**Name of journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO: 10210**

**Columns:** **REVIEW**

**Probiotics for antibiotic-associated diarrhea: Do we have a verdict?**

Issa I *et al*. Probiotics in the prevention of antibiotic associated diarrhea

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**Received:** March 19, 2014 **Revised:** May 16, 2014

**Accepted:** July 24, 2014

**Published online:**

**Abstract**

Probiotics use has tremendously increased over the past ten years. This was coupled with a surge of data relating their importance in clinical practice. Antibiotic-associated diarrhea, whose frequency has risen recently, was one of the earliest targets with data published more than ten years ago. Unfortunately, available trials suffer from severe discrepancies associated with variability and heterogeneity of several factors. Most published randomized controlled trials and subsequent meta-analysis suggest benefit for probiotics in the prevention of antibiotic-associated diarrhea. The same seems to also apply when the data is examined for *Clostridium difficile*-associated colitis. However, the largest randomized double-blind placebo controlled trial to date examining the use of a certain preparation of probiotics in antibiotic-associated diarrhea showed disappointing results, but it was flawed with several drawbacks. The commonest species of probiotics studied across most trials is Lactobacillus; however, other types have also shown similar benefit. Probiotics have enjoyed an impeccable safety reputation. Despite few reports of severe infections sometimes leading to septicemia, most of the available trials confirm their harmless behavior and show similar adverse events compared to placebo. Since a consensus dictating its use is still lacking, it would be advisable at this point to suggest prophylactic use of probiotics to certain patients at risk for antibiotic-associated diarrhea or to those who suffered previous episodes.

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**Key words:** Probiotics; Antibiotic-associated diarrhea; *Clostridium difficile*; Prevention; Lactobacillus; *Bifidobacterium*

**Core tip:** Probiotics use has been steadily increasing over the past ten years. One of the areas thoroughly examined includes prevention of antibiotic-associated diarrhea. Nonetheless, although trials are abundant, they are often confusing and conflicting. Adding insult to injury is the publication of the largest randomized controlled trial showing no benefit in prevention of antibiotic-associated diarrhea. We attempted to summarize, categorize and study the present literature detailing the important trials and their drawbacks in an attempt to come up with a reasonable consensus for their use.

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*World J Gastroenterol* 2014; In press

**INTRODUCTION**

Antibiotics use has been increasing steadily over the past decade; they are currently among the most prescribed medications worldwide. Their use elicits additional disturbances in the gut flora resulting in a multitude of symptoms on the clinical level. This ranges from mild diarrhea to electrolyte imbalance, sepsis, admission to the intensive care unit or even death[1]. Antibiotic-associated diarrhea (AAD) is referred to as unexplained diarrhea that occurs in association with antibiotic administration[2]. Its incidence has been noted to slowly increase over the past few years, reaching up to 30% in some instances[3,4]. Symptoms can vary from mild self-limited disease to the more serious and severe *Clostridium difficile*-associated diarrhea (CDAD). This issue may act as an important factor behind the non-adherence to antibiotic regimens[5]. Luckily, CDAD is only responsible for an estimated 10%-20% of cases of AAD[6]. Multiple risk factors for CDAD have been delineated, such as advanced age, hospitalization, acid suppression, chemotherapy, renal failure, gastrointestinal surgery and mechanical ventilation[3,7,8]. Reports from the United States have suggested a nearly 2-fold increase in mortality rate attributable to *Clostridium difficile* infect (CDI) diarrhea[9]. Another recent report from Canada has shown that regardless of the baseline above-mentioned risk factors, one out of every 10 patients who acquire C. diff will die[10].

Probiotics were first reported more than 100 years ago and they were defined as “live microorganisms which when administered in adequate amounts confer a health benefit on the host”[11]. They have been thought to restore the disturbed gut flora through a multitude of mechanisms. They help reduce colonization of pathogenic organisms by competitively inhibiting their adhesion on the mucosa surface[12]. They have also been shown to secrete acids to decrease intraluminal PH, thus inhibiting the growth of several pathogens including enterohemorrhagic *Escherichia coli*[13,14]. They may also produce direct acting antimicrobial molecules[14]. Another proposed mechanism of action includes their immunomodulatory effect, which may diminish the inflammation caused by certain strains of bacteria[15]. Probiotics have become widely available in the market ranging from capsules to dairy food supplements stored in health stores and supermarkets. Their appeal lies in their availability and ease of intake as well as their low cost and low incidence of associated adverse events[16]. We conducted a literature review to assess the efficacy and safety of the use of probiotics in AAD in the adult population, and attempted to come up with a reasonable consensus for their use.

**PROBIOTICS FOR THE PREVENTION OF AAD**

The effectiveness for the use of probiotics in the prevention of AAD has been thoroughly examined in the past few years[17-28] (Table 1). Nonetheless, drawing conclusions from these publications has proven difficult secondary to a multitude of flaws, such as small numbers of patients, selection bias, vast heterogeneity in study populations, different probiotic types or dosage and sometime different end-points. Initially, several good quality randomized controlled trials (RCT) with similar end-points showed a positive outcome on several variables including nausea, abdominal pain and diarrhea[29-32]. Two important meta-analysis were published in 2006, the first one included 25 RCTs and the second evaluated 16[33,34]. They both suggested that probiotics use was associated with a reduced risk of AAD. More recently, two large meta-analysis were released; the first by Videlock and Cremonini in 2012 included studies with concurrent administration of probiotics and antibiotics[35]. They analyzed 34 trials after exclusion and upon a random effects model they found a relative risk (RR) of AAD of 0.53 (95%CI: 0.44-0.63) when compared to placebo, their average number needed to treat (NNT) turned out to be eight (95%CI: 7-11). Hempel and colleagues performed the second one the same year, this review included RCTs that evaluated probiotics as adjuncts to antibiotics use[36]. Eighty-two trials met their inclusion criteria, of which 63 reported the number of patients with diarrhea, totaling 11811 participants. The RR to develop diarrhea compared with a control group was 0.58 (95%CI: 0.50-0.68). They also concluded a beneficial treatment with a NNT of 13. However, it is important to note that in this analysis RCTs were included only if probiotics were used to enhance the effect of antibiotics and therefore occurrence of diarrhea was not their primary end-point. A subgroup analysis involving only trials explicitly aiming to prevent or treat AAD showed similar results with an RR of 0.58 (95%CI: 0.49-0.68). Nonetheless, despite the fact that both these studies agreed there was sufficient evidence to support a preventive effect of probiotics supplementation on the incidence of AAD, they both suffered several limitations: lack of assessment of specific side effects, poor documentation of strains and of course large heterogeneity between the trials compared. A meta-analysis published few months ago aimed at drawing a better conclusion; they evaluated the efficacy of probiotics administered with antibiotics in reducing negatives outcomes[37]. They only included adult in-patients and excluded trials in which antibiotics were used for eradication of *Helicobacter pylori* as they were considered to represent a distinct clinical endpoint. They also discarded trials that were pilot of feasibility or tolerability because they did not define AAD incidence as an outcome, in addition to non-randomized comparisons or cohort studies. Due to their rigorous and strict inclusion criteria, they ended up with only 16 studies, all of which (except one) examined AAD as a primary outcome. Their meta-analysis demonstrated a statistically significant reduction in the risk of AAD with a RR of 0.61 (95%CI: 0.47-0.79), the NNT benefit was in the range of 11 (95%CI: 8-20). Their conclusion was favorable for probiotics in preventing AAD in the specific population of adult in-patients requiring antibiotics. The strength of their analysis was their policy of exclusive inclusion of trials with comparable outcome definition. Another was the focus on a specific target population thus decreasing heterogeneity between different publications. However, one significant limitation hindering most recent papers analyzing this issue is the surprising elevated rate of AAD found. In fact, three of the most recent RCTs reported rates as high as 34%-44%[38-40]. These high baseline event rates may have facilitated the detection of trends and significant outcomes despite small sample sizes. In general, most published papers agree to the benefit of probiotics in the context of AAD, however the largest RCT to date involving probiotics in the prevention of AAD failed to duplicate this result[41]. It is a multicenter randomized, double blind, placebo-controlled trial conducted by Allen and colleagues involving patients 65 years of age or older and exposed to at least one dose of antibiotics. They were randomized to either receive a preparation of Lactobacilli and bifidobacteria totaling 6 × 1010 organisms, once per day for 3 wk or a placebo. Their primary outcome was assessment of the occurrence of AAD within 8 wk. They screened more than 17000 patients of which 1493 were assigned to the probiotics arm *vs* 1488 to the placebo group. Their results showed no difference in the occurrence of AAD between the two groups with an RR of 1.04 (95%CI: 0.84-1.28). Their conclusion stated that this multi-strain preparation showed no benefit in preventing AAD in this specific population. Although the methodology of this trial appears impeccable and the authors even tested the viability of their preparation before the intervention (often missed in other trials), it still displays several limitations. The first one being their low recruitment rate, which was less than one per five patients screened, the main reason being refusal to add an additional medication to their already large repertoire. Additionally, ethnic diversity in the study population was not ensured and this limits the generalizability of the conclusion already narrowed by the age group selection. Third, the rate of AAD occurring in both the probiotic and the placebo groups (10.8% and 10.4% respectively) is quite low compared to all the recent data. This is consistent with the diminishing trend in England[42] and Wales[43] but not with the rest of the world. Most importantly, their calculated sample size, which amounted to around 3000, was based on their assumption that the placebo group will have an AAD incidence of 20% and CDAD of 4%. However, their actual incidence rates turned out to be much lower than that, this obviously under-powers their end-result. All of the above arguments and drawbacks invite us to suspect bias and question the conclusion of this publication.

**PROBIOTICS FOR THE PREVENTION OF CDAD:**

*Clostridium difficile*-associated diarrhea (CDAD) is considered a severe form of AAD, it usually affects 10%-20% of cases but some more recent studies have suggested that the actual figure may be closer to 30%[44,45]. CDI is a gram positive, spore-forming rod that was first described in 1935 in newborn infants[46]. Exposure to antibiotics constitutes a definite risk factor for CDAD but also for asymptomatic CDI carriage[47]. Additionally, cumulative antibiotic exposure increases the risk[48,49]. Of great concern since 2003 has been an increased frequency and severity of CDAD associated with emergence of the hyper virulent 027 strain[50]. Recently, a large retrospective review involving more than 5600 patients reported that quinolone antibiotics have a stronger association with CDAD, whereas other antibiotics posed an intermediate risk[51]. Furthermore, a prospective cohort study involving 101796 admissions over a 5-year period at a tertiary care medical center classified antibiotics as high or low risk with relation to CDAD. They found that commonly used antibiotics like fluoroquinolones, cephalosporins, macrolides, clindamycin and carbapenems were among the high-risk group while all others were considered as low[52]. In addition to the multitude of risk factors for CDAD mentioned earlier, a recent variable has emerged over the past 3-4 years. Acid suppressive therapy has been suggested as an important risk factor for the development of CDAD[53]. According to Tal *et al*[54] an association between proton pump inhibitors (PPI) and CDAD is found with an odds ratio (OR) of 2.1 (95%CI: 1.2-3.5). Moreover, Barletta and colleagues reported in a retrospective case-control study that the probability for CDI was higher when PPI use exceeded 2 d in patients without prior hospital admission and 1 d in patients previously admitted[55]. The literature suggests that CDAD can occur after just one dose of antibiotics and may appear up to several weeks after completion of antibiotic therapy[56]. However, disease may progress despite antibiotic discontinuation and usually requires treatment with metronidazole or vancomycin. Considering that CDAD is a severe form of AAD, it seems imperative and clinically relevant to assess if probiotic can help in prevention.

The 2010 Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for the treatment of CDI do not recommend the use of probiotics for the prevention of CDAD due to lack of evidence and risk of blood stream infection[57]. Since this publication, there has been a multitude of newer studies in the literature examining the use of probiotics in the prevention of CDAD. The PLACIDE trial mentioned earlier also examined patients with CDAD and found the same disappointing results as for AAD. However, the events that occurred were somewhat low; 12 out of 1470 (0.8%) in the probiotic arm and 17 out of 1471 (1.2%) in the placebo group (OR 0.7, 95%CI: 0.34-1.48)[41]. These figures raise a suspicious question since they are lower than most current numbers in the literature. In the subgroup analysis of their manuscript, Hempel et al. identified patients with CDI infection and showed that adjunct probiotic use extended the benefit to this severe section of patients as well with a RR of 0.52 (95%CI: 0.36-0.75)[16]. A large meta-analysis conducted in 2012 by Johnston *et al*[46] focused on probiotics in the prevention of CDAD. After their search and exclusion, they studied 20 RCTs deemed acceptable and included 1974 patients with positive CDI toxin *vs* 1844 placebo participants. They showed a large relative risk reduction in the incidence of CDAD of 66% corresponding to a RR of 0.34 (95%CI: 0.24-0.49). Authors concluded that there is moderate-quality evidence to support a protective effect of probiotics in the development of CDAD. This study failed, however to reach its estimated optimal information size, which may have led to an overestimation of the beneficial role. In the 2013 review published by Pattani *et al*[37], they also assessed the effect of probiotics on the incidence of CDAD. Their analysis was inclusive of 9 RCTs and more than 1000 patients. The event rates were 18 (3.1%) of 572 patients in the intervention arm and 55 (10.4%) of 572 patients in the placebo arm, suggesting a RR of 0.37 (95%CI: 0.22-0.61). Their conclusion was that probiotics had a favorable impact in preventing CDAD in adult in-hospital patients.

**FACTORS CONFOUNDING THE USE OF PROBIOTICS IN AAD**

Several confusing factors hinder our understanding of probiotics and flaw the studies aiming to detect their beneficial effects. Perhaps the most complex one is the type and composition of various probiotics used. Should we use single or multiple strains in our prevention? Are certain strains more beneficial than others are? Johnston *et al*[58] addressed this issue in their review and found that trials using multiple species showed a larger effect (RR 0.25, 95%CI: 0.15-0.41) than those using single strain (RR 0.5, 95%CI: 0.29-0.84) in preventing CDAD. The test for interaction suggested a low likelihood that chance alone explains such a difference (*P* = 0.06). They commented that the hypothesis is sufficiently credible to warrant further assessment through serious future studies[59].

Several strains of probiotics are currently available in the market, ranging from lactobacilli to bifidobacteria, saccharomyces, bacilli and others. When Pattani *et al*[37] pooled their studies by type of probiotic, reduction in AAD and CDAD persisted regardless whether a primarily lactobacillus-based probiotic or an S. boulardii-based formulation was used. The similarity in effect is reasonable and biologically plausible given that the benefit of probiotics is thought to derive (at least partly) from recolonization of the gastrointestinal tract with “normal”, non-pathologic flora rather than from species-specific effect[60]. Hempel *et al*[36] were even more thorough in their analysis of different blends of probiotics genera. They found 17 RCTs with Lactobacillus-based interventions which showed a pooled RR of 0.64 (95%CI: 0.47-0.86) with a number needed to treat for benefit of 14. The 15 yeast-based (saccharomyces) RCTs revealed a pooled RR of 0.48 (95%CI: 0.35-0.65), NNT was 10. The results of three older studies involving Enterococcus faecium was a RR of 0.51 (95%CI: 0.38-0.68) and a NNT of 12. Hence, their analysis of different probiotics strains and types showed benefit across the board regardless of the genus or species.

Another conflicting factor is the age of the targeted population. In the PLACIDE trial, the authors could not find benefit in preventing both AAD and CDAD through their probiotics preparation in their adult 65 years and older patients[41]. They had chosen this particular age group because of their predilection to develop antibiotic-associated diarrhea[2,3]. Hempel *et al*[35] stratified the trials they studied according to age, they found 14 RCTs involving adults (age 18-60 years). The effect was found to be positive with a RR of 0.54 (95%CI: 0.34-0.85). On the other hand, three RCTs included exclusively elderly patients and the pooled results for these trials was a RR of 0.81 (95%CI: 0.40-1.63). These results are in accordance with the PLACIDE trial and suggest that probiotics use maybe beneficial in adults but not necessarily in the older age group. On another level, a further review of the literature shows an additional four RCTs (other than the PLACIDE) involving exclusively patients in the older age group[39,40,61,62]. All of these trials show statistically significant benefit in prevention of AAD by the probiotic group. The largest of these was performed in 2008 by Stockenhuber *et al*[62] and involved 678 patients aged 65 and above. It revealed a significant difference in the incidence of AAD between the placebo and the intervention group (17/340 *vs* 63/338). Compiling all the 5 RCTs together into one meta-analysis results in a large number of patients (4023) and shows a statistically significant difference in favor of the probiotic arm (*Z* = 3.58, *P* = 0.0003)[41]. However, despite limiting the scope of the studies involved, substantial statistical heterogeneity persists (*P* < 0.0001) and undermines any conclusion that can be drawn from it. No logical reasoning can explain this discrepancy; we can theorize that maybe physiological changes occurring with aging make the gastrointestinal tract less susceptible to the effects brought about by the alteration of gut flora.

It is very difficult to draw conclusions from the available data and meta-analysis regarding the duration of treatment. The extent of heterogeneity between different studies precludes any reasonable analysis. This is also similar for the follow up period, as most publications do not precisely dwell on this issue.

**SAFETY OF PROBIOTIC USE**

Probiotics have enjoyed an impeccable reputation regarding safety. In general, little research attention has focused on adverse events in relation to their use in clinical practice[16]. This scarcity in data is partly a result of the Food and Drug Administration not regulating these products. One theoretical concern would be the potential transfer of antibiotic resistance, as many lactobacillus strains are naturally resistant to vancomycin. However, these resistance genes are chromosomal and not readily transferable to other pathogenic organisms[63]. Another theoretical risk would be the transfer of bacteria from the small intestine to other areas of the body, especially that infections suspected to be associated with the administered organisms were reported decades ago[16]. In some rare cases, probiotics have been linked to serious adverse effects such as fungemia and bacterial sepsis[64-70]. Few risk factors have been identified through these case reports and they include severe immune-suppression or infant prematurity. Additional factors have been shown to include insertion of central venous catheter, short gut syndrome, cardiac valvular heart disease or the presence of a jejunostomy tube[71]. An alarming study published in 2008 aimed at examining the effect of probiotics in hospitalized patients with a predicted severe acute pancreatitis[72]. Not only they failed to show any benefit regarding infectious complications in the probiotic arm but also they additionally revealed a statistically significant increase in mortality and an increased risk of bowel ischemia compared to placebo. They concluded that physicians should be careful in their use of probiotics especially in severely sick patients.

Examining available data for adverse events of probiotics is not an easy task; it is mostly under-reported in the literature. In their trial, Allen *et al*[41] found a statistically significant difference in flatus in the probiotic group. Almost 20% of participants had serious adverse events, but the frequency was similar in both groups. The most common were respiratory, mediastinal and thoracic disorders (5.9%). In the 2012 review performed by Johnston *et al*[58], they assessed 17 RCTs reporting on side effects[55]. Four reported no adverse events at all and three reported serious ones. However, the frequency of events was higher in the control group (12.6% *vs* 9.3%). The most commonly reported symptoms were abdominal cramping, nausea, fever, soft stools and flatulence. When Pattani *et al*[37] performed their meta-analysis; they found no life threatening adverse effects in the 16 RCTs studied. Furthermore, one of the largest meta-analysis to-date assessing probiotics is the one done by Hempel *et al*[36] in 2012, it included 84 RCTs, of which 59 did not report on probiotic-specific adverse events. The rest did not mention any serious side effects. More importantly, three recent systematic reviews have addressed the safety of probiotics[16,73,74]. The most comprehensive of them[16] searched 12 electronic databases; they included 208 RCTs. For short-term probiotic use compared with the control group they showed no statistically significant difference in the overall number of adverse events (RR 1.00, 95%CI: 0.93-1.07) including serious ones (RR 1.06, 95%CI: 0.97-1.16).

**CONCLUSION**

A substantial number of trials have been published examining the use of probiotics in the prevention of AAD. However, few of these were adequately powered enough to demonstrate a reduction in a relatively rare event (< 15%). Associations were shown and conclusions drawn through pooling results across inadequately powered RCTs. Several variables are still unclear in their interactions with probiotics. We have isolated only few RCTs exclusive to elderly patients, therefore potentially important but unknown factors might include the characteristics of the pre-treatment enteric flora, which varies between individuals and is affected by age. Additionally, the strain, dose and duration of probiotics used in the various studies vary widely, therefore making it difficult to draw strong conclusions regarding probiotic use. There are still many unanswered questions to be tackled by larger RCTs, such as: which patient population will benefit the most from probiotic supplementation; which probiotic strains are most effective and does this efficacy vary with the clinical indication or the dose; and finally what are the real risks and hazards associated with routine use of such medications.

The appeal of using probiotics comes clearly from their ready availability, low cost and acceptable known safety profile. With the current data at hand, it is difficult to draw any solid conclusion about the prophylactic use of probiotics in AAD. It would be reasonable to advise their use in some specific populations such as patients with a history of AAD or risk factors for the development of CDAD. Many physicians have been hesitant to adopt probiotics in their routine practice; it would be advisable at this point to stratify this use on case-by-case basis.

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**P-Reviewer:** Feuerstadt P, Maltz C **S-Editor:** Gou SX  **L-Editor: E-Editor:**

**Table 1 Most common trials in prevention of antibiotic-associated diarrhea/ *Clostridium difficile*-associated diarrhea through probiotics**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Study  | Outcome | Population | Rx grp | Plb grp |
| Allen *et al*[41] | AAD/CDI | 2941 in-patients | 1470 | 1471 |
| Armuzzi *et al*[29] | AAD | 60 out-patients | 30 | 30 |
| Beausoleil *et al*[40] | AAD/CDI | 89 in-patients | 44 | 45 |
| Beniwal *et al*[61] | AAD | 202 in-patients | 101 | 101 |
| Can *et al*[25] | AAD/CDI | 151 in-patients | 73 | 78 |
| Cimperman *et al*[23] | AAD | 31 in-patients | 15 | 16 |
| Cremonini *et al*[30] | AAD | 85 out-patients | 22,21,21 | 21 |
| Gao *et al*[38] | AAD/CDI | 255 in-patients | 86, 85 | 84 |
| Gotz *et al*[28] | AAD | 98 in-patients | 48 | 50 |
| Hickson *et al*[39] | AAD/CDI | 135 in-patients | 69 | 66 |
| Lewis *et al*[21] | AAD/CDI | 69 in-patients | 33 | 36 |
| McFarland *et al*[17] | AAD/CDI | 193 in-patients | 97 | 96 |
| Myllyluoma *et al*[31] | AAD | 47 out-patients | 24 | 23 |
| Nista *et al*[32] | AAD | 120 out-patients | 60 | 60 |
| Pozzoni *et al*[22] | AAD/CDI | 275 in-patients | 141 | 134 |
| Salminen *et al*[63] | AAD | 17 out-patients (HIV) | 9 | 8 |
| Sampalis *et al*[18] | AAD/CDI | 472 in-patients (ER) | 233 | 239 |
| Song *et al*[19] | AAD | 214 in-patients | 103 | 111 |
| Stockenhuber *et al*[62] | AAD/CDI | 678 in-patients | 340 | 338 |
| Surawicz *et al*[26] | AAD/CDI | 318 in-patients | 207 | 111 |
| Thomas *et al*[20] | AAD/CDI | 302 in-patients | 152 | 150 |
| Wenus *et al*[24] | AAD/CDI | 87 in-patients | 46 | 41 |
| Wunderlich *et al*[27] | AAD | 45 in-patients | 23 | 22 |

AAD: Antibiotic-associated diarrhea; CDI: *Clostridium difficile* infect; HIV: Human immunodeficiency virus; ER: Emergency room.