Estimation of the incidence of probiotic-associated bloodstream infection

The clinical information system was electronically queried for any inpatient prescribed Lactobacillus-, Saccharomyces-, or Bifidobacterium-based oral probiotics during the 8-year period from 2000 to 2008. The list was then cross-referenced against a list of any patient with blood cultures positive for any *Lactobacillus*, *Saccharomyces*, or *Bifidobacterium* species to identify patients with potential probiotic-related bloodstream infections. Infections were only considered probiotic-related if the patient had been prescribed probiotics in the previous 30 days and they exhibited signs and symptoms of infection, including persistent fever. Incidence rates were expressed as the number of potential probiotic-related bloodstream infections/number of patients prescribed that specific probiotic during the 8-year study period. The calculation of incidence rates of infection was restricted to only those probiotics with sufficiently large enough patient prescription rates to allow robust estimates.

3. Results

3.1. Characterization of probiotic use

Four hundred inpatients were prescribed probiotics from 2007 to 2008, yielding a frequency of 0.4% (579 probiotic inpatient courses/128 949 admissions). Three hundred eighty-five (96%) received *Lactobacillus acidophilus/Lactobacillus bulgaricus* and 15 (4%) received *S. boulardii*; none received Bifidobacterium. Patients on probiotics at the time of the admission (*n* = 18) and patients with incomplete medical records (*n* = 22) were excluded. In addition, patients receiving *S. boulardii* probiotics were also excluded because there were only a few cases. Thus, 345 patients receiving a single *L. acidophilus/L. bulgaricus* probiotic preparation were included in the analysis. Fifty-nine percent were female and 41% were male (*p* < 0.001), and the mean patient age was 65.9 ± 18 years. The median duration of inpatient probiotic treatment was 5 days (range 1–15 days).

Probiotics were prescribed by 191 different health care providers. Of these, 149 (78%) were physicians and 40 (21%) were physician assistants or nurse practitioners; job title was unknown for two (1%) prescribers. Probiotics were primarily prescribed by the medicine service (*n* = 148; 77%), followed by surgery (*n* = 8; 4%), medical rehabilitation (*n* = 5; 3%), pediatrics (*n* = 5; 3%), family medicine (*n* = 3; 2%), anesthesiology (*n* = 3; 2%), obstetrics/gynecology (*n* = 2; 1%), critical care medicine (*n* = 2; 1%), and others or unknown (*n* = 15; 8%).

The most common indications for probiotic use, which accounted for 72% of all indications, were treatment of *Clostridium difficile* infection or unspecified diarrhea, and prevention of antibiotic-associated diarrhea (see Table 1).

Table 1
Indications for probiotic use (N = 345)[a]

Indication	n (%)
Clostridium difficile treatment	103 (29.9)
Unspecified diarrhea treatment	91 (26.4)
Antibiotic-associated diarrhea prevention	55 (15.9)
Clostridium difficile prevention	21 (6.1)
Unknown	57 (16.5)
Other indications	18 (5.2)
Yeast infection	2 (0.6)
Liver encephalopathy	4 (1.2)
Peptic ulcer disease	2 (0.6)
Irritable bowel syndrome	2 (0.6)
Patient's request	1 (0.3)
Constipation	2 (0.6)
Cryptosporidium	1 (0.3)
Ischemic colitis	1 (0.3)
Unspecified colitis	3 (0.9)

[a] Each patient had only one probiotic indication.

With regard to probiotic use in patient risk categories, 161 of 345 patients (47%) patients had either moderate or severe immunosuppression: 124 (36%) were moderately immunosuppressed and 37 (11%) were severely immunosuppressed (see Table 2). One hundred fourteen of 345 patients (33%) had impaired intestinal integrity: 104 (30%) by abnormal abdominal imaging studies, 16 (5%) by abnormal colonoscopy, and eight (2%) by recent history of bowel surgery. Imaging studies and colonoscopies were done on 175 (51%) and 27 (8%) of the patients, respectively. Sixty-eight of 345 patients (20%) had abnormal heart valves: 62 (18%) identified as having moderate and/or severe heart valve abnormalities on echocardiogram and 14 (4%) as having a history of cardiac valve replacement or repair. Tricuspid regurgitation was the most common moderate heart valve abnormality seen (29 cases), followed by mitral regurgitation with 17 cases. For severe abnormalities, mitral regurgitation was the most common (eight cases), followed by tricuspid regurgitation (five cases). An echocardiogram was performed in 213 (62%) of the patients. Mitral valve replacement was the most common surgery performed (six cases), followed by aortic valve replacement (five), mitral valve repair (three), tricuspid valve repair (one), and tricuspid valve replacement (one).

3.2. Estimation of the incidence of probiotic-associated bloodstream infection

Two of 1176 (0.2%) patients developed what could be considered a potential probiotic-related bloodstream infection during the 8-year period (2000–2008).

The first case was a 66-year-old female with history of diabetes mellitus and end-stage renal disease, who was receiving a

Table 2
Immunosuppressive conditions (N = 345)[a]

Condition	n (%)
Elderly (≥80 years)	94 (27.2)
Chronic kidney disease	68 (19.7)
Diabetes mellitus	135 (39.1)
Cirrhosis	17 (4.9)
HIV	21 (6.1)
CD4+ <200/mm³	16 (4.6)
CD4+ >200/mm³	5 (1.4)
Systemic steroids	31 (9.0)
Non-hematologic cancer	54 (15.7)
Solid transplant patients	8 (2.3)
Neutropenia (<1000/μl)	14 (4.1)
Hematologic malignancies	10 (2.9)

[a] Some patients had more than one immunosuppressive condition.

probiotic containing *L. acidophilus/L. bulgaricus* for a recent *C. difficile* infection and who presented with fever and a right lower extremity cellulitis. Admission blood cultures grew *L. acidophilus* and group G Streptococcus. She was treated with ceftriaxone and vancomycin for her cellulitis and her condition improved.

The second case was a 73-year-old female with a history of diabetes mellitus, cholangiocarcinoma (status post chemotherapy), and hepaticojejunostomy. She presented with a 2-day history of fever, nausea, vomiting, and abdominal pain. Blood cultures grew Lactobacillus. Computed tomography showed an abdominal collection which was drained by interventional radiology; *Klebsiella pneumoniae* grew on culture. She was treated with piperacillin–tazobactam and improved. Just before she was admitted she had completed a course of metronidazole and *L. acidophilus/L. bulgaricus* for an unspecified diarrheal illness.

Given that this was a retrospective study and patient isolates were no longer available, molecular typing of the patient Lactobacillus isolates and the administered probiotic strains of Lactobacillus could not be accomplished.

4. Discussion

In general, the inpatient prescription of probiotics at our academic tertiary care facility, where probiotics have a non-formulary status, was infrequent. Nonetheless, we were able to identify 400 inpatients who were prescribed probiotics over a 1-year period.

Data indicate that when probiotics were prescribed, Lactobacillus-based products were chosen 96% of the time. Physicians wrote 78% of these prescriptions, primarily connected to the medical service, and did so mainly for the treatment of *C. difficile* infection or unspecified diarrhea and for the prevention of antibiotic-associated diarrhea (combined, 72% of indications). While there are data supporting the use of probiotics for *C. difficile* infection,[2] the Infectious Diseases Society of America, in conjunction with the Society for Healthcare Epidemiology of America, has stated that "Administration of currently available probiotics is not recommended to prevent primary *Clostridium difficile* infection, as there are limited data to support this approach and there is a potential risk of bloodstream infection."[27]

Overall, we were surprised to discover the frequency with which probiotics were given to patients who might be considered traditionally at high risk for probiotic-associated bloodstream infection. Forty-seven percent of the patients were either moderately or severely immunosuppressed. One third had impaired intestinal integrity and one fifth had abnormal heart valves. Sixty-nine percent had at least one risk factor and 24% had at least two risk factors for probiotic-associated infection.

The risk of probiotic-related bloodstream infection associated with the inpatient prescription of a *L. acidophilus/L. bulgaricus* probiotic was quite low at our institution (maximal estimate of 0.2%). Only two cases of potential probiotic-related infection were identified, the first patient was considered moderately immunosuppressed and the second patient had impaired intestinal integrity based on our criteria. Interestingly, both improved after broad-spectrum antibiotic therapy for unrelated concurrent infections (which also provided Lactobacillus coverage). Unfortunately, the two cases were not confirmed by typing. Therefore, we could not conclusively link probiotic intake with bloodstream infection, since these organisms can also routinely reside in the intestinal flora.[28,29]

Among the limitations of our study, it is important to mention that the criteria used for the degree of immunosuppression were somewhat arbitrary, so it is possible that immunosuppression could have been overestimated in some patients. In addition, only 10% of our patient sample had severe immunosuppression and the

risk of infection may have been underestimated in this patient category.

In conclusion, we found that the use of probiotics containing *L. acidophilus/L. bulgaricus* at our institution was relatively safe, even though they were frequently prescribed to inpatients who could be considered at high risk for probiotic-related bloodstream infection. However trivial the estimated risk of bloodstream infection associated with *L. acidophilus/L. bulgaricus*-based probiotic use appears, it needs to be part of a cost–benefit analysis that includes some evidence of clinical efficacy for the condition it is being prescribed for. Thus, until this type of information becomes available and the data are evaluated, it would seem prudent to continue not to recommend the widespread use of this probiotic based on its safety profile alone.

Ethical approval: This study was approved by the Montefiore Medical Center Institutional Review Board.

Conflict of interest: J. Simkins, A. Kaltsas, and B.P. Currie have no competing interests to declare. All authors had no financial support.

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