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Original Research Article

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

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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.

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 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). 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

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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 terms[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.