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Probiotics and the Prevention of Clostridioides difficile: A Review of Existing Systematic Reviews

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Abstract

Clostridioides difficile is the leading cause of infectious diarrhea (Vernaya et al., 2017). Probiotics have been proposed to provide a protective benefit against *Clostridioides difficile infection* (CDI). The objective of this literature review was to examine the research evidence pertaining to the use of probiotics for the prevention of CDI in individuals receiving antibiotic therapy. A systematic literature review of studies published between 2015 and 2019 was performed. Five databases were searched, which yielded 10 systematic reviews that met strict inclusion criteria. Overall, the majority of evidence indicated that probiotics versus no treatment, placebo, or usual care have the potential to reduce CDIs in patients on antibiotic therapy by 50% or greater. There was no increased risk of adverse events among those taking probiotics. Benefit is greater when the background risk of CDIs was over 5%. The optimal probiotic dose, duration, species, and formulation is not known, although multispecies or *Lactobacillus* probiotics may be more effective in addition to taking probiotics within one to two days of starting antibiotics. These findings are limited to patients that are not immune compromised, pregnant, elderly, critically ill, have not had recent surgery, and do not have prosthetic heart valves. Overall, due to the magnitude of the effect of probiotics and their favorable safety profile, providers should consider including a shared decision-making conversation with their patients taking antibiotics regarding their personal risk versus benefit option to take probiotics concurrently.

Keywords: clostridium difficile infection, clostridioides difficile infection, CDI, c. difficile, CDAD, clostridum difficile associated diarrhea, AAD, antibiotic associated diarrhea, probiotics, lactobacillus, saccharomyces, bifidobacterium,

Probiotics and the Prevention of *Clostridioides difficile*: A Review of Existing Systematic Reviews

Clostridioides difficile is the leading cause of infectious diarrhea (Vernaya et al., 2017). It is also the cause of significant morbidity and mortality (Shen et al., 2017; Vernaya et al., 2017). Antibiotics can disrupt the intestinal microbiota, leading to increased susceptibility to the *Clostridioides difficile* pathogen (Goldenberg et al., 2017). Lau and Chamberlain (2016) indicate that antibiotic therapy is known to be the most substantial risk factor for *Clostridioides difficile* infection (CDI). Probiotics are living microbial supplements that are used to restore colonic microflora (Vernaya et al., 2017). Probiotics are hypothesized to reduce the incidence and prevalence of CDI (Vernaya et al., 2017). Probiotics have the potential to protect against CDI and are a promising prophylactic therapy. The purpose of this research is to present a synthesis of the current evidence regarding probiotics for the prevention of CDI in patients receiving antibiotic therapy. The background of CDI and probiotics are explored, an overview of the current CDI preventative practices are provided, and the review methods are described. The literature review of studies published between 2015 and 2019 are discussed, including a review of study characteristics, synthesis of research findings, quality indicators, and gaps in the literature. In conclusion, implications for future research, clinical practice, and policy are recommended.

Background

Clostridioides difficile, formerly known as *Clostridium difficile*, is a "gram-positive, spore-forming, toxin-producing anaerobic bacterium" (Zhu et al., 2018, para. 2). This pathogen is responsible for causing half a million CDIs in 2011 in the United States (Lessa et al., 2015). Of those reported infections, 29,300 resulted in death within 30 days of diagnosis (Lessa et al.,

2015). Recent epidemiological estimates indicate that the national burden of CDIs is decreasing (Guh et al., 2020). A 36% decrease in healthcare associated CDIs was found between 2011 and 2017, no change was found in community acquired CDIs (Guh et al., 2020). While the incidence of healthcare associated CDIs was reported to be decreasing, it remains a prominent nosocomial infection and is responsible for 12.1% of all healthcare associated infections (Centers for Disease Control [CDC], 2018b).

The most significant risk factor for CDIs is antibiotic therapy (Lau & Chamberlain, 2016). Antibiotics reduce the ability of the gastrointestinal microflora to protect against CDIs by decreasing its ability to prevent colonization of the *Clostridioides difficile* pathogen (Parkes, 2009). Being on an antibiotic increases the risk of CDI by seven to 10 times for the duration of antibiotic therapy and for 30 days thereafter (CDC, 2018a). Certain antibiotic classes have also been found to increase the risk of CDIs; these classes are the fluoroquinolones, third and fourth generation cephalosporins, clindamycin, and carbapenems (CDC, 2018b). In addition, the concurrent use of two or more antibiotics increases the risk of CDI (Johnston et al., 2018). Lastly, certain patient populations are at an increased risk for CDIs. Those at an increased risk include those who (a) are over the age of 65, (b) are immune compromised from medications or disease states, (c) have stayed in a hospital or long term care facility, (d) have had a previous CDI or exposure to CDI, (e) are undergoing gastrointestinal surgeries or procedures, and possibly (f) are taking proton pump inhibitors or histamine 2 blockers (CDC, 2018b).

Probiotics, defined as “live microorganisms which when administered in adequate amounts confer a health benefit on the host” (Hill et al., 2014, p. 506) have come under consideration as a potential prophylactic therapy for preventing CDIs in patients receiving antibiotic therapy. Probiotics have been proposed to work, as shown in animal and cellular

studies, by preventing gastrointestinal colonization, adhesion, and invasion by the CDI pathogen in addition to stimulating the immune system (Parkes, 2009). The current approach for preventing CDIs includes placing patients with a known or suspected CDI into contact precautions, adherence to recommended hand hygiene practices, environmental cleaning with a CDI sporicidal agent, and utilizing antibiotic stewardship programs (CDC, 2019). Current guidelines do not recommend probiotics as a preventative strategy, despite having the highest quality evidence of the previously stated prophylactic strategies (Lytvyn et al., 2016).

The clinical significance of preventing CDIs is found in the sequela of CDI patients' experience, the economic burden of CDIs to the healthcare system, and the potential cost effectiveness of probiotics. In addition, the United States National Action Plan goal is to reduce CDIs by 50% by the year 2020 (CDC, 2015). Patients with CDIs experience distressing symptoms such as severe diarrhea, dehydration, and colitis (CDC, 2018a). More rare but serious consequences such as sepsis, toxic megacolon, and death are also possible consequences of CDIs (CDC, 2018a). In addition to experiencing the physical symptoms of pain and discomfort, patients also miss work and spend time hospitalized due to CDIs. The economic burden of CDIs is significant, with a reported cost of $5.4 billion dollars in 2014 between both community and healthcare associated costs (Desi et al., 2016). Probiotics may provide a cost effective strategy to reduce the incidence of CDIs, (Shen, Leff et al., 2017; Shen, Maw et al., 2017). Overall, reducing the incidence of CDIs would yield health and economic benefits to patients and healthcare systems alike as well as contribute to meeting The United States National Action Plan's CDI reduction goal.

The findings of this research have the potential to inform advanced practice registered nurse (APRN) practice and may cause APRNs to consider including a shared decision making

discussion about the potential benefit of probiotics with their patients that need antibiotic therapy. Furthermore, this research should be used to inform the development or reevaluation of current clinical guidelines regarding CDI prevention.

Based on the phenomena of interest, a clinical question was developed which utilized the PICO framework (Melnyk & Fineout-Overholt, 2015): population (P), intervention (I), comparison (C), and outcome (O). This literature review sought to answer the following PICO question: In individuals receiving antibiotic therapy (P) how does receiving probiotics (I) versus not receiving probiotics (C) prevention affect the prevention of *Clostridioides difficile* (O)?

Methods

A review of the literature was conducted with the following methods. To begin, the following databases were selected, CINAHL Plus with Full Text, Cochrane Database of Systematic reviews, MEDLINE, MEDLINE (PubMed), and EBSCOMegaFILE. Four of the databases were searched between January 2013 and November 2019. EBSCOMegaFILE was searched between January 2015 and November 2019, due to refined search criteria to include studies from the past five years. General search restrictions were used to identify full text, peer-reviewed, articles written in the English language. Details on specific search restrictions used for each database, along with the general subjects covered by database, have been provided (See Table 1 in the Appendix section).

The following keywords were used to search all databases: "*Clostridium difficile,"* "*Clostridioides difficile*," "*C. difficile*," "*C. diff,"* "CDAD," "*Clostridium difficile* associated diarrhea," "AAD," "antibiotic associated diarrhea," "*C. difficile* associated diarrhea," "*C. diff* associated diarrhea," "probiotic," "prevention," "prophylaxis." "CDI," "*Saccharomyces*, "*Lactobaccillus*" "*Bifidobacterium,"* and "systematic review." Details on specific keyword

combinations that were used and the number of hits for each search have been provided (See Table 2 in the Appendix section).

All cells in Table 2 that had 10 or less search hits were then reviewed. This review yielded 148 abstracts that were screened for inclusion or exclusion, 66 of these were duplicates. Inclusion criteria for Table 3 included (a) systematic reviews with or without meta-analysis of randomized controlled trials; (b) intervention needed to compare a probiotic to a placebo, no treatment, or usual care in patients being administered antibiotic therapy; (c) incidence of CDI needed to be reported as either a primary or secondary outcome; and (d) included adult and/or pediatric sample populations from inpatient or outpatient settings. Additionally, the systematic review could include any strain, formulation, duration, or dose of the probiotic intervention. Any systematic reviews that did not meet the criteria were then excluded. While the initial search period was between January 2013 and November 2019, articles were narrowed further to include only systematic reviews that were published in the year 2015 or after, in an effort to include the most recent evidence.

Ten systematic reviews were identified for inclusion in Table 4. Each systematic review was reviewed in its entirety. Nine of these systematic reviews included a meta-analysis. Seven of these studies reported CDI as a primary outcome and three of these studies reported CDI as a secondary outcome to antibiotic-associated diarrhea. Table 4 includes columns that describe each systematic review's design, number of randomized controlled trials, number of subjects, sample characteristics, description of probiotic intervention, and major findings.

Summary of the Literature: **Characteristics of Included Reviews**

Of the 10 systematic reviews included, the mean number of randomized controlled trials included in each review was 17.2, and ranged between 5 and 31. The number of subjects

included in each review ranged between 2,020 and 7,967. Seven of these studies reported CDI as a primary outcome, whereas three of these studies reported CDI as a secondary outcome to antibiotic-associated diarrhea. Five reviews included randomized controlled trials that included inpatients and outpatients, three reviews included inpatients only, one review included only outpatients, and one review did not specify inpatients or outpatients. Five reviews included adult and pediatric subjects, two reviews specified adult subjects (≥ 18 years old) only, two studies specified older adults only (adults ≥60 years old; adults ≥ 65 years old), one review did not specify whether adult or pediatric participants were included but reported a mean participant age of 43.2 years, no reviews included only pediatric subjects.

The characteristics of the probiotic interventions included amongst the reviews varied. Six reviews generally included randomized controlled trials that used any probiotic strain, any dose, any duration, and any formulation for the probiotic intervention (Cai et al., 2018; Goldenberg et al., 2017; Johnston et al., 2018; Lau & Chamberlain, 2016; Shen et al., 2017; Vernaya et al., 2017). In contrast, other reviews had specified criteria for characteristics of the probiotic intervention such as probiotic species, duration, and/or timing. One review by Xie et al. (2015) included six probiotic species, and no dose, duration, or formulation criteria were stated. The following genera of species were included in Xie et al. (2015): *Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus*, and *Bacillus* alone or in combination. Another review included only *Lactobacillus* alone or in combination, in any dose or duration (Sinclair et al., 2016). In the review by Szajewska and Kołodziej (2015) only *Saccharomyces boulardii,* in any dose or duration was included. Lastly, one review did not state inclusion criteria for probiotic species in their methods though reported that five different types of probiotics were described amongst their included randomized controlled trials (McFarland,

2015). The five types of probiotics included in McFarland (2015) were: *Saccharomyces boulardii*, *Lactobacillus rhamnosus GG, Lactobacillus Casei* DN114001, *L. acidophilus* + *Bifidobacterium bifidum*, and *Lactobacillus acidophilus* + *Lactobacillus casei* + *Lactobacillus rhamnosus.* One review specifically included only randomized controlled trials that indicated the probiotic intervention was administered within 3 days of the start of antibiotic therapy and continued for the duration of antibiotic course (Lau & Chamberlain, 2016).

Generally, all of the systematic reviews included subjects receiving any type of antibiotic regimen, who were receiving it for any indication. Therefore, the types of antibiotic therapy and indications for antibiotic therapy being administered to the intervention and control group subjects varied amongst all systematic reviews. Only one systematic review specified that only oral antibiotics were included (Cai et al., 2018).

Synthesis of Major Systemic Review Findings

Incidence of CDI

The incidence of CDIs reported in the subjects that received the probiotic intervention while on antibiotic therapy varied by systematic review, some reported statistically significant reductions in CDIs whereas others reported no preventative effect was found. These findings also varied amongst probiotic strains and patient populations. To begin, eight of the 10 systematic reviews reported findings to suggest efficacy of probiotics in the preventions of CDIs. A 58%-75% statistically significant reduction in the incidence of CDI in the pooled probiotic intervention groups was reported amongst five of the reviews (Goldenberg et al., 2017; Johnston et al., 2018; Lau & Chamberlain, 2016; Shen et al., 2017; Sinclair et al., 2016). Another reported a statistically significant odds reduction of CDI of 75% and 96% with regard to specific probiotic strains (Cai et al., 2017). McFarland (2015) found that four probiotic types were effective in the

prevention of CDI and these findings were also statistically significant. Two reviews reported no preventative effect of probiotic use (Vernaya et al., 2017; Xie et al., 2015). Finally, Szajewska and Kołodziej (2015) found probiotics to be statically significant in the reduction of CDI risk by 75% in the pediatric patient population.

Adverse Events

Adverse events were reported to be similar between probiotic and control groups amongst the four studies that reported on adverse events (Goldenberg et al., 2017; Johnston et al., 2018; Shen et al., 2017; Szajewska, & Kołodziej, 2015). None of these reviews found that there was a noteworthy increased risk of adverse events in the intervention groups taking probiotics. Two studies actually reported a somewhat reduced incidence of adverse events in the probiotic group (Goldenberg et al., 2017; Shen et al., 2017). Goldenberg et al. (2017) reported a statistically significant (P=0.02) incidence of adverse events of 14.3% in the probiotic group versus a 17% incidence in the control group (p. 15). Shen et al. (2017) found an adverse event incidence of 14.2% for the probiotic group in comparison to an incidence of 15.9% in the control group (p. 1894). Johnston et al. (2018) reported an incidence of 12.4% in the probiotic group compared to a 12.1% incidence in the control group (p. 775). Lastly, Szajewska and Kołodziej (2015) simply stated that there were similar rates of incidence between the control and probiotic groups but did not explicitly report the rates of adverse event incidence nor its statistical significance.

Commonly reported adverse events in the largest systematic review included abdominal cramping, fever, flatulence, nausea, and taste disturbance (Goldenberg et al., 2017, p. 15). Serious adverse events were identified as bacteremia, fungemia, and sepsis. These events were not reported in some reviews and others reported them but did not attribute them to the probiotic intervention (Goldenberg et al., 2017; Johnston et al., 2018; Shen et al., 2017).

Probiotic Species and Strain Specific Efficacy

Several studies identified probiotic species and/or strains with superior efficacy in prevention CDI. To begin, Johnston et al. (2017) found a statistically significant treatment effect, where multispecies probiotics significantly reduced CDIs when compared to no probiotics ($P<.0001$), this is in contrast to the statistically insignificant effect of single species probiotics ($P=.051$). A multispecies mix of probiotics was also found to be statistically significant by Lau and Chamberlain (2016) in addition to five single *Lactobacillus* strains (*L. GG, L. acidophilus, L. casei, L. rhamnosus, L.plantarum*) and the *Saccharomyces boulardii* strain. Sinclair et al. (2016) included only *Lactobacillus* species in their review and found a large statistically significant risk reduction associated with *Lactobacillus* prophylaxis, regardless if it was given alone or in combination with other strains. Shen et al. (2017) also found a favorable effect for *Lactobacillus* only and *Lactobacillus* in combinations with *Streptococcus* or *Streptococcus* + *Bifidobacterium* species subgroups, which were statistically significant. Of eight probiotic regimes Cai et al. (2018) found two *Lactobacillus* strains that had superior efficacy and were statistically significant in reducing the risk of CDIs, these are the *L. casei* and *L. acidophilus* strains. McFarland (2015) found two probiotic single strains to have a statistically significant effect; these are *Saccharomyces boulardii*, and *Lactobacillus Casei* DN114001. In addition, McFarland (2015) found two combinations of species and/or strains to have a statistically significant effect, *Lactobacillus acidophilus* + *Bifidobacterium bifidum* and *Lactobacillus acidophilus* + *Lactobacillus casei* + *Lactobacillus rhamnosus* (McFarland, 2015). *Saccharomyces boulardii*, was the only probiotic strain included in the review by Szajewska and Kołodziej (2015) which demonstrated a lower rate of CDI in the *Saccharomyces boulardii* intervention group, but it was not statistically significant in the pooled analysis. Likewise, Johnston et al. (2018) performed a

post hoc subgroup analysis of *Saccharomyces boulardii* in their study and found no significant difference in efficacy against CDIs when compared against trials using other species. Shen et al. (2017) found no statistically significant efficacy for a specific probiotic formulation, nor did Goldenberg et al. (2017).

Efficacy in Select Patient Populations

Several systematic reviews performed subgroup analyses on select patient populations including adults, pediatrics, inpatients, and outpatients. To begin, the findings in regard to the adult and pediatric populations are as follows. Three reviews, all which reported statistically significant reduction of CDIs in their pooled intervention groups, found no difference in probiotic efficacy across adult or pediatric age groups (Goldenberg et al., 2017; Johnston et al., 2018; McFarland, 2015). Similarly, Lau and Chamberlain (2016) found statistically significant efficacy for both adults and pediatric patients with a slightly higher risk reduction in pediatric patients, of 59.5% ($P<0.001$) and 65.9% ($P=0.008$) respectively. Only one review by Szajewska and Kołodziej, (2015) found that probiotics reduced the risk of CDIs in the pediatric population by 75% ($P=0.01$) but not in adults ($P=0.39$). Two reviews, that included only older adults, ≥60 years of age, found no efficacy of probiotics and prevention of CDI in the older patient population (Vernaya et al., 2017; Xie et al., 2015).

Next, there were several findings regarding inpatient and outpatient populations. The efficacy of probiotics in hospitalized adult patients was statistically significant at a 58% ($P<0.001$) risk reduction as reported by Shen et al (2017) and a 75% risk reductions by Sinclair et al (2016). A greater benefit was found in hospitalized patients, where a statistically significant risk reduction of 61% ($P=<0.001$) was found versus a statistically insignificant 69.4% ($P=0.468$) risk reduction in outpatients (Lau & Chamberlain, 2016, p. 31). One review included only

outpatients, which found two specific probiotic strains to be effective in reducing the odds of CDI in this population (Cai et al., 2018).

Timing of Probiotic Administration

Timing of administration of the probiotic intervention in relation to when antibiotic therapy is started was a major finding across two studies. Shen et al. (2017) was the only review to perform a sensitivity analysis to evaluate the effect of probiotic timing on the prevention of CDI, and all probiotics were found to be more effective when administered closest to the first dose of antibiotics. A statistically significant reduction in efficacy was found for every day probiotics were delayed (Shen et al., 2017). The highest efficacy was found when probiotics were started within two days of antibiotic therapy (Shen et al., 2017, p. 1894). Probiotics administered three to seven days after starting antibiotics had only a 30% CDI risk reduction whereas when administered within 1 to 2 days after starting antibiotics the efficacy increased to 68% (P=0.02) and was statistically significant (Shen et al., 2017, p. 1894). Moreover, the significant reduction (60.5%) in CDIs in the pooled probiotic intervention group reported by Lau and Chamberlain (2016) may in part be due to the inclusion of only randomized controlled trials where the probiotic intervention was initiated within three days of antibiotic therapy. This was the only review to do so among the included studies.

Baseline Risk

Another finding validated by several reviews was that the efficacy of probiotics for the prevention of CDIs when there is a certain level of baseline risk. A greater prophylactic benefit was found when the baseline risk of CDI was >5%, which increased the risk reduction to 70% (P=0.01) from 60% (Goldenberg et al., 2017, p. 17). Likewise, Sinclair et al. (2016) reported that a baseline risk of CDI of ≥ 6%, increased the risk reduction to 83% from 75% (p. e714-e715).

Finally, another review also found that a CDI incidence rate of ≥5% is likely to improve the efficacy of probiotics (Johnston et al., 2018, p. 777).

Quality Indicators

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criterion was used by six of the systematic review authors to transparently evaluate the quality of evidence regarding their findings on the efficacy of probiotics for preventing CDIs (Guyatt et al., 2008). While all 10 systematic reviews included in this review are considered to be grade I level evidence, the GRADE criterion helps further determine how much confidence readers can put into the findings of each systematic review (Guyett et al., 2008). The amount of confidence that can be put into the evidence can be impacted by: study limitations, inconsistency of results, indirectness of results, imprecision, and reporting bias (Guyett et al., 2008). There are four GRADE levels of quality: "very-low," "low," "moderate," and "high" (Guyett et al., 2008). Overall, the quality of the evidence varied amongst the six systematic reviews that utilized the GRADE approach. It was reported to be "very-low" by one study (Sinclair et al., 2016), "moderate" by four studies (Cai et al., 2017; Goldenberg et al., 2017; Johnston et al., 2018; Szajewska & Kolodziej, 2015), and "high" by one study (Shen et al., 2017). The remaining four systematic reviews did not report the quality of their evidence with the GRADE criterion.

Quality considerations for the remaining four systematic reviews that did not report a GRADE rating include heterogeneity, methodological quality, missing data, and bias. To start, heterogeneity amongst the included randomized controlled trials was a limitation noted by three of the remaining systematic reviews (Lau & Chamberlain, 2016; Vernaya et al., 2017). Lau and Chamberlain (2016) reported no significant heterogeneity between the randomized controlled studies that were included (I^2=0.000). Although Lau and Chamberlain (2016) acknowledged that

there was variation between enrollment criteria of subjects, probiotic intervention characteristics, antibiotic regimens, CDI testing and diagnosing, and the follow up period (Lau & Chamberlain, 2016). McFarland (2015) reported a low level of heterogeneity (I^2=17.2%). In contrast, Vernaya et al. (2017) found a moderate level of heterogeneity amongst their included randomized controlled trials (I^2=46%).

Two systematic reviews included a measure of methodological quality. Xie et al. (2015) reported that the overall quality of the randomized controlled trials in their systematic review were of moderate methodological quality, heterogeneity in their review was not explicitly stated nor measured. Furthermore, Vernaya et al. (2017) reported moderate to high methodological quality for the five randomized controlled trials in their review. Missing data was also discussed as a limitation by all three of the systematic reviews (Lau & Chamberlain, 2016; McFarland, 2015; Vernaya et al., 2017).

In addition, publication bias was assessed for in two of the reviews. A funnel plot was utilized by both Lau and Chamberlain (2016) and McFarland (2015), which found no evidence of publication bias in either review. Lastly, a concern for potential researcher bias was identified in the systematic review by McFarland (2016). McFarland (2016) disclosed a conflict of interest because of participation on the scientific advisory board for BioK+, one of the probiotic formulations included in the author's systematic review. The study included four randomized controlled trials that utilized the BioK+ formulation as an intervention (McFarland, 2016). This affiliation could affect the quality of this researcher's reporting of the data and findings.

Overall, there was vast variability in the designs, quality, and heterogeneity of the randomized controlled trials included amongst the 10 systematic reviews. Variability was identified amongst the types of probiotic species and strains, variability in antibiotics that

subjects were taking during the studies, and variability in the doses, duration, and formulations of probiotic interventions. These differences impact how much trust can be placed in the major findings. The major findings from this literature review of existing systematic reviews can be interpreted with these quality indicators in mind.

Discussion

The findings from this review of 10 existing systematic reviews leaves us with several important points regarding the efficacy, safety, optimal probiotic species, and timing of administration of probiotics as a prophylactic therapy for CDIs in patients receiving antibiotic therapy. Overall, the majority of the evidence reviewed suggests that probiotics have the potential to be an effective prophylactic therapy for preventing CDIs. As relative to no probiotics, placebo or usual care, six of the 10 meta-analyses reported CDI risk reduction rates of 58%-75% when probiotics were administered to patients receiving antibiotics (Goldenberg et al., 2017; Johnston et al., 2018; Lau & Chamberlain, 2016; Shen et al., 2017; Sinclair et al., 2016). Two additional reviews found efficacy for certain probiotic strains in reducing CDIs (Cai et al., 2018; McFarland, 2015). Two of the reviews on older adults found no preventative effect (Vernaya et al., 2017; Xie et al., 2015). One review found efficacy in the pediatric population but not adult (Szajewska & Kołodziej, 2015). It must be noted that the quality of the evidence varied amongst these reviews, ranging from "very-low" to "high." This variability in GRADE quality does affect the overall level of confidence we can put into the synthesized findings.

The finding regarding a superior probiotic species or strain was uncertain. Multispecies mixes were found to be beneficial (Johnston et al., 2017; Lau & Chamberlain, 2016; McFarland, 2016). Two single species of probiotics that demonstrated greater efficacy are the *Lactobacillus* and *Sacchromyces boulardii* species. Of the *Lactobacillus* strains, *Lactobacillus casei* was found

to be superior in two reviews (Cai et al., 2018; McFarland, 2016). Evidence on the *Sacchromyces boulardii* strain is mixed, two reviews indicated superior efficacy, whereas one other found no statistically significant efficacy (Lau & Chamberlain, 2016; McFarland, 2016; Szajewska & Kołodziej, 2015). Two reviews that reported large magnitudes of effect of probiotics reducing the incidence of CDIs did not identify a single probiotic species or formulation that was superior to another (Goldenberg et al., 2017; Shen et al., 2017). While a certain probiotic species, strains, or combinations thereof, may yield the greatest benefit, though this remains unknown. Furthermore, most probiotics are regulated as a dietary supplement, and thus do not require approval by the Food and Drug Administration (FDA) before being sold to consumers (National Center for Complimentary and Integrative Health [NCCIH], 2019). Consideration must also be given to the potential for variability in quality and purity amongst these over the counter products. Probiotics being sold to specifically treat a disease will have undergone testing for efficacy and safety and will have been approved by the FDA (NCCIH, 2019).

Probiotics appear to have a favorable safety and side effect profile as all of the reviews that reported on adverse events found a similar rate of adverse events between the probiotic intervention group and the control groups, some even reported a lower rate of adverse events in the probiotic groups. Common adverse events reported included: abdominal cramping, fever, flatulence, nausea, and taste disturbance (Goldenberg et al., 2017). Severe adverse events, bacteremia, fungemia, and sepsis, were reported but not attributed to probiotics.

Patients in both the adult and pediatric populations appeared to gain a protective benefit against CDIs from the administration of probiotics when on antibiotic therapy. The only population found not to confer a protective benefit from probiotics were patients' age 60 and older. Other populations that were found to benefit were inpatients and outpatients, but more

benefit was seen in hospitalized patients (Lau & Chamberlain, 2016; Shen et al., 2017; Sinclair et al., 2016). While benefit was found in these populations, it must be known that certain patient populations were excluded from many of the randomized controlled trials included in these reviews. Generally, those that were excluded include immune compromised, pregnant, elderly, critically ill, surgical patients, and patients with prosthetic heart valves. Therefore, the efficacy and safety of probiotics is not known for these unique populations.

This review also found that both the timing of administration and that the inherent background risks are important variables in increasing the efficacy of probiotics for the prevention of CDI. Several of the reviews reported increased efficacy of probiotics for the prevention of CDIs in populations that had a higher baseline risk of CDIs, reported as greater than 5-6% (Goldenberg et al., 2017; Johnston et al., 2018; Sinclair et al., 2016). The greater benefit seen in hospitalized patients in this review could perhaps be due to the inherently higher baseline CDI risk in this population. Hospitals and other inpatient care facilities should identify their unique baseline risk of CDIs to determine if their patient populations would confer an even greater protective benefit from probiotics. If a provider or facility decides to implement prophylactic probiotics, evidence suggests that it is best to begin probiotics at the time of beginning antibiotics or within one to two days for the greatest benefit (Shen et al., 2017).

Lastly, probiotics may be a cost-effective prophylactic intervention. One study found probiotics to be a cost-effective prophylactic therapy in hospitalized patients 65 years of age or older (Shen, Leff, Schneider et al., 2017). Likewise, Shen et al. (2017) reported that probiotics have the potential to save approximately 500 million dollars a year.

Future Implications

Clinical Practice Recommendations

APRN's are in a key role to help reduce the incidence of CDIs. This can be accomplished by first always adhering to the best practices for antibiotic stewardship in their practice. Second, when antibiotics are clinically indicated APRN's should engage in a shared decision-making conversation with their patients regarding their option to take probiotics, in those whom probiotics are deemed appropriate for. Those appropriate for probiotics would be patients that are not immune compromised, pregnant, elderly, critically ill, surgical patients, or patients with prosthetic heart valves The APRN could recommend a multispecies probiotic or one containing *Lactobacillus.* Furthermore, the APRN would emphasize the importance of starting the probiotic as close to the start of the antibiotic and for the duration of the course of antibiotics. Overall, this conversation should include a brief discussion on the current evidence on the efficacy and safety of probiotics in the prevention of CDIs, with the goal of fully informing our patients on their option to take probiotics concurrently with their antibiotic prescription.

Recommendations for Research

Several gaps in the literature have been identified through this review of the literature. First, while there is strong evidence of little to no adverse events in patients receiving probiotics, this finding is limited to certain patients as most randomized controlled trials examined in these 10 systematic reviews excluded similar patients. The types of patients generally excluded were, immune compromised, pregnant patients, elderly, critically ill patients, surgical patients, and patients with prosthetic heart valves. This yields a large gap in the literature regarding the safety and efficacy of the use of probiotics in these patients. Since several of these patient populations are at higher risk for CDI, consideration should be given to performing randomized controlled trials specifically in these populations to determine if they can be used safely and effectively.

Next, two systematic reviews with the smallest number of randomized controlled trials were those that included only patients 60 years of age and older. Since this is a patient population that is at increased risk for CDIs, more randomized controlled trials are necessary to determine if this population could confer benefit from probiotics.

Lastly, while the efficacy of probiotics in the prevention of CDIs was demonstrated in several systematic reviews, most of the systematic reviews included randomized controlled trials that included any probiotic species, dose, duration, or formulation, as well as any type of antibiotic. This leaves us with a large remaining question; just what is the optimal probiotic species (or mix of species), dose, duration of therapy, and formulation (pill, yogurt, liquid, powder)? Or furthermore, could a certain probiotic work best to prevent CDIs in patients that are on a specific antibiotic or antibiotic class. Large scale randomized controlled studies comparing single species probiotics, multispecies probiotics, doses, durations, and formulations while controlling for certain antibiotics could yield findings to identify optimal probiotic prophylaxis.

Education Recommendations

As discussed previously APRNs are in a key role to help reduce the incidence of CDIs. To accomplish this, APRNs must first receive formal education regarding the state of the current evidence on probiotics for the prevention of CDIs in patients receiving antibiotic therapy on which to guide their practice. Formal education on the findings of this literature review can be disseminated to the APRN population by the following means: published article, employer facilitated training, PowerPoint presentation, APRN curricula, and/or updated clinical practice guidelines.

Recommendations for Policy

The majority of the research reviewed suggests that probiotics are effective in preventing CDIs in patients on antibiotic therapy, in addition to having little to no adverse effects in a patient population that is not immunocompromised, pregnant, elderly, critically ill, surgical patients, and without prosthetic heart valves. While the optimal probiotic is not known, the evidence indicates that any probiotic versus no probiotic is generally more effective against CDIs. Current guidelines do not reflect this evidence, and consideration should be given to updating relevant guidelines to include a recommendation to providers on the individualized use of probiotics for CDI prophylaxis.

Conclusion

CDIs present a substantial burden to our healthcare systems, patients, and economy. The findings from this review of existing systematic reviews has the potential to reduce these burdens and help us meet the United States National Action Plans goal to reduce CDIs by 50% in 2020. The findings suggest that any probiotic versus no probiotic in patients receiving antibiotic therapy may help reduce their risk of CDIs. The optimal probiotic species, strain, dose, duration, and formulation is not known, but a multispecies probiotic or those containing Lactobacillus could be recommended. If probiotics are administered, they should be given ideally within one to two days of the start of antibiotics. Furthermore, patients that are immune compromised, pregnant, elderly, had recent surgery, or have a prosthetic heart valve should not receive probiotics due to the unknown efficacy and safety in these populations. Because current guidelines do not include a recommendation on prophylactic probiotic therapy, the decision to incorporate a probiotic into the patient's plan of care should be a shared decision between the provider and patient. This decision can be made once the patient has been fully informed about

the current state of the evidence and their individualized risk versus benefit of taking a probiotic concurrently with their prescribed antibiotic.

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Appendix

Table 1

Database Search Description

Database	Restrictions Added to Search	Dates Included in Database	General Subjects Covered by Database
CINAHL Plus with Full Text	Full Text, English Language, Peer reviewed	January 2013-November 2019	"Provides full text access to e-books about nursing and 29 core nursing journals. Also provides citations and abstracts to articles, books, dissertations, proceedings, and other materials about all aspects of nursing and allied health, including cardiopulmonary technology, emergency service, health education, medical/laboratory, medical assistant, medical records, occupational therapy, physical therapy, physician assistant, radiologic technology, social service/health care, and more" (Minnesota State University Mankato [MSU], n.d.)
Cochrane Database of Systematic Reviews	Full Text	January 2013-November 2019	"Cochrane Database of Systematic Reviews contains full text articles, as well as protocols focusing on the effects of healthcare. Data is evidence-based medicine and is often combined statistically (with meta-analysis) to increase the power of the findings of numerous studies, each too small to produce reliable results individually" (MSU, n.d.)

MEDLINE	Full Text, English Language, Peer reviewed, systematic review or meta-analysis or review	January 2013-November 2019	"Provides citations and abstracts to articles covering all medical topics, including "research, clinical practice, administration, policy issues, and health care services. Produced by the U.S. National Library of Medicine, MEDLINE contains all records published in Index Medicus and since 2002, most citations previously included in separate NLM specialty databases such as SPACELINE and HISTLINE" (MSU, n.d.).
MEDLINE (PubMed)	Full Text, Free Full Text, English Language, systematic reviews , meta-analyses, reviews	January 2013-November 2019	"Provides citations, abstracts, and selected full text to articles about "medicine, nursing, dentistry, veterinary medicine, the health care system, and the preclinical sciences" (MSU, n.d.).
EBSCO MegaFILE	Full Text, English Language, Peer Reviewed (scholarly)	January 2015-November 2019	"EBSCO MegaFILE is comprised of the complete content and functionality of the following databases, all of which are updated on a daily basis: Academic Search Premier, Business Source Premier, MasterFILE Premier, and Regional Business News." (MSU, n.d.)

Reference

Minnesota State University, Mankato.(n.d.). *Databases a-z: All.*

https://libguides.mnsu.edu/az.php?a=all

Table 2

Data Abstraction Process

Date of Search	**Key Words**	**Hits in CINAHL**	**Hits in Cochrane**	**Hits in Medline**	**Hits in MEDLINE (PubMed)**	**Hits in EBSCO**
11.27.19	"Clostridium Difficile"	442	**1**	**7**	551	730
	"Clostridioides difficile"	14	0	**0**	20	50
	"C. diff"	13	0	**2**	0	13
	"C. difficile"	147	0	96	241	364

	“CDAD”	13	0	**7**	11	23
	“Clostridium difficile Associated Diarrhea”	11	**1**	**7**	17	14
	“Clostridioides difficile Associated Diarrhea”	0	0	**1**	0	0
	“AAD”	90	0	44	61	279
	“Antibiotic Associated Diarrhea”	17	0	31	72	31
	“C. difficile associated diarrhea”	**2**	0	**0**	**8**	**2**
	“C. diff associated diarrhea”	**0**	0	0	0	0
	“probiotic*”	1015	11	810	701	2,213
	“prevention”	65,312	485	10354	34782	66,711
	“prophylaxis”	2,927	25	966	2405	4,941
	“Probiotic*” and “clostridium difficile”	20	**1**	25	30	25
	“probiotic*” and “prevention of clostridium difficile”	**3**	**1**	**1**	12	**2**
	“probiotic*” and “C. difficile”	**7**	0	**8**	**9**	12
	“Probiotic*” and “c. diff”	**1**	0	**1**	0	**1**
	“probiotic*” and “Clostridium difficile associated diarrhea"	**3**	**1**	14	**5**	0
	“probiotic*” and “AAD”	**2**	0	**6**	**7**	**5**
	“probiotic*” and “antibiotic associated diarrhea”	**10**	0	29	26	11
	“probiotic*” and “c. diff associated diarrhea”	**0**	0	**1**	**0**	0
	“probiotic*” and “c. difficile associated diarrhea”	**1**	0	**5**	**2**	**1**
	Probiotic* and clostridium difficile	20	**1**	24	68	25
	“CDI”	271		103	262	497
	“Probiotic* and CDI”	0	0	0	22	0
	“Probiotic*” and “Prevention” and “Clostridium difficile”	17	**1**	30	12	**10**
	“Saccharomyces” and	169	**0**	531	254	375

	"prevention" and "Clostridium difficile" or "clostridioides difficile" or "C. difficile" or "C. diff"					
	"lactobacillus" and "clostridium difficile" or "clostridioidies difficle" or "C. difficile" or "C. diff"	158	**0**	528	263	372
	"Bifidobacterium" and "clostridium difficile" or "clostridioides diffiicle" or "C. difficile" or "C. diff"	160	**0**	521	255	375
	"probiotic*" and "prevention" and "clostridium difficile" and "systematic review"	0	**0**	**6**	**7**	**1**
11/30/10	Bibliographic review					

BOLD = Articles reviewed for match with systematic review criteria

Table 3

Characteristics of Literature Included and Excluded

Reference	Included or Excluded	Rationale
Agamennone, V., Krul, C. A. M., Rijkers, G., & Kort, R. (2018). A practical guide for probiotics applied to the case of antibiotic-associated diarrhea in the netherlands. *BMC Gastroenterology*, *18*(1), N.PAG. https://doi.org /10.1186/s12876-018-0831-x	Excluded	Does not report on *Clostridioides difficile* as outcome
Al Momani, L. A., Abughanimeh, O., Boonpheng, B., Gabriel, J. G., & Young, M. (2018). Fidaxomicin vs vancomycin for the treatment of a first episode of clostridium difficile infection: A meta-analysis and systematic review. *Cureus, 10*(6), 1. http://dx.doi.org/10.7759/cureus.2778	Excluded	This did not address probiotics as interventions or *Clostridioides difficile* prevention as outcome

Allegretti, J. R., Kao, D., Phelps, E., Roach, B., Smith, J., Ganapini, V. C., Kassam, Z., Huiping, X., & Fischer, M. (2019). Risk of clostridium difficile infection with systemic antimicrobial therapy following successful fecal microbiota transplant: should we recommend anti-clostridium difficile antibiotic prophylaxis? *Digestive Diseases & Sciences, 64*(6), 1668–1671. https://doi.org/10.1007/s10620-018-5450-4	Excluded	Does not have probiotics as intervention.
Aragon, M. O. H., Martinez, M. F., Bologna Molina, R., Aranda Romo, S., Aragon-Martinez, O. H., & Martinez-Morales, F. (2019). Should dental care professionals prescribe probiotics for their patients under antibiotic administration? *International Dental Journal*, *69*(5), 331–333. https://doi.org/10.1111/idj.12459	Excluded	Not a systematic review reporting on probiotics as an intervention and outcome of *Clostridioides difficile* prevention
Aziz, A. M. (2013). Nursing management of clostridium difficile infection. *Nurse Prescribing*, *11*(1), 21–27. https://doi.org/10.12968/npre.2013.11.1.21	Excluded	Not a systematic review reporting on probiotics and the prevention of *Clostridioides difficile*
Biswal, S. (2014). Proton pump inhibitors and risk for clostridium difficile associated diarrhea. *Biomed Journal, 37*(4), 178-183. https://doi.org/10.4103/2319-4170.128002	Excluded	This not systematic review
Blaabjerg, S., Artzi, D. M., & Aabenhus, R. (2017). Probiotics for the prevention of antibiotic-associated diarrhea in outpatients-A systematic review and meta-analysis. *Antibiotics (Basel, Switzerland), 6*(4). http://dx.doi.org/10.3390/antibiotics6040021	Excluded	This is a systematic review, but it does not report CDI as an outcome only ADD.
Cai, J., Zhao, C., Du, Y., Zhang, Y., Zhao, M., & Zhao, Q. (2018). Comparative efficacy and tolerability of probiotics for antibiotic-associated diarrhea: Systematic review with network meta-analysis. *United European Gastroenterology Journal, 6*(2), 169-180. http://dx.doi.org/10.1177/2050640617736987	Included	This is a meta-analysis that addresses both ADD and CD prevention as outcomes of a probiotic intervention.
Cammarota, G., Ianiro, G., Bibbò, S., & Gasbarrini, A. (2014). Gut microbiota modulation: probiotics, antibiotics or fecal microbiota transplantation? *Internal & Emergency Medicine, 9(*4), 365–373. https://doi.org/10.1007/s11739-014-1069-4	Excluded	Not a systematic review reporting on probiotics and the prevention of *Clostridioides difficile*

Chanyi, R. M., Craven, L., Harvey, B., Reid, G., Silverman, M. J., & Burton, J. P. (2017). Faecal microbiota transplantation: Where did it start? What have studies taught us? Where is it going? *SAGE Open Medicine*, *5*. https://doi.org/10.1177/2050312117708712	Excluded	Not a systematic review
Clarkin, C., Quist, S., Shamis, R., King, A. E., & Shah, B. M. (2019). Management of clostridioides difficile infection. *Critical Care Nurse, 39(*5), e1–e12. https://doi.org/10.4037/ccn201984	Excluded	Not a systematic review reporting on probiotics and the prevention of *Clostridioides difficile*
Cohen, N.A., Ben Ami, R., Guzner-Gur, H., Santo, M.E., Halpern, Z., & Maharshak, N. (2015). Fecal microbiota transplantation for clostridium difficile-associated diarrhea. *The Israel Medical Association Journal: IMAJ, 17*(8), 510-514. https://www.ima.org.il/MedicineIMAJ/viewarticle.aspx?year=2015&month=08&page=510	Excluded	This did not address probiotics as interventions or *Clostridioides difficile* prevention as outcome
Crow, J. R., Davis, S. L., Chaykosky, D. M., Smith, T. T., & Smith, J.M. (2015). Probiotics and fecal microbiota transplant for primary and secondary prevention of clostridium difficile infection. *Pharmacotherapy, 35*(11), 1016–1025. https://doi.org/10.1002/phar.1644	Excluded	This article includes a review of select meta-analyses but includes studies are >5 years old.
Culligan, E. P., & Sleator, R. D. (2016). Advances in the microbiome: Applications to clostridium difficile infection. *Journal of Clinical Medicine, 5*(9) http://dx.doi.org/10.3390/jcm5090083	Excluded	This did not address probiotics as intervention or *Clostridioides difficile* prevention as outcome
Davey, P., Brown, E., Charani, E., Fenelon, L., Gould, I. M., Holmes, A., Ramsey, C., Wiffen, P. & Wilcox, M. (2013). Interventions to improve antibiotic prescribing practices for hospital inpatients. *The Cochrane Database of Systematic Reviews,* (4), 1. http://dx.doi.org/10.1002/14651858.CD003543.pub3	Excluded	This did not address probiotics as interventions or *Clostridioides difficile* prevention as outcome
Dinleyici, M., & Vandenplas, Y. (2019). Clostridium difficile colitis prevention and treatment. *Advances in Experimental Medicine and Biology, 1125*, 139-146. http://dx.doi.org/10.1007/5584_2018_322	Excluded	Unable to access, E-book.

Doll, M., Fleming, M., Stevens, M. P., & Bearman, G. (2019). *Clostridioides difficile*-associated diarrhea: Infection prevention unknowns and evolving risk reduction strategies. *Current Infectious Disease Reports, 21*(1), 1. http://dx.doi.org /10.1007/s11908-019-0659-8	Excluded	This did not address probiotics as intervention or *Clostridioides difficile* prevention as outcome
Goldberg, E. J., Bhalodia, S., Jacob, S., Patel, H., Trinh, K. V., Varghese, B., Yang, J., Young, S., Raffa, R.B. (2015). Clostridium difficile infection: A brief update on emerging therapies. *American Journal of Health-System Pharmacy,* 1007–1012. https://doi.org/10.2146/ajhp140645	Excluded	Not a systematic review reporting on probiotics and the prevention of *Clostridioides difficile*
Goldenberg, J. Z., Yap, C., Lytvyn, L., Lo, C. K., Beardsley, J., Mertz, D., & Johnston, B. C. (2017). Probiotics for the prevention of clostridium difficile-associated diarrhea in adults and children. *Cochrane Database of Systematic Reviews*, (12). https://doi.org/10.1002/14651858.CD006095.pub4	Included	This is a systematic review that includes the correct population, intervention, comparison, and outcome
Guh, A., Kutty, P., & Guh, A. (2018). Clostridioides difficile infection. *Annals of Internal Medicine*, *169*(7), ITC49–ITC64. https://doi.org/10.7326/AITC201810020	Excluded	This not systematic review
Hamed, A., Miller, A. C., & Zehtabchi, S. (2019). Coadministration of probiotics with prescribed antibiotics for preventing clostridium difficile diarrhea. *Academic Emergency Medicine*, *26*(4), 454–456. https://doi.org/10.1111/acem.13557	Excluded	Article written as a response to another study. Not a systematic review
Hopkins, R. J., & Wilson, R. B. (2018). Treatment of recurrent clostridium difficile colitis: A narrative review. *Gastroenterology Report, 6*(1), 21-28. http://dx.doi.org/10.1093/gastro/gox041	Excluded	Addresses treatment rather than prevention of *Clostridioides difficile*
Hudson, L., Anderson, S., Corbett, A., & Lamb, T. (2017). Gleaning insights from fecal microbiota transplantation and probiotic studies for the rational design of combination microbial therapies. *Clinical Microbiology Reviews*, *30*(1), 191–231. https://doi.org/10.1128/CMR.00049-16	Excluded	Not a systematic review
Hung, Y., Lee, J., Lin, H., Liu, H., Wu, Y., Tsai, P., & Ko, W. (2015). Clinical impact of Clostridium difficile colonization. *Journal of Microbiology, Immunology and Infection*, *48*(3), 241–248. https://doi.org/10.1016/j.jmii.2014.04.011	Excluded	This not systematic review

Hungin, A., Mulligan, C., Pot, B., Whorwell, P., Agréus, L., Fracasso, P., … de Wit, N. (2013). [Review of systematic review: Probiotics in the management of lower gastrointestinal symptoms in clinical practice – an evidence-based international guide]. *Alimentary Pharmacology & Therapeutics*, *38*(8), 864–2813. https://doi.org/10.1111/apt.12460	Excluded	Does not have probiotics as intervention or CD infection as outcome.
Jarrad, A., Karoli, T., Blaskovich, M., Lyras, D., Cooper, M., & Jarrad, A. (2015). Clostridium difficile drug pipeline: challenges in discovery and development of new agents. *Journal of Medicinal Chemistry*, *58*(13), 5164–5185. https://doi.org/10.1021/jm5016846	Excluded	This not a systematic review
Johnston, B. C., Goldenberg, J. Z., & Guyatt, G. H. (2013). Probiotics for the prevention of clostridium difficile-associated diarrhea. *Annals of Internal Medicine, 158*(9), 706–707. https://doi.org/10.7326/0003-4819-158-9-201305070-00019	Excluded	This is a journal article commentary, incorrect study type.
*Johnston, B. C., Lytvyn, L., Lo, C. K., Allen, S. J., Wang, D., Szajewska, H., Miller, M. Ehrhardt, S., Sampalis, J. Duman, D. G., Pozzoni, P., Colli, A., Lönnermark, E., Selinger, C. P.,Wong, S., Plummer, S., Hickson, M., Pancheva, R., Hirsch, S…Mertz, D. (2018). Microbial preparations (probiotics) for the prevention of *Clostridium difficile* infection in adults and children: An individual patient data meta-analysis of 6,851 participants. *Infection Control and Hospital Epidemiology, 39*(7), 771-781. https://doi.org/10.1017/ice.2018.84	Included	This is a systematic review of RCT's, with meta-analysis. Probiotics are the intervention, and CD infections are the outcome.
Kalakuntla, A. S., Nalakonda, G., Nalakonda, K., Pidikiti, C. V., & Aasim, S. A. (2019). Probiotics and clostridium difficile: A review of dysbiosis and the rehabilitation of gut microbiota. *Cureus, 11*(7), 1. http://dx.doi.org/10.7759/cureus.5063	Excluded	This did not address probiotics as interventions or *Clostridioides difficile* prevention as outcome
Keller, D. L. (2013). Probiotics for the prevention of clostridium difficile-associated diarrhea. *Annals of Internal Medicine, 157*(12), 878-88. https://doi.org/10.7326/0003-4819-158-9-201305070-00017	Excluded	This is a journal article commentary, incorrect study type.
Killeen, S., Martin, S. T., Hyland, J., O'Connell, P. R., & Winter, D. C. (2014). Clostridium difficile enteritis: A new role for an old foe. *The Surgeon: Journal of the Royal Colleges of Surgeons of Edinburgh and Ireland, 12*(5), 256-262. http://dx.doi.org /10.1016/j.surge.2014.01.008	Excluded	Does not address probiotics as an intervention.

Kleinman, L., Talbot, G., Hunsche, E., Schüler, R., & Nord, C. (2018). The cdi-daysyms: Content development of a new patient-reported outcome questionnaire for symptoms of clostridium difficile infection. *Value in Health*, *21*(4), 441–448. https://doi.org/10.1016/j.jval.2017.08.3017	Excluded	This is not a systematic review
Knoll, B., Hammond, S., Koo, S., Issa, N., Tullius, S., Baden, L.,Pomahac, B., & Marty, F. (2013). Infections following facial composite tissue allotransplantation—single center experience and review of the literature. *American Journal of Transplantation*, *13*(3), 770–779. https://doi.org/10.1111/ajt.12013	Excluded	Does not address probiotics as intervention or *Clostridioides difficile* prevention as outcome
Komatsu, S., Sakamoto, E., Norimizu, S., Shingu, Y., Asahara, T., Nomoto, K., & Nagino, M. (2016). Efficacy of perioperative synbiotics treatment for the prevention of surgical site infection after laparoscopic colorectal surgery: A randomized controlled trial. *Surgery Today, 46*(4), 479–490. https://doi.org/10.1007/s00595-015-1178-3	Excluded	Not a systematic review.
Lau, C. S., & Chamberlain, R. S. (2016). Probiotics are effective at preventing *Clostridium difficile*-associated diarrhea: A systematic review and meta-analysis. *International Journal of General Medicine, 9*, 27-37. https://doi.org/10.2147/IJGM.S98280	Included	This is a systematic review with meta-analysis that has probiotics as intervention and CD infections as outcome.
Leedahl, D. D., Personett, H. A., Nagpal, A., & Barreto, E. F. (2019). Prevention of clostridium difficile infection in critically ill adults. *Pharmacotherapy, 39(*3), 399–407. https://doi.org/10.1002/phar.2200	Excluded	Is not a systematic review of RCT's.
Ling, Z., Liu, X., Cheng, Y., Luo, Y., Yuan, L., Li, L., & Xiang, C. (2015). Clostridium butyricum combined with bifidobacterium infantis probiotic mixture restores fecal microbiota and attenuates systemic inflammation in mice with antibiotic-associated diarrhea. *BioMed Research International*,1–9. https://doi.org/10.1155/2015/582048	Excluded	Incorrect subject, mice.
Liu, Y., Tran, D. Q., & Rhoads, J. M. (2018). Probiotics in disease prevention and treatment. *Journal of Clinical Pharmacology*, *58*, S164–S179. https://doi.org/10.1002/jcph.1121	Excluded	Not a systematic review reporting on probiotics as an intervention and outcome of *Clostridioides difficile* prevention

Marshall, L. L., Peasah, S., & Stevens, G. A. (2017). Clostridium difficile infection in older adults: Systematic review of efforts to reduce occurrence and improve outcomes. *The Consultant Pharmacist: The Journal of the American Society of Consultant Pharmacists, 32*(1), 24-41. http://dx.doi.org/10.4140/TCP.n.2017.24	Excluded	Does not address probiotics as an intervention and *Clostridoides difficile* prevention as outcome
McFarland, L. V. (2015). Probiotics for the primary and secondary prevention of c. difficile infections: A meta-analysis and systematic review. *Antibiotics (Basel, Switzerland), 4*(2), 160-178. http://dx.doi.org/10.3390/antibiotics4020160	Included	This is a meta analysis and systematic review of probiotics as intervention and CDI as outcome
Meng, F., Chen, T., Ma, D., Wang, X., Zhao, X., Tian, P., Wang, H., Tang, X., Wang, X. & Xin, H. (2017). Reclamation of herb residues using probiotics and their therapeutic effect on diarrhea. *Mediators of Inflammation*, 1–8. https://doi.org/10.1155/2017/4265898	Excluded	This is not a systematic review of RCT's.
Mills, J., Rao, K., & Young, V. (n.d.). Probiotics for prevention of clostridium difficile infection. *Current Opinion Gastroenterology*, *34*(1), 3–10. https://doi.org/10.1097/MOG.0000000000000410	Excluded	Not a systematic review.
Mohajeri, M. H., Brummer, R. J. M., Rastall, R. A., Weersma, R. K., Harmsen, H. J. M., Faas, M., & Eggersdorfer, M. (2018). The role of the microbiome for human health: From basic science to clinical applications. *European Journal of Nutrition,* 57, 1–14. https://doi.org/10.1007/s00394-018-1703-4	Excluded	Not a systematic review
Morris, O., Tebruegge, M., Pallett, A., Green, S. M., Pearson, A. D., Tuck, A., Clarke, S. C., Roderick, P., & Faust, S. N. (2013). Clostridium difficile in children: A review of existing and recently uncovered evidence. *Advances in Experimental Medicine and Biology, 764*, 57-72. https://doi.org/10.1007/978-1-4614-4726-9_4	Excluded	This did not address probiotics as intervention or clostridioides difficile prevention as outcome
Morrow, L. E., & Wischmeyer, P. (2017). Blurred lines: dysbiosis and probiotics in the icu. *CHEST, 151*(2), 492–499. https://doi.org/10.1016/j.chest.2016.10.006	Excluded	This is not a systematic review of RCT's.
Mullane, K. (2014). Fidaxomicin in *Clostridium difficile* infection: Latest evidence and clinical guidance. *Therapeutic Advances in Chronic Disease, 5*(2), 69-84. http://dx.doi.org /10.1177/2040622313511285	Excluded	This did not address probiotics as interventions or *Clostridioides difficile* prevention as outcome

Natarajan, M., Walk, S., Young, V., & Aronoff, D. (2013). A clinical and epidemiological review of non-toxigenic Clostridium difficile. *Anaerobe*, *22*, 1-5. https://doi.org/10.1016/j.anaerobe.2013.05.005	Excluded	Not a systematic review
Nazir, Y., Hussain, S. A., Abdul Hamid, A., & Song, Y. (2018). Probiotics and their potential preventive and therapeutic role for cancer, high serum cholesterol, and allergic and hiv diseases. *BioMed Research International*, *2018*, 1–17. https://doi.org/10.1155/2018/3428437	Excluded	Not a systematic review reporting on probiotics as an intervention and outcome of clostridioides difficile prevention
Nelson, R. L., Gladman, E., & Barbateskovic, M. (2014). Antimicrobial prophylaxis for colorectal surgery. *The Cochrane Database of Systematic Reviews,* (5), 1. http://dx.doi.org/ 10.1002/14651858.CD001181.pub4	Excluded	This did not address probiotics as interventions or *Clostridioides difficile* prevention as outcome
Oscherwitz, S. (2013). Probiotics for the prevention of *Clostridium difficile*-associated diarrhea. *Annals of Internal Medicine, 158*(9), 706. https://doi.org /10.7326/0003-4819-158-9-201305070-00018	Excluded	This is a journal article commentary, incorrect study type.
Paasché, S. (2013). Fecal microbiota transplantation: An innovative approach to treating *Clostridium difficile* disease. *JAAPA: Official Journal of the American Academy of Physician Assistants, 26*(8), 46-49. https://doi.org/10.1097/01.jaa.0000432570.98817.16	Excluded	This did not address probiotics as interventions or *Clostridioides difficile* prevention as outcome
Papatheodorou, P., Barth, H., Minton, N., & Aktories, K. (2018). Cellular uptake and mode-of-action of *Clostridium difficile* toxins. *Advances in Experimental Medicine and Biology, 1050*, 77-96. http://dx.doi.org/10.1007/978-3-319-72799-8_6	Excluded	This did not address probiotics as interventions or *Clostridioides difficile* prevention as outcome
Pattani, R., Palda, V. A., Hwang, S. W., & Shah, P. S. (2013). Probiotics for the prevention of antibiotic-associated diarrhea and *Clostridium difficile* infection among hospitalized patients: Systematic review and meta-analysis. *Open Medicine: A Peer-Reviewed, Independent, Open-Access Journal, 7*(2), e56-e67. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3863752/	Excluded	This article meets all inclusion criteria but was excluded because it was published prior to 2015.
Pérez-Cobas, A. E., Moya, A., Gosalbes, M. J., & Latorre, A. (2015). Colonization resistance of the gut microbiota against *Clostridium difficile*. *Antibiotics (Basel, Switzerland), 4*(3), 337-357. http://dx.doi.org/10.3390/antibiotics4030337	Excluded	This not systematic review

Permpalung, N., Upala, S., Sanguankeo, A., & Sornprom, S. (2016). Association between NSAIDs and -associated diarrhea: A systematic review and meta-analysis. *Canadian Journal of Gastroenterology and Hepatology*, 9. https://doi.org/10.1155/2016/7431838	Excluded	This a meta-analysis but it does not address probiotics as intervention or *Clostridioides difficile* prevention as outcome
Phatharacharukul, P., Thongprayoon, C., Cheungpasitporn, W., Edmonds, P., Mahaparn, P., Bruminhent, J., & Edmonds, P. J. (2015). The risks of incident and recurrent *Clostridium difficile*-associated diarrhea in chronic kidney disease and end-stage kidney disease patients: a systematic review and meta-analysis. *Digestive Diseases & Sciences, 60(*10), 2913–2922. https://doi.org/ 10.1007/s10620-015-3714-9	Excluded	Incorrect patient population.
Polito, N. B., & Avery, L. M. (2018). Mitigating risk of bloodstream infection related to inpatient probiotic use. *American Journal of Health-System Pharmacy, 75(*10), 595–596. https://doi.org/10.2146/ajhp180092	Excluded	Not a systematic review
Rineh, A., Kelso, M., Vatansever, F., Tegos, G., & Hamblin, M. (2014). [Review of *Clostridium difficile infection: molecular pathogenesis and novel therapeutics*]. *Expert Review of Anti-infective Therapy*, *12*(1), 131–150. https://doi.org/10.1586/14787210.2014.866515	Excluded	This not a systematic review and it does not address probiotics as intervention or *Clostridioides difficile* prevention as outcome
Rondanelli, M., Faliva, M., Perna, S., Giacosa, A., Peroni, G., & Castellazzi, A. (2017). [Review of *using probiotics in clinical practice: Where are we now? A review of existing meta-analyses*]. *Gut Microbes*, *8*(6), 521–543. https://doi.org/10.1080/19490976.2017.1345414	Excluded	This is not a meta-analysis that addresses probiotics as intervention and prevention of CDI
Rubin, Z. A., Martin, E. M., & Allyn, P. (2018). Primary prevention of *Clostridium difficile*-associated diarrhea: Current controversies and future tools. *Current Infectious Disease Reports, 20*(9), 32. http://dx.doi.org/10.1007/s11908-018-0639-4	Excluded	This did not address probiotics as an intervention as compared to no probiotics. It is not a meta-analysis of RCT's.

Sartelli, M., Di Bella, S., Mcfarland, L., Khanna, S., Furuya-Kanamori, L., Abuzeid, N., Abdu Zidan, F.M., Ansaloni, L., Augustin, G., Bala, M., Ben-Ishay, O., Biffl, W. L., Brecher, S. M., Camocho-Ortiz, A., Cainzos, M. A., Chan, S., Cherry-Bukoweic, J. R., Clanton, J., Coccolini, F… Catena, F. (2019). 2019 update of the WSES guidelines for management of infection in surgical patients. *World Journal of Emergency Surgery, 14*(1), 8. https://doi.org/10.1186/s13017-019-0228-3	Excluded	This is not a systematic review
Scott, K. P., Jean-Michel, A., Midtvedt, T., & Van Hemert, S. (2015). Manipulating the gut microbiota to maintain health and treat disease. *Microbial Ecology in Health & Disease,* 26, 1–N. https://doi.org/10.3402/mehd.v26.25877	Excluded	Not a systematic review
Seddik, H., Boutallaka, H., Elkoti, I., Nejjari, F., Berraida, R., Berrag, S., … Benkirane, A. (2019). *Saccharomyces boulardii* CNCM I-745 plus sequential therapy for helicobacter pylori infections: a randomized, open-label trial. *European Journal of Clinical Pharmacology*, *75*(5), 639–645. https://doi.org/10.1007/s00228-019-02625-0	Excluded	Not a systematic review reporting on outcome of *Clostridioides difficile* prevention
Seo, M., Inoue, I., Tanaka, M., Matsuda, N., Nakano, T., Awata, T., Katayama, S., Alpers, S., & Komoda, T. (2013). *Clostridium butyricum* MIYAIRI 588 improves high-fat diet-induced non-alcoholic fatty liver disease in rats. *Digestive Diseases & Sciences*, *58*(12), 3534–3544. https://doi.org/10.1007/s10620-013-2879-3	Excluded	Incorrect subject rats.
*Shen N. T., Maw, A., Tmanova, L. L., Pino, A., Ancy, K., Crawford, C. V… Evans, A. T. (2017). Timely use of probiotics in hospitalized adults prevents *Clostridium difficile* infection: A systematic review with meta-regression analysis. *Gastroenterology,* 152, 18889. https://doi.org/10.1053/j.gastro.2017.02.003	Included	This is a systematic review with meta-analysis that has probiotics as intervention and CD infections as outcome.
Shin, J. H., Chaves-Olarte, E., & Warren, C. A. (2016). *Clostridium difficile* infection. *Microbiology Spectrum, 4*(3). http://dx.doi.org/10.1128/microbiolspec.EI10-0007-2015	Excluded	Does not address probiotics as intervention or CD prevention as outcome. It is a chapter in a textbook and is only available for preview.

Simpson, M., & Lyon, C. (2019). Do probiotics reduce C diff risk in hospitalized patients? *Journal of Family Practice*, *68*(6), 351–354. https://www.mdedge.com/clinicianreviews/article/211620/infectious-diseases/do-probiotics-reduce-c-diff-risk-hospitalized	Excluded	Not a systematic review reporting on probiotics and the prevention of *Clostridioides difficile*
Sinclair, A., Xie, X., Saab, L., Dendukuri, N. (2016). *Lactobacillus* probiotics in the prevention of diarrhea associated with *Clostridium difficile*: A systematic review and Bayesian hierarchical meta-analysis. *Canadian Medical Associated Journal Open, 4(*4), E706-E718. https://doi.org/10.9778/cmajo.20160087	Included	This is a systematic review with meta-analysis that has probiotics as intervention and CD infections as outcome.
Spinler, J., Ross, C., & Savidge, T. (2016). Probiotics as adjunctive therapy for preventing *Clostridium difficile* infection – What are we waiting for? *Anaerobe*, *41*, 51–57. https://doi.org/10.1016/j.anaerobe.2016.05.007	Excluded	Not a systematic review
Stier, H., & Bischoff, S. C. (2016). Influence of *Saccharomyces boulardii* CNCM I-745 on the gut-associated immune system. *Clinical and Experimental Gastroenterology, 9*, 269-279. https://doi.org/10.2147/CEG.S111003	Excluded	This did not address probiotics as interventions or *Clostridioides difficile* prevention as outcome
Szajewska, H., & Kołodziej, M. (2015). Systematic review with meta-analysis: *Lactobacillus rhamnosus* GG in the prevention of antibiotic-associated diarrhoea in children and adults. *Alimentary Pharmacology & Therapeutics, 42*(10), 1149–1157. https://doi.org 10.1111/apt.13404	Included	This is a systematic review with meta-analysis that reports on CD infection as an outcome.
Valdés-Varela, L., Gueimonde, M., & Ruas-Madiedo, P. (2018). Probiotics for prevention and treatment of clostridium difficile infection. *Advances in Experimental Medicine and Biology, 1050*, 161-176. http://dx.doi.org/10.1007/978-3-319-72799-8_10	Excluded	This is not a meta-analysis
*Vernaya, M., McAdam, J., & Hampton, M. D. (2017). Effectiveness of probiotics in reducing the incidence of Clostridium difficile-associated diarrhea in elderly patients: A systematic review. *JBI Database of Systematic Reviews and Implementation Reports, 15*(1), 140. https://doi.org/10.11124/JBISRIR-2016-003234	Included	This is a systematic review with meta-analysis that has probiotics as intervention and CD infections as outcome.

Vitko, H. A., Schreiber, M. A., & Sekula, L. K. (2017). Probiotics for trauma patients: Should we be taking a precautionary approach? *Journal of Trauma Nursing*, *24*(1), 46–52. https://doi.org/10.1097/JTN.0000000000000263	Excluded	Not a systematic review
Walker, T. (2013). Probiotics can considerably minimize *C difficile* in hospitals. *Formulary*, *48*(2), 51. https://www.formularywatch.com/clinical-pharmacology/probiotics-can-considerably-minimize-c-difficile-hospitals	Excluded	Journal article commentary. Not a systematic review
Weed, H. G. (2013). Review: Probiotics prevent *C. difficile*-associated diarrhea in patients using antibiotics. *Annals of Internal Medicine, 159*(8), JC7. https://doi.org/10.7326/0003-4819-159-8-201310150-02007	Excluded	This is a journal article commentary, incorrect study type.
Wilkins, T., Sequoia, J., & Wilkins, T. (2017). Probiotics for gastrointestinal conditions: A summary of the evidence. *American Family Physician*, *96*(3), 170–178. http://www.aafp.org/link_out?pmid=28762696	Excluded	This did not address probiotics as an intervention or *Clostridioides difficile* prevention as outcome
Williams, D., & Adcock, L. (2018). Probiotics for antibiotic-associated diarrhea and *Clostridium difficile* infection: a review of clinical effectiveness. *Canadian Agency for Drugs and Technologies in Health,* 1-29. https://www.ncbi.nlm.nih.gov/books/NBK538350/	Excluded	This is a review of systematic reviews/meta-analyses
Wong, S., Jamous, A., Sekhar, R., Lewis, S., Mckeown, E., & Hirani, S. (2015). Effectiveness of probiotic in preventing and treating antibiotic-associated diarrhoea and/or *Clostridium difficile*-associated diarrhoea in patients with spinal cord injury: A protocol of systematic review of randomised controlled trials. *Systematic Reviews*, *4*(154), 170. https://doi.org/10.1186/s13643-015-0159-3	Excluded	This is a protocol, full article has not been published yet.
Wu, Z., Du, X., & Zheng, J. (2013). Role of *Lactobacillus* in the prevention of *Clostridium difficile*-associated diarrhea: A meta-analysis of randomized controlled trials. *Chinese Medical Journal, 126*(21), 4154-4161. https://journals.lww.com/cmj/fulltext/2013/11050/Role_of Lactobacillusin_the_prevention.27.aspx	Excluded	This article meets all inclusion criteria but was excluded because it was published prior to 2015.
Zhu, D., Sorg, J., & Sun, X. (2018). Biology: Sporulation, germination, and corresponding therapies for infection. *Frontiers in Cellular and Infection Microbiology*, *8*, 29. https://doi.org/10.3389/fcimb.2018.00029	Excluded	Microbiology of CDI is beyond the scope of this review

Zwetchkenbaum, S. R., Overbeck, K. J., & Pomerantz, S. C. (2015). Antibiotic-associated diarrhea and the older dental patient: how do dentists respond? *Special Care in Dentistry*, *35*(6), 279–284. https://doi.org/10.1111/scd.12130	Excluded	Not a systematic review

*Identified through bibliographic review

Table 4

Literature Review of All Studies Included

Citation	**Study Design**	**RCT's**	**Subjects**	**Sample Characteristics**	**Intervention & Control**	**Major Findings**
Cai, J., Zhao, C., Du, Y., Zhang, Y., Zhao, M., & Zhao, Q. (2018). Comparative efficacy and tolerability of probiotics for antibiotic-associated diarrhea: Systematic review with network meta-analysis. *United European Gastroenterology Journal, 6*(2), 169-180. https://doi.org/10.1177/2050640617736987	Systematic review with meta-analysis	21	6623	Outpatients only Any oral antibiotic and indication	Probiotics, any dose, strain, or duration. Vs. Active or placebo control	-*L. casei* strain found to have best efficacy for reducing CD infection (0.04 (0.00, 0.77). -*L. acidophilus* (0.25 (0.12, 0.52) -GRADE: moderate quality
Goldenberg, J. Z., Yap, C., Lytvyn, L., Lo, C. K., Beardsley, J., Mertz, D., & Johnston, B. C. (2017). Probiotics for the prevention of *Clostridium difficile*-associated diarrhea in adults and children. *The Cochrane Database of Systematic Reviews, 12*, CD006095. https://doi.org/10.1002/14651858.CD006095.pub4	Systematic Review with Meta-Analysis	31	8,572	Inpatients & Outpatients Adults & Pediatrics Any antibiotic, any indication	Probiotics, any strain, dose, or duration. Vs. Placebo, alternative prophylaxis, or no treatment	-Probiotics reduced risk of CDAD by 60% (Z=6.54, P<0.00001) -GRADE: moderate quality -Probiotics reduced risk of adverse events by 17% (Z=2.30, P=0.02) -Among trials with a baseline CDI risk of >5% demonstrated a 70% risk

Citation	Study Design	RCT's	Subjects	Sample Characteristics	Intervention & Control	Major Findings
						reduction of CDAD (*P*=0.01)
Johnston, B. C., Lytvyn, L., Lo, C. K., Allen, S. J., Wang, D., Szajewska, H., Miller, M. Ehrhardt, S., Sampalis, J. Duman, D.G., Pozzoni, P., Colli, A., Lönnermark, E., Selinger, C.P.,Wong, S., Plummer, S., Hickson, M., Pancheva, R., Hirsch, S…Mertz, D.. (2018). Microbial preparations (probiotics) for the prevention of *Clostridium difficile* infection in adults and children: An individual patient data meta-analysis of 6,851 participants. *Infection Control and Hospital Epidemiology, 39*(7), 771-781. https://doi.org/10.1017/ice.2018.84	Systematic Review with Meta-analysis	18	6,851	Inpatients & Outpatients Adults & Pediatrics Any antibiotic regimen	Probiotics, any strain, dose, or duration. Vs. Placebo, alternative prophylaxis, or no treatment	-Probiotics reduced the odds of CDI by 63% (OR 0.37, *P*<0.0001) -GRADE: moderate quality -Probiotics may be more effective when baseline CDI risk is ≥5% -Risk of SAEs not significantly different between probiotic (12.1%) and control group (12.4%) -Multispecies probiotics had statistically significant treatment effect (p<.0001)
Lau, C. S., & Chamberlain, R. S. (2016). Probiotics are effective at preventing *Clostridium difficile*-associated diarrhea: A systematic review and meta-analysis. *International Journal of General Medicine, 9*, 27-37. https://doaj.org/article/51f1955b2e5f4726bd07f25e3710797c	Systematic Review with Meta-analysis	26	7957	Inpatients & Outpatients Adults & Pediatrics Any antibiotic regimen	Probiotics, any strain, any dose. Started 3 days of antibiotics and continued for entire antibiotic duration Vs. Placebo or no treatment	-60.5% reduction in CDAD for probiotic group compared to placebo group (*P*<0.001) -Beneficial in both adults, 59.5% risk reduction, (*P*=<0.001) and children, 65.9% risk reduction (*P*=0.008) -More beneficial in hospitalized patients, 61% risk

Citation	Study Design	RCT's	Subjects	Sample Characteristics	Intervention & Control	Major Findings
						reduction, (*P*=<0.001) versus outpatients, 69.4% risk reduction which was not statistically significant (*P*=0.468) -Multispecies, 5 *Lactobacillu*s strains, and *Saccharomyces boulardi* statistically significant
McFarland, L. V. (2015). Probiotics for the primary and secondary prevention of *C. difficile* infections: A meta-analysis and systematic review. *Antibiotics, 4*(2), 160-178. https://doi.org/10.3390/antibiotics4020160	Systematic review with meta-analysis	25		Inpatients and outpatients. Adults and pediatrics Any antibiotic and indication	5 different probiotics. Any dose, formulation or duration Vs. Placebo, active control, or no treatment	-2 probiotics strains, and 2 combinations effective for primary prevention of CD infection, and statistically significant -No difference between adults or pediatrics -No difference for daily probiotic dose ≥10cfu/day vs <10cfu/day
Shen N. T., Maw, A., Tmanova, L. L., Pino, A., Ancy, K., Crawford, C. V., Simon, C.V., & Evans, A.T. (2017). Timely use of probiotics in hospitalized adults prevents *Clostridium difficile* infection: A systematic review with meta-regression analysis. *Gastroenterology,* 152,	Systematic review with Meta-analysis	19	6261	Inpatients only. Adults only (18 ≥ years old) Any antibiotic, and indication	Probiotics any strain or dose Vs. Placebo or no treatment	-Risk reduction was 58% for hospitalized adults taking probiotics (*P*<0.001) -GRADE: High quality -Incidence of adverse events similar in both groups (14.2% probiotic group vs.

Citation	Study Design	RCT's	Subjects	Sample Characteristics	Intervention & Control	Major Findings
18889. https://doi.org/10.1053/j.gastro.2017.02.003						15.9% control group) -Timing of probiotic administration was a significant predictor of CDI efficacy, most effective if started within 2 days of antibiotics (P=0.02) -Lactobacillus alone or in combination statistically significant
Sinclair, A., Xie, X., Saab, L., Dendukuri, N. (2016). *Lactobacillus* probiotics in the prevention of diarrhea associated with *Clostridium difficile:* A systematic review and Bayesian hierarchical meta-analysis. *Canadian Medical Associated Journal Open, 4(*4), E706-E718. https://doi.org/10.9778/cmajo.20160087	Systematic Review with Meta-analysis	10	4,841	Inpatients only. Adults only Any antibiotic and indication	Probiotics containing *Lactobacillus* only, any dose. Varying duration. Vs. placebo	-Pooled statistically significant relative risk reduction of 75% for probiotic group (no p value given) -*Lactobacillus* effective alone or in combination -GRADE: very low quality -Pooled RR was 0.17 in the studies in which the observed risk of CD diarrhea ≥ 6% and statistically significant
Szajewska, H., & Kołodziej, M. (2015). Systematic review with meta-analysis: *Saccharomyces boulardii* in the prevention of	Systematic review with meta-analysis	11	2020	Adults & pediatrics Does	*Saccharomyces boulardii* only, any dose or duration	-CD diarrhea was lower in the probiotic group compared to placebo group but not significant

Citation	Study Design	RCT's	Subjects	Sample Characteristics	Intervention & Control	Major Findings
antibiotic-associated diarrhoea. *Alimentary Pharmacology & Therapeutics*, *42*(7), 793–801. https://doi.org/10.1111/apt.13344				not specify inpatients or outpatients Any antibiotic and indication	Vs. Placebo or no treatment	(P=0.07) –Subgroup analysis showed probiotic reduced risk of CD in children (P=0.01) but not adults (P=.39) -GRADE: moderate quality -AEs similar between probiotic and control groups
Vernaya, M., McAdam, J., & Hampton, M. D. (2017). Effectiveness of probiotics in reducing the incidence of *Clostridium difficile*-associated diarrhea in elderly patients: A systematic review. *JBI Database of Systematic Reviews and Implementation Reports, 15*(1), 140. https://doi.org/10.11124/JBISRIR-2016-003234	Systematic Review with Meta-analysis	5	3,461	Inpatients only. Older adults only (≥60 years old) Any antibiotic and indication	Probiotics, any dose, strain or duration. Vs. Placebo	-Probiotics no more effective than placebo in the reduction of CDAD incidence in elderly hospitalized patients than placebo (*P*=0.38)
Xie, C., Li, J., Wang, K., Li, Q., & Chen, D. (2015). Probiotics for the prevention of antibiotic-associated diarrhoea in older patients: A systematic review. *Travel Medicine and Infectious Disease*, *13*(2), 128–134. https://doi.org/10.1016/j.tmaid.2015.03.001	Systematic review	6	3562	Older Adults ≥65 years old Any antibiotic and indication	*Lactobacillus, Bifidobacteriu,m, Saccharomyces, Streptococcus*, *Enterococcus* and *Bacillus*, alone or in combination Vs.	-Found no preventative effect for ADD or CD infection

Citation	Study Design	RCT's	Subjects	Sample Characteristics	Intervention & Control	Major Findings
					Placebo or no treatment	