Probiotics for the Prevention of Antibiotic Associated Diarrhea and Clostridium Difficile Infection among Hospitalized Patients: A Systematic Review and Meta-Analysis

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R Pattani participated in designing the study methodology, contributed to data extraction and analysis, and was the principal writer of the manuscript. VA Palda conceived the project, outlined the qualitative study methods, and contributed to data extraction and analysis. SW Hwang assisted in designing study methods and in the data extraction and analysis. PS Shah outlined quantitative methods, conducted the quantitative analysis, and participated in writing the manuscript. All of the authors reviewed and edited drafts of the manuscript for important intellectual content and each author approved the final version of the manuscript.

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None

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**ABSTRACT**

**Background**: Antibiotic associated diarrhea (AAD) and Clostridium difficile infection (CDI) are associated with high morbidity, mortality, and health care costs. Probiotics may mitigate the existing disease burden. Our objective was to systematically review and meta-analyze studies of co-administration of probiotics with antibiotics for prevention of AAD and CDI in adult inpatients.

**Methods:** Systematic searches of MEDLINE (1946 – May 2012), EMBASE (1980 – May 2012) and Cochrane Central Register of Controlled Trials (CCTR) were undertaken to identify relevant publications on May 31, 2012. We searched for randomized controlled trials published in the English language of adult inpatients receiving antibiotics and randomized to the co-administration of probiotics or to usual care with or without the use of placebo. Studies were included if they reported on either AAD or CDI as outcomes. Data were extracted on predetermined criteria evaluating study characteristics, methods, and risk of bias. Trials were given a global rating of good, fair, or poor by at least two reviewers. Meta-analyses were performed using a random effect model, and pooled relative risks (RR) and 95% confidence intervals (CI) were calculated.

**Results:** Sixteen trials were included in this review. Four studies were good quality, five were fair quality, and seven were poor quality. Pooled analyses revealed significant reduction in the risk of AAD (RR 0.61, 95% CI 0.47, 0.79) and CDI (RR 0.37, 95% CI 0.22, 0.62) among patients randomized to the co-administration of probiotics. The number needed to treat for benefit was 11 (95% CI 8, 20) for AAD and 14 (95% CI 8, 50) for CDI. With subgroup analysis, significant reductions in both AAD and CDI rate were retained in the subgroups of good quality trials, trials assessing a primarily Lactobacillus-based formulation, and trials for which the follow-up period was less than 4 weeks.

**Interpretation**: Probiotics used concurrently with antibiotics reduce the risk of AAD and CDI.

Introduction

A rise in the use of antibiotics has resulted in a marked increase in antibiotic-associated diarrhea (AAD) and Clostridium Difficile Infection (CDI) (1). There is a spectrum of adverse sequelae associated with CDI, including diarrhea, electrolyte abnormalities, sepsis and septic shock, toxic megacolon requiring colectomy, ICU admission, and death (2). In response to this devastating infection, non-antibiotic strategies such as toxin-binding agents, active immunization, Intravenous Immune Globulin (IVIG) administration, and fecal transplantation have been attempted with variable success (3). Many hospitals are emphasizing infection control measures and antimicrobial stewardship to mitigate disease burden (4). The administration of probiotics with antibiotics has also been studied as a preventive intervention against AAD and CDI.

Randomized controlled trials (RCTs) assessing probiotics for the prevention of AAD and CDI have been marred by low case volumes. Existing systematic reviews and meta-analyses (5-9) have grouped disparate populations such as inpatients with outpatients or adults with children, and have considered clinically distinct entities as combined outcomes such as prevention and treatment or AAD and CDI.

Given the high morbidity of AAD and CDI among inpatients, we conducted a systematic review and meta-analysis to evaluate the efficacy of probiotics administered with antibiotics in reducing these outcomes. AAD and CDI were examined as separate outcomes and we limited our review to adult inpatients, because hospitalization is a potent risk factor for CDI colonization (10).

Methods

Data Sources and Searches

This review is reported according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (11). Systematic searches of MEDLINE (1946 – May 2012), EMBASE (1980 – May 2012) and Cochrane Central Register of Controlled Trials (CCTR) were undertaken to identify relevant publications on May 31, 2012. We employed a sensitive search strategy (Appendix 1) using broad keywords to identify the condition of interest (clostridium difficile, antibiotic-associated diarrhea, and phrase variants) as well as the intervention of interest (“probiotics” and specific probiotic genera). A manual search of the reference lists of identified manuscripts was also performed in order to identify and retrieve relevant research studies.

Study Selection

One extractor screened all abstracts for relevance to the topic. Among relevant articles, two independent reviewers screened abstracts for possible inclusion. We included randomized controlled trials (RCTs) published in the English language of adult inpatients (hospitalized patients admitted to medical, surgical, or acute care of the elderly wards) receiving antibiotics who were randomized to the co-administration of probiotics or to usual care, with or without the use of placebo. To be included in the review, the study must have reported either AAD or CDI prevention as outcomes. AAD and CDI were defined as the number of patients who developed diarrhea and C. difficile positivity by toxin assay or stool culture, respectively, while on antibiotics, divided by the number of patients with available endpoints. We contacted primary authors to obtain original data for our quantitative analysis if the necessary data were not reported in an included publication. If the authors could not provide it, their studies were included in the systematic review but excluded from meta-analysis. We excluded studies of probiotics to prevent CDI recurrence in patients previously diagnosed with CDI. We further excluded trials in which antibiotics were used for Helicobacter pylori eradication, as this represents a distinct clinical endpoint of treatment augmentation and is a condition for which management occurs almost exclusively in the outpatient setting. We excluded studies that were pilot trials of feasibility or tolerability because these studies did not define AAD or CDI incidence as outcomes of interest. We also excluded studies presented only at conferences, studies of before-after comparison, as well as non-randomized comparison and cohort studies. Letters, commentaries, reviews, and editorials were excluded if they did not contain original data.

Data Extraction and Assessment of Risk of Bias

The included manuscripts received a full-text review by two reviewers. Risk of bias among included studies was assessed on the basis of the US Preventative Services Task Force (USPSTF) recommendations which includes domains of randomization, blinding, comparable groups, adequate follow-up (>80%), clear interventions and outcomes, intention to treat analysis, and adequate study power (12). A data extraction form was used to record the findings from each trial. Studies were given a rating of good, fair or poor by two reviewers based on a predetermined global quality rating scale combining the aforementioned criteria (Appendix 2). Disagreement on quality rating was resolved by a third reviewer.

Data Synthesis

Meta-analytic software (RevMan 5.0 from the Cochrane Collaboration) was used to synthesize the results. Relative risk (RR), risk difference (RD) and number needed to treat to benefit or to harm (NNTB/H), with their respective 95% confidence intervals (CI) were calculated using the Der-Simonian Laird method. Mantel Haenszel method was used to determine the weighting of the studies in the meta-analyses because rare events were being assessed. We expected clinical and statistical heterogeneity among the studies. Thus, we used the random effect model for meta-analyses because it accounts for random variability both within studies and among studies. Subgroup analyses were planned a priori to assess the effect on results of study quality (good vs. fair vs. poor), type of probiotic (Lactobacillus-based vs. Saccharomyces boulardii-based), and follow-up duration ( < 4 weeks or  4 weeks). No adjustments were made for multiple analyses. *Post-hoc* meta-regression was performed to identify independent effects of type of probiotics.

Heterogeneity and publication bias assessment

Clinical heterogeneity was assessed for population characteristics, type of probiotic supplementation, and quality of studies. Statistical heterogeneity was assessed using Cochrane Q test and by calculating I-squared (I2) values. A funnel plot was created to assess for the possibility of publication bias.

Source of Funding and Ethics Approval

No external funding was received for this review. Data are available in published articles, thus no ethics approval was necessary.

Results

Sixteen studies (13-28) were included. Details of the selection process are shown in Figure 1. Baseline characteristics of these studies are reported in Table 1. Only five studies were multi-center (14, 16-18, 27) and the majority of studies were conducted in the United States or the United Kingdom. Among all of the trials, the range of mean ages among patients randomized to probiotic was 33 – 79.9 years and to placebo was 33 – 78.5 years. Male patients comprised 43 – 89% of participants in the probiotics groups and 40 – 94.9% in the placebo groups; however, the upper limits for enrolled males were influenced by one study (25). The majority of studies included fewer than 75% males.

All but one of the sixteen studies (19) examined AAD as a primary outcome. Only one trial (18) assessed two endpoints of AAD with different definitions, and in that case, the definition that most closely approximated the outcome definitions in other studies was used for meta-analysis. One study (13) examined a dose-response relationship using a Lactobacillus acidophilus and Lactobacillus casei co-formulation. Patients were randomized to a high-dose probiotic group, a low-dose probiotic group, or a placebo group. For the purpose of this meta-analysis, data from the low dose and placebo groups were used, since this comparison most closely approximated the dosing regimens of the other included RCTs. Ten studies (13-15, 17-20, 23, 24, 28) used a Lactobacillus-based probiotic, five studies (16, 21, 22, 25, 26) evaluated Saccharomyces boulardii, and one study (27) assessed Enterococcus species. Thirteen studies (13-17, 19-22, 24-26) sought to evaluate CDI as an outcome, with one having CDI as the primary endpoint (19). Of the thirteen studies evaluating CDI, four were initially excluded. Two of these studies (21, 24) did not report CDI event rates because there was insufficient data to detect a difference. An additional two studies (16, 20) did not identify CDI cases according to their original study protocols. Primary authors of these studies were contacted, but only one publication’s original data could be obtained to generate outcome information that was comparable to the other included studies (24). Therefore all four studies were included in the systematic review and only the one study for which original data were acquired (24) was ultimately added in the meta-analysis.

Meta-analysis of included studies demonstrated statistically significant reduction in the risk of AAD (RR 0.61, 95% CI 0.47, 0.79; I2=44%; RD -0.09, 95% CI -0.13, -0.05; NNTB 11, 95% CI 8, 20). For CDI, there was a large drop-off in the number of patients with available endpoints. The event rates were 18 [3.1%] of 574 patients in the intervention arm and 55 [10.3%] of 533 patients in the placebo arm (RR 0.37, 95% CI 0.22, 0.62; I2=0%; RD -0.07, 95% CI -0.12, -0.02; NNTB 14, 95% CI 8, 50). The forest plot displaying the effect size by trial as well as the aggregate effect size is shown in Figure 2. It should be noted that due to small sample sizes and the rarity of outcomes, several of the studies have confidence intervals that cross unity. Studies were heterogeneous in sample size and the funnel plot (Figure 3) demonstrates a moderate degree of publication bias.

The quality rating of all of the studies is provided in Table 2. The results of subgroup analyses by study quality, probiotic type, and follow-up duration are reported in Table 3.

When stratified by study quality, the four good quality studies (13-16) demonstrated reduction in AAD and CDI with the use of probiotics. They shared features that led to their high rating: clear inclusion criteria, interventions, and outcomes. These studies used validated scales or precise qualitative explanations to define the outcome measures and had reasonable long-term follow-up between 3 to 7 weeks. The fair quality studies (17-21), when pooled, demonstrated reduction in AAD and CDI that was not significant. These studies received a lower quality rating because of a lack of clarity or validity in their outcomes measures, with the use of very liberal, subjective criteria for AAD and CDI that may have resulted in over-reporting. Specifically for CDI, two of the studies (19, 21) tested for C. difficile toxin on formed stool, which may have led to the inclusion of cases of C. difficile colonization as opposed to the clinically relevant outcome of C. difficile infection. All but one (22) of the seven poor quality studies (22-28) showed statistically significant RR in AAD with the use of probiotics. Four of the poor quality trials (22, 24-26) assessed CDI as a secondary outcome, and none of them demonstrated significant risk reduction. In general, these poor quality studies were limited by unclear interventions and outcomes. These studies lacked formal reporting of key study methods, such as randomization process, blinding methods, and duration of the intervention or follow-up.

When studies were pooled by type of probiotic, reductions in AAD and CDI were observed regardless of whether a primarily Lactobacillus-based probiotic or an S. boulardii-based formulation was used. However, only the combined analysis of Lactobacillus-based formulations resulted in a reduction that was statistically significant. The similarity in effect size between both groups has some biologic plausibility, given that probiotic utility is thought to derive its benefit, at least in part, from re-colonizing the gastrointestinal tract with “normal”, non-pathogenic flora, rather than from species-specific effects.

The literature suggests that AAD and CDI can occur after just one dose of antibiotics and up to several weeks after completion of therapy (29). As such, an adequate follow-up period is needed to ensure that most cases are appropriately identified. Our subgroup analysis by follow-up period was dichotomized to before or after 4 weeks, because this time frame reflects a practical and clinically applicable cutoff for ongoing patient surveillance. While the effect size observed was more robust with longer follow-up, only reduction in AAD, and not CDI, remained significant. Statistical heterogeneity was moderately increased for the subgroup of patients that had follow-up ≥ 4 weeks, I2 of 54% for AAD and 57% for CDI.

Post-hoc meta-regression analysis by type of probiotic confirmed the findings of subgroup analysis. Specifically, the primarily Lactobacillus-based formulation remained significantly effective in reducing AAD. Due to wide variability in duration of follow-up, we were unable to perform meta-regression of duration of follow-up as a continuous measure.

No life-threatening adverse probiotic effects were reported in these RCTs. Despite case reports of toxicity among patients with extenuating circumstances (30-32), probiotics had an excellent safety profile; the most common side effect was gastrointestinal upset.

Discussion

Probiotics can confer health benefits in several ways: by creating nutrient competition, altering gut flora favorably, serving as a barrier against pathogen-receptor binding, elaborating immunomodulators (such as IgA) or trophic factors, and reducing osmotic diarrhea (33). With recent epidemiologic patterns showing a rise in AAD and CDI occurrence among healthier, previously spared populations, as well as among patients most vulnerable to its complications (34-36), there is an urgent need to find innovative solutions for prevention.

Our findings indicate that probiotics given concurrently with antibiotics reduce the risk of AAD and CDI. The results of our meta-analysis are concordant with several prior systematic reviews and meta-analyses (5-9), which have varied in the patients assessed and outcomes defined. A recent meta-analysis by Hempel et al (8) assessed probiotics in both the prevention and treatment of AAD and reported benefit. This study included 82 trials of significant heterogeneity; in addition to examining both prevention and treatment trials, they assessed trials of both inpatients and outpatients, evaluated all age groups, and included 24 trials in which patients were receiving antibiotics for H. pylori eradication.

One of the strengths of this review is the emphasis placed on ensuring that comparable outcome definitions were used in meta-analyzing the data. This was achieved by carefully selecting the study arms to include for trials that had more than two intervention groups, and by contacting primary authors for original data when needed. These actions will mitigate some of the impact of the clinical heterogeneity observed between the trials. Another major strength is that the review focused on a specific patient population: inpatients. Reducing the incidence of CDI will improve individual patient outcomes while curtailing spread in the high-risk setting of hospitals. Thus these results have implications for the health of other, non-infected inpatients. Finally, this meta-analysis shows that benefit is retained regardless of study quality, type of probiotic used, and follow-up duration. However, the results are only significant for both AAD and CDI concurrently for the subgroups of good quality studies, studies assessing Lactobacillus-based formulations, and studies in which the follow-up was < 4 weeks.

Several limitations in the individual studies and in our meta-analysis merit discussion. A notable limitation among some of the more recent studies is the high baseline rates of AAD and CDI observed in the placebo arms. Three of the recent, good quality RCTs (13-15) reported AAD rates of 34 – 44% and CDI rates at 16 – 24% in the control groups. These high baseline event rates may have facilitated the detection of a significant effect size despite a small sample size. The extent to which this may have been influenced by different local practices in antimicrobial stewardship and environmental infection control is unknown, and thus their effect sizes may not be duplicated in other settings where baseline rates of AAD and CDI are lower.

The included trials shared certain methodological issues that also limit broad interpretation of the results. Some of the studies had lower enrolment than planned for detecting the expected differences, a factor of particular importance for the negative trials (20, 21). Almost all of the studies that we assessed excluded patients that might otherwise be considered candidates for a hospital-wide intervention like probiotics. For example, patients who had received a course of antibiotics as an outpatient in the weeks preceding trial enrolment were excluded to avoid inclusion of cases of community-associated CDI. Furthermore, patients with preexisting gastrointestinal pathology were excluded to avoid inclusion of patients suffering from diarrhea not related to antibiotics. These steps may limit the interpretation of how probiotics will affect a more inclusive inpatient population. Two of the fair quality studies (18, 21) reported possible probiotic under-dosing. A high rate of attrition > 20%, was observed in four studies (22-24, 26), necessitating a poor quality rating.

Our meta-analysis also suffers from some important limitations. There was evidence of moderate publication bias as demonstrated in Figure 3. Three trials were excluded because they were not in English (37-39). Furthermore, among all of the patients assessed for AAD, 1200 patients did not have endpoints for CDI.

We chose to convey outcome information using RDs and NNTs. We acknowledge the limitation of utilizing NNTs to convey outcome information given the clinical and statistical heterogeneity among the studies included in this review. Admittedly, NNT is difficult to interpret when such heterogeneity exists, and so we caution readers and decision-makers against using this information without putting it in the context of the variability of the studies and considering the local prevalence of CDI in their population.

Conclusions

Our findings illuminate the benefits of probiotics in preventing both AAD and CDI among the specific patient population of inpatient adults requiring antibiotics. On the basis of the current review, probiotics are recommendable in such patients in the absence of contraindications; however, prevalence of AAD and CDI should be taken into consideration before making guidelines. The literature does not clearly indicate a favored choice of probiotic, although there is stronger evidence for Lactobacillus-based formulations.

Many health care providers have been hesitant to adopt probiotics in routine practice despite impressive effect sizes. This may be because of the small sample sizes in the individual trials, high baseline rates of AAD and CDI in the larger, more recent trials, the clinical and statistical heterogeneity between trials, and the publication bias seen in this and other meta-analyses. While there may be a signal towards clinical equipoise, future RCTs should strive to recruit more patients and strengthen power in order to help bring probiotics to the bedside. Other research that will add to our current knowledge might address whether there is greater benefit with the use of combination therapy over single-species probiotic formulations. The hypothesis of a dose-response effect requires further validation.

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Potentially relevant citations identified in literature search:

MEDLINE n = 573

EMBASE n = 1185

CCTR n = 253

Total n = 2011

Abstracts assessed by two reviewers:

n = 257

Duplicates excluded: n = 131;

Articles excluded on basis of abstract by single reviewer because not relevant to the question: n = 1623

Excluded, not English: n = 3;

Excluded, not RCT: n = 9;

Excluded, pediatrics: n = 182;

Excluded, outpatient: n = 7;

Excluded, HPylori study: n = 13

Excluded, treatment not prevention study: n = 17;

Excluded, pilot trial or tolerability study: n = 3; Excluded, conference abstract: n = 2;

Excluded for multiple concurrent reasons: n = 5;

Total: n = 241

Included articles

n = 16

Figure 1: Flow diagram of study selection process



Figure 2: Meta-analysis of all randomized controlled trials demonstrating effect of probiotics on (a) AAD and (b) CDI

(b) CDI

(a) AAD



|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Source** | **Characteristics of Study Population** | **Probiotic Agent & Duration** | **Additional Follow-Up** | **Primary & Secondary Outcome** | **N randomized**  **Total (Probiotic, Placebo)** | **N analyzed**  **Total (Probiotic, Placebo)** | **Attrition Primary Outcome**  **(%)** |
| **GOOD QUALITY** | | | | | | | |
| Gao et al, 2010 | Adult inpatients  Mean age: 60 yrs (both groups),  Gender: 51% vs. 50% male (probiotic vs. placebo)  Single centre, China | Lb-A, Lb-C within 36 hr to 5 d post-antibiotics | 21 d | AAD  CDI | 255 (high 86 / low 85, 84) | AAD: 255 (high 86 / low 85, 84)  CDI: 255 (high 86 / low 85, 84) | 0 |
| Hickson et al, 2007 | Adult inpatients on orthopedic, medical, and care of the elderly wards  Mean age: 73.7 vs 73.9 yrs (probiotic vs. placebo)  Gender: 43% vs. 48% male (probiotic vs. placebo)  Three hospitals, United Kingdom | Lb-C, ST, LB-B within 48 hr to 7 d post-antibiotics | 28 d | AAD  CDI | 135 (69, 66) | AAD: 113 (57, 56)  CDI: 109 (56, 53) | 16 |
| Beausoleil et al, 2007 | Adult inpatients  Mean age: 68.8 vs 72.9 yrs (probiotic vs. placebo)  Gender: 45.5% vs. 51.1% male (probiotic vs. placebo)  Single tertiary care center, Canada | Lb-A, Lb-C within 48 hr for duration of antibiotics | 21 d | AAD  CDI | 89 (44, 45) | AAD: 89 (44, 45)  CDI: 89 (44, 45) | 0 |
| McFarland et al, 1995 | Adult inpatients receiving at least 1 -lactam antibiotic  Mean age: 40.7 vs. 42.3 yrs (probiotic vs. placebo)  Gender: 63.9% vs 65.6% male (probiotic vs. placebo)  Four centers, United States | SB within 72 hr to 3 days post-antibiotics | 31-46 d | AAD  CDI \* | 193 (97, 96) | AAD: 193 (97, 96)  CDI: 24 (10, 14) | 0 |
| **FAIR QUALITY** | | | | | | | |
| Psaradellis et al, 2010 | Adult inpatients in emergency dept. or ward  Mean age: 59.5 vs. 58.1 yrs (probiotic vs. placebo)  Gender: 54.2% vs. 48.4% (probiotic vs. placebo)  Eight centers, Canada | Lb-A, Lb-C within 24 hr to 5 days post-antibiotics | 21 d | AAD  CDI | 472 (233, 239) | AAD: 437 (216, 221)  CDI: 46 (16, 30) | 8 |
| Song et al, 2010 | Adult inpatients  Mean age: 61 vs. 60 yrs (probiotic vs. placebo)  Gender: 61.2% vs. 62.2% male (probiotic vs. placebo)  Ten tertiary hospitals, Korea | Lb-A, Lb-R within 48 hr for 14 d | 14 d | AAD-1  AAD-2 | 214 (103, 111) | AAD-1: 214 (103, 111)  AAD-2: 214 (103, 111) | 0 |
| Plummer et al, 2004 | Adult inpatients on medical, and care of the elderly wards  Baseline characteristics not provided (mean age, gender, etc.)  Single centre, United Kingdom | Lb-A, BB within 36 hr for 20 d | 0 d | CDI | 138 (69, 69) | CDI: 138 (69, 69) | 0 |
| Thomas et al, 2001 | Adult inpatients on a medical ward  Mean age: 57.2 vs. 54.4 yrs (probiotic vs. placebo)  Gender: 51.1% vs. 56.0% (probiotic vs. placebo)  Single centre, United States | Lb-R within 24 hr for 14 d |  7 d | AAD  CDI \* | 302 (152, 150) | AAD: 267 (133, 134)  CDI: 267 (133, 134) | 12 |
| Lewis et al, 1998 | Adult inpatients on a medical ward  Mean age: 75 vs. 77 yrs (probiotic vs. placebo)  Baseline gender characteristics not provided  Single centre, United Kingdom | SB within 24 hr for duration of antibiotics | Treatment Duration | AAD  CDI \* | 72 (not indicated) | AAD: 69 (33, 36)  CDI: 69 (33, 36) | 4 |
| **POOR QUALITY** | | | | | | | |
| Pozzoni et al, 2012 | Adult inpatients  Mean age: 79.9 vs. 78.5 yrs (probiotic vs. placebo)  Gender: 49.6% vs. 50.0% (probiotic vs. placebo)  Single centre, Italy | SB within 48 hr for 7 days post-antibiotics | 84 d | AAD  CDI | 275 (141, 134) | AAD: 204 (106, 98)  CDI: 204 (106, 98) | 26 |
| Cimperman et al, 2011 | Adult inpatients on medical wards  Mean age: 42.8 vs. 63.6 yrs (probiotic vs. placebo)  Gender: 54% vs. 40% male (probiotic vs. placebo)  Single centre, United States | Lb-Reut within 96 hr for 28 d | Treatment Duration | AAD | 31 (15, 16) | 23 (13, 10) | 26 |
| Wenus et al, 2008 | Adult inpatients  Mean age: 58.8 vs. 56.2 yrs (probiotic vs. placebo)  Gender: 65.2% vs. 51.2% male (probiotic vs. placebo)  Single centre, Norway | Lb-R, BB-12, Lb-A within 72 hr for 14 d | Treatment Duration | AAD  CDI | 87 (46, 41) | AAD: 63 (34, 29)  CDI: 55 (Not Reported) | 28 |
| Can et al, 2006 | Adult inpatients receiving chemotherapy  Mean age not provided, range: 25-50 yrs (both groups)  Gender: 89.0% vs. 94.9% male (probiotic vs. placebo)  Single centre, Turkey | SB within 48 hr, duration not noted | 28 d | AAD  CDI | 151 (73, 78) | AAD: 151 (73, 78)  CDI: 151 (73, 78) | 0 |
| Surawicz et al, 1989 | Adult inpatients  Mean age: 48.8 vs. 45.4 yrs (probiotic vs. placebo)  Gender: 66% vs. 73% male (probiotic vs. placebo)  Single centre, United States | SB within 48 hr to 14 days post-antibiotics | Treatment Duration | AAD  CDI | 318 (Not Reported) | AAD: 180 (116, 64)  CDI: 138 (91, 47) | 43 |
| Wunderlich et al, 1989 | Adult inpatients  Mean age: 33 yrs overall  Gender: 48% male overall  Five centres, Switzerland | Enterococcus SF 68 for 7 d | Treatment Duration | AAD | 45 (23, 22) | 45 (23, 22) | 0 |
| Gotz et al, 1979 | Adult inpatients on medical wards receiving Ampicillin  Mean age: 64 vs. 65 yrs (probiotic vs. placebo)  Gender: 36.1% vs. 51.2% male (probiotic vs. placebo)  Single centre, United States | Lb-A, Lb-B within 24 hr for 5 d | Treatment Duration | AAD | 98 (48, 50) | AAD: 79 (36, 43) | 19 |

Table 1: Source Table

Lb-A Lactobacillus Acidophilus, Lb-B Lactobacillus Bulgaricus, Lb-R Lactobacillus Rhamnosus, Lb-Reut Lactobacillus Reuteri Lb-C Lactobacilus Casei, BB Bifidobacterium Bifidum, Bifidobacterium Bifidum 12 BB-12, ST Streptococcus Thermophilus, SB S Boulardii; AAD-1 loose or watery stools more than 3 times per day for at least 2 days within 14 days of enrolment, AAD-2 more than 2 times per day over same period; NR Not reported

\* Not included in Meta-analysis

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **RCT** | **Randomized** | **Blinded** | **Comparable Groups (Start and End)** | **F/u > 80%** | **Clear Interventions** | **Clear, relevant Outcomes** | **Valid, reliable, equal measures used** | **Intention to Treat Analysis** | **Confounders noted** | **Power calculation reported and appropriate** |
| **GOOD QUALITY** | | | | | | | | | | |
| Gao et al, 2010 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Hickson et al, 2007 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Beausoleil et al, 2007 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| McFarland et al, 1995 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| **FAIR QUALITY** | | | | | | | | | | |
| Psaradellis et al, 2010 | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | No |
| Song et al, 2010 | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes |
| Plummer et al, 2004 | Yes | Yes | Not Reported | Yes | Yes | Yes | Yes | Yes | No | No |
| Thomas et al, 2001 | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | No |
| Lewis et al, 1998 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | No |
| **POOR QUALITY** | | | | | | | | | | |
| Pozzoni et al, 2012 | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | No |
| Cimperman et al, 2011 | Yes | Yes | No | No | Yes | Yes | Yes | No | No | No |
| Wenus et al, 2008 | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes |
| Can et al, 2006 | Yes | Yes | Not Reported | Yes | Yes | Yes | No | Yes | No | No |
| Surawicz et al, 1989 | Yes | Yes | Yes | No | Yes | Yes | Yes | No | Yes | Yes |
| Wunderlich et al, 1989 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No |
| Gotz et al, 1979 | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | No |

Table 2: Risk of bias among included studies

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Subgroup** | | **# of Studies** | **Probiotic**  **(N events, N analyzed)** | **Placebo**  **(N events, N analyzed)** | **RR (95% CI)** | **RD (95% CI)** | **I2 (%)** |
|  | |  |  |  |  |  |  |
| **AAD** | |  |  |  |  |  |  |
| **All studies** | | **15** | **178, 1169** | **266, 1127** | **0.61 (0.47, 0.79)** | **-0.09, (-0.13, -0.05)** | **44** |
| Study Quality | Good | 4 | 45, 283 | 86, 281 | 0.54 (0.39, 0.73) | -0.14 (-0.21, -0.06) | 0 |
|  | Fair | 4 | 97, 485 | 118, 502 | 0.85 (0.67, 1.08) | -0.03 (-0.08, 0.01) | 3 |
|  | Poor | 7 | 36, 401 | 62, 344 | 0.42 (0.23, 0.76) | -0.11 (-0.18, -0.04) | 42 |
| Probiotic Type\* | Lactobacillus | 9 | 134, 721 | 207, 733 | 0.64 (0.48, 0.84) | -0.11 (-0.17, -0.04) | 35 |
|  | S Boulardii | 5 | 42, 425 | 53, 372 | 0.68 (0.37, 1.24) | -0.05 (-0.11, 0.00) | 53 |
| Follow-Up | < 4 weeks | 10 | 146, 823 | 208, 789 | 0.57 (0.41, 0.79) | -0.09 (-0.14, -0.04) | 29 |
|  | ≥ 4 weeks | 5 | 32, 346 | 58, 338 | 0.47 (0.23, 0.94) | -0.09 (-0.18, -0.01) | 54 |
|  |  |  |  |  |  |  |  |
| **CDI** | |  |  |  |  |  |  |
| **All studies** | | **9** | **18, 574** | **55, 533** | **0.37 (0.22, 0.62)** | **-0.07 (-0.12, -0.02)** | **0** |
| Study Quality | Good | 3 | 9, 185 | 36, 182 | 0.24 (0.08, 0.73) | -0.15 (-0.21, -0.09) | 29 |
|  | Fair | 2 | 3, 85 | 9, 99 | 0.42 (0.12, 1.52) | -0.05 (-0.11, 0.02) | 0 |
|  | Poor | 4 | 6, 304 | 10, 252 | 0.47 (0.18,1.24) | -0.02 (-0.05, 0.01) | 0 |
| Probiotic Type | Lactobacillus | 6 | 12, 304 | 46, 310 | 0.33 (0.18, 0.60) | -0.09 (-0.15, -0.04) | 0 |
|  | S Boulardii | 3 | 6, 270 | 9, 223 | 0.49 (0.17, 1.40) | -0.02 (-0.06, 0.02) | 2 |
| Follow-Up | < 4 weeks | 6 | 15, 339 | 42, 304 | 0.35 (0.20, 0.62) | -0.07 (-0.11, -0.03) | 0 |
|  | ≥ 4 weeks | 3 | 3, 235 | 13, 229 | 0.31 (0.03, 2.77) | -0.05 (-0.13, 0.03) | 57 |

Table 3: Subgroup Analyses