Original Article

Survey and Systematic Literature Review of Probiotics Stocked in Academic Medical Centers within the United States

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Abstract

Background: Probiotics have a wide variation in their effectiveness in preventing or treating conditions due to the varying beneficial effects of specific probiotic strains. In other words, there is no “generic equivalency” between different probiotic species. However, it has been noted that many practitioners consider probiotics in generic terms and may not realize the impact of these differences between probiotics.

Objective: The aims of this study were to identify probiotics used in US academic medical centers and to determine whether those probiotics were supported by a reliable evidence base.

Methods: A phone survey of 126 inpatient pharmacies in US academic medical centers was conducted to determine which probiotics were stocked. A systematic search was conducted to identify relevant studies that were then critically evaluated to determine whether the identified probiotics are supported by a reliable evidence base.

Results: There was a 90.5% (114/126) response rate of academic medical centers that were contacted through the phone survey. Ten probiotic products were identified through the phone survey. The probiotic most often stocked in academic medical centers was *Culturelle* (27.2%) followed by *Lactinex* (25.4%). The systematic search identified evidence that evaluated *Culturelle*, *Florastor*, *Lactinex*, and *VSL #3*. Of those 4 probiotics, none were supported by a strong evidence base. However, the results suggested that both *Culturelle* and *Florastor* appear to be supported by more evidence compared to other probiotics.

Conclusion: A majority of academic medical centers did not stock a probiotic that was supported by a reliable evidence base.

Key Words—academic medical centers, dietary supplements, health care survey, hospital formularies, probiotics

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The term *probiotic* can be used to describe microorganisms that have the potential to provide beneficial health effects to the host.^{1,2} Although there are thousands of commercially available probiotics, there is much debate as to what beneficial effects they might provide and which specific organisms may be most beneficial for particular uses.^{1–5} Microorganisms that are commonly used in probiotic preparations

include the bacterial genera *Lactobacillus*, *Bifidobacterium*, *Escherichia*, *Enterococcus*, or *Bacillus* and the fungal genus *Saccharomyces*.^{2,5}

Different probiotic species and strains can have substantially different effects on the host. Several species and strain-specific factors play a role in determining what, if any, effects a probiotic may have. To exert a beneficial effect, a probiotic must first be

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able to colonize the gastrointestinal (GI) tract. The initial step that is required for GI colonization by probiotics is adhesion to GI mucosa.⁶ Although not fully understood, current evidence suggests that the adhesive characteristics of probiotics may be due to differences in large surface proteins expressed and their interaction with mucus-binding proteins.⁶ However, this is not a characteristic that is shared among all probiotic species and strains.^{5,6}

Probiotics that are able to colonize the GI tract effectively are then able to also resist colonization of potentially harmful bacteria, and they may have additional properties that make them beneficial to the host.⁵ For example, *Lactobacillus* can produce antimicrobial compounds, known as bacteriocins, which may inhibit a wide range of pathogens such as *Bacillus*, *Staphylococcus*, and *Enterococcus* species. Additionally, a specific strain of *Lactobacillus acidophilus* (La-14) produces a bacteriocin that has shown some inhibitory action against different variations of *Listeria innocua* and *Listeria monocytogenes*.³

Due to the variation in probiotic species and strains, the effectiveness of probiotics for preventing or treating different conditions can also vary substantially.³⁻⁵ With this in mind, it is important to recognize that there is no “generic equivalency” between probiotic species and strains. For example, one *Lactobacillus acidophilus* strain cannot be assumed to be equivalent to another *Lactobacillus acidophilus* strain in terms of its effectiveness in a human host. Therefore, it is important for clinicians to use or recommend specific commercially available probiotics, or a combination of probiotics, that have specifically been shown to have beneficial effects in clinical trials.

Anecdotally, it has been noted that many practitioners consider probiotics in generic terms and may not recognize the important differences between different probiotic products. Similarly, many health care facilities stock a probiotic, but they will substitute one commercial probiotic for another based on cost or availability and without regard for the evidence that may or may not exist for the specific probiotics.

To address this issue, a survey of academic medical centers in the United States was first conducted to determine which specific commercial probiotics were being stocked most commonly throughout the country. Using this survey data, a systematic literature review was conducted to determine whether those specific probiotics were supported by clinical research. This analysis will determine whether academic medical

centers are currently using commercial probiotics that are specifically supported by a reliable evidence base.

METHODOLOGY

Phone Survey

To gather data about which commercial probiotics are stocked in US academic medical centers, a phone survey was conducted between February 23, 2011 and April 20, 2011. The inpatient pharmacy department was contacted by phone at 126 academic medical centers. These academic medical centers were identified through available online lists and by manual search. Each academic medical center pharmacy was asked to identify which specific commercial probiotics they stocked or used in their facility. This list of probiotics was tabulated into a spreadsheet.

Systematic Search

To identify whether clinical research was available for the specific commercial probiotics used by US academic medical centers, a systematic literature search was conducted utilizing PubMed and Natural Medicines Comprehensive Database (NMCD). The search terms that were used focused on identifying literature for the specific commercial products identified by the survey. The search terms included “Bacid,” “Lactinex,” “Culturelle,” “Florastor,” “Flora-Q,” “Flora-Q2,” “Floranex,” “Florajen3,” “Probiotic 123,” “VSL #3,” “acidophilus,” “bulgaricus,” “paracasei,” “lactis,” “plantarum,” “bifidum,” “breve,” “lactis,” “longum,” “thermophilus,” “lactobacillus AND GG,” and “Saccharomyces boulardii.” The search was limited to randomized controlled trials (RCTs) conducted in humans and published in English.

Studies were included for review if they evaluated a commercially available brand name probiotic used for at least 1 of the following inpatient-focused indications: rotaviral diarrhea, antibiotic-associated diarrhea, ventilator-associated pneumonia (VAP), *Clostridium difficile*-associated disease (CDD) recurrence, or necrotizing enterocolitis. These indications were chosen based on the authors’ discretion. Studies were excluded if they evaluated a probiotic preparation that was not identified through the phone survey.

Critical Analysis of Evidence and Evidence Ratings

A critical analysis was conducted of each RCT identified to assess the risk of bias. The risk of bias of the individual studies was assessed based on 3 primary factors: randomization, allocation concealment, and

Table 1. Frequency and composition of brand probiotics stocked in academic medical centers in the United States

Probiotic brand	Probiotic strains	Academic medical centers that stocked a commercial probiotic, n (%)
<i>Culturelle</i>	<i>Lactobacillus rhamnosus</i> GG (ATCC 53103)	31 (27.2%)
<i>Lactinex</i>	<i>Lactobacillus gasseri</i> <i>Lactobacillus bulgaricus</i>	29 (25.4%)
<i>Floranex</i>	<i>Lactobacillus acidophilus</i>	16 (14.0%)
<i>Florastor</i>	<i>Saccharomyces boulardii</i>	11 (9.6%)
<i>Bacid</i>	<i>Bifidobacterium bifidum</i> <i>Lactobacillus acidophilus</i> <i>Lactobacillus bulgaricus</i> <i>Streptococcus thermophilus</i>	9 (7.9%)
VSL #3	<i>Bifidobacterium breve</i> <i>Bifidobacterium longum</i> <i>Bifidobacterium infantis</i> <i>Lactobacillus acidophilus</i> <i>Lactobacillus plantarum</i> <i>Lactobacillus paracasei</i> <i>Lactobacillus bulgaricus</i> <i>Streptococcus thermophilus</i>	4 (3.5%)
<i>Florajen3</i>	<i>Bifidobacterium lactis</i> <i>Bifidobacterium longum</i> <i>Lactobacillus acidophilus</i>	1 (0.9%)
<i>Flora-Q</i>	<i>Bifidobacterium</i> <i>Lactobacillus acidophilus</i> <i>Lactobacillus paracasei</i> <i>Streptococcus thermophilus</i>	1 (0.9%)
<i>Flora-Q2</i>	<i>Bifidobacterium</i> <i>Lactobacillus acidophilus</i> <i>Lactobacillus paracasei</i> <i>Streptococcus thermophilus</i>	1 (0.9%)
<i>Probiotic 123</i>	<i>Bifidobacterium bifidum</i> <i>Bifidobacterium lactis</i> <i>Lactobacillus acidophilus</i>	1 (0.9%)

study blinding. These criteria were used based on an adaptation of guidelines for assessing the risk of bias for individual studies included in systematic reviews by the Cochrane Collaboration.⁷ Based on these 3 factors, each study was given either a low, unknown, or high risk of bias rating. A study with a low risk of bias adequately met all assessment criteria (randomized, double-blind, and allocation is adequately concealed), a study with an unknown risk of bias had 1 or more

of the assessment criteria unknown or not described, and a study with a high risk of bias had at least 1 of assessment criteria inadequately performed.

Each commercially available probiotic identified in the phone survey was also assigned an overall evidence rating of either A (strong evidence base), B (moderate evidence base), or C (low/no evidence base) for the body of literature supporting that specific product in a specific indication. These evidence ratings

Figure 1. Flow diagram of systematic search and study selection process.

were assigned based on 3 factors: (1) risk of bias in individual studies, (2) study outcomes, and (3) consistency of study outcomes among identified studies. An A evidence rating meant that a probiotic was supported by consistent and low risk of bias RCTs for a specific indication, a B evidence rating meant that a probiotic was supported by mostly consistent and low to unknown risk of bias RCT(s) for a specific indication, and a C evidence rating meant that a probiotic was supported by little to no evidence or supported by high risk of bias RCT(s) or inconsistent findings for a specific indication.

RESULTS

Phone Survey

The phone survey resulted in a 90.5% (114/126) response rate of academic medical centers who were contacted. Fifteen (13.2%) of those 114 respondents did not stock a probiotic, 78 (68.4%) stocked only 1 probiotic, and 20 (17.5%) stocked more than 1 different probiotic product (Table 1).

Systematic Search Results

The systematic literature search yielded a total of 24 relevant RCTs that met the inclusion criteria (Figure 1). These studies are summarized in the Appendix. The 24 RCTs evaluated a total of 4 different commercially available brand probiotics including *Culturelle*, *Florastor*, *Lactinex*, and *VSL #3*. No studies meeting the inclusion criteria were identified

for the other commercially available probiotics identified in the survey.

Culturelle

Out of the 24 RCTs identified by the systematic search, 14 were related to *Culturelle* (Table A1). Of these studies, 7 were related to the use of *Culturelle* for rotaviral diarrhea, 5 for antibiotic-associated diarrhea, 1 for VAP, 1 for necrotizing enterocolitis, and none for CDD recurrence. The risk of bias in these studies ranged from low to high. Eleven of the studies were found to have a low risk of bias, 2 had an unknown risk of bias, and 1 had a high risk of bias.⁸⁻²¹

Fifty percent of the evidence identified evaluated the use of *Culturelle* in rotaviral diarrhea. Four (57%) of these studies showed a statistically significant benefit for decreasing the duration of diarrhea, while 3 (43%) did not show any benefit. Additionally, 2 (29%) of these studies showed a statistically significant benefit for decreasing duration of hospitalization, 4 studies (57%) showed no benefit, and 1 (14%) study did not evaluate duration of hospitalization.⁸⁻¹⁴ Overall, *Culturelle* had a low/no evidence base for rotaviral diarrhea.

Of the 5 RCTs identified regarding the use of *Culturelle* for antibiotic-associated diarrhea, 2 (40%) of the studies showed a statistically significant benefit for decreasing the incidence of antibiotic-associated diarrhea, while the other 3(60%) studies did not show any benefit with *Culturelle* therapy. However, no studies showed

Table 2. Summary of the randomization, allocation concealment, study blinding, and overall risk of bias in selected studies

Reference	Randomization	Allocation concealment	Study blinding	Risk of bias
Studies evaluating <i>Culturelle</i>				
Isolauri (1991) ⁸	Yes	Unknown	Double-blind	Unknown
Shornikova (1997) ⁹	Yes	No	Double-blind	High
Arvola (1999) ¹⁵	Yes	Yes	Double-blind	Low
Vanderhoof (1999) ¹⁶	Yes	Yes	Double-blind	Low
Guandalini (2000) ¹⁰	Yes	Yes	Double-blind	Low
Armuzzi (2001) ¹⁷	Yes	Unknown	Double-blind	Unknown
Thomas (2001) ¹⁸	Yes	Yes	Double-blind	Low
Dani (2002) ²¹	Yes	Yes	Double-blind	Low
Salazar - Lindo (2004) ¹¹	Yes	Yes	Double-blind	Low
Basu (2007) ¹²	Yes	Yes	Double-blind	Low
Basu (2009) ¹³	Yes	Yes	Double-blind	Low
Misra (2009) ¹⁴	Yes	Yes	Double-blind	Low
Szajewska (2009) ¹⁹	Yes	Yes	Double-blind	Low
Morrow (2010) ¹²⁰	Yes	Yes	Double-blind	Low
Studies evaluating <i>Florastor</i>				
Surawicz (1989) ²³	Yes	Unknown	Double-blind	Unknown
McFarland (1994) ²⁷	Yes	Unknown	Unknown	Unknown
McFarland (1995) ²⁴	Yes	Yes	Double-blind	Low
Lewis (1998) ²⁵	Yes	Unknown	Unknown	Unknown
Surawicz (2000) ²⁸	Yes	Yes	Double-blind	Low
Duman (2005) ²⁶	Yes	Unknown	Open-label	High
Biloo (2006) ²²	Yes	Unknown	Unknown	Unknown
Studies evaluating <i>Lactinex</i>				
Gotz (1979) ²⁹	Yes	Unknown	Double-blind	Unknown
Tankanow (1990) ³⁰	Yes	Unknown	Double-blind	Unknown
Studies evaluating <i>VSL #3</i>				
Dubey (2008) ³¹	Yes	Yes	Double-blind	Low

a benefit in decreasing the duration of antibiotic-associated diarrhea.¹⁵⁻¹⁹ Overall, *Culturelle* had a low/no evidence base for antibiotic-associated diarrhea.

Two RCTs were identified for VAP and necrotizing enterocolitis. One RCT showed a statistically significant benefit for decreasing the incidence of VAP.²⁰ The other RCT identified found no benefit for the use of *Culturelle* in necrotizing enterocolitis.²¹ Overall, *Culturelle* had a moderate evidence base for VAP and a low/no evidence base necrotizing enterocolitis.

Florastor

Seven studies out of the 24 RCTs identified were related to *Florastor* use (Table A2). Of those studies,

1 was related to the use of *Florastor* for rotaviral diarrhea, 4 for antibiotic-associated diarrhea, and 2 for CDD recurrence. The risk of bias in these studies ranged from low to high. While 29% of the studies were found to have a low risk of bias, 57% had an unknown risk of bias, and 14% had a high risk of bias.²²⁻²⁸

A majority (57%) of the evidence identified evaluated the use of *Florastor* in antibiotic-associated diarrhea. Three (75%) of these studies showed a statistically significant benefit for decreasing the incidence of antibiotic-associated diarrhea, while 1 (25%) did not report a statistically significant benefit. Additionally, 1 (25%) study showed a statistically

Table 3. Evidence ratings^a of identified probiotics in select indications

	Rotaviral diarrhea	Antibiotic associated-diarrhea	VAP	CDD recurrence	Necrotizing enterocolitis
<i>Culturelle</i>	C	C	B	C	C
<i>Florastor</i>	B	B	C	B	C
<i>Lactinex</i>	C	C	C	C	C
VSL #3	B	C	C	C	C

Note: CDD = *Clostridium difficile*-associated disease; VAP = ventilator-associated pneumonia.

^aA = strong evidence base; B = moderate evidence base; C = low/no evidence base.

significant benefit for decreasing hospitalization duration, 1 (25%) showed no benefit, and 2 (50%) studies did not evaluate duration of hospitalization.²³⁻²⁶ Overall, *Florastor* had a moderate evidence base for antibiotic-associated diarrhea.

Of the 2 RCTs identified regarding the use of *Florastor* for CDD recurrence, 1 study showed a statistically significant benefit for decreasing the incidence of CDD recurrence in patients with recurrent CDD, while that same study found no benefit in those with an initial CDD. The other study showed no benefit for the use of *Florastor* in CDD recurrence in patients who received vancomycin or metronidazole.^{27,28} Overall, *Florastor* had a moderate evidence base for CDD recurrence.

There was 1 RCT identified for the use of *Florastor* in rotaviral diarrhea. This RCT showed a statistically significant benefit for decreasing the incidence and duration of rotaviral diarrhea. Overall, *Florastor* had a moderate evidence base for rotaviral diarrhea.²²

Lactinex

Two studies out of the 24 RCTs identified were related to *Lactinex* use (Table A3). Both of these studies evaluated the use of *Lactinex* in antibiotic-associated diarrhea and were of unknown risk of bias. Both of these studies found no significant benefit in decreasing the incidence of antibiotic-associated diarrhea. Overall, *Lactinex* had a low/no evidence base for antibiotic-associated diarrhea.^{29,30}

VSL #3

One study related to VSL #3 use in rotaviral diarrhea was identified (Table A4). The risk of bias in this study was low. The results of the study were reported in the incidence of recovery, improvement, and failure of VSL #3 or placebo. Study results showed that in patients who received VSL #3, there was a greater percentage of diarrhea recovery compared to improvement or failure. However, there was no

comparison between VSL #3 and placebo.³¹ Overall, VSL #3 had a moderate evidence base for rotaviral diarrhea.

DISCUSSION

Probiotics have been shown to elicit various biological effects through their ability to colonize the GI tract, produce compounds such as bacteriocins, and other strain-specific actions. Because these effects are specific for each probiotic strain or combination of strains, benefits from probiotics observed in studies are not generalizable to other probiotics, even within the same species of bacteria or fungus. Therefore, the use of a probiotic in an academic medical center should be supported by a reliable evidence base specific to that probiotic product.

Of the 114 academic medical centers that responded to the phone survey, 10 unique commercially available probiotics were identified as being utilized. However, evidence for only 4 (*Culturelle*, *Florastor*, *Lactinex*, VSL #3) of those 10 probiotics was identified that evaluated the use of a probiotic in rotaviral diarrhea, antibiotic-associated diarrhea, VAP, CDD, or necrotizing enterocolitis. Overall, 24 RCTs were identified. Of these 24 studies, 2 (8.3%) had a high risk of bias, 8 (33.3%) had an unknown risk of bias, and 14 (58.3%) had a low risk of bias (Table 2). This shows that a majority of the literature identified was high quality.

Based on this current study that evaluated RCTs, no probiotics that were identified were supported by a strong evidence base (Table 3). Although a majority of the literature identified was high quality, no probiotics were supported with a strong evidence base mainly due to the lack of consistent benefit observed throughout the studies. These results suggest that currently no probiotic used in academic medical centers is supported by consistent evidence base for its use in several common inpatient indications. Therefore, the question remains, if no probiotics are

supported by a strong evidence base, which probiotic should be stocked in an inpatient pharmacy or should any be stocked at all?

Although no probiotics were supported by a strong evidence base, both *Culturelle* and *Florastor* appear to be supported by more evidence compared to *Lactinex* and *VSL #3*, which had low/no evidence to moderate evidence base for all of the indications identified. Only 27.2% and 9.6% of academic medical centers stocked *Culturelle* and *Florastor*, respectively, whereas 51% of academic medical centers stocked at least 1 probiotic that was supported by low/no evidence. These results suggest that a majority of academic medical centers stock a probiotic that lacks a reliable evidence base. More studies should be conducted to evaluate the use of a specific probiotic product in inpatient indications. However, the selection of probiotics used in inpatient pharmacies should always be based on which one has the most evidence base for a specific indication. Therefore, it is reasonable to suggest that more than 1 different probiotic product may be stocked in the same pharmacy if each probiotic is to be used for a different indication.

One limitation of this study was that the survey did not assess which indication the probiotics were used for in the academic medical centers. Therefore, the study investigators may not have evaluated the relevant inpatient indications. Because this survey was a cross-sectional study, it only provided a snapshot of probiotic usage at that moment. Therefore, the results may not accurately reflect the probiotics that are stocked within academic medical centers over time. Additionally, the systematic search, evaluation, and review of individual studies were conducted by 1 study investigator.

CONCLUSION

In conclusion, a majority of academic medical centers currently do not stock a probiotic that is supported by a strong evidence base. Academic medical centers should assess the supporting evidence for each probiotic prior to stocking it in their pharmacy. Additionally, further research of commercially available probiotics is needed to provide more data that institutions can use to make informed formulary and purchasing decisions.

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APPENDIX

Table A1. A summary of randomized controlled trials evaluating *Culturelle* in select indications^a

Reference	Study population	Intervention and comparator, duration of therapy	Outcomes
Rotaviral diarrhea			
Isolaure (1991) ⁸	Children between 4 and 45 months of age with acute diarrhea (82% rotavirus) <7 days	<u>Intervention:</u> LGG (10 ¹⁰⁻¹¹ CFU) bid (n = 23) <u>Comparator:</u> LGG fermented milk product 125 g (10 ¹⁰⁻¹¹ CFU) bid (n = 24) <u>Comparator:</u> Placebo (fermented-then-pasteurized) yogurt 125 g bid (n = 24) <u>Duration of therapy:</u> 5 days	<u>Duration of diarrhea in hospital, mean (SD):</u> LGG: 1.4 days (0.8) LGG fermented milk product: 1.4 days (0.8) Placebo: 2.4 days (1.1) (<i>P</i> < .001, between groups) <u>Duration of hospitalization:</u> LGG: 3.2 days (1.2) LGG fermented milk product: 3.5 days (1.6) Placebo: 3.6 days
Shornikova (1997) ⁹	Children between 1 and 36 months of age with acute diarrhea (27% rotavirus) <5 days	<u>Intervention:</u> LGG (5 ⁹ CFU) bid (n = 59) <u>Comparator:</u> Placebo (cellulose powder) bid (n = 64) <u>Duration of therapy:</u> 5 days	<u>Duration of diarrhea in hospital, mean (SD):</u> LGG: 2.7 days (2.2) Placebo: 3.8 days (2.8) (<i>P</i> = .02) <u>Duration of hospitalization, mean (SD):</u> LGG: 7.6 days (5.6) Placebo: 9.2 days (6.3) (<i>P</i> = .15)
Guandalini (2000) ¹⁰	Children between 1 and 36 months of age with acute diarrhea <5 days	<u>Intervention:</u> LGG (10 ¹⁰ CFU / 250 mL ORS) given as needed for rehydration (n = 56; 100% rotavirus) <u>Comparator:</u> Placebo (ORS) given as needed for rehydration (n = 45; 100% rotavirus) <u>Duration of therapy:</u> Variable	<u>Duration of diarrhea in hospital, mean (SD):</u> LGG: 56.2 hours (16.9) Placebo 76.6 hours (41.6) (<i>P</i> < .008) <u>Duration of hospitalization, mean (SD):</u> LGG: 76.5 hours (15) Placebo 97.9 hours (16.5) (<i>P</i> = .04)
Salazar-Lindo (2004) ¹¹	Male children between 3 and 36 months of age with acute diarrhea <2 days	<u>Intervention:</u> LGG (10 ⁹ CFU / mL milk form) given as needed for rehydration (n = 90; 39.4% rotavirus) <u>Comparator:</u> Placebo (milk formula) (n = 89; 24.4% rotavirus) <u>Duration of therapy:</u> <5 days	<u>Duration of diarrhea, mean (SD):</u> LGG: 58.5 hours (30.2) Placebo: 50.4 hours (28) (<i>P</i> = .15) <u>Duration of hospitalization, mean (SD):</u> LGG: 81.2 hours (32.6) Placebo: 74.7 hours (33.7) (<i>P</i> = .28)

(continued)

Table A1. A summary of randomized controlled trials evaluating *Culturelle* in select indications^a (CONT.)

Reference	Study population	Intervention and comparator, duration of therapy	Outcomes
Basu (2007) ¹²	Children with acute watery diarrhea (75.85% rotavirus)	Intervention: LGG (6 x 10 ⁷ CFU / 100 mL ORS) bid (n = 323) Comparator: Placebo (ORS) bid (n = 323) Duration of therapy: > 7 days	Duration of diarrhea, mean (SD): LGG: 6.8 days (2.1) Placebo: 6.6 days (2.3) (nonsignificant; no P value given) Duration of hospitalization, mean (SD): LGG: 9.3 days (1.3) Placebo: 9.2 days (1.2) (nonsignificant; no P value given)
Basu (2009) ¹³	Children with acute watery diarrhea	Intervention: LGG (10 ¹⁰ CFU / 100 mL ORS) bid (n = 188; 59.04% rotavirus) Intervention: LGG (10 ¹² CFU / 100 mL ORS) bid (n = 186; 56.99% rotavirus) Comparator: Placebo (ORS) bid (n = 185; 55.14% rotavirus) Duration of therapy: >7 days	Duration of diarrhea, mean (SD): LGG (10 ¹⁰ CFU): 5.02 days (1.32) LGG (10 ¹² CFU): 5.12 days (1.16) Placebo: 7.23 (1.27) (statistically significant; no P value given) Duration of hospitalization, mean (SD): LGG (10 ¹⁰ CFU): 6.21 days (1.24) LGG (10 ¹² CFU): 5.12 days (1.16) Placebo 9.75 (2.06) (statistically significant; no P value given)
Misra (2009) ¹⁴	Children < 36 months old with diarrhea (25.7% rotavirus)	Intervention: LGG (10 ⁹ CFU) qd (n = 105) Comparator: Placebo (crystalline micro cellulose) qd (n = 105) Duration of therapy: Not stated	Duration of diarrhea, mean: LGG: 2.94 days Placebo: 3.25 days (P = .2)
Antibiotic-associated diarrhea			
Arvola (1999) ¹⁵	Children 2 weeks to 12.8 years old treated with oral antibiotics for treatment of acute respiratory infections	Intervention: LGG (2 x 10 ¹⁰ CFU) bid (n = 61) Comparator: Placebo (n = 58) Duration of therapy: During antibiotic treatment	Incidence of AAD during first 2 weeks: LGG: 5% Placebo: 16% (P = .05)

(continued)

Table A1. A summary of randomized controlled trials evaluating *Culturelle* in select indications^a (CONT.)

Reference	Study population	Intervention and comparator, duration of therapy	Outcomes
Vanderhoof (1999) ¹⁶	Children between 6 months and 10 years of age treated with 10-day antibiotic regimen	<u>Intervention:</u> Children < 12 kg: LGG (1 x 10 ¹⁰ CFU) qd Children >12 kg: LGG (2 x 10 ¹⁰ CFU) qd (n = 93) <u>Comparator:</u> Placebo (inulin) qd (n = 95) <u>Duration of therapy:</u> Not stated	<u>Incidence of AAD during antibiotic administration:</u> LGG: 8% Placebo: 26% (no <i>P</i> value given) <u>Duration of AAD mean:</u> LGG: 4.7 days Placebo: 5.88 (<i>P</i> = .05)
Armuzzi (2001) ¹⁷	Healthy asymptomatic <i>Helicobacter pylori</i> -positive patients taking 1 week of rabeprazole 20 mg bid, clarithromycin 500 mg bid, and tinidazole 500 mg bid	<u>Intervention:</u> LGG (6 x 10 ⁹ CFU) bid (n = 30) <u>Comparator:</u> Placebo (n = 30) <u>Duration of therapy:</u> 2 weeks	<u>Incidence of AAD:</u> LGG: 3.3% Placebo: 26.6% (<i>P</i> = .01)
Thomas (2001) ¹⁸	Hospitalized patients receiving antibiotics	<u>Intervention:</u> LGG (2 x 10 ¹⁰ CFU) qd (n = 133) <u>Comparator:</u> Placebo qd (n = 134) <u>Duration of therapy:</u> 2 weeks	<u>Incidence of AAD:</u> LGG: 29.3% Placebo: 29.9% (<i>P</i> = .93)
Szajewska (2009) ¹⁹	Children between 5 and 17 years old with confirmed <i>H. pylori</i> taking 1 week of amoxicillin 25 mg/kg daily, clarithromycin 10 mg/kg bid, and omeprazole 0.5 mg/kg bid	<u>Intervention:</u> LGG (10 ⁹ CFU) bid (n = 34) <u>Comparator:</u> Placebo (maltodextrin) bid (n = 32) <u>Duration of therapy:</u> 1 week	<u>Incidence of AAD:</u> LGG: 6% Placebo: 20% Relative risk (95% CI): 0.3 (0.07-1.2)
Ventilator-associated pneumonia			
Morrow (2010) ²⁰	Mechanically ventilated adults >18 years of age at high risk of developing VAP	<u>Intervention:</u> LGG (2 x 10 ⁹ CFU) bid (n = 73) <u>Comparator:</u> Placebo (inulin) bid (n = 73) <u>Duration of therapy:</u> Not stated	<u>Incidence of microbiologically confirmed VAP:</u> LGG: 17.8% Placebo: 38.4% (<i>P</i> = .006)
Necrotizing enterocolitis			
Dani (2002) ²¹	Preterm infants <33 weeks of age or birth weight <1,500 g	<u>Intervention:</u> LGG (6 x 10 ⁹ CFU) bid (n = 295) <u>Comparator:</u> Placebo (n = 290) <u>Duration of therapy:</u> About 48 days	<u>Incidence of NEC:</u> LGG: 1.4% Placebo: 2.7% (nonsignificant; no <i>P</i> value given)

Note: AAD = antibiotic-associated diarrhea; bid = twice daily; CFU = colony-forming unit; LGG = *Lactobacillus rhamnosus* GG; NEC = ORS = oral rehydration solution; qd = once daily; VAP = ventilator-associated pneumonia.

^aRotaviral diarrhea, antibiotic-associated diarrhea, ventilator-associated pneumonia, *Clostridium difficile*-associated disease recurrence.

Table A2. A summary of randomized controlled trials evaluating *Florastor* in select indications^a

Reference	Study population	Intervention and comparator, duration of therapy	Results
Rotaviral diarrhea			
Biloo (2006) ²²	Children between 2 months and 12 years of age with acute diarrhea	<u>Intervention:</u> <i>S. boulardii</i> 250 mg bid, ORS, and nutritional support (n = 50; 16% rotavirus) <u>Comparator:</u> ORS and nutritional support (n = 50; 20% rotavirus) <u>Duration of therapy:</u> 5 days	<u>Incidence of diarrhea at end of 2 months, mean:</u> <i>S. boulardii</i> : 0.32 Comparator: 0.56 (<i>P</i> = .04) <u>Duration of diarrhea:</u> <i>S. boulardii</i> : 3.5 days Comparator: 4.8 days (<i>P</i> = .001)
Antibiotic-associated diarrhea			
Surawicz (1989) ²³	Patients receiving antibiotics	<u>Intervention:</u> <i>S. boulardii</i> 250 mg bid (n = 116) <u>Comparator:</u> Placebo (n = 64) <u>Duration of therapy:</u> Not stated	<u>Incidence of AAD:</u> <i>S. boulardii</i> : 9.5% Comparator: 21.8% (<i>P</i> = .038) <u>Duration of AAD:</u> <i>S. boulardii</i> : 5.2 days Comparator: 4 days (<i>P</i> = .31)
McFarland (1995) ²⁴	Hospitalized patients receiving a beta-lactam antibiotic, with no acute diarrhea	<u>Intervention:</u> <i>S. boulardii</i> two 250 mg bid (n = 97) <u>Comparator:</u> Placebo (n = 96) <u>Duration of therapy:</u> 3 days after antibiotic was stopped	<u>Incidence of AAD:</u> <i>S. boulardii</i> : 7.2% Placebo: 14.6% (<i>P</i> = .02)
Lewis (1998) ²⁵	Patients >65 years of age who had been prescribed antibiotics within the past 24 hours	<u>Intervention:</u> <i>S. boulardii</i> 113 mg bid (n = 33) <u>Comparator:</u> Placebo (n = 36) <u>Duration of therapy:</u> Entirety of antibiotic therapy	<u>Duration of hospitalization, median:</u> <i>S. boulardii</i> : 7 days Placebo: 9 days (<i>P</i> = .01) <u>Incidence of AAD:</u> <i>S. boulardii</i> : 21.2% Placebo: 13.9% (no <i>P</i> value given)
Duman (2005) ²⁶	Patients with peptic ulcer disease (PUD) or non-ulcer dyspepsia who received clarithromycin, amoxicillin, and omeprazole for <i>Helicobacter pylori</i> eradication for 14 days	<u>Intervention:</u> <i>S. boulardii</i> two 250 mg capsules bid (n = 204) <u>Comparator:</u> None (n = 185) <u>Duration of therapy:</u> 2 weeks	<u>Incidence of AAD:</u> <i>S. boulardii</i> : 6.9% Comparator: 15.6% (<i>P</i> = .007)

(continued)

Table A2. A summary of randomized controlled trials evaluating *Florastor* in select indications^a (CONT.)

Reference	Study population	Intervention and comparator, duration of therapy	Results
<i>Clostridium difficile</i> –associated disease recurrence			
McFarland (1994) ²⁷	Adults with active CDD currently on vancomycin or metronidazole	<u>Intervention:</u> <i>S. boulardii</i> 1 g daily <u>Comparator:</u> Placebo (n = 124) <u>Duration of therapy:</u> 4 weeks	<u>CDD recurrence in patients with recurrent CDD:</u> <i>S. boulardii</i> : 34.6% Placebo: 64.7% (<i>P</i> = .04) <u>CDD recurrence in patients with initial CDD:</u> <i>S. boulardii</i> : 19.3% Placebo: 24.2% (<i>P</i> = .86)
Surawicz (2000) ²⁸	Adults with recurrent CDD given a 10-day course of high-dose vancomycin (2 g/day), low-dose vancomycin (500 mg/day), or metronidazole (1 g/day)	<u>Intervention:</u> <i>S. boulardii</i> two 250 mg capsules bid and high-dose vancomycin (n = 18) <u>Intervention:</u> <i>S. boulardii</i> two 250 mg capsules bid and low-dose vancomycin (n = 45) <u>Intervention:</u> <i>S. boulardii</i> two 250 mg capsules bid and metronidazole (n = 27) <u>Comparator:</u> Placebo and either high-dose vancomycin (n = 14), low-dose vancomycin (n = 38), or metronidazole (n = 26) <u>Duration of therapy:</u> 4 weeks	<u>CDD recurrence:</u> <i>S. boulardii</i> and high-dose vancomycin: 16.7% Placebo and high-dose vancomycin: 50% (<i>P</i> = .05) <i>S. boulardii</i> and low-dose vancomycin: 51.1% Placebo and low-dose vancomycin: 44.7% (nonsignificant; no <i>P</i> value given) <i>S. boulardii</i> and metronidazole: 48.1% Placebo and metronidazole: 50% (nonsignificant; no <i>P</i> value given)

Note: AAD = antibiotic-associated diarrhea; bid = twice daily; CDD = *Clostridium difficile*–associated disease; ORS = oral rehydration solution; *S. boulardii* = *Saccharomyces boulardii*.

^aRotaviral diarrhea, antibiotic-associated diarrhea, ventilator-associated pneumonia, *Clostridium difficile*–associated disease recurrence.

Table A3. A summary of randomized controlled trials evaluating *Lactinex* in select indications^a

Reference	Study characteristics	Intervention and comparator, duration of therapy	Outcomes
Antibiotic-associated diarrhea			
Gotz (1979) ²⁹	Patients who had started oral or intravenous ampicillin therapy	Intervention: <i>Lactinex</i> qid (n = 36) Comparator: Placebo qid (n = 43) Duration of therapy: 5 days	Incidence of diarrhea: <i>Lactinex</i> : 8.3% Placebo: 21% (<i>P</i> = .21)
Tankanow (1990) ³⁰	Children between 5 months and 6 years who had started amoxicillin therapy	Intervention: <i>Lactinex</i> (1 g packets) qid (n = 15) Comparator: Placebo (lactose) qid (n = 23) Duration of therapy: 10 days	Incidence of diarrhea: <i>Lactinex</i> : 66% Placebo: 69.5% (<i>P</i> = .563)

Note: qid = four times a day.

^aRotaviral diarrhea, antibiotic-associated diarrhea, ventilator-associated pneumonia, *Clostridium difficile*-associated disease recurrence.

Table A4. A summary of randomized controlled trials evaluating *VSL #3* in select indications^a

Reference	Study characteristics	Intervention and comparator, duration of therapy	Outcomes
Rotaviral diarrhea			
Dubey (2008) ³¹	Children 6 months to 2 years old with acute watery diarrhea for < 72 hours duration with confirmed rotavirus infection	Intervention: <i>VSL #3</i> <5 kg = 2 sachets/day 5 to 10 kg = 4 sachets/day (n=113) Comparator: Placebo (n=111) Duration of therapy: 4 days	<i>VSL #3</i> : Recovery: 101 (89.4%), Improvement: 4 (3.5%) Failure 8 (7.1%) (<i>P</i> < .001) Placebo: Recovery: 44 (39.6%) Improvement: 24 (21.6%) Failure 43 (38.7%) (no <i>P</i> value given)

^aRotaviral diarrhea, antibiotic-associated diarrhea, ventilator-associated pneumonia, *Clostridium difficile*-associated disease recurrence.