HHS Public Access

Author manuscript

Am J Infect Control. Author manuscript; available in PMC 2024 September 05.

Published in final edited form as:

Am J Infect Control. 2016 May 01; 44(5): 548–553. doi:10.1016/j.ajic.2015.12.001.

Prevalence of probiotic use among inpatients: A descriptive study of 145 U.S. hospitals

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Abstract

Background: To inform clinical guidance, public health efforts, and research directions, probiotic use in U.S. health care needs to be better understood. This work aimed to assess the prevalence of inpatient probiotic use in a sample of U.S. hospitals.

Methods: Probiotic use among patients discharged in 2012 was estimated using the MarketScan Hospital Drug Database. In addition, the annual trend in probiotic use (2006-2012) was assessed among a subset of hospitals.

Results: Among 145 hospitals with 1,976,167 discharges in 2012, probiotics were used in 51,723 (2.6%) of hospitalizations occurring in 139 (96%) hospitals. Patients receiving probiotics were 9 times more likely to receive antimicrobials ($P < .0001$) and 21 times more likely to have a *Clostridium difficile* infection diagnosis ($P < .0001$). The most common probiotic formulations were *Saccharomyces boulardii* (32% of patients receiving probiotics), *Lactobacillus acidophilus* and *Lactobacillus bulgaricus* (30%), *L acidophilus* (28%), and *Lactobacillus rhamnosus* (11%). Probiotic use increased from 1.0% of 1,090,373 discharges in 2006 to 2.9% of 1,006,051 discharges in 2012 ($P < .0001$).

Conclusions: In this sample of U.S. hospitals, a sizable and growing number of inpatients received probiotics as part of their care despite inadequate evidence to support their use in this population. Additional research is needed to guide probiotic use in the hospital setting.

Keywords

Probiotic; hospital; prevalence; microbial; *Lactobacillus* ; *Saccharomyces* ; *Bifidobacterium* ; Dietary supplement

Probiotics, commonly defined as “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host” [1] are used among the general population for health maintenance purposes. Use of probiotics for prevention and treatment of antibiotic-associated diarrhea (AAD) and *Clostridium difficile* infection (CDI) is receiving increasing

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APPENDIX: SUPPLEMENTARY MATERIAL

Supplementary data related this article can be found at doi:10.1016/j.ajic.2015.12.001.

Conflicts of Interest: None to report.

attention[2] as patients, clinicians, and researchers search for ways to mitigate the effects of antibiotic use.[3] However, the evidence supporting their efficacy and safety when used for this purpose is inconclusive.

Pooled analyses of data from randomized controlled trials of probiotics used for prophylaxis suggest reduced risk of AAD[4-6] and *C difficile*–associated diarrhea[5,7] in adults and children receiving antibiotics. In the meta-analyses for prevention of AAD, however, moderate to substantial statistical heterogeneity between the trials was observed.[4-6] In addition, a recent, well-powered study of hospitalized adults ≥65 years of age that used a high-dose multistrain probiotic (1 *Bifidobacterium bifidum*, 1 *Bifidobacterium lactis*, and 2 *Lactobacillus acidophilus* strains) highlights the need to tease out this heterogeneity. Despite the strengths in the design, risk of AAD and *C difficile*–associated diarrhea was equivalent between the probiotic and placebo arms.[8] Such findings indicate the need for focused evidence using specific strains, antimicrobials, timing, dosing, and patient populations evaluated in studies of sufficient power to better understand under what circumstances probiotics are effective.

Probiotics can be marketed as dietary supplements, which require compliance with Good Manufacturing Practices and premarketing notification to the U.S. Food and Drug Administration for a new dietary supplement ingredient documenting a reasonable expectation for safety. Premarketing demonstration of product efficacy and obtaining Food and Drug Administration approval based on evidence of product efficacy and safety, which are required for New Drug Applications, however, are not required for the marketing of dietary supplements.[9] A recent survey of U.S. academic medical centers found 87% of 114 respondents stocked or used at least 1 probiotic, with a total of 10 probiotic products among the centers.[10] In a separate study in an academic medical center, 0.4% of patients were prescribed a probiotic in 2007-2008, with 96% of these patients receiving a combination product (*L acidophilus–Lactobacillus bulgaricus*) and 4% receiving a product containing *Saccharomyces boulardii*.[11] Prevention and treatment of CDI, treatment for unspecified diarrhea, and prevention of AAD comprised 78.3% of the justifications for probiotic use in this center.

Although these studies provide a useful starting point in the description of probiotic utilization in the inpatient setting, the former did not quantify inpatient prescribing practices, and the latter reported the experience of only 1 medical center. A study with a larger sample of hospitals that quantifies inpatient probiotic utilization and provides clinical context is needed to inform clinical guidance, public health efforts, and research directions. The primary objective of this study, therefore, was to assess and characterize the prevalence of probiotic use from a sample of 145 U.S. hospitals.

METHODS

Study design

An observational study was conducted to describe the prevalence of probiotic use in the inpatient setting. The study was divided into 2 parts: a cross-sectional study of prevalence of probiotic use in 2012 and a longitudinal study of probiotic use among the subset of hospitals

reporting yearly from 2006-2012, inclusive. Because the data were deidentified at the patient and hospital levels, this work was determined not to involve human subjects and therefore was exempt from the regulations governing the protection of human subjects in research under 45 CFR 46.101(b)(5).[12] This work was conducted under the provisions of the Centers for Disease Control and Prevention–MarketScan Data Use Agreement.

Data source

The Truven Health MarketScan Hospital Drug Database (HDD) from the years 2006-2012, inclusive, was used to estimate probiotic use in the inpatient setting. The HDD is a relational database developed from hospital charge detail master data, containing all charges accumulated during the hospitalization, including room and board, supplies, procedures, laboratory testing, and pharmacy products. The drug data are derived from free-form text fields, which are then mapped to a drug classification system by a clinical coder. Codes of interest are obtained through text string searches of the generic drug name in the description field of the corresponding drug reference table. The database also includes standard administrative elements, such as patient demographics, hospitalization diagnosis and procedure codes, and facility characteristics.

To facilitate an informal comparison with a nationally representative sample, the Healthcare Utilization Project's National Inpatient Sample (NIS) estimates from 2012 were compared with study sample estimates whenever possible (Supplemental Tables S1 and S2).

Population

Data were restricted to those of hospitals reporting directly to Truven Health. Within these data, the study population consisted of all discharges, unless otherwise noted. Individual patients may have been present multiple times in the data as a result of multiple hospitalizations. Prior to database release, any discharges identified as having critical errors were removed. Critical errors include patient age <0 or >124 years, missing or invalid primary diagnosis or procedure codes, and diagnoses or procedures not corresponding to age or sex of the patient.

Identification of probiotics

To identify probiotic use, text strings were searched in the HDD reference tables consisting of terms at the genus, species, and strain level and terms indicative of probiotics that were identified from several sources.[13-16] These terms included the following: probiotic, *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *rhamnosus*, *plantarum*, *acidophilus*, *casei*, *johnsonii*, *boulardii*, *helveticus*, *bulgaricus*, *infantis*, and *reuteri* (see Supplemental Table S3 for a longer list). In addition to these root terms, different spelling permutations were searched using the Perl Regular Expression function PRXMATCH (SAS Institute, Cary, NC).[17] Identified codes and corresponding descriptions were reviewed by hand. Codes with terms or phrases in the descriptions inconsistent with a probiotic were removed (examples are shown in Supplemental Table S4). To ensure identification of all possible codes specific to probiotics, sections of the reference tables were also hand checked. Ultimately, 8 unique generic probiotic formulations consisting of ≥1 species were identified in the HDD drug reference tables (see Supplemental Table S5 for additional

details). Dose was not considered in the identification process because relevant information (eg, number of colony forming units per dose) was not available.

Identification of antimicrobials

The process for identifying antimicrobial use was conducted in a similar manner to that for probiotics. A previously developed list of term[18] was used, which included antibacterial, antifungal, antiviral, and antiparasitic agents. Route of administration was restricted to inhalation, oral, and parenteral.

Analytic and statistical methods

Prevalence of probiotic use was defined as the number of patients receiving a probiotic during hospitalization divided by the total number of patients discharged in 2012. Distributions of patient-, facility-, and hospitalization-level characteristics were tallied by probiotic group. For categorical variables, the denominator consisted of the number of discharges unless otherwise noted. For continuous variables, the mean, 95% confidence interval (CI), and median were presented. Unadjusted comparisons of patient- and hospital-level characteristics between patients with and without probiotic use were conducted using the independent samples t test for continuous variables and χ^2 test for categorical variables.

To describe trends in the prevalence of probiotic use over time, annual prevalence of probiotic use from 2006-2012 was calculated among the subset of hospitals reporting data during each of these years. The need to adjust for facility-level effects was confirmed using the covtest option in SAS's PROC GLIMMIX (SAS Institute). The final model was adjusted for within-facility residual correlations using PROC GENMOD with a first-order autoregressive correlation structure and assuming a gamma distribution. Robust SEMs were used to safeguard against misspecification of correlation structure. The annual and overall change in prevalence was estimated using this model.

RESULTS

Cross-sectional study

In 2012, 145 hospitals with 1,976,167 pediatric and adult hospital discharges submitted data directly to Truven Health. Probiotics were used in 51,723 (2.6%) of the hospitalizations and in 139 (96%) hospitals. At the hospital level, probiotic use ranged from 0.3%-8.5% (5th-95th percentile, 139 hospitals) of discharges.

Patients with any probiotic use were older (median age, 70 vs 57 years; $P < .0001$), had a longer mean length of stay (8.8 vs 4.4 days, $P < .0001$), and incurred higher charges ($63,732 vs $34,130, $P < .0001$) than patients without probiotic use. The probiotic group was also 21 times more likely to have a discharge diagnosis of *C difficile* infection (95% CI, 20.4-21.7; $P < .0001$), almost 9 times as likely to have used antimicrobials (odds ratio [OR], 8.6; 95% CI, 8.3-8.8; $P < .0001$), more likely to be admitted from another inpatient health care facility (OR, 1.4; 95% CI, 1.4-1.5; $P < .0001$), and more likely to be transferred to another health care facility at discharge (OR, 2.9; 95% CI, 2.8-2.9; $P < .0001$) than the nonprobiotic group (Table 1).

A total of 54,242 probiotic courses were used; 95% of patients in the probiotic group received just 1 probiotic formulation during their hospitalization, and the remaining 5% received 2-3 formulations. Each formulation contained between 1 and 4 organisms identified at the species level. As detailed in Table 2, the most commonly used probiotic formulations were *S boulardii* (32% of discharges in the probiotic group), *L acidophilus* and *L bulgaricus* (30%), *L acidophilus* (28%), and *Lactobacillus rhamnosus* (11%), not mutually exclusive.

Infectious, inflammatory, and gastrointestinal conditions comprised the bulk of the most common primary diagnostic categories in the probiotic group (Table 3). Obstetric and cardiovascular conditions were more common in both the nonprobiotic group (Table 3), the overall HDD sample, and the NIS (Supplemental Table S6).

Longitudinal study

Sixty hospitals submitted annually from 2006-2012 and therefore were included in the trend analysis. In 2006, 1.0% of discharges received at least 1 course of probiotics. Usage increased annually 1.2-fold (95% CI, 1.1-1.3; $P < .0001$) through 2012, in which 2.9% of discharges received at least 1 course of probiotics for an overall 2.9-fold (95% CI, 1.8-4.5; $P < .0001$) increase between 2006 and 2012 (Fig 1, Supplemental Table S7).

DISCUSSION

Summary

In this sample of 145 U.S. hospitals, a sizable number of patients received probiotics as part of their care. Although the proportion of probiotic use among discharges was small, the magnitude was considerable because almost 52,000 hospitalizations included probiotic use as part of prescribed medical care in 2012. Projected nationally, probiotics may have been utilized in the care of approximately 850,000 patients discharged from US hospitals (based on weights provided by Truven Health; additional details in Supplemental Appendix). In addition, the consistent increase in probiotic use from year to year between 2006 and 2012 suggests probiotic use is continuing to increase. The most common categories of diagnosis codes among the patients with probiotic use were associated with infectious diseases, antibiotic use, increased severity of illness, or exposure to health care.

Comparability with other studies

These findings are similar to survey results on the increasing use of probiotic use among nonhospitalized persons. A recent study of probiotic use among a sample of noninstitutionalized adults in the United States also showed an increase in probiotic use over time. Recorded probiotic use in the prior 30 days grew from 0.4% (projected national estimate of 865,000) of adults in 2007 to 1.6% (3,857,000) in 2012.[19] In the same time span, use among children was 0.3% (number not estimated) in 2007 and 0.5% (294,000) in 2012.[20]

We identified 7 probiotic formulations in use across 96% of the 145 hospitals, with 71% of hospitals using 1-2 formulations (mean, 2.1; range, 1-6) per hospital in 2012. This finding is comparable with the aforementioned survey of probiotic use among U.S. academic

medical centers in which 10 products were identified in stock or in use across 87% of the 114 responding centers, with 79% of the centers reported stocking or using only 1 product.[10] At the species level, the top 4 probiotic products most frequently reported across the centers[10] were also similar to those used in the current study, consisting of *L rhamnosus*, *Lactobacillus gasseri* and *L bulgaricus*, *Lactobacillus acidophilus*, and *S boulardii*.

Limitations

A limitation of this study is the utilization of a nonprobability (convenience) sample of hospitals, which increases the potential for selection bias,[21] The Northeast region was under-represented at 0.3% of discharges in the HDD sample compared with 19.1% in the Healthcare Utilization Project's NIS, a nationally representative sample of hospital discharge data. Despite this regional difference, more clinically relevant measures, including top hospital discharge diagnoses, average length of stay, and discharge disposition, were similar to national estimates (Supplemental Table S6). Therefore, our findings may reflect an estimate of U.S. inpatient hospital probiotic use, although this extrapolation must be interpreted with caution. A second limitation is that this study relied on administrative data collected primarily for billing purposes. Administrative data lack clinical detail beyond what is needed for the purposes of tracking costs and charges in particular. Third, although the probiotic formulations were identified at the species level, strain identity (the unit at which probiotic activity is determined), product potency (eg, number of colony forming units at the time of expiration), and product source (eg, name of brand or manufacturer) were generally absent. These details would have been helpful in verifying the product identities. Fourth, because estimation of probiotic use was based on drug charge data, the prevalence may be underestimated. Unaccounted for sources of probiotics include foods containing probiotics (eg, yogurt) provided by the hospital and dietary supplements and foods containing probiotics brought to the hospital by the patient or patient's family.

Need for additional research

Manipulation or remediation of the microbiome may be an important strategy for prevention of health care–associated infections in the future. Whether probiotics are effective in preserving or restoring a healthy microbiome remains unknown, but the high prevalence of probiotic use among hospitalized patients may indicate a growing belief among clinicians that these agents may be an effective strategy for doing so. Currently, there is not enough evidence to support use of currently available probiotics in this clinical setting. Correspondingly, several professional societies directly state that they do not yet recommend probiotics for the prevention of CDI because of the need for further research in the areas of efficacy and safety.[22-25]

Recently, the Agency for Health Research and Quality sponsored the development of an evidence report to compile safety assessments of probiotic agents containing specific microorganisms used in research studies for risk reduction, prevention, and treatment of disease. As a result of issues, including lack of safety assessments, inconsistent reporting, and poor documentation of interventions, one of the major conclusions of the report was that "the current literature is not well equipped to answer questions on the safety of probiotic interventions with confidence."[13] Adverse events among probiotic users that have

been reported in case reports and clinical trials include bacteremia, fungemia, endocarditis, functional ileus, bowel distension, bowel ischemia, diarrhea, and increased risk of death.[26,27] Risk may be increased among patients with central venous catheterization, bacterial translocation, immunosuppression, critical illness, pancreatitis, and organ transplants.[26] Patients with these conditions are likely to be prescribed antibiotics, which places them at increased risk for microbiome disruption. Because the patients most likely to benefit are also most at risk for an adverse event, preclinical research focused on the selection of likely probiotics and carefully designed clinical trials with systematic assessment of safety is particularly important.

In the planning process of trials of probiotic efficacy and safety, issues to be mindful of include product labeling inaccuracies at the species and even genus level for reasons such as difficulty in identification, desire for consumer recognition,[28] and cross-contamination during manufacturing[29]; varying susceptibility of strains to antibiotics[30]; and product viability at the time of ingestion. The general questions needing to be answered include the following: which strain-specific organisms, which patient populations, at what doses, and in what time frames (related to antibiotic use in particular) are both safe and effective in the prevention or treatment of which diseases?

CONCLUSIONS

This study found a sizable and growing number of hospitalized patients who receive probiotics as part of their care. These findings, given the lack of sufficient evidence for the efficacy and safety of probiotic use in hospitalized patients, suggest that research is critically needed to guide the use of these agents in the hospital setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank Dan Budnitz, MD, MPH, and Nadine Shehab, PharmD, MPH, of Division of Healthcare Quality Promotion for review of the manuscript.

Funding/Support: Supported through salary funds from the Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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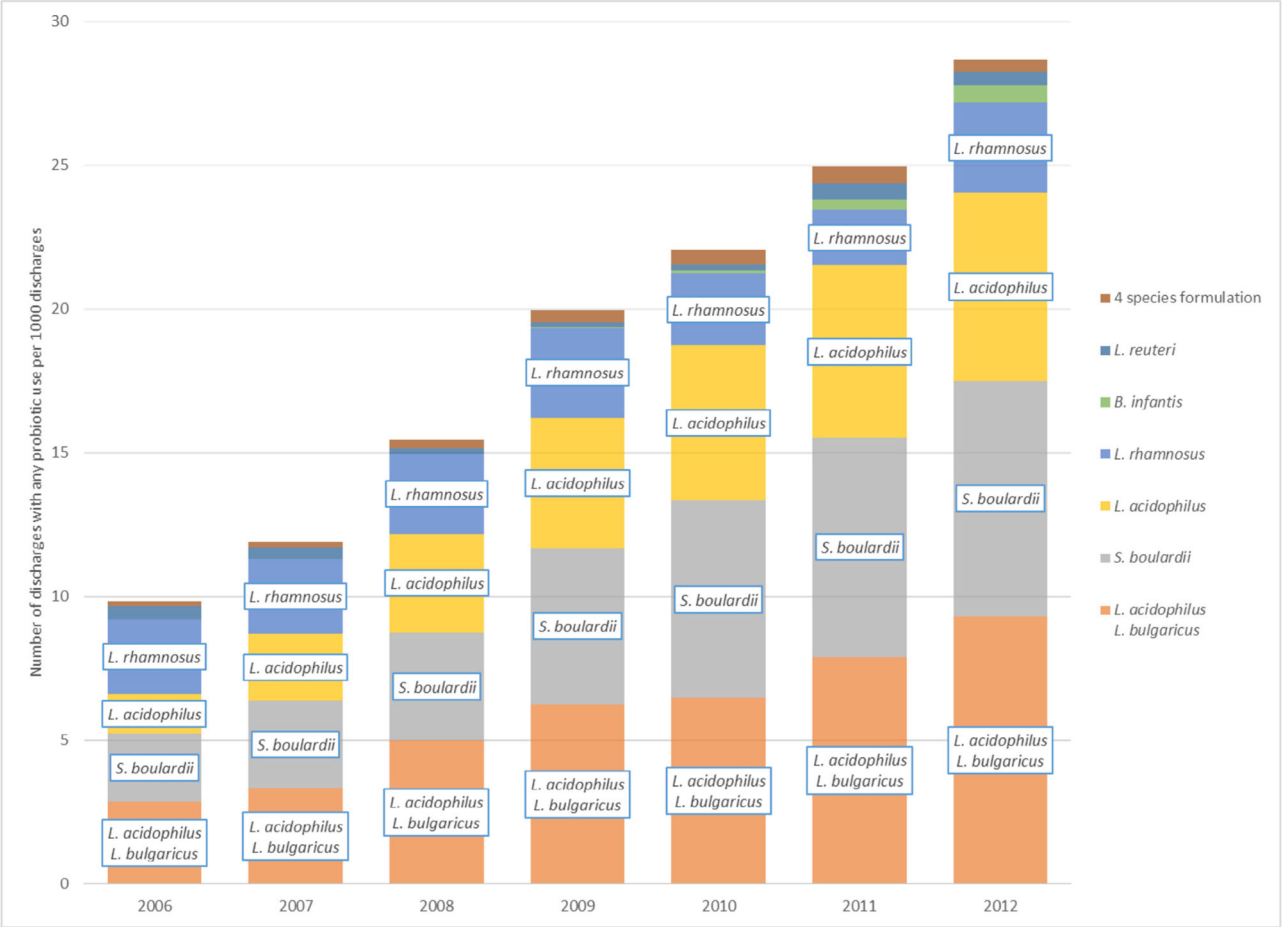

Fig 1.

Trend in probiotic use among 60 U.S. hospitals reporting annually, HDD, 2006-2012. Corresponding data table is displayed in Supplemental Table S7. *HDD*, MarketScan Hospital Drug Database; 4 species formulation consists of *Lactobacillus acidophilus*, *Streptococcus thermophilus*,*Lactobacillus paracasei*, and *Bifidobacterium animalis*.

Table 1

Characteristics of discharges with and without probiotic use during hospitalization, HDD 2012

Variable	Value	Probiotic	No probiotic	*P* value
Discharges, n		51,723	1,924,444	
Hospitals, n		139	145	
Patient characteristics				
Age category, %	0 y	1.1	10.3	<.0001
	1-17 y	2.4	2.7	
	18-64 y	34.4	48.4	
	65-84 y	44.5	29.6	
	≥85 y	17.7	9.1	
Sex, %	Male	42.2	42.9	.0021
	Female	57.8	57.1	
Principal payer, %	Medicare	67.4	42.4	<.0001
	Medicaid	9.7	20.0	
	Private	15.9	26.2	
	Other	2.8	3.3	
	Self-pay	4.1	7.7	
	No charge	<0.1	0.1	
	Unknown	0.1	0.4	
Hospital characteristics				
Census region, %	Northeast	0.7	0.3	<.0001
	Midwest	12.6	19.2	
	South	76.5	65.5	
	West	10.1	14.9	
Urban-rural, %	Rural	14.6	11.3	<.0001
	Urban	85.4	88.7	
Bed category, %	1-199 beds	23.6	21.9	<.0001
	200-299 beds	21.0	19.1	
	300-499 beds	33.3	32.2	
	≥500 beds	22.1	26.8	

Variable	Value	Probiotic	No probiotic	*P* value
Teaching		4.3	9.6	<.0001
Hospitalization characteristics				
Admission type, %	Elective, routine	12.2	21.4	<.0001
	Emergency admit	67.5	50.3	
	Newborn delivery	0.5	9.6	
	Other	0.4	0.6	
	Urgent	19.4	18.1	
Admission source, %	Inpatient health care facility	9.0	6.5	<.0001
	Referral	90.0	83.0	
	Newborn	0.5	9.6	
	Other	1.0	1.0	
Discharge disposition, %	Transferred to another health care facility	32.7	14.5	<.0001
	Discharged to home	63.9	82.4	
	Left against medical advice	0.5	1.0	
	Died	2.8	1.9	
	Missing	0.1	0.2	
Length of stay, d	Mean	8.8	4.4	<.0001
	Median	6.0	3.0	
Charge, $	Mean	63,732	34,130	<.0001
	Median	35,570	20,459	
Any stay in ICU, %		37.2	26.2	<.0001
CDI diagnosis, %	Primary code (ICD-9-CM code: 008.45)	5.3	0.2	<.0001
	Secondary code	7.2	0.4	<.0001
	Any code	12.5	0.7	<.0001
Antimicrobial use, %		91.9	57.1	<.0001

CDI, *Clostridium difficile* infection; *HDD*, MarketScan Hospital Drug Database; *ICU*, intensive care unit.

Table 2

Utilization of specific probiotic formulations by age among discharges with any probiotic use, HDD, 2012

Binary name (genus, species)	No. of hospitals		All ages		0 y*	1-17 y	18-64 y	65-84 y	≥85 y
Any probiotic, N	139		51,723 discharges		575	1217	17,772	23,025	9,134
Lactobacillus acidophilus, Lactobacillus bulgaricus	77	55%	15,483†	30%‡	52%	28%	28%	31%	31%
Saccharomyces boulardii	74	53%	16,358	32%	5%	18%	29%	33%	36%
Lactobacillus acidophilus	71	51%	14,645	28%	12%	15%	32%	27%	26%
Lactobacillus rhamnosus	41	29%	5,789	11%	29%	37%	11%	10%	9%
Lactobacillus acidophilus, Streptococcus thermophilus, Lactobacillus paracasei, Bifidobacterium animalis§	17	12%	831	2%	0%	0%	2%	2%	1%
Lactobacillus reuteri	7	5%	510	1%	3%	3%	1%	1%	1%
Bifidobacterium infantis	3	2%	629	1%	–	1%	2%	1%	1%

NOTE. Only 7 of the 8 formulations identified from the HDD reference tables were actually used.

HDD, MarketScan Hospital Drug Database.

*Age <1 year or those missing age.

†Summation of probiotic courses across formulations will add up to 54,242 total probiotic courses.

‡Percent = (No. of courses) ÷ (51,723 patient discharges with probiotic use). Summation of this value (%) across formulations will exceed 100% because 5% of discharges received 2-3 formulations.

§Actual text description in HDD reference table: *LA, LA-PCAS, STREP, BIF ANIMALIS*. Potential identity: *Lactobacillus acidophilus, Streptococcus thermophilus, L. paracasei, Bifidobacterium animalis*.

Table 3

Ten most frequent diagnostic categories based on primary ICD-9-CM diagnosis codes among discharges from 145 U.S. hospitals with and without probiotic use, HDD, 2012

		Probiotic*		No probiotic†		Comparison
CCS‡	CCS category description	Rank	%	Rank	%	*P* value§
2	Septicemia (except in labor)	1	10.5	3	2.9	<.0001
122	Pneumonia (except that caused by tuberculosis or sexually transmitted disease)	2	6.6	4	2.7	
135	Intestinal infection	3	6.5	54	0.5	
197	Skin and subcutaneous tissue infections	4	4.3	19	1.6	
159	Urinary tract infections	5	3.7	17	1.6	
237	Complication of device, implant, or graft	6	3.2	13	1.7	
127	Chronic obstructive pulmonary disease and bronchiectasis	7	2.9	9	1.9	
108	Congestive heart failure, nonhypertensive	8	2.8	5	2.6	
238	Complications of surgical procedures or medical care	9	2.6	24	1.3	
254	Rehabilitation care, fitting of prostheses, and adjustment of devices	10	2.6	35	0.7	
218	Live-born	48	0.5	1	9.6	
203	Osteoarthritis	16	1.7	2	2.9	
106	Cardiac dysrhythmias	17	1.5	6	2.4	
657	Mood disorders	52	0.4	7	2.2	
100	Acute myocardial infarction	20	1.2	8	2.0	
109	Acute cerebrovascular disease	23	1.0	10	1.8	

CCS, Clinical Classifications Software; *HDD*, MarketScan Hospital Drug Database.

*Probiotic: 51,723 discharges.

†No probiotic: 1,924,444 discharges.

‡Clinical Classifications Software. Healthcare Cost and Utilization Project (HCUP). June 2015. Agency for Healthcare Research and Quality, Rockville, MD. www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp.

§Comparison: probiotic versus no probiotic by 11 categories (top 10 CCS categories and all others): $\chi^2_{10} = 52{,}087$, $P < .0001$.