The Use of Probiotics for Decreasing Antibiotic-Associated Diarrhea

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"The term antibiotic-associated diarrhea (AAD) usually refers to a benign, self-limiting diarrhea following the use of antimicrobials. Typically, no pathogens are identified and most patients respond to supportive measures and discontinuation of antibiotics" (Deshpande, D., Pimentel, R., & Choure, A, 2015). However, AAD may occasionally progress in severity to result in colitis, dehydration, electrolyte disturbance, bowel perforation, and megacolon, leading to patient discomfort, potential loss of adherence to treatment, and increased healthcare costs (Allen et al., 2013; Videlock & Cremonini, 2012). It occurs in both in-patient and outpatient settings with a prevalence rate of 5-25% depending on the type of antibiotic that is administered (Allen et al., 2013; Song et al., 2010;). "The occurrence of AAD can be a limiting factor to adherence to antibiotic regimens and to successful completion of treatment" (Videlock & Cremonini, 2012).

A common cause of severe AAD is infection by clostridium difficile. "Clostridium difficile-associated diarrhea (CDAD) refers to a wide spectrum of diarrheal illnesses caused by the toxins produced by this organism, including cases of severe colitis with or without the presence of pseudomembranes" (Deshpande et al., 2015). CDAD has increased in incidence and severity over the last decade due to the use of broad-spectrum antibiotics (Allen et al., 2013). It is a major public health concern and accounts for significant morbidity and mortality, especially in the elderly and patients with recurring episodes (Allen et al., 2013).

Current treatments for AAD and CDAD are limited. Whereas most cases are typically "treated with discontinuation of the antibiotic and with dietary changes, severe cases often require bed rest, intravenous fluids, and additional antibiotics such as metronidazole or

vancomycin" (Allen et al., 2013). However, 25% of patients treated with antibiotics for CDAD will relapse within 2 months (Allen et al., 2013).

AAD is caused by a change in the composition and function of the intestinal flora. One of the main roles of normal gut microflora is to protect against colonization by intestinal pathogens. Once this protective barrier is broken, patients are more susceptible to infection (Song et al., 2010). In these settings, supplementation with probiotics during antibiotic treatment has been proposed to enhance the gut mucosal barrier function of the host to minimize risk against pathogen susceptibility (Videlock & Cremonini, 2012).

The supplementation with probiotics during antibiotic treatment is currently not a standard of care, but there is growing interest in their use for the treatment of AAD and CDAD because of the wide availability of probiotics as dietary supplements and concern over recent outbreaks of severe C. difficile disease in Canada, the United Kingdom, and the United States (Song et al., 2010; Videlock & Cremonini, 2012). Probiotics have been proposed to treat and prevent AAD and CDAD as several meta-analyses have concluded that various probiotic strains can decrease the incidence of both, and have been shown to enhance the host flora by stimulating immune function, suppressing pathogenic bacteria colonization, and clearing pathogens and their toxins from the host (Allen et al., 2013; Song et al., 2010).

This evidence, in addition to personal experience with clinical patients who either complained of AAD or discontinued antibiotic use because of it, led to the formation of the initial PICO(T) "In patients receiving oral antibiotics, should probiotics also be prescribed to reduce gastrointestinal distress?" Deciding it was too vague and needed clarification, it was changed to "For patients receiving oral antibiotics, will a simultaneous prescription of probiotics aid in decreasing antibiotic associated diarrhea?" The reasons for the changes were to emphasize

the co-prescription of probiotics as prophylactic, rather than as an after-the-fact treatment, and to focus on the primary reasons for why either the patient or health care provider discontinues antibiotics.

Methods

Search Strategy

Initially, three primary databases were searched with limiters set to ten years (2005-2015) and only those studies in English. Those databases were PubMed, CINHAL, and Google Scholar. The search terms included combinations of the following keywords: probiotic, antibiotic, gastrointestinal, diarrhea, side effects, and distress. An additional search was performed in PubMed limiting the results to only RCTs, Meta-Analyses, and Systematic Reviews. A manual search of references listed on the retrieved studies was also conducted to identify additional studies of interest.

Surprisingly, there was a large selection of literature available, most of it directly related to the PICO question. Several RCTs have been conducted in the past ten years testing the efficacy of different probiotic strains on AAD and CDAD, and the populations of those studied varied. All relevant articles located were evaluated using Evidence Appraisal forms (see Appendix A) and a Systematic Evidence Evaluation Table was created (see Appendix B). Finally, the information gathered from all articles was analyzed for common themes and populated in an Evidence Synthesis table (see Appendix C).

Literature Synthesis/Presentation of Evidence

In 2010, Gao et al. published what was at the time was the largest RCT studying the effects of probiotic therapy for ADD and CDAD, and the first to study dose-ranging outcomes. In a double-blind placebo-controlled study, 255 inpatients in a single hospital were randomized

to three different groups: two placebo capsules per day (n=84), one probiotic capsule and one placebo capsule per day (Pro-1, n=85), and two probiotic capsules per day (Pro-2, n=86). The probiotics were started within 36hrs of the start of antibiotics and continued for 5 days past the therapy period. The investigators followed the patients for an additional 21 days as ADD can occur up to two months after the cessation of antibiotic therapy. The incidence of AAD for the placebo, Pro-1, and Pro-2 were 44.1%, 28.2%, and 15.5% respectively. Where at first this appears significant, the probiotic percentages still fall into the known range for AAD of 5-25% of adult patients. The most usable data gained from this study was that the duration of AAD was decreased from 6.4 days for the placebo to only 2.8 days for the Pro-2 group. Most importantly, the respective rates of CDAD for the placebo, Pro-1, and Pro-2 groups were 23.8%, 9.4%, and 1.2%. This research supports the hypothesis that increased dosages of probiotics may be directly related to a significant decrease in both the number of days of AAD and the incidence of CDAD.

In 2010, Song et al. published their results from a randomized, double-blinded, multicenter study on the effect of a lactobacillus supplement (Lacidofil Cap) for the prevention of AAD in 214 patients receiving a 14-day course of antibiotics for respiratory tract infections. Patients were asked to record bowel frequency and stool consistency during the time period, and the primary outcome was loose or watery stools more than 2 times per day for at least 2 days. Final analysis saw no difference in the rate of occurrence of AAD between the study and control groups, as AAD occurred in 3.9% and 7.2% respectively. However, the study group was able to maintain their bowel habits to a greater extent than the control group, as they were less likely to experience non-AAD changes in bowel frequency and consistency during the entire 14-day period. Whereas the resulting data was inconsistent with previous studies that found success with

probiotics in preventing AAD, the authors admitted that only studying the effects of probiotics on antibiotics specific to respiratory illnesses may have been a significant limitation.

Videlock and Cremonini (2012) performed a meta-analysis of 34 randomized, double-blinded, placebo-controlled trials that studied the effects of administering probiotics during the entire course of antibiotic treatment. The aim was to estimate the risk of AAD when probiotics were administered, and to identify the factors associated with those reductions. Specific factors the authors were interested in were whether different strains were more effective in reducing the risk of ADD and were there variances between children and adults. A major difference of this meta-analysis from others performed was that any studies that analyzed CDD and colitis were excluded. Thee authors found that the preventive effect of probiotics remained significant when grouped by probiotic species, population age group, relative duration of antibiotics and probiotics, study risk of bias and probiotic administered (Videlock & Cremonini, 2012).

Rather than focusing on AAD, Johnston et al. (2012) instead performed a meta-analysis with the intent of reviewing RCTs and extracting only the data pertinent to CDAD. Twenty trials including 3,818 patients were analyzed to determine the efficacy and safety of any strain and dose of probiotics in preventing CDAD in both adults and children who were receiving antibiotics. Their results indicated CDAD was decreased by as much as 66% when probiotics were taken during antibiotic therapy; only 3% in a population of 1,000 persons.

The most recent of the reviewed literature was the multicenter, randomized, double-blinded, placebo-controlled RCT performed by Allen et al. (2013) on 2,981 inpatients 65 years and older. On the basis of previous evidence, the researchers used a high dose, multi-strain combination of lactobacilli and bifidobacteria, those strains most frequently used in other clinical trials, to determine the efficacy of probiotics in the prevention of AAD and CDAD in older

inpatients. Patients were given either the placebo or probiotic for 21 days and monitored for AAD for the first 8 weeks and for CDAD for the first 12 weeks. By far the largest RCT ever performed on this subject, the results were in complete contradiction to all other studies performed prior. Not only did the evidence reveal that probiotics had no affect on ADD (10.8% for the probiotic versus 10.4% for the placebo) or CDAD (0.8% for the probiotic versus 1.2% for the placebo), but there was also no decrease in other symptoms such as severity of diarrhea, frequency of abdominal symptoms, length of hospital stay, and quality of life.

Summary of Findings & Discussion

All articles reviewed were directly related to the proposed PICO(T) question. Though not all were able to provide a definitive answer regarding the use of probiotics to limit AAD or CDAD, the majority reported favorable outcomes when probiotics where administered simultaneously with a course of antibiotics. Common themes studied were whether probiotics use in conjunction with antibiotics decreased incidence of AAD and the severity of symptoms, and if increased dosages of probiotics had a positive influence. Populations varied from adolescents to elderly, included both in- and outpatients, and several strains of probiotics were studied in conjunction with various antibiotics.

The articles by Gao et al. (2010) and Allen et al. (2013) conducted the most significant research and provided interesting yet opposing results. Gao et al. (2010) was the first to look at whether increasing the dosage of a probiotic might reduce the occurrence of AAD and CDAD, and found higher dosages indeed had favorable results. However, Allen et al. (2013) refuted that study (and the majority of all previous studies) by using a large dose of a combination probiotic and testing it on more than 10 times as many patients as anyone else had, finding no differences in the rate of occurrence of AAD.

One finding all authors agreed upon was that probiotics were safe to use and patients rarely experienced any side effects specific to their use. The common recommendation in all articles was that larger populations needed to be studied, and different strains of probiotics needed to be analyzed to determine if specific probiotics worked better in conjunction with specific antibiotics.

Summary Statement

After reviewing the literature, this author recommends the concurrent use of probiotics for patients prescribed a course of oral antibiotics, even though the largest trial revealed no decrease in either ADD or CDAD. This recommendation is based on the facts that there are no known serious adverse effects with using probiotics, and the majority of the literature reports a decrease in both AAD and CDAD for those patients receiving both antibiotics and probiotics. Due to the relatively low cost of probiotics, in addition to other known benefits, their use may eventually be found to decrease the incidence of AAD and CDAD, healthcare costs, and morbidity/mortality, especially if strains, combinations, and dosages are discovered that target specific bacterium.

References

Allen, S. J., Wareham, K., Wang, D., Bradley, C., Hutchings, H., Harris, W., … Mack, D. (2013). Lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhoea and clostridium difficile diarrhoea in older inpatients (PLACIDE): A randomised, double-blind, placebo-controlled, multicentre trial. *The Lancet, 382*(9900), 1249-1257. doi:10.1016/S0140-6736(13)61218-0

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Gao, X. W., Mubasher, M., Fang, C. Y., Reifer, C., & Miller, L. E. (2010). Dose-response efficacy of a proprietary probiotic formula of lactobacillus acidophilus CL1285 and lactobacillus casei LBC80R for antibiotic-associated diarrhea and clostridium difficile-associated diarrhea prophylaxis in adult patients. *American Journal of Gastroenterology, 105*(7), 1636-1641. doi:10.1038/ajg.2010.11

Hempel, S., Newberry, S. J., Maher, A. R., Wang, Z., Miles, J. N., Shanman, R., … Shekelle, P. G. (2012). Probiotics for the prevention and treatment of antibiotic-associated diarrhea. *The Journal of the American Medical Association, 307*(18), 1959 -1969. doi:10.1001/jama.2012.3507

Johnston, B. C., Ma, S. S., Goldenberg, J. Z., Thorlund, K., Vandvik, P. O., Loeb, M., Guyatt, G. H. (2012). Probiotics for the prevention of clostridium difficile–associated diarrhea. *Annals of Internal Medicine, 157*(12), 878-888. doi:10.7326/0003-4819-157-12-201212180-00563

Song, H. J., Kim, J., Jung, S., Kim, S., Park, H., Jeong, Y., … Kim, E. Y. (2010). Effect of probiotic lactobacillus (Lacidofil® Cap) for the prevention of antibiotic-associated diarrhea: A prospective, randomized, double-blind, multicenter study. *Journal of Korean Medical Science, 25*(12), 1784-1791. doi:10.3346/jkms.2010.25.12.1784

Videlock, E. J., & Cremonini, F. (2012). Meta-analysis: Probiotics in antibiotic-associated diarrhea. *Alimentary Pharmacology & Therapeutics, 35*(12), 1355–1369. doi:10.1111/j.1365-2036.2012.05104.x

Appendix A

Evidence Appraisal Form

First Author	Gao	
Article Citation	Gao, X. W., Mubasher, M., Fang, C. Y., Reifer, C., & Miller, L. E. (2010). Dose-response efficacy of a proprietary probiotic formula of lactobacillus acidophilus CL1285 and lactobacillus casei LBC80R for antibiotic-associated diarrhea and clostridium difficile-associated diarrhea prophylaxis in adult patients. American Journal of Gastroenterology, 105(7), 1636-1641. doi:10.1038/ajg.2010.11	
Brief Title	Dose – Response Efficacy of a Proprietary Probiotic Formula of Lactobacillus acidophilus	
Study Question	Two hypotheses: First, would probiotic prophylaxis lower the incidence of AAD and CDAD in hospitalized adults receiving antibiotic therapy? Second, would this effect occur in a dose-dependent manner?	
Design Type	Single center, three-arm, randomized, double-blind, placebo-controlled dose-ranging study	
Sample / Size	What was the sample size?	1120 eligible, 865 excluded, 255 enrolled, 19 did not complete
	Is the sample patients or non-patients?	Patients
	If patients, what was the male/female count?	131:124
	What was the sampling method?	Random
	What was the response rate (if applicable)?	N/A
Outcome Variables & Definitions	**IV:** Two probiotic capsules per day (Pro-2, n = 86), one probiotic capsule and one placebo capsule per day (Pro-1, n = 85), or two placebo capsules per day (n = 84). **DV:** AAD, CDAD, and gastrointestinal symptoms	
Measures	Self report for abdominal pain abdominal distension, loose stool, and constipation. CDAD incidence was not reported how it was determined. No criteria for how loose stool/diarrhea was determined.	
Analytical Approach	Categorical variables, e.g. incidence of AAD, are presented as n (%). Further group comparisons were assessed with χ 2 -test or Fisher ' s exact test. No adjustments were made for multiplicity.	
Findings	Results showed a significantly lower incidence of AAD and, in particular, CDAD for both probiotic treatment groups compared to the placebo group. Furthermore, a distinct dose – response effect was observed with higher probiotic dosages resulting in greater efficacy, shorter time with continuous AAD, and fewer gastrointestinal symptoms.	
Limitations	1) Present results are specific to the product studied and cannot be generalized to other probiotic products. 2) Although AAD and CDAD often begin between 4 and 9 days after antibiotic use is stopped, they can occur up to 8 weeks later. Therefore, it is plausible that some late cases of AAD and CDAD were missed. 3) Only patients aged 50 – 70 years were enrolled in this study, which may limit applicability to younger patients. 4) The length of antibiotic therapy in this study was between 3 and 14 days. Therefore, the effects of probiotic administration on AAD /CDAD with prolonged antibiotic treatment are unknown. 5) Patients in this study were solely of Asian descent. Therefore, caution must be exercised when applying these study outcomes to patients of other ethnic origins.	
Hierarchy of Evidence Rating System	☐ I	Evidence from a systematic review or meta-analysis of all relevant randomized controlled trials, or evidence-based clinical practice guidelines based on systematic reviews of RCT's
	☒ II	Evidence obtained from at least one well-designed RCT
	☐ III	Evidence obtained from well-designed control trials without randomization
	☐ IV	Evidence from well-designed case control and cohort studies
	☐ V	Evidence from systematic reviews of descriptive and qualitative studies
	☐ VI	Evidence from a single descriptive or qualitative study
	☐ VII	Evidence from the opinion of authorities and/or reports of expert committees
		Strongest ↕ Weakest

Level of Quality	***Grade***	***Level***	***Research***	***Non-research***
	☐ **A**	**High**	Consistent results, sufficient sample size, adequate control and definitive conclusions; consistent recommendations based on extensive literature review that includes thoughtful reference to scientific evidence	Expertise is clearly evident.
	☒ **B**	**Good**	Reasonable consistent results, sufficient sample size, some control, and fairly definitive conclusions; reasonable consistent recommendations based on fairly comprehensive literature review that includes some reference to scientific evidence	Expertise appears to be credible.
	☐ **C**	**Low/ Major flaw**	Little evidence with inconsistent results, insufficient sample size, conclusions cannot be drawn	Expertise is not discernible or is dubious.

General Comments	

Evidence Appraisal Form

First Author	Song	
Article Citation	Song, H. J., Kim, J., Jung, S., Kim, S., Park, H., Jeong, Y., … Kim, E. Y. (2010). Effect of probiotic lactobacillus (Lacidofil® Cap) for the prevention of antibiotic-associated diarrhea: A prospective, randomized, double-blind, multicenter study. Journal of Korean Medical Science, 25(12), 1784-1791. doi:10.3346/jkms.2010.25.12.1784	
Brief Title	Effect of Probiotic Lactobacillus (Lacidofil® Cap) for the Prevention of Antibiotic-associated Diarrhea	
Study Question	What is the efficacy of the probiotic lactobacillus (Lacidofil Cap) in the prevention of antibiotic-associated diarrhea?	
Design Type	A Prospective, Randomized, Double-blind, Multicenter Study	
Sample / Size	What was the sample size?	214
	Is the sample patients or non-patients?	Patients
	If patients, what was the male/female count?	132:82
	What was the sampling method?	Random
	What was the response rate (if applicable)?	172
Outcome Variables & Definitions	**IV:** Placebo and Lacidofil cap. **DV:** diarrhea	
Measures	Self report of symptoms	
Analytical Approach	Chi-square test; multiple logistic regression analysis; effect estimates	
Findings	In this study, the number of AAD cases was not statistically different between the 2 groups and the prevalence of AAD was low (3.9-7.2%) compared with a previous report (2-25%) as assessed by ITT analysis.	
Limitations	1) The incidence of AAD was much lower than in previous studies. Patients were followed up for only 2 weeks after antibiotic therapy. As AAD can occur up to 2 months after stopping antibiotic treatment, some cases might have been missed. 2) The patients were not normally distributed. Some centers recruited more patients than allocated, and others had fewer cases. 3) The difference between hospitals in the main antibiotic prescribed is a potential weakness because the incidence of AAD differs between groups of antibiotics. However, there was no significant difference in antibiotic use between the 2 groups. 4) Although the required sample size was 220, the study was performed using 214 patients. The most frequent limitation of previous studies may also have been insufficient power to detect significant differences	
Hierarchy of Evidence Rating System	☐ I	Evidence from a systematic review or meta-analysis of all relevant randomized controlled trials, or evidence-based clinical practice guidelines based on systematic reviews of RCT's
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	☐ **C**	**Low/ Major flaw**	Little evidence with inconsistent results, insufficient sample size, conclusions cannot be drawn	Expertise is not discernible or is dubious.

General Comments	

Evidence Appraisal Form

First Author	Videlock	
Article Citation	Videlock, E. J., & Cremonini, F. (2012). Meta-analysis: Probiotics in antibiotic-associated diarrhea. Alimentary Pharmacology & Therapeutics, 35(12), 1355–1369. doi: 10.1111/j.1365-2036.2012.05104.x	
Brief Title	Meta-analysis: probiotics in antibiotic-associated diarrhea.	
Study Question	What is the estimated reductionin risk of AAD with administration of probiotics in randomized placebo-controlled trials, and what identified factors are associated with such reduction?	
Design Type	Meta-analysis of randomised, double-blinded, placebo-controlled trials	
Sample / Size	What was the sample size?	34 studies (including 4138 patients)
	Is the sample patients or non-patients?	Non-patients
	If patients, what was the male/female count?	N/A
	What was the sampling method?	Purposive
	What was the response rate (if applicable)?	N/A
Outcome Variables & Definitions	**IV:** antibiotics and probiotic administered for at least the duration of the antibiotic treatment. **DV:** the incidence of diarrhea irrespective of the presence of Clostridium difficile or the development of pseudomembranous colitis.	
Measures	MEDLINE, Cochrane Controlled Trial Register and EMBASE databases (1966–2011). The search was limited a priori to studies that were double-blinded, placebo-controlled, parallel group	
Analytical Approach	N/A	
Findings	The preventive effect of probiotics remained significant when grouped by probiotic species, population age group, relative duration of antibiotics and probiotics, study risk of bias and probiotic administered.	
Limitations	1) Inclusion criteria and search strategy may have missed clinical trials with non-diarrhea primary outcomes but in which the incidence of diarrhea was explicitly measured. 2) Authors did not systematically extract data related to adverse events and thus number needed to harm was not calculated.	
Hierarchy of Evidence Rating System	☒ I	Evidence from a systematic review or meta-analysis of all relevant randomized controlled trials, or evidence-based clinical practice guidelines based on systematic reviews of RCT's
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First Author	Johnston	
Article Citation	Johnston, B. C., Ma, S. S., Goldenberg, J. Z., Thorlund, K., Vandvik, P. O., Loeb, M., Guyatt, G. H. (2012). Probiotics for the prevention of clostridium difficile–associated diarrhea. Annals of Internal Medicine, 157(12), 878-888. doi:10.7326/0003-4819-157-12-201212180-00563	
Brief Title	Probiotics for the Prevention of Clostridium difficile–Associated Diarrhea	
Study Question	What is the efficacy and safety of probiotics (any strain or dose) for the prevention of CDAD in adults and children receiving antibiotics?	
Design Type	A Systematic Review and Meta-analysis	
Sample / Size	What was the sample size?	Twenty trials including 3818 participants met the eligibility criteria.
	Is the sample patients or non-patients?	Non patients
	If patients, what was the male/female count?	N/A
	What was the sampling method?	Purposive
	What was the response rate (if applicable)?	N/A
Outcome Variables & Definitions	**IV:** Placebo and probiotics (any strain and any dose), **DV:** AAD, CDAD	
Measures	Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, Allied and Complementary Medicine Database, Web of Science, and 12 gray-literature sources.	
Analytical Approach	Heterogeneity was investigated by using the chi-square test and I^2 statistic.	
Findings	Moderate-quality evidence suggests that probiotic prophylaxis results in a large reduction in CDAD without an increase in clinically important adverse events.	
Limitations	1) The studies demonstrated some inconsistency in CDAD diagnostic methods. 2) Although the CI around the pooled estimate of effect on CDAD is narrow, the total sample size across studies did not meet the OIS (5676 persons). 3) There is considerable variability in the control group risk for CDAD across studies. 4) Of the 20 included trials, 13 excluded patients who were immunodeficient or who were receiving immunosuppressive therapy.	
Hierarchy of Evidence Rating System	☒ I	Evidence from a systematic review or meta-analysis of all relevant randomized controlled trials, or evidence-based clinical practice guidelines based on systematic reviews of RCT's
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General Comments				

Evidence Appraisal Form

First Author	Allen	
Article Citation	Allen, S. J., Wareham, K., Wang, D., Bradley, C., Hutchings, H., Harris, W., … Mack, D. (2013). Lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhoea and clostridium difficile diarrhoea in older inpatients (PLACIDE): A randomised, double-blind, placebo-controlled, multicentre trial. The Lancet, 382(9900), 1249-1257. doi:10.1016/S0140-6736(13)61218-0	
Brief Title	Lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhea	
Study Question	Will the administration of a microbial preparation would reduce the frequency of AAD and CDD in an at-risk population?	
Design Type	Multicenter, randomized, double-blind, placebo-controlled, two-group, pragmatic, efficacy trial	
Sample / Size	What was the sample size?	17420 (only 2981 used).
	Is the sample patients or non-patients?	Patients
	If patients, what was the male/female count?	1,456:1,525
	What was the sampling method?	Random
	What was the response rate (if applicable)?	N/A
Outcome Variables & Definitions	**IV:** Placebo and probiotic. **DV:** The primary outcomes were the occurrence of AAD within 8 weeks and CDD within 12 weeks of recruitment. Secondary outcomes were severity and duration of AAD and CDD, abdominal symptoms, serious adverse events, duration of hospital stay, the acceptability of the microbial preparation, and quality of life.	
Measures	Diarrhea defined as three or more loose stools (consistency 5–7 on the Bristol Stool Form Scale) in a 24 h period or as stools described as looser than normal in participants unable to use the scale. Quality of life was assessed by the generic 12-item short form survey (SF12 v2), which was administered by research nurses at baseline, and 4 and 8 weeks.	
Analytical Approach	χ^2 tests and Mann-Whitney methods used for comparative purposes.	
Findings	AAD (including CDD) occurred in 159 (10·8%) participants in the microbial preparation group and 153 (10·4%) participants in the placebo group (relative risk [RR] 1·04; 95% CI 0·84–1·28; p=0·71). CDD was an uncommon cause of AAD and occurred in 12 (0·8%) participants in the microbial preparation group and 17 (1·2%) participants in the placebo group (RR 0·71; 95% CI 0·34–1·47; p=0·35). No evidence that a multi-strain preparation of lactobacilli and bifidobacteria was effective in prevention of AAD or CDD.	
Limitations	Recruited fewer than one in five eligible patients. The main reason for non-participation was the unwillingness of people already receiving medicines to take an additional preparation.	
Hierarchy of Evidence Rating System	☐ I	Evidence from a systematic review or meta-analysis of all relevant randomized controlled trials, or evidence-based clinical practice guidelines based on systematic reviews of RCT's
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	☐ **B**	**Good**	Reasonable consistent results, sufficient sample size, some control, and fairly definitive conclusions; reasonable consistent recommendations based on fairly comprehensive literature review that includes some reference to scientific evidence	Expertise appears to be credible.
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General Comments				

Appendix B

Systematic Evidence Evaluation Table

Citation	Relevance to PICOT	Design Type	Sample / Size	Outcome Variables & Definitions	Measures	Analytical Approach	Findings	Limitations	Evidence Rating/ Level of Quality
(Allen et al., 2013)	++++	RCT	2,981	IV: Probiotic; placebo DV: diarrhea	Self-report of # of loose stools based on Bristol Stool Chart. Nurse collected 12-item QOL survey	Chi square, Mann-Whitney	-No evidence that a multi-strain preparation of lactobacilli and bifidobacteria was effective in prevention of AAD or CDD.	-Lack or participation -Only 1 in 5 eligible pts opted to participate	II/A
(Gao et al., 2010)	++++	RCT	255	IV: Probiotics capsule; placebo DV: Abx-associated diarrhea (AAD), c-diff (CDAD), other GI symptoms	Self-report of GI symptoms. Lab test for c-diff	Chi square, Fisher's exact	-Significantly lower incidence of AAD and CDAD for probiotic treatment groups compared to the placebo group. -A distinct dose response effect with higher probiotic dosages resulting in greater efficacy, shorter time with continuous AAD, and fewer gastrointestinal symptoms.	Results limited to products studied; pts not followed for long-enough time; older pts (50-70yoa); only studied short-term abx therapy (3-14 days); only Asian pts	II/B
(Johnston et al., 2012)	++++	Systematic Review and Meta-analysis	20 trials with 3,818 participants	IV: probiotics, placebo DV: CDAD	Electronic search of multiple databases	Chi-square test and I^2 statistic	-Probiotic prophylaxis results in a large reduction in CDAD without an increase in clinically important adverse events.	-Some inconsistency in CDAD diagnostic methods. -Considerable variability in the control group risk for CDAD across studies. -13 of the 20 trials excluded patients who were immunodeficient or who were receiving immunosuppressive	I/A

								therapy.	
(Song et al., 2010)	++++	RCT	214	IV: Lacidofil capsule (probiotic), placebo DV: Diarrhea	Self-report of symptoms	Chi square and Student's t-test	-No statistically different rates of report of AAD between the two groups	-Short-f/u time after therapy -patients not normally distributed between test sites -Difference in strengths of abx -Sample size was 6 pts less than what was needed according to the power analysis	II/B
Videlock et al, 2012)	++++	Systematic Review and Meta-analysis	34 studies (including 4138 patients)	IV: antibiotics and probiotic administered for at least the duration of the antibiotic treatment. DV: the incidence of diarrhea irrespective of the presence of Clostridium difficile or the development of pseudomembranous colitis.	Electronic search of multiple databases	N/A	-The preventive effect of probiotics remained significant when grouped by probiotic species, population age group, relative duration of antibiotics and probiotics, study risk of bias and probiotic administered.	1) Inclusion criteria and search strategy may have missed clinical trials with non-diarrhea primary outcomes but in which the incidence of diarrhea was explicitly measured. 2) Authors did not systematically extract data related to adverse events and thus number needed to harm was not calculated.	I/B

Appendix C

Evidence Synthesis Table

Article	LOE	Probiotic Used	AAD / CDAD
(Johnston et al., 2012)	**I/A**	**Yes**	↓
(Videlock et al, 2012)	**I/B**	**Yes**	↓
(Allen et al., 2013)	**II/A**	**Yes**	↔
(Gao et al., 2010)	**II/B**	**Yes**	↓
(Song et al., 2010)	**II/B**	**Yes**	↔

Note. LOE = level of evidence; AAD = antibiotic associate diarrhea; CDAD = C. difficile-associated diarrhea.