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REVIEW

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

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Abstract

Probiotics use has increased tremendously 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-analyses 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 a 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.

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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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 at the clinical level. This ranges from mild diarrhea to electrolyte imbalance, sepsis, admission to the intensive care unit or even death[1]. Antibiotic-associated

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.

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* (*C. 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. difficile* 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 of 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 (RCTs) with similar end-points showed a positive outcome on several variables including nausea, abdominal pain and diarrhea[29-32]. Two important meta-analyses 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-analyses were released; the first by Videlock and Cremonini[35] in 2012 included studies with concurrent administration of probiotics and antibiotics. They analyzed 34 trials after exclusion and, with the use of 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 8 (95%CI: 7-11). Hempel *et al*[36] performed the second one the same year; this review included RCTs that evaluated probiotics as adjuncts to antibiotic use. 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 effect 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 a 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 studies 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 *et al*[41] 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 6×10^{10} 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 was 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

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 risk[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 probiotics 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*[16] 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). A large meta-analysis conducted in 2012 by Johnston *et al*[58] 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). The 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 a 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 of 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 probiotic 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 AAD[2,3]. Hempel *et al*[36] 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 result 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 showed 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 since 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 did they fail 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], 17 RCTs reporting on side effects were assessed[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-analyses to-date assessing probiotics is the one performed 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 there was 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.

REFERENCES

1 **Hurley BW**, Nguyen CC. The spectrum of pseudomembranous enterocolitis and antibiotic-associated diarrhea. *Arch Intern Med* 2002; **162**: 2177-2184 [PMID: 12390059]

2 **Bartlett JG**. Clinical practice. Antibiotic-associated diarrhea. *N Engl J Med* 2002; **346**: 334-339 [PMID: 11821511]

3 **McFarland LV**. Epidemiology, risk factors and treatments for antibiotic-associated diarrhea. *Dig Dis* 1998; **16**: 292-307 [PMID: 9892789]

4 **Barbut F**, Meynard JL. Managing antibiotic associated diarrhoea. *BMJ* 2002; **324**: 1345-1346 [PMID: 12052785]

5 **Szajewska H**, Mrukowicz JZ. Probiotics in prevention of antibiotic-associated diarrhea: meta-analysis. *J Pediatr* 2003; **142**: 85 [PMID: 12569905]

6 **Högenauer C**, Hammer HF, Krejs GJ, Reisinger EC. Mechanisms and management of antibiotic-associated diarrhea. *Clin Infect Dis* 1998; **27**: 702-710 [PMID: 9798020]

7 **Silva Júnior M**. Recent changes in Clostridium difficile infec-

tion. *Einstein* (Sao Paulo) 2012; **10**: 105-109 [PMID: 23045838]

8 **Cheng SH**, Lu JJ, Young TG, Perng CL, Chi WM. Clostridium difficile--associated diseases: comparison of symptomatic infection versus carriage on the basis of risk factors, toxin production, and genotyping results. *Clin Infect Dis* 1997; **25**: 157-158 [PMID: 9243055]

9 **Zilberberg MD**, Shorr AF, Kollef MH. Increase in adult Clostridium difficile-related hospitalizations and case-fatality rate, United States, 2000-2005. *Emerg Infect Dis* 2008; **14**: 929-931 [PMID: 18507904]

10 **Oake N**, Taljaard M, van Walraven C, Wilson K, Roth V, Forster AJ. The effect of hospital-acquired Clostridium difficile infection on in-hospital mortality. *Arch Intern Med* 2010; **170**: 1804-1810 [PMID: 21059973]

11 Report of a Joint FAO/WHO Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics in Food Including Powder Milk with Live Lactic Acid Bacteria. Argentina: WHO; 2001

12 **Sherman PM**, Johnson-Henry KC, Yeung HP, Ngo PS, Goulet J, Tompkins TA. Probiotics reduce enterohemorrhagic Escherichia coli O157: H7- and enteropathogenic E. coli O127: H6-induced changes in polarized T84 epithelial cell monolayers by reducing bacterial adhesion and cytoskeletal rearrangements. *Infect Immun* 2005; **73**: 5183-5188 [PMID: 16041036]

13 **Alvarez-Olmos MI**, Oberhelman RA. Probiotic agents and infectious diseases: a modern perspective on a traditional therapy. *Clin Infect Dis* 2001; **32**: 1567-1576 [PMID: 11340528]

14 **Doron S**, Gorbach SL. Probiotics: their role in the treatment and prevention of disease. *Expert Rev Anti Infect Ther* 2006; **4**: 261-275 [PMID: 16597207]

15 **Morrow LE**, Gogineni V, Malesker MA. Probiotics in the intensive care unit. *Nutr Clin Pract* 2012; **27**: 235-241 [PMID: 22473797]

16 **Hempel S**, Newberry S, Ruelaz A, Wang Z, Miles JN, Suttorp MJ, Johnsen B, Shanman R, Slusser W, Fu N, Smith A, Roth B, Polak J, Motala A, Perry T, Shekelle PG. Safety of probiotics used to reduce risk and prevent or treat disease. *Evid Rep Technol Assess* (Full Rep) 2011; (**200**): 1-645 [PMID: 23126627]

17 **McFarland LV**, Surawicz CM, Greenberg RN, Elmer GW, Moyer KA, Melcher SA, Bowen KE, Cox JL. Prevention of beta-lactam-associated diarrhea by Saccharomyces boulardii compared with placebo. *Am J Gastroenterol* 1995; **90**: 439-448 [PMID: 7872284]

18 **Sampalis J**, Psaradellis E, Rampakakis E. Efficacy of BIO K+ CL1285 in the reduction of antibiotic-associated diarrhea - a placebo controlled double-blind randomized, multi-center study. *Arch Med Sci* 2010; **6**: 56-64 [PMID: 22371721]

19 **Song HJ**, Kim JY, Jung SA, Kim SE, Park HS, Jeong Y, Hong SP, Cheon JH, Kim WH, Kim HJ, Ye BD, Yang SK, Kim SW, Shin SJ, Kim HS, Sung JK, Kim EY. Effect of probiotic Lactobacillus (Lacidofil® cap) for the prevention of antibiotic-associated diarrhea: a prospective, randomized, double-blind, multicenter study. *J Korean Med Sci* 2010; **25**: 1784-1791 [PMID: 21165295]

20 **Thomas MR**, Litin SC, Osmon DR, Corr AP, Weaver AL, Lohse CM. Lack of effect of Lactobacillus GG on antibiotic-associated diarrhea: a randomized, placebo-controlled trial. *Mayo Clin Proc* 2001; **76**: 883-889 [PMID: 11560298]

21 **Lewis SJ**, Potts LF, Barry RE. The lack of therapeutic effect of Saccharomyces boulardii in the prevention of antibiotic-related diarrhoea in elderly patients. *J Infect* 1998; **36**: 171-174 [PMID: 9570649]

22 **Pozzoni P**, Riva A, Bellatorre AG, Amigoni M, Redaelli E, Ronchetti A, Stefani M, Tironi R, Molteni EE, Conte D, Casazza G, Colli A. Saccharomyces boulardii for the prevention of antibiotic-associated diarrhea in adult hospitalized patients: a single-center, randomized, double-blind, placebo-controlled trial. *Am J Gastroenterol* 2012; **107**: 922-931 [PMID: 22472744]

23 **Cimperman L**, Bayless G, Best K, Diligente A, Mordarski B, Oster M, Smith M, Vatakis F, Wiese D, Steiber A, Katz J. A randomized, double-blind, placebo-controlled pilot study of Lactobacillus reuteri ATCC 55730 for the prevention of antibiotic-associated diarrhea in hospitalized adults. *J Clin Gastroenterol* 2011; **45**: 785-789 [PMID: 21552138]

24 **Wenus C**, Goll R, Loken EB, Biong AS, Halvorsen DS, Florholmen J. Prevention of antibiotic-associated diarrhoea by a fermented probiotic milk drink. *Eur J Clin Nutr* 2008; **62**: 299-301 [PMID: 17356555]

25 **Can M**, Beşirbellioglu BA, Avci IY, Beker CM, Pahsa A. Prophylactic Saccharomyces boulardii in the prevention of antibiotic-associated diarrhea: a prospective study. *Med Sci Monit* 2006; **12**: PI19-PI22 [PMID: 16572062]

26 **Surawicz CM**, Elmer GW, Speelman P, McFarland LV, Chinn J, van Belle G. Prevention of antibiotic-associated diarrhea by Saccharomyces boulardii: a prospective study. *Gastroenterology* 1989; **96**: 981-988 [PMID: 2494098]

27 **Wunderlich PF**, Braun L, Fumagalli I, D'Apuzzo V, Heim F, Karly M, Lodi R, Politta G, Vonbank F, Zeltner L. Double-blind report on the efficacy of lactic acid-producing Enterococcus SF68 in the prevention of antibiotic-associated diarrhoea and in the treatment of acute diarrhoea. *J Int Med Res* 1989; **17**: 333-338 [PMID: 2676650]

28 **Gotz V**, Romankiewicz JA, Moss J, Murray HW. Prophylaxis against ampicillin-associated diarrhea with a lactobacillus preparation. *Am J Hosp Pharm* 1979; **36**: 754-757 [PMID: 111546]

29 **Armuzzi A**, Cremonini F, Bartolozzi F, Canducci F, Candelli M, Ojetti V, Cammarota G, Anti M, De Lorenzo A, Pola P, Gasbarrini G, Gasbarrini A. The effect of oral administration of Lactobacillus GG on antibiotic-associated gastrointestinal side-effects during Helicobacter pylori eradication therapy. *Aliment Pharmacol Ther* 2001; **15**: 163-169 [PMID: 11148433]

30 **Cremonini F**, Di Caro S, Covino M, Armuzzi A, Gabrielli M, Santarelli L, Nista EC, Cammarota G, Gasbarrini G, Gasbarrini A. Effect of different probiotic preparations on anti-helicobacter pylori therapy-related side effects: a parallel group, triple blind, placebo-controlled study. *Am J Gastroenterol* 2002; **97**: 2744-2749 [PMID: 12425542]

31 **Myllyluoma E**, Veijola L, Ahlroos T, Tynkkynen S, Kankuri E, Vapaatalo H, Rautelin H, Korpela R. Probiotic supplementation improves tolerance to Helicobacter pylori eradication therapy--a placebo-controlled, double-blind randomized pilot study. *Aliment Pharmacol Ther* 2005; **21**: 1263-1272 [PMID: 15882248]

32 **Nista EC**, Candelli M, Cremonini F, Cazzato IA, Zocco MA, Franceschi F, Cammarota G, Gasbarrini G, Gasbarrini A. Bacillus clausii therapy to reduce side-effects of anti-Helicobacter pylori treatment: randomized, double-blind, placebo controlled trial. *Aliment Pharmacol Ther* 2004; **20**: 1181-1188 [PMID: 15569121]

33 **McFarland LV**. Meta-analysis of probiotics for the prevention of antibiotic associated diarrhea and the treatment of Clostridium difficile disease. *Am J Gastroenterol* 2006; **101**: 812-822 [PMID: 16635227]

34 **Sazawal S**, Hiremath G, Dhingra U, Malik P, Deb S, Black RE. Efficacy of probiotics in prevention of acute diarrhoea: a meta-analysis of masked, randomised, placebo-controlled trials. *Lancet Infect Dis* 2006; **6**: 374-382 [PMID: 16728323]

35 **Videlock EJ**, Cremonini F. Meta-analysis: probiotics in antibiotic-associated diarrhoea. *Aliment Pharmacol Ther* 2012; **35**: 1355-1369 [PMID: 22531096]

36 **Hempel S**, Newberry SJ, Maher AR, Wang Z, Miles JN, Shanman R, Johnsen B, Shekelle PG. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. *JAMA* 2012; **307**: 1959-1969 [PMID: 22570464]

37 **Pattani R**, Palda VA, Hwang SW, Shah PS. Probiotics for

the prevention of antibiotic-associated diarrhea and Clostridium difficile infection among hospitalized patients: systematic review and meta-analysis. *Open Med* 2013; **7**: e56-e67 [PMID: 24348885]

38 **Gao XW**, Mubasher M, Fang CY, Reifer C, Miller LE. 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. *Am J Gastroenterol* 2010; **105**: 1636-1641 [PMID: 20145608]

39 **Hickson M**, D'Souza AL, Muthu N, Rogers TR, Want S, Rajkumar C, Bulpitt CJ. Use of probiotic Lactobacillus preparation to prevent diarrhoea associated with antibiotics: randomised double blind placebo controlled trial. *BMJ* 2007; **335**: 80 [PMID: 17604300]

40 **Beausoleil M**, Fortier N, Guénette S, L'ecuyer A, Savoie M, Franco M, Lachaine J, Weiss K. Effect of a fermented milk combining Lactobacillus acidophilus Cl1285 and Lactobacillus casei in the prevention of antibiotic-associated diarrhea: a randomized, double-blind, placebo-controlled trial. *Can J Gastroenterol* 2007; **21**: 732-736 [PMID: 18026577]

41 **Allen SJ**, Wareham K, Wang D, Bradley C, Hutchings H, Harris W, Dhar A, Brown H, Foden A, Gravenor MB, Mack D. 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. *Lancet* 2013; **382**: 1249-1257 [PMID: 23932219 DOI: 10.1016/S0140-6736(13)61218-0]

42 Results from the mandatory Clostridium difficile reporting scheme. Health Protection Agency: United Kingdom; 2012

43 All Wales Commentaries: Clostridium difficile reports. Public Health Wales: United Kingdom, 2012

44 **Bauer MP**, Notermans DW, van Benthem BH, Brazier JS, Wilcox MH, Rupnik M, Monnet DL, van Dissel JT, Kuijper EJ. Clostridium difficile infection in Europe: a hospital-based survey. *Lancet* 2011; **377**: 63-73 [PMID: 21084111 DOI: 10.1016/S0140-6736(10)61266-4]

45 **Kachrimanidou M**, Malisiovas N. Clostridium difficile infection: a comprehensive review. *Crit Rev Microbiol* 2011; **37**: 178-187 [PMID: 21609252]

46 **Schroeder MS**. Clostridium difficile--associated diarrhea. *Am Fam Physician* 2005; **71**: 921-928 [PMID: 15768622]

47 **Bignardi GE**. Risk factors for Clostridium difficile infection. *J Hosp Infect* 1998; **40**: 1-15 [PMID: 9777516 DOI: 10.1016/S0195-6701(98)90019-6]

48 **Bartlett JG**, Gerding DN. Clinical recognition and diagnosis of Clostridium difficile infection. *Clin Infect Dis* 2008; **46** Suppl 1: S12-S18 [PMID: 18177217]

49 **Seniakovich VM**, Leont'ev AF, Dvoriakovskiĭ IV, Dvoriakovskaia GM, Markov BA, Ormantaev AK. [Control of decompressive portacaval anastomosis in children after radical treatment of portal hypertension]. *Vestn Khir Im I I Grek* 1990; **144**: 78-79 [PMID: 2165330]

50 **Warny M**, Pepin J, Fang A, Killgore G, Thompson A, Brazier J, Frost E, McDonald LC. Toxin production by an emerging strain of Clostridium difficile associated with outbreaks of severe disease in North America and Europe. *Lancet* 2005; **366**: 1079-1084 [PMID: 16182895 DOI: 10.1016/S0140-6736(05)67420-X]

51 **Pépin J**, Saheb N, Coulombe MA, Alary ME, Corriveau MP, Authier S, Leblanc M, Rivard G, Bettez M, Primeau V, Nguyen M, Jacob CE, Lanthier L. Emergence of fluoroquinolones as the predominant risk factor for Clostridium difficile-associated diarrhea: a cohort study during an epidemic in Quebec. *Clin Infect Dis* 2005; **41**: 1254-1260 [PMID: 16206099]

52 **Howell MD**, Novack V, Grgurich P, Soulliard D, Novack L, Pencina M, Talmor D. Iatrogenic gastric acid suppression and the risk of nosocomial Clostridium difficile infection. *Arch Intern Med* 2010; **170**: 784-790 [PMID: 20458086]

53 **Leonard J**, Marshall JK, Moayyedi P. Systematic review of the risk of enteric infection in patients taking acid suppression. *Am J Gastroenterol* 2007; **102**: 2047-2056; quiz 2057 [PMID: 17509031]

54 **Tal S**, Gurevich A, Guller V, Gurevich I, Berger D, Levi S. Risk factors for recurrence of Clostridium difficile-associated diarrhea in the elderly. *Scand J Infect Dis* 2002; **34**: 594-597 [PMID: 12238576 DOI: 10.1080/00365540210147525]

55 **Barletta JF**, El-Ibiary SY, Davis LE, Nguyen B, Raney CR. Proton Pump Inhibitors and the Risk for Hospital-Acquired Clostridium difficile Infection. *Mayo Clin Proc* 2013; **88**: 1085-1090 [PMID: 24012413]

56 **Kelly CP**, Pothoulakis C, LaMont JT. Clostridium difficile colitis. *N Engl J Med* 1994; **330**: 257-262 [PMID: 8043060]

57 **Cohen SH**, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, Pepin J, Wilcox MH. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). *Infect Control Hosp Epidemiol* 2010; **31**: 431-455 [PMID: 20307191]

58 **Johnston BC**, Ma SS, Goldenberg JZ, Thorlund K, Vandvik PO, Loeb M, Guyatt GH. Probiotics for the prevention of Clostridium difficile-associated diarrhea: a systematic review and meta-analysis. *Ann Intern Med* 2012; **157**: 878-888 [PMID: 23362517]

59 **Sun X**, Briel M, Walter SD, Guyatt GH. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. *BMJ* 2010; **340**: c117 [PMID: 20354011]

60 **Bengmark S**. Ecological control of the gastrointestinal tract. The role of probiotic flora. *Gut* 1998; **42**: 2-7 [PMID: 9505873]

61 **Beniwal RS**, Arena VC, Thomas L, Narla S, Imperiale TF, Chaudhry RA, Ahmad UA. A randomized trial of yogurt for prevention of antibiotic-associated diarrhea. *Dig Dis Sci* 2003; **48**: 2077-2082 [PMID: 14627358]

62 **Stockenhuber A**, Kamhuber C, Leeb G, Adelmann K, Prager E, Mach K, Stockenhuber F. Preventing antibiotic associated diarrhoea using a probiotic Lactobacillus casei preparation. *Gut* 2008; **57** Suppl II: A20

63 **Salminen MK**, Tynkkynen S, Rautelin H, Poussa T, Saxelin M, Ristola M, Valtonen V, Järvinen A. The efficacy and safety of probiotic Lactobacillus rhamnosus GG on prolonged, noninfectious diarrhea in HIV Patients on antiretroviral therapy: a randomized, placebo-controlled, crossover study. *HIV Clin Trials* 2004; **5**: 183-191 [PMID: 15472792]

64 **Fredenucci I**, Chomarat M, Boucaud C, Flandrois JP. Saccharomyces boulardii fungemia in a patient receiving Ultra-levure therapy. *Clin Infect Dis* 1998; **27**: 222-223 [PMID: 9675488]

65 **Lestin F**, Pertschy A, Rimek D. [Fungemia after oral treatment with Saccharomyces boulardii in a patient with multiple comorbidities]. *Dtsch Med Wochenschr* 2003; **128**: 2531-2533 [PMID: 14648435]

66 **Piechno S**, Seguin P, Gangneux JP. [Saccharomyces boulardii fungal sepsis: beware of the yeast]. *Can J Anaesth* 2007; **54**: 245-246 [PMID: 17331940]

67 **Riquelme AJ**, Calvo MA, Guzmán AM, Depix MS, García P, Pérez C, Arrese M, Labarca JA. Saccharomyces cerevisiae fungemia after Saccharomyces boulardii treatment in immunocompromised patients. *J Clin Gastroenterol* 2003; **36**: 41-43 [PMID: 12488707]

68 **Trautmann M**, Synowzik I, Nadji-Ohl M, Con Voigt T, Reiter W. Fungemia due to Saccharomyces cerevisiae var. boulardii. *Chemotherapie J* 2008; **17**: 57-61

69 **Zunic P**, Lacotte J, Pegoix M, Buteux G, Leroy G, Mosquet B, Moulin M. [Saccharomyces boulardii fungemia. Apropos of a case]. *Therapie* 1991; **46**: 498-499 [PMID: 1819157]

70 **Land MH**, Rouster-Stevens K, Woods CR, Cannon ML, Cnota J, Shetty AK. Lactobacillus sepsis associated with probiotic therapy. *Pediatrics* 2005; **115**: 178-181 [PMID: 15629999]

71 **Boyle RJ**, Robins-Browne RM, Tang ML. Probiotic use in clinical practice: what are the risks? *Am J Clin Nutr* 2006; **83**: 1256-1264; quiz 1446-1447 [PMID: 16762934]

72 **Besselink MG**, van Santvoort HC, Buskens E, Boermeester

MA, van Goor H, Timmerman HM, Nieuwenhuijs VB, Bollen TL, van Ramshorst B, Witteman BJ, Rosman C, Ploeg RJ, Brink MA, Schaapherder AF, Dejong CH, Wahab PJ, van Laarhoven CJ, van der Harst E, van Eijck CH, Cuesta MA, Akkermans LM, Gooszen HG. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. *Lancet* 2008; **371**: 651-659 [PMID: 18279948 DOI: 10.1016/S0140-6736(08)60207-X]

73 **McFarland LV**. Systematic review and meta-analysis of Saccharomyces boulardii in adult patients. *World J Gastroenterol* 2010; **16**: 2202-2222 [PMID: 20458757 DOI: 10.3748/wjg.v16.i18.2202]

74 **Whelan K**, Myers CE. Safety of probiotics in patients receiving nutritional support: a systematic review of case reports, randomized controlled trials, and nonrandomized trials. *Am J Clin Nutr* 2010; **91**: 687-703 [PMID: 20089732]

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