Lactobacillus sp as a Probiotic for the Prevention of *Clostridium difficile* Associated Diarrhea

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**ABSTRACT**

**Background:** Antibiotic treatment can disturb the resistance of the gastrointestinal flora to colonization. This may result in complications, the most serious of which is *Clostridium difficile* associated diarrhea (CDAD). The aim of this study was to determine the effectiveness of probiotics for the prevention of CDAD.

**Method:** The databases used were Scopus, Proquest, CINAHL, Medline, Pubmed and ScienceDirect, limited to having been published in the last 5 years. A literature review followed the keyword search. The keywords used were probiotics, *Clostridium difficile*, associated, diarrhea, randomized, control and trial using "AND" and "OR". Twelve trials with 5102 participants were included. Eight trials reported a preventive effect for CDAD using a mixture of 2 strains of lactobacillus, a mixture of 4 combination strains, a mixture of lactobacillus and Saccharomyces or a mixture of Bifidobacterium, Lactobacillus and Saccharomyces.

**Result:** Our findings indicate that probiotics may prevent CDAD. Most probiotics contain a singular strain. The combination with *lactobacillus sp* was the most effective at preventing CDAD.

**Conclusion:** In addition, 6 out of 8 trials had an in relation to preventing CDAD containing lactobacillus sp. Four studies said that there were some factors that meant that the probiotic could not reduce or prevent the CDAD.


**KEYWORDS**

Lactobacillus sp; probiotic; *Clostridium difficile*; diarrhea

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**INTRODUCTION**

A healthy body normally has *Clostridium difficile* (CD) bacteria in the intestine. *Clostridium difficile* (CD) is a Gram positive anaerobic bacterium. The use of antibiotics for an unknown period showed that *Clostridium difficile* disrupts the colonic microbiota, so then the growth of *Clostridium difficile* is faster and produces toxins A and B. This causes an increase in pseudomembrane colitis with fever and diarrhea (Mizui et al., 2013). The major cause of antibiotic associated diarrhea in hospitals is *Clostridium difficile*(Li et al, 2018). According this study, the antibiotics used included clindamycin, cephalosporins and fluoroquinolones. The use of these antibiotics is not obligatory (Squellati, 2018). Administering antibiotics as a treatment can interfere with the colonization of the normal flora in the digestive tract, resulting in various symptoms and effects, especially diarrhea. This process results in *Clostridium difficile* Associated Diarrhea (CDAD)(Li et al., 2018).

Patients who have a sustained *Clostridium difficile* infection can contract *Antibiotic Associated Diarrhea* (AAD). It is also known that *Clostridium difficile* associated diarrhea is a trend that is currently evident, with more than 500,000 people exposed to *Clostridium difficile*. It may cause major death with inflammation in patients and around 10% will die (Squellati, 2018). The Centers for Disease Control and Prevention (CDC) conducted a survey about *Clostridium difficile* in an infection-focused program. There was 34 countries that used 10 sites and other countries showed that CDAD has increased by 453,000 with 29,300 deaths (Approach, 2017)
The complexity of diarrhea generally establishes whether a physician will discontinue or change the antibiotics, and whether a stool specimen needs to be analyzed for the appearance of Clostridium difficile toxins. Other nosocomial infections, long hospital stays, medical care costs, and diagnostic procedures can make the patient at risk for developing AAD (Xie, Li, Wang, Li, & Chen, 2015).

Probiotics can potentially prevent the development of CDAD and it can make the growth of the normal gastrointestinal flora increased and compensate for the negative microbiota effects of antibiotics. Therefore, probiotics have been greatly used to mediate a variation of conditions influencing the gastrointestinal tract, including diarrhea, inflammatory bowel disease, irritable bowel syndrome, bacterial overgrowth and especially Clostridium difficile infection (Xie et al., 2015). Probiotics also help to take down Clostridium difficile colonization by adhering to the epithelial and mucosal membranes in the colon. But probiotics should not be taken in the ICU, because some patients have an unsuitable reaction as they are already compromised due to the patient’s underlying condition (Squellati, 2018).

Probiotics are becoming advanced, existing as capsules and dairy-based food supplements sold in health food stores, medicine stores and on the modern market. If probiotics are effective, then the incidence of Clostridium difficile becomes reduced and adverse events decline, meaning that the cost that the hospital pays is lower. Probiotics make an attractive choice for the prevention of Clostridium difficile associated diarrhea (Johnston et al., 2013). We were guided by systematically reviewing the literature to determine the effectiveness and safety of probiotics (any strain or dose) for the prevention of Clostridium difficile associated diarrhea and looking at the wellbeing of patients who were also receiving antibiotics.

**MATERIALS AND METHODS**

**Research Design**

The systematic review was used to determine the effectiveness of probiotics for the prevention of CDAD. The use of studies was limited to the latest research, namely for the last 5 years and using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) approach.

**Search Strategy**

The literature search was carried out focused on several databases such as Scopus, Proquest, CINAHL, Medline, Pubmed and Science Direct. The literature review used the following keywords: probiotics, Clostridium difficile, associated, diarrhea, randomized, control and trial, in addition to using "AND" and the keywords RCT, randomized control and trial using "OR". After a number of articles were obtained, the researcher then selected them again according to the specified inclusion and exclusion criteria.

**Inclusion and Exclusion Criteria**

The desired articles were published from 2013 to 2018, and the age restriction was applied, focusing on the keywords in the search for matching articles. The design method searched for was RCT’s that compared interventions based on a variety of strains where a combination of probiotics and doses were eligible. We scanned the lists of identified articles to obtained additional trial articles. Articles with samples that did not focus on humans but that used rats or mice, the discussion of articles outside of the probiotics of Clostridium difficile associated diarrhea, articles with design methods that were not RCT, as well as articles that were systematic reviews, narrative reviews, theses, books or chapters, abstracts and editorials issued in this study were not included according to our exclusion criteria.

**Article Searching Process**

The searching of the articles was done using the keyword ‘surgical scrubs’, ‘scrubbing’ and ‘microorganisms’ in accordance with the PICOT method that was determined and we also used the Boolean logic search method on the Ebscho, Science Direct, Springer link, Scopus and ProQuest databases with a time limitation of 2012 - 2018. In the search process, 189 articles were found and 11 articles were in accordance with the inclusion criteria to be
12 articles were chosen to review. The probiotics used that were Lactobacillus casei Shirota, Lactobacillus helveticus NFCM, Lactobacillus sp, Streptococcus sp and Saccharomyces sp. The probiotics included the following:

- **Lactobacillus casei Shirota**
- **Lactobacillus helveticus** NFCM
- **Lactobacillus sp**
- **Streptococcus sp**
- **Saccharomyces sp**

The probiotics which prevented CDAD were from 4 major genuses. There was a combination probiotic treatment associated with significant *Clostridium difficile* associated diarrhea on these studies. Eight trials reported a preventive effect against CDAD with a mixture of *Lactobacillus casei* and *Lactobacillus paracasei* CNCCM 1-1518(Alberda, Marcushamer, Hewer, Journault, & Demetrios Kutsogiannis, 2018) and a mixture of 4 strains containing *Lactobacillus acidophilus* NFCM, *Lactobacillus paracasei* Lpc-37, *Bifidobacterium lactis* Bi-07 and *B. lactis* Bi-04(Barker et al., 2017)(Ouwehand et al., 2014). There was also a mixture of *Lactobacillus helveticus* R0052, *Lactobacillus rhamnous* R0011(Evans, Salewski, Christman, Girard, & Tompkins, 2016) and *Saccharomyces boulardii* CNCCM 1-745(SB)(Kabbani et al., 2017). VSL#3 contains a mixture of *Bifidobacterium breve*, *Bifidobacterium longum* and *Bifidobacterium infantis*. The probiotics used that were *Streptococcus sp* included *Streptococcus thermophiles* and *Streptococcus boulardii*. The probiotics used that were *Saccharomyces sp* included *Saccharomyces boulardii* and *Saccharomyces CNCM 1-745*.

Diarrhea was defined as consisting of 2 main variations, which were ≥ 3 loose stools in 24 h and ≥ 2 loose or watery stools per day.

**Probiotics Affecting Clostridium Difficile Associated Diarrhea**

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Streptococcus thermophiles (Selinger et al., 2013), Saccharomyces boulardii (Shan et al., 2013) and Lactobacillus casei Shirotu (Wong et al., 2014). Six studies reported that Lactobacillus sp was the most effective probiotic at preventing Clostridium difficile associated diarrhea (Barker et al., 2017) (Barker et al., 2017), (Evans et al., 2016), (Kabbani et al., 2017), (Ouwehand et al., 2014), (Selinger et al., 2013).

Across the 4 trials, it was reported there was no important impact on Clostridium difficile associated diarrhea when using a mixture of 2 strains, namely Lactobacillus acidophilus (CU600 and CU121) and two strains of Bifidobacterium (Bifidobacterium bifidum CU120 and Bifidobacterium lactis CU34) (Allen et al., 2013). There was also a mixture examined consisting of Lactobacillus acidophilus LA-5 and Bifidobacterium BB-12 (Chatterjee et al., 2013), Saccharomyces boulardii (Ehrhardt et al., 2016) and ACTIMEL containing Lactobacillus casei, Lactobacillus bulgaricus and Streptococcus thermophiles (Mallina et al., 2018).

**DISCUSSION**

The result of this review found that the age group most affected by CDAD was adults (the youngest being 6 months through to old age in the study overall), although this was not statistically significant. One study stated that being of an age >18 years old may increase the risk by about 2% concerning being infected by Clostridium difficile in the health care setting. However, the level of infection was neither studied nor evaluated deeply. Old age individuals are more susceptible to Clostridium difficile infection because it is related to their humoral immune response (Patel, Wieczorkiewicz, & Tuazon, 2016). In addition, CDAD infection often happens at an old age where, in the health care setting, they have consumed broad spectrum antibiotic (Allen et al., 2013).

Based on the review, the duration of consumed probiotics in the studies varied and it was between a minimum of 7 days to a maximum of several weeks. The other studies said that a short treatment duration (<8 weeks) may be more effective than a long duration (>8 weeks) in reference to bowel inflammation. This is related to the quality of the patient's life because longer term or even the continuous supplementation of probiotics may be required to detect significant alterations in the symptoms (Zhang et al., 2016).

We found 4 journals that said that probiotics cannot reduce CDAD. This was found because ineffective probiotic results were related to the limitations of the trial. For example, probiotics that were not according to a doctor's recommended dosage. There were some patients who had not only received probiotics but they had also received a high dosage of antibiotics so the probiotics given at the time no longer have an effect (Box, Oxtwine, & Goicoechea, 2016). Another thing to consider is that the number of study participants was 80.5% for those not eligible and the patients who were eligible may have been relatively healthy. One must consider a different design for the trial to get better results (Ehrhardt et al., 2016).

On the other hand, our review showed that the probiotics that can reduce CDAD were from 4 different genuses. These were Lactobacillus, Bifidobacterium, Streptococcus and Saccharomyces. It also was explained by Johnston and colleagues. Their systematic review consisted of 20 RCTs with 3818 patients to determine if probiotics are effective at preventing CDAD. They found evidence that shows that probiotics reduce the chance of CDAD to a large extent, with only a small percentage of adverse reactions. The probiotics used were Bifidobacterium, Lactobacillus, Saccharomyces, and Streptococcus (Johnston et al., 2013). It was explained that probiotics are the most effective if given closer to the first antibiotic dose, with a decrement in efficacy for every day of delay in starting probiotics (Shan et al., 2013).

Probiotics Bifidobacterium, Lactobacillus, Saccharomyces, and Streptococcus may have effects that can be attributed to its actions on intestinal immunity. They may improve the number of IgA and other immunoglobulin secreting cells in the intestinal mucosa and it can also stimulate the local release of interferons. It could also function through the advancing of the barrier function, immunomodulation, and competitive adherence to the intestinal mucosa by avoiding or ameliorating various infective or inflammatory diseases (Chatterjee et al., 2013).

On the other hand, this review has shown that Lactobacillus is a great species determinant for the prevention of CDAD. For example, Lactobacillus casei becomes practical when it is flavored. It was shown by Alberda teams (Alberda et al., 2018) said that 32 participants in trial. AAD was documented in 12.5% of the probiotic Lactobacillus casei drink group and 31.3% in the control group.

Most of the studies stated that probiotics were more effective against bacterial diarrhea. For instance, when the efficacy of Lactobacillus GG was analyzed in a meta-analysis, as for separate etiologies, it was evident that this probiotic was most effective for rotavirus diarrhea (Guandalini, 2011).

One trial said that Lactobacillus sp strains have been shown to survive passage through the gastrointestinal tract when healthy volunteers were given eubacteriaes, causing diarrhea. In in-vitro studies, these strains have shown the ability to adhere to human epithelial cells, to maintain the gut barrier and to stimulate an anti-inflammatory response, in addition to blocking pathogen adhesion. It is feasible that these mechanisms have a role in reducing the duration of diarrhea events (Evans et al., 2016).

Lactobacillus can also reduce CDAD according to Ouwehand et al. as seen in a trial. Their result showed there to be a significant dose response effect in CDAD with an incidence of 12.5, 19.6, and 24.6 with the high dose, low dose and placebo (p=0.02). They said that abdominal pain was reduced only in the high-dose...
Lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhea and Clostridium difficile diarrhea in older inpatients (PLACIDE): a randomised, double-blind, placebo-controlled, multicentre trial. The Lancet, 6726(Cdd), 1–9. https://doi.org/10.1016/S0140-6736(13)61218-0


