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Comparison of Conjunctive Probiotic Use Versus No Probiotic Use in Outcomes of Antibiotic-Associated Diarrhea

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by

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Abstract

Antibiotics are utilized in the medical community for the treatment of bacterial infections. Consequently, the use of antibiotics may result in certain gastrointestinal side effects. Antibiotic-associated diarrhea is one side effect that can be seen in patient populations that are on an antibiotic regimen. Due to this side effect profile, patient compliance on an antibiotic regimen may be compromised. This lack in patient compliance led to increased interest to determine if there are treatment options available to prevent or reduce instances of antibiotic-associated diarrhea. One treatment option of interest includes the use of probiotics. The purpose of this literature review is to determine if conjunctive use of probiotic supplementation during an antibiotic regimen demonstrates protective effects in preventing or reducing the incidence of antibiotic-associated diarrhea. Studies that were included analyzed probiotic use versus a placebo in treatment of antibiotic-associated diarrhea in pediatric, adult, and elderly populations in an outpatient or inpatient clinical setting. The data available at this time suggests that supplementing with probiotics during an antibiotic regimen may be effective in prevention and reduction of antibiotic-associated diarrhea in pediatric and adult populations.

Keywords: antibiotics, probiotics, and antibiotic-associated diarrhea

Introduction

Antibiotics have been a staple in medical treatment since the discovery of penicillin in the 20th century. Antibiotics play an essential role in fighting off infections that were once life-threatening to humans. Unfortunately, with all the great benefits of antibiotics, they have also been known to create adverse effects within the body. One such common adverse effect includes antibiotic-associated diarrhea. The essence of antibiotics is to destroy infectious bacteria through various mechanisms, but in this process, they end up destroying important symbiotic bacteria that are necessary for maintaining certain biological processes within the human body. Most of these symbiotic bacteria reside in the human intestinal tract. Therefore, disruption of this bacteria via antibiotic use can lead to a variety of pathological consequences, such as diarrhea.

Because the benefits of these symbiotic bacteria are crucial for maintaining human health, research began to explore various treatment methods to combat the destructive nature of antibiotics. One such method includes the use of probiotics during and after treatment with an antibiotic. Probiotics are simply a variety of live microorganisms that have been identified as beneficial to the human body. Examples of microorganisms used in many probiotic supplements include the genera Lactobacillus and Bifidobacterium. The purpose of this research is to investigate whether supplementing the human intestinal tract with probiotic microorganisms will have a positive influence in reducing the adverse effects that occur with antibiotic use.

Statement of the Problem

Antibiotic-associated diarrhea is a common manifestation in the clinical setting due to the abundant use of prescription antibiotics to treat various bacterial infections. Between 1 and 40% of patients taking an antibiotic will report an incidence of antibiotic-associated diarrhea. This is variable based on patient population, risk factors, and research setting (DynaMed, 2018). Due to

the frequency of prescription antibiotic use and the resultant antibiotic-associated diarrhea, understanding possible effective therapies to treat this common clinical manifestation is pertinent to current medical practice. Research on the efficacy of probiotic therapy on antibiotic-associated diarrhea is on-going in the medical community. Knowing whether this therapy method would be an appropriate option for medical providers to incorporate in their daily medical practice would be beneficial in limiting a common adverse effect that accompanies antibiotic use, which may ultimately improve patient compliance and satisfaction.

Research Question

In patients on a current antibiotic regimen, is there a statistically significant difference with conjunctive use of prescription probiotics versus no probiotic use in the reduction of antibiotic-associated diarrhea?

Methods

A literature review was performed using electronic search databases; PubMed, CINHAL, Cochrane Library, ClinicalKey, and DynaMed. Search criteria included the keyword search terms probiotics and antibiotic-associated diarrhea. These keyword terms were entered in all databases. MeSH terms in PubMed were based on the keyword searches. MeSH terms included diarrhea, probiotics, intestines, and anti-bacterial agents. Each keyword term was automatically mapped to a MeSH term in PubMed. The literature review generated a total of 861 articles. Some articles were repeated in these databases. Inclusion criteria included an initial search time frame that was limited to 10 years, but this demonstrated limited data, so the time frame was expanded to 15 years. The population of patients included in this research consisted of men, women, and children of all age ranges, in an inpatient or outpatient setting, who were on an antibiotic regimen during the timeframe of the study. Research studies reviewed were primary and secondary

sources including randomized controlled trials, meta-analyses, and systematic reviews. Upon further review of the selected literature, one article was removed due to it not meeting the inclusion criteria. Exclusion criteria included duplicate or repeated articles, any article that was published beyond the 15-year time frame, and any article that included secondary disorders such as spinal cord injuries. This literature review focused on the prevalence of antibiotic-associated diarrhea, the overall efficacy of probiotics during an antibiotic regimen, the type and dosage of probiotic microorganisms utilized, and any variables that may have had an impact on outcomes, such as patient age.

Prevalence of Antibiotic-Associated Diarrhea

Antibiotics are utilized in medicine to treat bacterial infections. In addition to this, it is known that antibiotics may cause a variety of gastrointestinal side effects, such as diarrhea. The prevalence of antibiotic-associated diarrhea is an area of interest in research. Evans, Salewski, Christman, Girard, and Tomkins (2016) conducted a 10-week randomized, double-blind, placebo-controlled trial to investigate the effect of probiotic supplementation on antibiotic-associated diarrhea in healthy adults. The study included a proposed sample size of 160 participants that were randomly selected to either the placebo or probiotic group. A 7-day course of oral 875 mg amoxicillin/125 mg clavulanic acid antibiotic was administered twice a day to all participants. The probiotic supplementation administered in this study was Lacidofil® STRONG, which contained *Lactobacillus helveticus* R0052 at 0.2 billion colony-forming units (CFUs) and *Lactobacillus rhamnosus* R0011 at 3.8 billion CFUs. The primary outcome of this study was to measure the difference between the placebo and probiotic groups in the weekly mean of stool consistency and frequency. This was done by using the Bristol Stool Scale (BSS), which categorizes stool into seven types based on how long the stool has spent in the bowel. For

example, a type 1 stool is characterized as hard, separated lumps that are hard to pass, whereas a type 7 stool is considered watery with no solid pieces. The secondary outcomes were to evaluate the number of participants that reported diarrhea-like defecations and gastrointestinal symptoms using the Gastrointestinal Symptom Rating Scale (GSRS). The GSRS is based on a 7-point graded scale where a score of 1 indicates no troublesome gastrointestinal symptoms and a score of 7 indicates severe symptoms. Furthermore, the secondary outcomes assessed the safety of the participants via vital signs and blood parameters and any adverse effects from the treatments that were reported within the study.

From the initially enrolled participants, 14 of them withdrew during the study for personal reasons or lack of follow-up. Therefore, 76 participants remained in the probiotic group and 70 in the placebo group. The results of this study concluded that both the placebo and probiotic groups demonstrated an increase in BSS scores and prevalence of antibiotic-associated diarrhea during the antibiotic treatment, $p < .001$ (Evans, Salewski, Christman, Girard, & Tomkins, 2016). There was a statistically significant difference in the duration of diarrhea-like defecations found within the probiotic group compared to the placebo group, $p = .037$. Those taking the probiotic supplementation were found to have an average duration of 2.70 days versus the placebo group of 3.71 days (Evans et al., 2016). No significant difference was found in GSRS scores when comparing the placebo versus probiotic groups. Each group reported a weekly mean GSRS score of less than 2, which indicates minimal to no abdominal discomfort, constipation, or indigestion symptoms (Evans et al., 2016).

The strengths of this study include the population of subjects and study design. The population of participants in this study included both males and females who have been screened and identified as a healthy adult without a history of gastrointestinal disorders or immune-

compromised conditions. This allows the results of the study to be applied to the general population. The double-blind and randomized design of this study reduces the likelihood of bias influencing the study results. Another strength of this study includes the evaluation of two probiotic strains. This provides evidence towards determining if specific strains of probiotics are more effective than others. One weakness of this study includes a small sample size of 146 participants. Furthermore, there was not an equal number of males and females within this study. Although the study size was small and unequal distribution of gender was present, the study demonstrated appropriate methodology with a statistically significant result that may warrant further research.

The prevalence of antibiotic-associated diarrhea in the pediatric population was determined by Olek et al. (2017), who conducted a randomized, double-blind, placebo-controlled study to determine if the single strain probiotic, *Lactobacillus plantarum* DSM9843 (LP299V), reduced the frequency of gastrointestinal symptoms and diarrhea associated with antibiotic use in the pediatric population. A total of 438 children between the ages of 1 to 11 years were included in the study. The children in the study were randomized into two groups, the LP299V receiving group (n = 218) and the placebo group (n = 220). The primary outcome of determining the incidence of diarrhea was evaluated via the Bristol Stool Scale. The secondary outcome of determining the duration and frequency of antibiotic-associated diarrhea was based on the World Health Organization's guidelines of classify antibiotic-associated diarrhea. This guideline classifies it as greater than or equal to three loose or watery stools within 24 hours after starting an antibiotic regimen. The study provided additional information that the researchers gathered from the World Health Organization, which indicated that the prevalence of antibiotic-associated

diarrhea in the pediatric population averages between 11 to 40% of children on an antibiotic regimen (Olek et al., 2017).

Olek et al. (2017) concluded in this study that the incidence of children experiencing loose or watery stools during an antibiotic regimen was high at 44.5% for the placebo group and 39% for the LP299V group. However, when comparing the LP299V and placebo groups, there were no statistically significant differences found in the incidence or mean number of loose or watery stools when both groups were administered an antibiotic regimen. Furthermore, there were no statistically significant differences found in the incidence or frequency of gastrointestinal symptoms found between the two groups.

The strengths of this study include outcome measures that were simple for parents of the children to record or document at home with minimal error and within an appropriate time frame that allowed for sufficient data to be collected. Furthermore, the use of one strain of probiotic in this study provided further information towards determining if certain strains of probiotics are more effective than others in the prevention of antibiotic-associated diarrhea. The limitations of this study include a smaller sample size of 438 children in the narrow age range of 1 to 11 years. This leaves out the ability to apply the results of this study towards the entirety of the pediatric population, including infants and adolescents. Although the results of this study indicated no statistically significant benefit of the probiotic strain, *Lactobacillus plantarum*, it warrants consideration of further research into the other strains of probiotics to determine if a statistical significance is present.

The Efficacy of Probiotic Use Versus Placebo During an Antibiotic Regimen in Reduction of Antibiotic-Associated Diarrhea

Due to the prevalence of diarrhea caused by antibiotic use, a question of research is to determine if there are treatment options available to reduce the occurrence of antibiotic-associated diarrhea. The use of probiotic supplementation is one treatment option that is being studied; however, the efficacy of this treatment option is not fully understood. Blaabjerg, Artzi, and Aabenhus (2017) performed a systematic review and meta-analysis to assess the potential benefits or harms with probiotic use in the prevention of antibiotic-associated diarrhea. A total of 17 prospective, randomized, controlled trials with 3631 participants were included in the review. The patient population included male and female adults and children in the outpatient setting on an oral antibiotic regimen. Multiple strains of probiotics were included in the studies. The duration of probiotic treatment ranged from seven days to five weeks. The oral antibiotic treatments used in most studies included combination amoxicillin and clarithromycin or combination levofloxacin and amoxicillin. Several studies did not specify which antibiotic was being used. The primary outcome of this meta-analysis was to compare the incidence of antibiotic-associated diarrhea in the probiotic versus placebo groups. Secondary outcomes included adverse events and mean duration of diarrhea. Preliminary evidence was provided for a dose-response relationship. The incidence of diarrhea was patient-reported based on each study's definition of diarrhea. Seven studies utilized the World Health Organization's definition of diarrhea, which includes three or more loose stools in a 24-hour period. Three studies used a modified De Boer questionnaire to define diarrhea in a none, mild, moderate, or severe category. Four studies did not include any definitions of diarrhea. The Grading of Recommendations, Assessment, Development, and Education (GRADE) criteria and Cochrane Collaboration's tool were utilized to assess the quality of evidence and risk of bias.

Blaabjerg et al. (2017) concluded in this systematic review and meta-analysis that the incidence of antibiotic-associated diarrhea was more prevalent in the placebo groups at 17.7% versus the probiotic groups at 8.0%. This was a pooled result of the 17 studies. Because of these results, it was concluded that there was a statistically significant reduction in antibiotic-associated diarrhea with probiotic use, RR .49, 95% CI [.36, .66]. However, the quality of evidence is moderate due to the high risk of bias and heterogeneity that was detected, $p = .001$. Within the pooled results, a meta-analysis was performed to evaluate the different strains of probiotics. The two strains that resulted in a statistically significant reduction in antibiotic-associated diarrhea included, *Lactobacillus rhamnosus* GG, RR .29, $p < .001$, 95% CI [.15, .57], and *Saccharomyces boulardii*, RR .41, $p < .001$, 95% CI [.30, .57]. The quality of evidence for this was found to be high. Four studies reported on the mean duration of diarrhea. Three of the four studies found a reduction in the mean duration of diarrhea in the probiotic groups, with an average of 2.93 days compared to the placebo groups of 4.65 days. A total of 10 studies reported on a dose-response relationship. A dosage of greater than 5 billion CFUs per day was found to have fewer incidences of antibiotic-associated diarrhea, $p = .002$.

The strengths of this systematic review and meta-analysis include the patient population with a broad age range of both males and females. This improves the ability to apply the results of the studies to the general population. The outcomes of certain studies yielded statistically significant results with a high quality of evidence based on the GRADE criteria. Limitations of this systematic review and meta-analysis include the small sample size in several of the studies and a lack of double-blinding found in 11 of the studies, which categorized these studies with a high risk of bias. Furthermore, the broad inclusion criteria created a high degree of heterogeneity. The results of this systematic review and meta-analysis with the use of

randomized trials, quality methodology, and statistically significant results warrant further research with larger sample sizes, stringent approaches with defined outcomes, and further attention on the dosage of probiotic strains.

Because of the prevalence of antibiotic-associated diarrhea indicated in the pediatric population, it is important to determine the response by this age group to probiotic supplementation during an antibiotic regimen. A Cochrane review conducted by Guo, Goldenberg, Humphrey, El Dib, and Johnston (2019) systematically reviewed 33 eligible studies to assess the safety and efficacy of probiotic supplementation for the prevention of antibiotic-associated diarrhea in the pediatric population. All studies included in this review were prospective, randomized, controlled trials. A total of 6352 participants between the ages of 0 to 18 years were included in the studies. One primary outcome of the review was to determine if probiotics have an influence on the incidence of antibiotic-associated diarrhea. Of the 33 studies, seven placebo-controlled, one active-controlled, and eight no treatment-controlled studies demonstrated that probiotics may decrease the incidence of antibiotic-associated diarrhea, $p = .05$ (Guo, Goldenberg, Humphrey, El Dib, & Johnston, 2019). The remaining studies did not find a difference in the incidence of antibiotic-associated diarrhea with probiotic supplementation. One secondary outcome of the review was to evaluate if probiotics have an influence on the mean duration of antibiotic-associated diarrhea. Eight studies reported on the mean duration of antibiotic-associated diarrhea; however, the quality of the evidence presented was low due to inconsistency and reporting bias. Further objectives of this review were to determine if the type of species, number of strains, and dosage of probiotics had an impact on antibiotic-associated diarrhea. Of the 33 trials, the two species, *Lactobacillus rhamnosus* and *Saccharomyces boulardii*, were found to have the most statistically significant protective effect against diarrhea.

Specifically, 8% of *Lactobacillus rhamnosus* participants experienced diarrhea compared to 22% with the control group, RR .37, $p < .001$, 95% CI [.24, .55]. Additionally, 8% of *Saccharomyces boulardii* participants experienced diarrhea compared to 21% with the control group, RR .36, $p < .001$, 95% CI [.24, .54] (Guo et al., 2019). In reference to number of strains, both single, RR .42, $p < .001$, 95% CI [.32, .56], and multi-strain probiotics, RR .53, $p < .001$, 95% CI [.37, .75], were found to have a statistically significant effect on antibiotic-associated diarrhea (Guo et al., 2019). Thirty-two of the 33 studies reported on the dosage of probiotics. It was found that a probiotic supplement with a dosage of greater than 5 billion CFUs exhibited the most evidence for the protective effects of probiotics (Guo et al., 2019).

The strengths of this systematic review include the use of the GRADE criteria to evaluate the validity of the evidence given for each outcome. A second strength of the review includes a large number of participants with a wide range of ages from 3 days to 18 years within the pediatric population. Furthermore, the participants consisted of both males and females from diverse socioeconomic backgrounds from 17 countries across the world. This allows the results of the research to be generalized to healthy children who are on an antibiotic regimen. Limitations of this systematic review include a limited number of studies that were examined to answer certain primary or secondary outcomes. For example, with the information reviewed from the 33 studies, only eight of them reported on the duration of antibiotic-associated diarrhea, whereas 32 of the 33 studies reported on probiotic dosage. Therefore, the limited studies used for certain objectives do not provide a proper representation of all available data. A second limitation of this review includes the risk of bias that was present in many of the studies. A total of 20 of the 33 studies were categorized as high risk of bias due to incomplete outcome data and lack of blinding. This bias may cause inconsistency in the results of the research. Despite these

limitations, the large and diverse population, proper methodology, and the importance placed on determining the validity of outcomes warrant the possibility of probiotics being a beneficial addition to current medical practice when placing a pediatric patient on an antibiotic regimen.

The results of the systematic review above are similar to a meta-analysis conducted by Szajewska, Ruszczyński, and Radzikowski (2006) who evaluated the effectiveness of several strains of probiotics in the prevention of antibiotic-associated diarrhea in the pediatric population. A total of 766 children, ages 1 month to 14 years, were included in the study. The primary outcome of this meta-analysis was to determine if probiotic supplementation reduces the incidence of antibiotic-associated diarrhea. The secondary outcomes included the adverse events, the need for intravenous rehydration, and the mean duration of diarrhea. The definition of diarrhea or antibiotic-associated diarrhea varied between each of the six studies. The definitions ranged from a single reported loose stool in a 24-hour period to three loose stools reported in a 48-hour period.

The results of this meta-analysis concluded that the studies that utilized the probiotic strain, *Lactobacillus rhamnosus* GG, were found to have a statistically significant effect in reducing antibiotic-associated diarrhea in the pediatric population, RR .29, $p < .001$, 95% CI [.15, .57]. The study that utilized the strain, *Saccharomyces boulardii*, was also found to have a statistically significant effect, RR .19, $p = .002$, 95% CI [.07, .55] (Szajewska, Ruszczyński, & Radzikowski, 2006). Lastly, the study that utilized the strains, *Bifidobacterium lactis* and *Streptococcus thermophilus*, also was found to have a statistically significant reduction of antibiotic-associated diarrhea, RR .52, $p = .03$, 95% CI [.29, .59] (Szajewska et al., 2006). The mean duration of diarrhea was reported between studies in an inconsistent manner. Therefore, a meta-analysis of this outcome was not able to be properly performed. Nevertheless, it was

included that one study reported a reduction of the mean duration of diarrhea by approximately 1.18 days in the probiotic group compared to the placebo group, $p = .05$ (Szajewska et al., 2006).

The strengths of this meta-analysis include the use of randomized, placebo-controlled trials for each of the selected studies. Furthermore, a thorough search strategy was performed to identify valid controlled trials. The limitations of this meta-analysis include the variability in the defined criteria of diarrhea or antibiotic-associated diarrhea. This alters the reliability of outcome measures. The small sample sizes with limited age ranges of some of the studies also presents as a limitation of this meta-analysis. Lastly, the search strategy was thorough but lacked in identifying any unpublished trials to include in the analysis. The inconsistencies and small sample sizes may present the information concluded in this meta-analysis as less valid or meaningful. However, it does warrant further research to the idea of specific strains of probiotics that have more or less of an effect on antibiotic-associated diarrhea with a focus on attaining reliable data from well-conducted studies.

Additional research has been done on the efficacy of probiotics versus placebo in the reduction of antibiotic-associated diarrhea. Hempel et al. (2012) conducted a systematic review and meta-analysis of 82 randomized controlled trials to evaluate the available evidence on probiotics for treatment and prevention of antibiotic-associated diarrhea. Participants in the studies were of all ages. Several genera of probiotics were utilized for intervention within the studies. Multiple different antibiotics were used in the studies, which primarily included amoxicillin, clarithromycin, and azithromycin. The primary outcome of this systematic review and meta-analysis was to determine if there was a difference in the prevalence of antibiotic-associated diarrhea between the probiotic and placebo groups. Secondary outcomes included the severity of diarrhea and related adverse effects. The Cochrane Risk of Bias tool was used to

assess for risk of potential bias. The relative risk was calculated during the meta-analysis by using the DerSimonian-Laird algorithm. The definition of diarrhea varied amongst the several studies. The definitions included diarrhea being either two or three or more loose stools in a 24- or 48-hour period.

The results of the systematic review and meta-analysis concluded that the use of probiotics was associated with a lower relative risk of experiencing antibiotic-associated diarrhea compared to the placebo groups, RR .58, $p < .001$, 95% CI [.50, .68] (Hempel et al., 2012). Most of the studies that reported on the incidence of antibiotic-associated diarrhea found decreased incidence in the probiotic groups compared to the placebo groups, $p = .047$. There were no statistically significant differences found in the effectiveness of probiotics based on individual strains (Hempel et al., 2012).

The strengths of this systematic review and meta-analysis include the use of randomized controlled trials in all studies chosen for the review. Also, the large number of studies with patient populations across all age ranges allowed the information of this study to be applicable to the general population. Of the 82 studies selected, 44 were double-blinded, which decreases the likelihood of skewed results from potential bias. However, the remaining studies were not double-blinded, which may increase the likelihood of bias impacting the results provided from these selected trials. This contributes to the limitations of this systematic review and meta-analysis. Furthermore, the small sample size in many of the studies and the lack of reporting power calculation by nearly half of the studies make it difficult to ascertain the probability that the outcomes have a statistically significant effect. Despite the limitations present, this systematic review and meta-analysis demonstrated a well-designed methodology and randomization with results that indicate a notable ratio of the probability that probiotics may

reduce the risk of antibiotic-associated diarrhea during an antibiotic regimen. This finding warrants further investigation with larger sample sizes and double-blinding testing practices to minimize the potential risk of bias.

With the interest of probiotic supplementation for the treatment of antibiotic-associated diarrhea in healthy adult and pediatric populations, it is necessary to assess the efficacy in individuals in a compromised state of health in an inpatient setting. Selinger et al. (2013) conducted a double-blind, randomized, placebo-controlled clinical trial to investigate whether the probiotic preparation VSL#3 prevents antibiotic-associated diarrhea and *Clostridium difficile*-associated diarrhea in hospitalized patients. The study included a sample size of 229 average-risk adults in the inpatient setting who were on an antibiotic regimen. However, during the study, a total of 103 patients were withdrawn due to poor adherence and loss of follow-up after hospital discharge. Therefore, a final 122 patients completed the trial in accordance with the study's protocol. The 122 participants were divided equally into probiotic and placebo groups. The probiotic was given during the entire length of the antibiotic course plus an additional seven days thereafter. The VSL#3 preparation consisted of eight strains of probiotics with a dosage of 450 billion CFUs. The definition of diarrhea was based on the Bristol Stool Scale of more than two loose stools for two or more days.

The results of this study determined a statistically significant effect of the probiotic VSL#3 towards the prevention of antibiotic-associated diarrhea. Specifically, it was reported that 11.4% of the placebo group experienced diarrhea during the antibiotic regimen, whereas 0% of participants in the probiotic group experienced such symptoms, $p = .006$. Furthermore, a reduction in length of hospital stay by two days was found in the probiotic group. However, these results were not considered statistically significant (Selinger et al., 2013).

The strengths of this study include the study design. The double-blind, randomized design of this study reduces the probability of the results being skewed by potential bias. Limitations of this study include the inclusion criteria for participants that have taken an antibiotic four weeks prior to the study or have had a history of bowel pathology. This may inhibit the results of the study to be applied to the general population. The small sample size in this study is an additional limitation. Despite the study limitations, the outcomes of this study are promising and suggest a potential benefit of probiotics on antibiotic-associated diarrhea.

Additionally, Videlock and Cremonini (2012) performed a meta-analysis of 34 randomized, double-blinded, placebo-controlled trials to evaluate if probiotic use reduces the incidence of antibiotic-associated diarrhea during an antibiotic regimen. A total of 4138 participants were included in the studies. They consisted of children and adults in the inpatient and outpatient settings. The outcome objectives of the meta-analysis were to determine if probiotics reduced the incidence of antibiotic-associated diarrhea, if there is a variation in effect between adults and children, and if there are certain strains of probiotics that are more effective than others. The duration of antibiotic and probiotic supplementation varied between the studies with a range between three days to several weeks.

The results of the meta-analysis determined a lower risk of antibiotic-associated diarrhea in those who were in the probiotic groups versus those in the placebo groups, RR .53, $p < .001$, 95% CI [.44, .63] (Videlock & Cremonini, 2012). This was a pooled result from both pediatric and adult studies. No variations were found when comparing children versus adults in the overall effectiveness of probiotics. When comparing the different strains of probiotics used in each study, there were no differences found between strains in the overall effectiveness of probiotics

on the reduction of antibiotic-associated diarrhea. All strains within the studies yielded a protective effect (Videlock & Cremonini, 2012).

The strengths of this meta-analysis include a thorough methodology and a larger number of studies that were used for the analysis. Furthermore, focus was placed on assessing and reporting the risk of bias for each study in the meta-analysis. Limitations of this meta-analysis include the small sample sizes and lack of double-blinding in several of the studies. A high risk of bias was reported in several of the studies. The variability in length of antibiotic regimens between each study also prevented a reliable analysis to be made. The results of this meta-analysis showed a preventative effect of probiotics on antibiotic-associated diarrhea; however, the variability in study protocols and high risk of bias may limit the application of these results to the general population.

The Effect of Probiotics on Duration, Frequency, and Gastrointestinal Symptoms Related to Antibiotic-Associated Diarrhea

Research has also been conducted to investigate the efficacy of probiotics on a variety of aspects related to antibiotic-associated diarrhea, including frequency, duration, and type of gastrointestinal symptoms. Blaabjerg et al. (2017) concluded that the mean duration of antibiotic-associated diarrhea was less in the groups receiving a probiotic supplement compared to the placebo groups. Specifically, it was determined that an average of 2.93 days duration of diarrhea was found in the probiotic groups, whereas a total of 4.65 days duration was noted in the placebo groups. And Szajewska et al. (2006) found a reduction in the mean duration of diarrhea by 1.18 days in the probiotic when compared to the placebo group. Conversely, Evans et al. (2016) found no significant difference in the consistency and frequency of bowel movements between the probiotic and placebo groups. Furthermore, no significant difference was found between groups

regarding mean GSRS scores. Both the probiotic and placebo groups reported low scores, which indicates minimal to no abdominal discomfort, constipation, or indigestion symptoms. However, this study did find that there was a reduction in the duration of diarrhea symptoms by one day within the probiotic group (Evans et al., 2016). Olek et al. (2017) also concluded that there were no statistically significant differences found in the incidence or frequency of gastrointestinal symptoms found between the probiotic and placebo groups.

The Variability in Type of Organism and Dosage of Probiotics and the Influence in Overall Effectiveness

The efficacy of probiotics towards the reduction of antibiotic-associated diarrhea has been discussed. Additional factors that should be considered with probiotic supplementation include the type of organism and dosage of probiotic utilized for treatment. Cai et al. (2017) performed a systematic review and network meta-analysis to compare the overall effectiveness and tolerability amongst different probiotic agents in the prevention of antibiotic-associated diarrhea. Fifty-one randomized controlled trials with a total of 9569 participants were included in this systematic review and meta-analysis. Ten probiotic interventions were identified in the studies. Eight of the probiotic interventions were single strains, whereas the remaining two consisted of multiple genera of probiotics. The probiotics were administered during and after an antibiotic regimen. The primary outcome included assessing the efficacy of different probiotic strains on the incidence of antibiotic-associated diarrhea. Secondary outcomes assessed tolerability to treatment and occurrence of adverse events. Risk of bias and quality of evidence was assessed using the Cochrane Collaboration tool and the GRADE criteria.

Cai et al. (2017) concluded in this systematic review and network meta-analysis that all 10 of the probiotic interventions reduced the incidence of antibiotic-associated diarrhea.

However, six of the probiotic therapies were found superior in overall efficacy when compared to the placebo groups. *Lactobacillus rhamnosus* GG was ranked the highest in efficacy towards reducing the incidence of antibiotic-associated diarrhea, OR .28, 95% CI [.17, .47]. The remaining five effective therapies include *Lactobacillus casei*, OR .29, 95% CI [.13, .68], *Bacillus clausii*, OR .33, 95% CI [.11, .99], *Saccharomyces* boulardii, OR .41, 95% CI [.29, .57], *Lactobacillus* acidophilus, OR .57, 95% CI [.43, .76], and Multi-genera II, OR .60, 95% CI [.45, .81]. A meta-regression found no statistically significant difference in the efficacy of probiotics based on dosage and duration of therapy.

A strength of this study is that this was the first network meta-analysis designed to study probiotic efficacy on antibiotic-associated diarrhea. With this approach of study, multiple interventions of probiotics were able to be systematically evaluated and ranked in order of overall clinical effectiveness. The use of direct and indirect evidence was integrated into the study design, which increases the statistical precision of the results. Additional strengths include the use of a non-splitting approach and design-by-treatment interaction model to address possible inconsistencies and the GRADE criteria to determine the quality of evidence. These approaches, along with a large sample size, enabled this study to provide a precise estimate of the proposed clinical outcomes. Limitations of this systematic review and network meta-analysis include those that were present from the studies chosen for the review, such as incomplete data and possible selective reporting. Some of the studies also had small sample sizes, which may limit the clinical interpretation of these results. Despite these limitations, the results of this high-quality systematic review and network meta-analysis indicating that certain strains of probiotics demonstrate superiority in overall efficacy warrants a need for further well-designed trials and quality meta-analyses.

Blaabjerg et al. (2017) also found a difference in the effectiveness of probiotics on antibiotic-associated diarrhea based on strain and dosage of the probiotic. Specifically, it was determined that the strains, *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii*, demonstrated the most statistically significant reduction in antibiotic-associated diarrhea. A total of 10 studies found that a probiotic dosage of 5 billion CFUs per day or greater was associated with fewer incidences of antibiotic-associated diarrhea. Guo et al. (2019) concluded that the probiotic strains, *Lactobacillus rhamnosus* and *Saccharomyces boulardii*, were found to have the most statistically significant protective effect against antibiotic-associated diarrhea. It was also found that a dosage of 5 billion CFUs or greater exhibited the most evidence for the protective effects of probiotics. Similarly, Szajewska et al. (2006) also concluded that the probiotic strain, *Lactobacillus rhamnosus* GG, was found to have the most statistically significant reduction in antibiotic-associated diarrhea in the pediatric population. Other strains also found to be statistically significant, include *Saccharomyces boulardii*, *Bifidobacterium lactis*, and *Streptococcus thermophilus*. In reference to probiotic preparations, Selinger et al. (2013) found that the probiotic preparation, VSL#3, was determined to have a statistically significant effect on the prevention of antibiotic-associated diarrhea. VSL#3 is a preparation of eight probiotic strains at a dosage of 450 billion CFUs.

A meta-analysis performed by Johnston, Supine, and Vohra (2006) assessed the overall effectiveness of probiotics in the prevention of antibiotic-associated diarrhea in the pediatric population. Focus was placed on determining if certain probiotic strains and dosages have more significant effects than others. A total of 707 participants ranging in ages from 2 weeks to 15 years were included in the studies. In each study, the probiotic therapies were administered during the entirety of an antibiotic regimen, which ranged between 7 to 14 days. Several classes

of antibiotics and probiotic strains with differing dosages were included in the studies. The 5-point Jadad scale was used to assess double-blinding and randomization methods within each study.

The results of this meta-analysis concluded that five of the six studies found a statistically significant reduction in antibiotic-associated diarrhea in the probiotic groups compared to the placebo groups, RR .43, $p = .003$, 95% CI [.25, .75]. However, moderate statistical heterogeneity was found amongst the study results. Evaluation of probiotic strains revealed that *Lactobacillus rhamnosus* GG, RR .29, $p < .001$, 95% CI [.15, .57], and *Saccharomyces boulardii*, RR .19, $p = .002$, 95% CI [.07, .55], resulted in the greatest protective effect towards incidence of antibiotic-associated diarrhea (Johnston, Supine, & Vohra, 2006). A comparison of dosage of probiotics found that the treatment groups that used an amount of 5 billion CFUs or greater resulted in a clinically significant protective effect, RR .36, $p < .001$, 95% CI [.25, .53], whereas those that were less than 5 billion CFUs did not (Johnston et al., 2006).

Strengths of this meta-analysis include a comprehensive search strategy and the use of randomized controlled trials with attention placed on determining potential bias that may skew study results. An additional strength includes a thorough comparison of dosages and strains of probiotics with adequate data reporting. Limitations of this meta-analysis include the small number of studies selected for the analysis with half of the studies indicating an unclear quality based on the 5-point Jadad scale. This may indicate a possible risk of bias, which should be taken into consideration when clinically interpreting these results. The results of this meta-analysis, with its comprehensive methodology and randomization, provides promising evidence that certain strains and dosages of probiotics are statistically more protective against antibiotic-associated diarrhea. Further investigation with a larger number of studies should be considered in

order to draw a conclusion on the efficacy of probiotics on antibiotic-associated diarrhea in the pediatric populations.

Multiple strains of probiotics have been concluded to be protective against antibiotic-associated diarrhea. Conversely, Olek et al. (2017) found that the probiotic strain, *Lactobacillus plantarum* DSM 9843 (LP299V), did not result in a statistically significant difference in the incidence of antibiotic-associated diarrhea when compared to the placebo group. Furthermore, Evans et al. (2016) also determined that the probiotic strains, *Lactobacillus helveticus* R0052 and *Lactobacillus rhamnosus* R0011, at a dosage of 3.8 billion CFUs did not result in a statistically significant reduction in the consistency or frequency of bowel movements when compared to the placebo group.

The Variability in Outcomes Between Age Groups

A variability in outcomes between age groups has subsequently been studied when determining the efficacy of probiotics in the reduction of antibiotic-associated diarrhea. In reference to the pediatric population, Johnston et al. (2006) concluded that the use of probiotics in the pediatric population, ages 2 weeks to 15 years, resulted in a statistically significant reduction in antibiotic-associated diarrhea compared to the placebo groups. Szajewska et al. (2006) also found that probiotic use during an antibiotic regimen was correlated with a statistically significant reduction in the incidence of antibiotic-associated diarrhea within the pediatric population. The ages of the participants ranged from 1 month to 14 years. Conflictingly, the results of the study conducted by Olek et al. (2017) did not correlate a statistically significant reduction in antibiotic-associated diarrhea in the pediatric population with the use of probiotics. However, the strain of probiotic utilized in this study may have influenced the results of this study.

When comparing adult and pediatric populations, no variations in the overall effectiveness of probiotics were determined. Both populations experienced a lower risk of antibiotic-associated diarrhea with the use of probiotic supplementation during an antibiotic regimen (Videlock & Cremonini, 2012).

The results indicated in the studies above indicate minimal variability in outcomes between children, adolescents, and adults. However, whether similar outcomes would occur in the elderly population is important to consider. Xie, Li, Wang, Li, and Chen (2014) systematically reviewed six randomized controlled trials to evaluate the effectiveness of probiotics for the prevention of antibiotic-associated diarrhea and *Clostridium difficile* infection in older patients. A total of 3563 patients 65 years and older were included in this review. The six studies compared several genera of probiotics to the placebo groups. Risk ratios were used to measure differences in placebo versus treatment groups. All but one study defined diarrhea as greater than or equal to 3 loose stools within a 24-hour period. The Cochrane Risk of Bias tool was used to assess the quality of each study's methodology. The results of this systematic review found that only one of the six studies found a protective effect of probiotics in preventing antibiotic-associated diarrhea in older patients, RR .50, 95% CI [.29, .86]. The genera, *Bacillus licheniformis*, was utilized in this study. The remaining studies found no statistically significant difference in the reduction of antibiotic-associated diarrhea from the probiotic versus the placebo groups.

The strengths of this systematic review include a methodology that was thorough and utilized multiple electronic search databases. Furthermore, five out of the six studies were double-blinded, randomized controlled trials, which decreases the likelihood of bias skewed study results. Limitations of this systematic review include the small sample sizes in five of the

studies. Also, the one study that indicated a preventative effect of probiotics on antibiotic-associated diarrhea was without double-blinding, indicating a high risk of bias. The focus of a population strictly to those 65 and older may mask potential biases as well. The results of this systematic review, though limited with small sample size and potential bias, provides further insight into factors that may result in no beneficial effect of probiotics on antibiotic-associated diarrhea, such as age and strain of probiotic. However, further investigation with larger sample sizes is warranted to apply these results to the general population.

Discussion

The results of this literature review indicate that conjunctive use of probiotic supplementation during an antibiotic regimen demonstrate a statistically significant reduction in the overall instance of antibiotic-associated diarrhea. This was concluded by Blaadjerg et al. (2017) after noting that the incidence of antibiotic-associated diarrhea was more prevalent in the placebo groups versus the probiotic groups. Guo et al. (2019) found similar results in the pediatric population. These studies were conducted on healthy adults, children, and adolescents. In an inpatient setting, Selinger et al. (2013) determined in their study that hospitalized adult patients given a probiotic preparation resulted in no instances of antibiotic-associated diarrhea. Furthermore, this group resulted in a reduced hospital stay by two days when compared to the placebo group.

The efficacy of probiotics towards the reduction of antibiotic-associated diarrhea is influenced by the type of strain and dosage of probiotic. The two strains of probiotic found most statistically significant in multiple studies include *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii* (Blaabjerg et al., 2017; Cai et al., 2017; Guo et al., 2019; Szajewska et al., 2006). In reference to dosage, it was consistent that an amount of 5 billion CFUs or greater

resulted in a clinically significant protective effect (Blaabjerg et al., 2017; Johnston et al., 2006; Guo et al., 2019).

The statistical significance of the efficacy of probiotic supplementation towards the reduction of antibiotic-associated diarrhea also presents with limitations. The variability in outcomes based on age is notable. Johnston et al. (2006) and Szajewska et al. (2006) both indicated within their studies that probiotics given during an antibiotic regimen resulted in a statistically significant reduction of antibiotic-associated diarrhea in the pediatric population. When comparing adults versus children and adolescents, no variation in outcomes was found. Both age groups demonstrated a reduced risk of diarrhea with conjunctive use of probiotic supplementation during an antibiotic regimen (Videlock & Cremonini, 2012). The elderly population did not have similar outcomes. A systematic review by Xie et al. (2014) discovered that all but one of the studies in the review noted that individuals 65 years and older given a probiotic supplement did not result in a reduction in antibiotic-associated diarrhea when compared to the placebo group.

Additional limitations that exist include the efficacy of probiotics on specific gastrointestinal symptoms that are identified in antibiotic-associated diarrhea, including abdominal pain, bloating, and flatulence. Evans et al. (2016) and Olek et al. (2017) indicated that probiotic supplementation did not result in a statistically significant difference in the incidence or frequency of gastrointestinal symptoms found between the probiotic and placebo groups.

Current research investigating the efficacy of conjunctive use of probiotics during an antibiotic regimen in the reduction of antibiotic-associated diarrhea has included systematic reviews, meta-analyses, and double-blinded studies. The results of these studies suggest that probiotic supplementation demonstrates a protective effect in the prevention and reduction of

antibiotic-associated diarrhea. Nevertheless, with the limitations in outcomes that exist, it is difficult to establish a definite evidence-based conclusion towards the overall efficacy of probiotics. Further research is required to determine the safety and efficacy of probiotics in all patient populations in different clinical settings.

Applicability to Clinical Practice

The information provided in this literature review will assist medical providers in making an evidence-based decision on whether to include a probiotic during an antibiotic regimen to reduce the occurrence of antibiotic-associated diarrhea. The use of probiotics offers a potentially effective method to treat a common adverse effect of antibiotic use. This may aid medical providers in improving patient satisfaction and compliance with treatment.

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