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A Systematic Search and Review on the Efficacy, Safety, and Cost-Effectiveness of Utilizing Lactobacillus Probiotics in Concurrence with Prescribing Antibiotics to Reduce Clostridium difficile Infection Rates in Hospitalized Patients

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A Systematic Search and Review on the Efficacy, Safety, and Cost-Effectiveness of Utilizing Lactobacillus Probiotics in Concurrence with Prescribing Antibiotics to Reduce *Clostridium difficile* Infection Rates in Hospitalized Patients

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Abstract

Incidence of *Clostridium difficile* infection, (CDI) in patients receiving antibiotics is significant. In 2017, there were approximately 223,900 cases of CDI in hospitalized patients alone (Center for Disease Control [CDC], 2017). Despite enhanced infection control measures, CDI rates remain prevalent and are associated with increased costs to healthcare. An integrative literature review and synthesis was performed. Studies were analyzed to delineate if Lactobacillus containing probiotics, when administered concurrently with high risk antibiotics, decrease CDI rates for patients in the inpatient hospital setting. Additional analysis of probiotic safety and a cost versus benefit analysis was researched. The purpose of the review and analysis was to determine the strength of evidence for utilization of probiotics. Within this review, the use of probiotics to combat incidence of CDI was associated with low risk of adverse effects with probiotic use, and moderate effect on reducing CDI rates. Significant cost savings to inpatient facilities is also noted. The research findings suggest use of probiotics is associated with improved patient outcomes by decreasing incidence of CDI, reduced hospital length of stay, and the prevention of the physical and emotional consequences from CDI. A concept map was constructed to guide readers through the correlational relationship of a Lactobacillus probiotic on CDI rates, institutional cost savings, and adverse events. Despite promising findings in safety, cost reduction, and decreased incidence of CDI, due to high heterogenicity between studies, details regarding prescribing practices remain unclear. Therefore, precise recommendations for practice remain unknown and further research is

warranted. These findings provide a foundation of knowledge that may be utilized by the advanced practice nurse and other healthcare providers. Monitoring for new research that emerges, or encouragement for further research to be performed, within the hospital setting, is needed. Until then, the data found within this review provides education related to the benefits of utilizing probiotics for patients receiving high risk antibiotics with a subsequent result of decreased incidence of CDI, decreased mortality related to CDI, and long-term cost savings to an institution. Robust clinical trials are needed to validate the effectiveness of particular dosages, duration, and species of probiotics. Therefore, institutional based prescribing guidelines cannot be formed at this time and prescribing should be left to the judgement of the prescribing provider.

TABLE OF CONTENTS

Page

TABLE OF CONTENTS (*continued*)

LIST OF TABLES

Table Page

LIST OF TABLES (*continued*)

LIST OF FIGURES

Figure Page

Section I

Introduction to Inquiry

Introduction

Clostridium difficile infection (CDI) is a gram-positive bacterium that is highly virulent and is the leading cause of hospital acquired antibiotic associated diarrhea (Lau & Chamberlain 2016, p. 27). The diagnosis of CDI results in detrimental outcomes as increased length of hospital stays, increased risk for systemic infection, and increased risk of morbidity. In addition, CDI results in increased costs to institutions due to costs accumulated from additional treatment of infection, increased length of hospital stay, and additional safety measures to prevent the spread of the infection (personal protective gowns and specialized bleach cleaners), which is often not reimbursed by insurance. Despite enhanced infection control measures CDI rates remain prevalent in the hospital setting affecting on average thirteen per one-thousand patients (Center for Disease Control (CDC), 2017). According to the Cochrane Database, the use of probiotics has been studied for its effects on CDI rates for many years (Chaturaka, 2018). This leads to the question of the use of probiotics and can they be efficacious, safe, and cost-effective method to combatting hospital acquired CDI.

To address the inquiry question, this scholarly inquiry project reviewed current literature regarding probiotic's effects on reducing hospital acquired CDI rates. Background and rationale of the impact of CDI and the biochemical chemical effects of probiotics are explained. The significance of hospital acquired *Clostridium difficile* in terms of mortality rates and cost burdens are highlighted. Purpose and PICOT formed question is presented to clearly inform the reader, the intent of this scholarly inquiry paper. Methods and procedures used for content analysis are provided.

Background and Rationale

CDI is an opportunistic gastrointestinal infection that occurs when normal intestinal microbiome is disrupted. Symptoms may range from mild diarrhea to severe colitis. In severe cases, CDI may result in sepsis, ischemic colon, possible colostomy, and/or death. The criteria of mild to severe CDI along with recommended treatment is described in Table Al *Clinical Definition and Recommended Treatment for Clostridium difficile Infection in Adults*. Use of antibiotics, advanced age, recent hospitalization, and an immunocompromised state of health are the leading precipitating factors to CDI (Tilton & Johnson, 2018, p. 280). Risks of developing CDI are further increased for patients receiving high risk antibiotics such as: Cefepime, Clindamycin, Piperacillin, Ciprofloxacin, Fluoroquinolones, and Vancomycin, due to the increased disruption of normal gastrointestinal flora (Tilton & Johnson, 2018, p. 282). Increased incidence of CDI in hospitals is due to higher presence of the virulent *Clostridium difficile* strain in hospital settings (CDC, 2017). Research has shown, up to 20-50 % of hospital surfaces contain *Clostridium difficile* spores (McFarland, Ship, Auclair, & Millette, 2018, p. 444). The high virulence of CDI is due to the Clostridium difficile spores being resistant to hand sanitizer and many typical disinfectant cleaners, requiring handwashing and cleaners with bleach to disinfect surfaces (CDC, 2019)

Health care associated CDI is defined as *Clostridium difficile* infection diagnosed more than 48 hours after hospital admission and/or less than four weeks after discharge from a hospital facility (Starn, Harpe, & Cline, 2016, p. 238). CDI has become one of the top causes of health care associated infections in America. According to the CDC's

Antibiotic Resistance Threats report, in 2017 there were approximately 223,900 cases of CDI (CDC, 2019).

Clostridium difficile infection results in a financial burden of nearly five billion dollars for American hospitals (CDC, 2017). On average, each incident of hospital acquired CDI, in the United States, costs between 18,676- 27,408 dollars and this does not include quality of life adjustments (Heimann, Aguilar, Mellinghof, & Vehreschild, 2018, p. 24). Additional costs accrued are due to increased length of hospital stay, additional treatment methods (antibiotics, antifungals), need for personal protective gowns, specialized bleach cleaning products, and additional room cleaning methods (Zhang et al., 2016). CDI is often coded as a healthcare associated infection resulting in little to no reimbursement for hospitals that participate in Center for Medicaid Service programs (CDC, 2017).

Mortality rates associated with CDI are high. According to the CDC (2017), one out of 11 patients who are 65 years or older die within 30 days of diagnosis of CDI (CDC, 2017). Mortality rate after 90 days is further increased to 22% (McFarland et al., 2018, p. 444). For those who do survive, the infection may leave an impact and burden on one's physical, mental, and emotional health. In a qualitative study by Guillemin et al. (2014), the authors conclude that CDI was a traumatic and frightening experience for patients. One patient describes the fatigue she experienced topped with the embarrassment of being in an isolation room, she then describes when she returned home, she could not return to work for a few weeks due to the increased frequency of her bowel movements. The authors bring light to the burden associated with CDI with hopes that

the study may encourage providers to take extra precautions to prevent occurrence of the infection (Guillemin et al., 2014, p. 97).

Despite the CDC's initiative to promote antibiotic stewardship through decreased prescribing practices of antibiotic and increased education of modified contact precautions in the inpatient hospital setting, infection rates remain significant (McFarland et al., 2018, p. 444). Use of probiotics to support gastrointestinal health has been speculated for quite some time (Chaturaka, 2018). In a meta-analysis performed by McFarland et al. (2018), authors note that probiotics helped to restore the intestinal microbiome and reduced bioavailability which resulted in decreased *Clostridium difficile* growth. Additionally, probiotics may neutralize toxins released by *Clostridium difficile* resulting in reduced inflammation in the gastrointestinal tract (McFarland et al., 2018, p. 444). The role probiotics play in decreasing bioavailability and in turn decreasing *Clostridium difficile* proliferation seems plausible (Lewis, Lundberg, Tharp, & Runnels, 2017, p. 849). However, due to lack of sufficient research, prescriber use of probiotics as a prophylactic measure to decrease the incidence of CDI remains variable.

Purpose and PICOT Question

The purpose of the integrative literature review was to analyze studies in which probiotics are used as a measure to prevent CDI, analyze the safety of probiotic formularies, and determine costs savings related to probiotic implementation. Therefore, the aim of the review is to determine whether probiotics are safe and beneficial in the prevention of *Clostridium difficile* for patients who are receiving antibiotic therapy most prone to causing CDI. Concurrently, the secondary aim was to determine if there was evidence that probiotics resulted in cost savings to institutions.

To effectively perform a review of literature and explore the clinical inquiry, a PICOT question was formed. PICOT is a format used to develop a clinical question that guides a review of literature. PICOT is an acronym for the following elements: P- population of interest, I- intervention described, C-comparison for the intervention, O- outcomes to be measured, and T- timeline (Gray, Grove, & Sutherland, 2017, p. 459). The PICOT question developed was:

"For adult patients in the hospital setting who receive high risk antibiotics associated with the development of CDI, (Cefepime, Piperacillin, Ciprofloxacin, Fluoroquinolones, Vancomycin, Clindamycin, and Cephalosporin); is the practice of prophylactically administering a Lactobacillus containing probiotic concurrently with a course of antibiotic treatment compared to no probiotic intervention, a efficacious, safe, and cost-effective method to reduce rates of hospital acquired *Clostridium difficile* infection?"

Method Used for the Inquiry

Systematic and exhaustive search methods were conducted from January 2019-November 2019. Six research databases were utilized, including: CINAHL, PubMed, Cochrane, OVID, EBSCO host, and Google Scholar. Keywords and search terms utilized were: prophylactic probiotic, *Clostridium difficile*, antibiotics, patient experience, probiotics, economic burden, infection reduction, cost analysis, and cost saving. Table A1. *Database Search*, delineates the dates of searches, database used, keywords utilized, and number of hits obtained. All databases that were used were filtered to articles less than ten years old, printed in English, and had human subjects.

Purpose of the review of literature was to obtain systematic reviews, meta-analysis, and strong randomized control trials to support the above-mentioned clinical

question. Special attention was made to find studies that examined a probiotic intervention against a placebo or no intervention, probiotics administered concurrently with antibiotics, (as a prophylactic measure), and probiotic formularies that contained Lactobacillus or were multi-strained with Lactobacillus. Primary focus was placed on finding studies that reported the effects of utilizing probiotics on rates of CDI and evaluated the safety of probiotics. Secondary focus was placed on studies that evaluated cost-effectiveness of implementing probiotics in the in-patient hospital setting.

Nineteen articles were reviewed. The SALSA framework, (Search, Appraisal, Synthesis, and Analysis), was the structural base and process used to guide this scholarly inquiry project (Grant & Booth, 2009). Critical appraisal of each individual study was performed utilizing appraisal guidelines described in Gray, Grove and Sutherland, (2007) text. Articles were scored for their level of evidence guided by: Ackley, Swan, Ladwig, and Tucker (2008). Hierarchy of evidence description can be viewed in Table B1. *Level of Evidence.* By utilizing "SALSA" framework and the critiquing guidelines presented by Gray et al. (2009), and Ackley et al. (2008), Nineteen studies were noted to be most useful for the purpose of this review and are included in Tables C1- C19., *Literature Review*. For each article critiqued; objectives, evaluation of the sample population, methods of study design, variables, and measurement tools were noted. Implications and applicability for practice are described.

Section II

Literature Review

Introduction

Due to the controversial nature surrounding the topic of probiotic therapy, the efficacy of probiotics for prevention of CDI has been moderately studied (Vanden-Nieuwboer, & Claassen, 2019). As a result, nine of the nineteen articles examined were systematic reviews and meta-analyses. Of the remaining articles, one was a qualitative review, and nine were individual studies ranging from cohort studies to multi-center randomized control trials.

Several themes emerged following the review of literature. These themes included: variation in study sampling methods/flaws, variation in interventions, and study findings. To help guide the reader; a theme matrix may be found in Table D1. *Theme Matrix*. This theme matrix was constructed to delineate each individual study with the matching themes. Each theme was subsequently described in detail in the literature review section.

Theme One: Study Methods

Study methods concerning sampling flaws, bias, and exclusion of high-risk patients poses a problem for prescribing providers as confidence in study findings may be lowered due to these factors. Sampling flaws, selection bias, and presence of heterogeneity lower the strength of the research findings. The issue of excluding high risk patients may decrease transferability of study findings into practice. Variability of what is considered a high-risk patient is high across the studies examined.

Study heterogeneity and selection bias. Multiple authors of the systematic reviews, such as Lau and Chamberlain (2016), noted the complexity of ensuring heterogeneity while maintaining low risk of publication bias. This issue may leave providers unable to determine the interventions that are most effective in the reduction of CDI cases. Numerous variations in variables between each randomized control study poses a problem for systematic reviews and meta-analysis. This variability from study to study can result in a high level of heterogeneity. Due to the many differences between studies, the researcher is not able to verify the reliability of the study methods, due to the lack of replication in study designs.

Three of the nine systematic reviews provided strong evidence to support low study heterogeneity, low risk of publication, and low selection bias. Johnston et al. (2012), Lau and Chamberlain (2016), and Shen et al. (2017), do not show any apparent risk of selection bias and reported statistics of low heterogeneity. This gave these studies good strength and credibility. These findings suggest that the studies being combined were alike and the data from the meta-analysis was credible. Low selection bias in these three studies suggested there was no researcher bias in the selection of the studies that were included in the analysis.

A meta-analysis performed by the Cochrane group, authored by Goldenberg et al (2018), reported low risk of publication bias and no significant heterogeneity when analyzing studies that focused on CDI reduction. However, publication bias was present when the study focus was switched to adverse events instead of CDI reduction, resulting in significant level of heterogeneity. This was due to the lack of volume of studies that

reported adverse events. Therefore, selection bias was eminent and resulted in a downgrade of certainty of evidence to low (Goldenberg et al., 2017, p. 24).

The remaining five systematic reviews/meta-analysis poorly reported processes of controlling and analyzing for publication bias and ensuring heterogeneity (Hassan, Rompola, Glaser, Kinsey, & Philips, 2018; Leal, Heitman, Conly, Henderson, & Manns, 2016; Li et al., 2018; Pattani, Palda, Hwang, & Shah, 2013; Redman, Philips, & Ward, 2014). Both Leal et al. (2016) and Li et al. (2018) did not report any statistics regarding heterogeneity, nor mention a process to determine publication bias. Hassan et al. (2018), Pattani et al. (2013), and Redman et al. (2014), vaguely reported presence of moderate publication bias. Yet, no further statistical values were given to determine the extent of bias present. Although these studies seem to provide valuable information and statistical analysis, complete confidence in their value cannot be determined due to these two factors. This is the biggest flaw of these studies. Through analysis of each individual study, the complexity of finding a group of individual studies that have similar variables is apparent. Little to no study replication was found in this review of literature.

Poor sampling methods/study design. When the individual studies were analyzed, (disregarding systematic review and meta-analysis), all ten of the individual studies had flaws in sampling methods and study designs. Despite the flaws, each study is believed to contribute value that can be used for further research.

Seven of the studies were retrospective design studies (Box, Ortwine, & Goicoechea, 2018; Carvour et al., 2019; Dudzicz, Kujawa-Szewieczek, Kwiecien, Wiecke, & Adamczak, 2018; Kujawa-Szewieczek et al., 2015; Lewis et al., 2017; Maziade, Andriessen, Pereira, Currie, & Goldstein, 2013; Sadanand, Newland, &

Bednarski, 2019). Retrospective designed studies pose the problem of a lack of randomization. This study method lacks control, as a result, risk factors or extraneous variables that may contribute to CDI reduction or proliferation may not be measured (Gray et al., 2017 p. 241). Due to high rates of internal and external threats to validity in retrospective designed studies, determining cause and effect relationships may be confounded (Tofthagen, 2012, p. 181). However, there is value to retrospective studies. These factors include financial feasibility, (compared to large randomized control studies), and design success and/or failures that can be used for design of further studies (Tofthagen, 2012, p. 181).

All seven retrospective designed studies were single center cohort studies. Therefore, external validity, (extent to which research results can be generalized to other populations), cannot be fully determined. Another downfall of single center studies is insight to other unmeasured study variables or phenomena, such as differences in standards of care, cannot be determined unless specifically stated (Gray et al., 2017, p. 199). However, these studies still provide insight that can be useful for further research.

The last two studies by Selinger et al. (2013) and Guillemin et al. (2014), had sampling flaws. The Selinger et al. (2013) study, despite being a strong randomized control trial with good rigor, had a low power analysis. The power required for adequate sample size was calculated to be greater than 382 participants; the final number of participants was 122 (Selinger et al., 2013, p.161). Selinger et al. (2013) initially did have a higher total population sample (initial enrollment was 231). The study had a poor attrition rate resulting in a final study sample of 122 patients. This was lower than the required power analysis set at five percent level of significance.

Lastly, Guillemin et al. (2014) performed a qualitative study on the mental, physical, and emotional impact associated with the diagnosis of CDI. In this study, sampling methods initially were purposive. However, a portion of the sample population ended up being recruited under convenience sampling. The initial study was designed to control for selection bias by having a third-party agency enroll patients. Yet, a clinician who was involved directly with this patient population, helped to recruit patients (Guillemin et al., 2014, p. 99).

These examples convey the need for further randomized control trials that are large enough to meet a power analysis of five percent level of significance, have rigor in sample selection methods, and have strong control on variables. Once high-quality individual studies are performed and further replicated, systematic reviews and meta-analysis will then have less significant levels of heterogeneity between each individual study analyzed. In turn, the lower level of heterogeneity may provide researchers higher confidence in the meta-analysis findings.

Exclusion of high-risk patients. Many of the studies analyzed excluded "high risk" patients due to concerns for risk of adverse events. For each of these studies the definition of high risk varied. Variability of "high risk" poses a problem for providers when analyzing these studies. Exclusion of high-risk patients may also decrease a provider's ability to apply the concepts of the research into clinical practice. Determining the risk versus benefit ratio of probiotics for high-risk patient groups is difficult, due to lack of studies that include high risk patients. Probiotics may be safe and hold benefit for these high-risk patient population groups. A few studies found within this literature

review did include a high-risk population sample, such as the article by Dudzcicz et al. (2018).

Several studies report exclusion of high-risk patients (Lau and Chamberlain, 2016; Lewis et al., 2017; Pattani et al., 2013; Selinger et al., 2013; Shen et al., 2017). Each study's definition of high risk is defined differently. For example, Shen et al. (2017) defined "high risk" as: pregnancy, human immunodeficiency virus, previous organ transplant, undergoing chemo-therapy and/or radiation, prosthetic heart valves, admitted to an intensive care unit for any reason, and pre-existing gastrointestinal disorders of any type (Shen et al., 2017, p. 1891). Lewis et al. (2017) reported an exclusion of high-risk patients similar to Shen's except the addition of the presence of a central venous catheter and unable to take medications orally (Lewis et al., 2017, p. 849). Both exclusion criteria are similar, yet different, leaving the high-risk exclusion criteria unclear. Of these five studies that do not include high risk patients, all have findings which supported the use of probiotics, but state that further research is needed due to study limitations.

Several studies in this review did contain high-risk patient populations (Dudzicz et al., 2018; Hassan et al., 2018; Kujawa-Szewieczek et al., 2015; Maziade et al., 2013; Redman et al., 2014). These studies focused on high-risk patient population groups or included high risk patients. All five of the studies were based outside of the United States, however, were still in well-developed countries. For example, the study by Maziade et al. (2013), was performed in Quebec, Canada and included patients that have been excluded from prior Canadian randomized control trials for the following: recent chemotherapy use, presence of cardiac valves, patients within the intensive care units, and presence of central venous catheters (Maziade et al., 2013 pp. 1342-1343). The study

by Dudzicz et al. (2018) is based in a nephrology and post transplantation ward. In the Dudzicz et al. (2018) study, all the post-transplant patients were receiving immunosuppressive medications, resulting in an immunocompromised state. No significant adverse side effects, bacteremia or fungemia related sepsis, linked to probiotic administration were found in these studies.

The culture of not prescribing probiotics to "high-risk" patient populations comes from multiple individual case studies citing the link of probiotics to sepsis. However, a recent systematic review by Costa et al. (2018) noted a lack of significant evidence to support this practice. Costa et al. (2018) performed a systematic review and meta-analysis of individual clinical reports and case studies related to serious effects related to Lactobacillus probiotic usage. The author found that there have been a total of 93 cases of septicemia and/or fungaemia related to all probiotic species types since 1976-2018 and of those 93 cases 26 were related to Lactobacillus probiotics since (Costa et al., 2018, p. 4). Studies analyzed within this review of literature, (19 articles, of which nine are systematic reviews), did not note any patients who experienced major adverse health events related to Lactobacillus administration. This leaves the provider questioning if such stringent inclusion criteria are necessary or if adequate research has yet to be performed.

Theme Two: Intervention Methodologies

High variability in intervention practices was an emerging theme in this review. Every study had differences in species, concentration/dosage, timing of initiation, and duration of the probiotics administered. This impedes providers from utilizing the highest evidence in practice. Determination of which strain, concentration, and timing of

administration was most beneficial for reducing CDI outcomes was unclear, due to lack of rigor within studies and lack of replication of studies.

Probiotic species and dosage. Based on recommendations by the Cochrane group, the aim of the article review was to use studies that focused on probiotics that contained *Lactobacillus* (Goldenberg et al., 2017, p. 23). This was a difficult goal as many of the systematic reviews included different types of probiotic strains such as Bifidobacterium, and Saccharomyces boulardii. Even with studies that only focused on Lactobacillus probiotics, high variability across all the studies in concentration/colony forming units per dosage, and dosing frequency, were found. Once again, this factor was a major contributor to the high heterogenicity seen within all the systematic reviews.

Many of the systematic reviews did not control specifically for the species type and dosage of the probiotics. For example, the systematic review by Hassan et al. (2018), performed statistical analysis of pooled data from 25 studies, in which the main population studied was cancer patients. Eighteen of the 25 studies reviewed contained a Lactobacillus probiotic. The results of the study appeared promising in the efficacy of probiotics. Yet, the authors disclosed that no conclusion of probiotic safety and efficacy could be determined due to the vast interventional heterogeneity present in the studies (Hassan et al., 2018, p. 2509). This was a common phrase and theme found in many of the systematic reviews. Goldenberg et al. (2018), Hassan et al. (2018), Johnston et al. (2012), Lau and Chamberlain (2016), Leal et al. (2016), Li et al. (2018), Pattani et al. (2013), Redman et al. (2013), and Shen et al. (2017), all lacked rigor in their intervention design in regards to probiotic species and dosing frequency, and do not exclusively use probiotics containing Lactobacillus. In the study by Pattani et al, (2013), authors

researched multiple probiotic species but only the probiotics which contained a Lactobacillus species showed significant reduction in CDI (relative risk of 0.33, risk difference -.010, CI [-.5-.05] $I^2 = 0$.) (Pattani et al., 2013, p. *e*64).

Box et al.'s (2018) retrospective cohort study attempted to control variability by only analyzing patients who received a probiotic formulation (which contained Lactobacillus), called "Bio-K". Yet, because probiotic prescribing was left to the digression of the primary provider, high variability in dosage amount and frequency of dosing was found. As a result, high degree of prescribing bias was present (Box et al., 2018, p. 2). There was a chance that only patients who providers believed were high risk for CDI were prescribed the probiotic. Due to the lack of a control group, confidence in the study findings are low.

Seven of the articles reviewed controlled the intervention by using a specific type of probiotic, all which contained Lactobacillus, these articles also specified the dosing amount and frequency (Dudzcicz et al., 2018; Kamdeu et al., 2012; Kujawa-Szewieczek et al., 2015; Lewis et al., 2017; Maziade et al., 2013; Sadanand et al., 2019; Selinger et al., 2013). For example, Dudzcicz et al. (2018), had a strong designed study with high rigor. This study analyzed CDI outcomes for patients in a nephrology and transplantation unit by administering a Lactobacillus containing probiotic called "LP299v". The probiotic was administered orally, once daily, at the start of antibiotic administration, and continued for the duration of the antibiotic treatment. Due to the high quality of the study, Dudzicz et al. (2017) may be a landmark study to guide further research.

Timing of probiotic administration. Timing of the administration of probiotics appeared to be an important factor on the effects of CDI reduction (Shen et al., 2017).

Within this review, there was high variability between studies on when interventional probiotics were administered. From analysis of the articles research it appeared the closer probiotics were started to the time of the initial antibiotic administration, the better the outcome in reference to CDI reduction (Shen et al.,2017).

The effects of timing on probiotic administration and duration of treatment for CDI rates were analyzed by Shen et al. (2017). They reported statistically significant reduction in CDI rates in patients who received probiotics within one to two days of antibiotic administration, (relative risk 0.32, 95% CI .22-.48), compared to patients who received probiotics within three to seven days, (relative risk .70, 95% CI .40-1.23). This resulted in a significant difference in infection rates (p = .02), (Shen et al., 2017, p. 1896). Understanding of how probiotics work, and how antibiotics disrupt the micro bacterial state of the gastro-intestinal tract, this concept of starting a probiotic near the start of an antibiotics seems reasonable (Pattani et al., 2013, p. *e*65). Seven studies were clear on their probiotic initiation and administration time frame: Dudzicz et al. (2018), Kamdeu-Fansi et al. (2012), Kujawa-Szewieczek et al. (2015), Lewis et al. (2017), Maziade et al. (2013), Selinger et al. (2013) and Shen et al. (2013), all initiated probiotics either at the time of antibiotic administration or within three days of antibiotic start.

One large well-designed randomized control trial called the PLACIDE study by Allen et al. (2013), failed to initiate a probiotic intervention in a timely manner. This study found lowered but not significant findings on probiotic efficacy in reducing CDI rates. However, in the study's intervention process probiotics were initiated up to seven days after antibiotic start. Therefore, when implementing Shen et al.'s (2017) findings to

this study, the timing variable alone could be one of the factors as to why probiotics did not significantly reduce CDI rates within this study.

Information on timing/ initiation of probiotics was not always included in the studies. This is problematic as this variable appeared to be an important factor on the efficacy of probiotics. More research is needed to determine when the administration of probiotics results in the highest benefit. In this review, probiotics started at the time of first antibiotic administration and up to two days after seemed to hold the most benefit in significant reduction of CDI (Dudzicz et al., 2018; Kamdeu-Fansi et al., 2012; Kujawa-Szewieczek et al., 2015; Lewis et al., 2017; Maziade et al., 2013; Selinger et al., 2013; Shen et al., 2013).

Theme Three: Findings

Returning to the main purpose of the review; the efficacy of probiotics on reducing the rates of CDI in hospitalized patients undergoing antibiotic therapy, determining if they are cost effective, and safe. As noted with the previous themes discussed, there are many hinderances in both the background methods and interventional methods that make a final conclusion on the efficacy and safety of probiotics difficult. However, in this literature review, Lactobacillus probiotics appeared to have a positive effect on reducing CDI rates, appeared to be cost-effective, and do not seem to have more adverse events/side effects than a control or placebo intervention.

Decreased *Clostridium difficile* infection rates. Twelve out of the 16 studies that had an outcome measure analyzing the effect of probiotics on CDI rates, provided evidence to support the use of probiotics as a means of CDI prevention. However, due to the many flaws previously mentioned in this review, most of the studies disclose that

future studies are needed to fully support the use of probiotics with high confidence. The lack of rigor and poor study designs leave the validity of the research findings unclear.

Goldenberg et al. (2018), which is considered a landmark study on the subject of probiotic efficacy, found prophylactic probiotics are effective but most useful in hospitals in which preintervention rates of CDI is greater than five percent. In environments with baseline CDI rates greater than five percent, the implementation of probiotics may result in a 70% risk reduction (Goldenberg, et al., 2018, p. 19). Among the other studies that were of moderate quality, the average risk reduction of CDI ranged from 33-40% with an average of 35.6% reduced risk of CDI (Johnston et al., 2012; Leal et al., 2018; Pattani et al., 2013; Shen et al., 2017).

Although the article by Dudzicz et al. (2018) was a retrospective single center study, their design had high rigor, (in terms of dosing, timing of administration and duration of probiotic treatment). Their inclusion of high-risk patient population and rigor within the study design, may make this study a future landmark study. Their findings showed a significant decrease in rate of CDI during the implementation period of a Lactobacillus containing probiotic called “LP299v” administered once per day with the start of any antibiotic. The incidence rate of CDI declined from 10.3 cases per 1,000 patients, down to 1.1 cases per 1000 patients, (p = 0.0003). This was a significant finding. When researchers discontinued probiotics in phase three of their study, CDI rates again increased and matched preintervention rates (Dudzicz et al., 2018, pp. 5-7). Despite study flaws and poor designs seen within many of the studies, probiotics consistently seem to be effective as a prophylactic measure for CDI reduction (Butler et al., 2016, p. 21). The Cochrane hand book discusses study designs and lack of study replication to be the major

reason for why they termed evidence of probiotic efficacy as moderate quality (Goldenberg et al., 2017, p.5).

The studies that do not support probiotics as a CDI reduction method also have many flaws. For example, high prescriber bias, was seen in the study by Box et al. (2018), where probiotic prescribing was left solely to the digression of the prescribing provider. This further supported that probiotics may be efficacious when noting the quality of the studies that did not support probiotics had lower appraised quality than their counter part. However, the lack of overall quality, rigor, and heterogeneity between studies leaves the researcher unable to state with high level of certainty that probiotics are effective. Due the study design flaws, this research review finds that probiotics are likely effective for reducing CDI rates, but only can be concluded with a low to moderate level of certainty due to poor study design.

Cost effectiveness. Cost effectiveness was an important finding to analyze. Cost effective analysis is often needed to gain support from stakeholders in a hospital setting (Melnyk & Fineout-Overholt, 2015, p.474). Six studies discussed the cost related savings and benefits of using probiotics. Dudzicz et al. (2018), Kamdeu et al. (2012) and Li et al. (2018), provided the most evidence of cost savings in this literature review.

Dudzicz et al. (2018) performed a study in which patients in a nephrology and transplantation ward received a probiotic called “LP299v” orally, once per day. The result was a decrease in CDI rates from 10.3 per 1,000 patients to 1.1 cases per 1,000 patients, (p = 0.0003) (Dudzicz et al., 2018, p.5). Cost to implement a probiotic as a prophylactic measure, for an average of 14 days was about four dollars and fifty cents. Utilizing the number needed to treat, which was 15, the cost to prevent one case of CDI

was about 68.9 dollars. This is a significant finding, as one case of CDI can cost an average of 8,000 dollars to treat (Dudzicz et al., 2018, p. 9).

Kamdeu-Fansi et al. (2012) performed a formal cost benefit analysis on a study that was previously performed by Gao et al. (2010). Despite the study being originally performed in China, Kamdeu-Fansi et al. (2012) performed adjustments for the differences in currency value to match costs of American pharmaceuticals and hospital products. They performed this by utilizing the American Consumer Price Index to determine the cost adjustments. In the study there were three cohorts; one placebo group, one group who received one "Bio-K+" probiotic daily, and one group that received two capsules of the "Bio-K+" probiotic, once per day. The authors made five major assumptions based on typical care practices. They assumed CDI testing would be performed by a microbiological screening test. They assumed, after CDI diagnosis, 58% of patients would be treated with Metronidazole and 42% would receive Vancomycin. They assumed Metronidazole would fail in 26% of the cases (based off current literature findings). They also assumed that patients with CDI would have a prolonged length of hospital stay (Kamdeu-Fansi et al., 2012, pp. 56-57). For cohort one (placebo), they found an average additional length of hospital stay was six toseven days. Cohort two average hospital length of stay was four days, and cohort three average length of hospital stay was two to three days. For those who were diagnosed with CDI, the additional hospitalization costs were about 1,424.16 dollars per day (Kamdeu Fansi et al., 2012, p.56). Therefore, utilizing these assumptions and study findings, if all patients who are at risk of CDI are given one probiotic once per day, due to the subsequent decrease in total CDI cases, the total cost savings may result in 1,968 dollars per patient given the Bio-K+

probiotic. In the scenario for those who received two capsules of the Bio- K+ probiotic, the cost savings were closer to 2,661 dollars, per patient treated with the probiotic (Kamdeu-Fansi et al., 2012, p. 56). Utilizing the average CDI rate per 1,000 patients in American hospitals, prophylactically treating 1,000 patients with two capsules of probiotics, once per day, during their antibiotic course, could result in a cost savings of 1,680,000 dollars annually (Kamdeu-Fansi et al. (2012, p.59). This study was based solely on hospital costs and did not take into account quality of life cost adjustments.

Li et al. (2018) also analyzed in-hospital costs but adjusted the analysis to include burden on quality of life indicators. Li et al. (2018) suggest cost savings to an institution was higher when taking into consideration the quality of life effects. They reported savings were closer to 3,686 dollars per patient treated with probiotics due to the decreased overall rates of CDI and decreased quality of life burden (Li et al., 2018, p. 473).

These findings are highly significant when discussing cost savings to an institution. Each case of CDI was associated with increased length of hospital stay, increased need in medical cares, and increased mortality rates. Quality of life adjustments with this infection are equally important to consider. In a qualitative study by Guillemin et al. (2014), authors explored the perceived burden associated with CDI from the patient's lived experience. They highlight that the diagnosis and symptoms associated with CDI were highly burdensome and found data saturation on the negative effects the infection had on psychological and emotional health of patients. They find increased negative effects on an individual's professional life and an increased financial burden experienced by the patients. The financial burden experienced was mostly due to

increased required payment for hospital services and additional time off work that was required post hospital discharge (Guillemin et al., 2014, p. 100). The article was an excellent example of how healthcare associated costs to a facility are not the only aspects to consider when a cost-benefit analysis is performed. Quality of life measurement continues to be an important aspect to consider in an analysis of cost versus benefit (Li et al., 2018). As shown in the Guillemin et al., (2016) study, CDI affected patients' lives due to the increased length of hospital stay, increased embarrassment felt by the patient, and financial implications due to lost time at work (Guillemin et al., 2016).

Adverse side effects. The last finding analyzed was to determine if there were significant differences in adverse side effects with the use of an interventional Lactobacillus probiotic group compared to a placebo group. This was a very important variable to determine for future studies as implementation of an intervention that is known to be harmful to a patient would be unethical. As noted in the exclusion of high-risk patient section, there is hesitancy to use probiotics on patients due to a concern for increased chance of blood stream infections related to probiotic use. This practice was based off individual clinical reports and case studies. Again, according to Costa et al. (2018) there was significant lack of evidence to support this practice. Six studies were included in this review based on their inclusion of "high-risk" patients. All six of the studies found no significant difference in adverse effects related to a probiotic group versus a placebo group.

Hassan et al. (2018) focused on a sample population group with cancer. They found that adverse events in the intervention group (n = 237) were lower than that in the control group (n = 314) (Hassan et al., 2018, p.2506). Hassan et al. (2018) did not

provide a statistical analysis to determine if this finding was significant. However, their inclusion of the high-risk patient population is important to note. Sadanand et al. (2019) performed a single -center retrospective study on pediatric hemopoietic stem cell transplant patients. These patients received a Lactobacillus containing probiotic as a treatment method for graft versus host disease. No cases of blood stream infections while patients were on probiotics were found. (Sadanand et al., 2019, p. 304). Although this study did not exclusively look at CDI infection, the study is included as an important supporting factor for the safety of probiotics. These post transplantation pediatric patients were receiving immunosuppressive medication. Yet, there were no severe adverse events, such as probiotic related septicemia, seen in this study related to probiotic usage (Sadanand et al., 2019, p. 305).

Goldenberg et al. (2018), Johnston et al. (2012), and Shen et al (2017) all performed analysis on adverse event variables and provided statistical data to support their findings. Goldenberg et al. (2018) found statistically significant data which supported less adverse side effects in the probiotic group over placebo. However, due to the high publication bias present within the systematic review and meta-analysis, this study's findings were inconclusive (Goldenberg et al., 2018). Johnston et al. (2012), found when comparing the adverse events in a placebo group versus a probiotic treatment group, there was a relative risk reduction of 0.82, with a 95% confidence interval of 0.65-1.05. Thus, the authors supported the safety of the probiotic intervention. The authors noted the evidence classified as moderate quality evidence (Johnston et al., 2012, p. 884). Shen et al. (2017) stated there was no significant difference in adverse effects from the

placebo group to intervention group ($p = 0.35$), in their study (Shen et al., 2017, pp. 1894-1895).

Literature Review Summary

The efficacy of probiotics remains unclear. There likely is benefit to the use of probiotics as a prophylactic measure to reduce CDI occurrence within the hospital setting. The main hinderance to this subject's clarity is the lack of strong study methods and backgrounds and high heterogeneity between many of the studies analyzed within the systematic reviews analyzed. Individual studies lacked rigor and randomization. This conclusion was consistent with findings and recommendations posted by the Agency for Healthcare Research and Quality (AHRQ), Comparative Effectiveness Review. They listed probiotics as a treatment option with low quality of evidence but consistent findings of efficacy (Butler et al., 2016, p.21). They also found the prevention methods: antibiotic stewardship and handwashing, to also have low quality of evidence. Other measures such as chlorhexidine bathing, ultraviolet room cleaning, and hydrogen peroxide cleaners, do not have sufficient evidence to support these practices as evidence-based methods (Butler et al., 2016, p. 15). Therefore, Butler et al. (2016) argued that the low quality of evidence should not rule out usage of probiotics as antibiotic stewardship and handwashing continues to be a widely accepted hospital practice.

A theme noted in many of the studies was exclusion of the high-risk patient population. This concept stemmed from a few case studies where blood stream infections were believed to be from the use of a probiotic. A compelling article by Costa et al. (2018) found this concept to be rare and not a reliable reason to exclude high risk patients. Multiple articles within this review were selected due to their inclusion of a

high-risk population group- such as stem cell transplantation patients and cancer patients. No adverse events were found in any of the studies contained within this review of literature. Therefore, in order to strengthen support for the use of probiotics more high-quality randomized controls studies that have rigor and high control need to be performed and less stringent exclusion criteria may need to be considered.

Within this review, a few intervention methodologies were sought including a probiotic intervention that contained Lactobacillus, and studies that analyzed the effect of the timing of initiation of a probiotic. The concept of focusing on studies that contain a Lactobacillus component was guided by current recommendations from the Cochrane group (Goldenberg et al., 2017). Studies that analyzed the effect on the timing of probiotic administration noted higher success with CDI reduction when a probiotic intervention was initiated within three days of antibiotic administration (Dudzicz et al., 2018; Kamdeu-Fansi et al., 2012; Kujawa-Szewieczek et al., 2015; Lewis et al., 2017; Maziade et al., 2013; Selinger et al., 2013; and Shen et al., 2013).

Overall findings for the initial PICOT question are difficult to answer due to the study flaws previously mentioned. Therefore, overall support for the use of probiotics is supported within this review with only low to moderate confidence. This matches the current Cochrane handbook's consensus of their review of the literature (Goldenberg et al., 2017). They too noted the quality of evidence to support the use of probiotics as a preventative measure for CDI as "moderate". The AHRQ noted the evidence for use of probiotics as low but was consistently effective for reduction of CDI rates. The low rating was due to high heterogeneity between studies analyzed (Butler et al., 2016, p.121). Twelve of the 16 studies reviewed showed reduced incidence of CDI rates when a

probiotic treatment was implemented. Of the remaining four articles, two did not support the use of probiotics (Box et al.,2018; Carvour et al., 2019). These two studies had severely flawed study methods which rendered the quality of the studies as low. The remaining two articles suggested reduction in cases of CDI; however, findings were not statistically significant (Johnston et al., 2012; Li et al., 2018).

Cost effectiveness of probiotics is supported by this review of the literature. Cost savings could be as high a 2,661 dollars per patient treated with a probiotic as a prophylactic measure (Kamdeu-Fansi et al., 2012, p. 56). This finding was due to the resultant overall decrease in hospital acquired cases of CDI (Kamdeu-Fansi et al., 2012, p. 56). Utilizing the average CDI rate per 1,000 patients in American hospitals, the implementation of treating 1,000 patients with two capsules of probiotics once per day, during their antibiotic course, may result in a cost savings of 1,680,000 dollars (Kamdeu-Fansi et al., 2012, p. 56).

No significant difference in adverse effects experienced by a probiotic intervention group over a control group was found in this literature review. Inclusion of studies with high risk patients was performed to aid in analyzing the safety of probiotics (Dudzuczet al., 2018; Hassan et al., 2018, Kujawa-Szewieczek et al., 2015; Mazaide et al., 2013; Reman et al., 2014; Sadanand et al., 2019). No major adverse events were found in the high-risk population groups that were exposed to probiotic treatment. These compounded findings support the safety of the use of probiotics.

Overall, the literature contained within this review supports the use of a Lactobacillus containing probiotic when initiated within three days of antibiotic start, as a measure to reduce CDI incidence within a hospital setting. The evidence within this

review supports probiotics as a safe and cost-effective measure to reduce *Clostridium difficile* incidence within the hospital setting. Due to the flaws within each study confidence in these findings can only be rated as low to moderate. However, as stated by Goldenberg et al, (2018) probiotics have the highest quality evidence among cited prophylactic therapies including handwashing, daily room cleaning, contact isolation, and antibiotic stewardship, yet are not included in prophylactic clinical practice guidelines (Goldenberg, et al., 2018, p. 21) Yet to move forward, support for further high-quality, large, randomized control trial research is needed before institutional prescribing guidelines can be formulated.

Section III

Conceptual Framework

Introduction

A conceptual framework was constructed to aid readers to better understand the phenomenon of interest- Lactobacillus probiotics. As can be viewed in Table E1. *Conceptual Analysis Components,* the concept of interest was identified, antecedents and consequences are explained, and the level of evidence, (which was used to support this framework), was provided. The purpose of the pictorial framework provided in *Figure 1*., was to provide visual explanation of how each of the variables related to one another and show the consequential relationship or outcome of the concept.

Relationships Identified

As can be viewed in *Figure 1*., a negative relationship was seen for the variables of *Clostridium difficile* infection rates. This indicates that as the concept of interest is implemented (a Lactobacillus containing probiotic), rates of CDI are decreased, (Dudzicz et al., 2018; Goldenberg et al., 2018; Johnston et al., 2012; Kamdeu Fansi et al., 2012; Kujawa-Szewieczek et al., 2015; Lau & Chamberlain, 2016; Leal et al., 2016; Lewis et al., 2017; Li et al., 2018; Mazaide et al., 2013; Pattani et al., 2013; and Shen et al., 2017).

When probiotics were administered there was neither a positive or a negative relationship seen in terms of adverse events. There was no significant difference seen between the control or intervention group (Goldenberg et al., 2018; Hassan et al., 2018;

Johnston et al., 2012; Kujawa-Szewieczek et al., 2015; Lau & Chamberlain, 2016; Mazaide et al., 2016; Redman et al., 2014; and Sadanand et al., 2019).

The final consequence examined was cost versus benefit. As the concept of a *Lactobacillus* probiotic was implemented, there was a positive relationship on institutional cost savings (Dudzicz et al., 2018; Hassan et al., 2018; Kamdeu-Fansi et al., 2012; Leal et al., 2016; Lewis et al., 2017; Li et al., 2018; Shen et al., 2017).

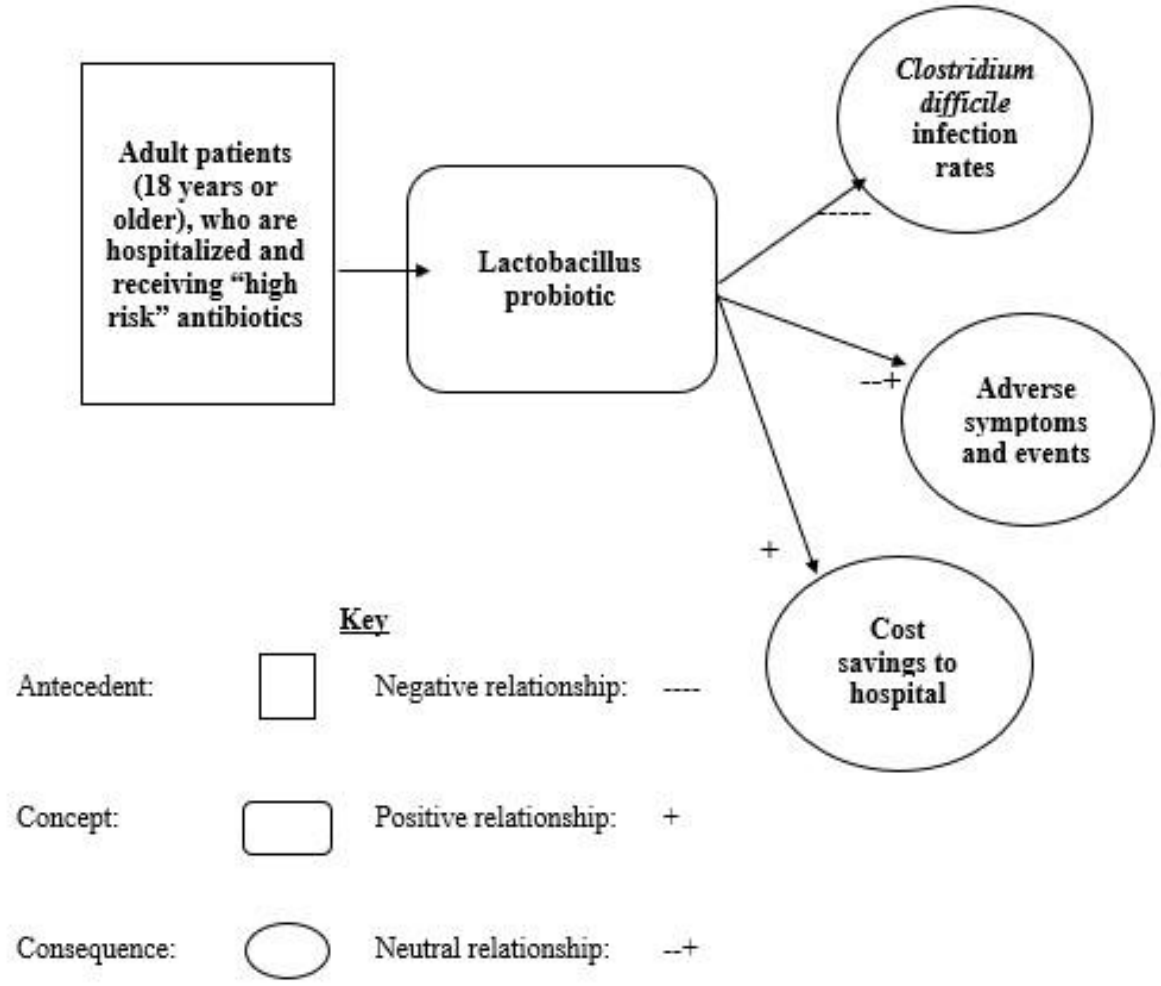

Figure 1. Conceptual Relationship Diagram. A pictorial relationship of the effects of a Lactobacillus probiotic used in a hospital setting on *Clostridium difficile* rates, adverse symptoms, and cost savings to an institution

Section IV

Conclusions/Recommendations, and Implications

Introduction

Heath care acquired CDI is a highly virulent bacterial infection associated with increased patient mortality rates, increased costs to hospitals, and an increased burden on a patient's overall quality of life (Center for Disease Control, 2017; Guillemin et al., 2014). Strategies that are known to decrease the incidence of CDI should be examined. Probiotics utilized for the prevention of CDI has been highly speculated and remains a controversial topic in healthcare (Vanden-Nieuwboer & Claassen, 2019). This literature review, aimed to investigate the effects probiotics have on reducing incidence of CDI in patients who were hospitalized and on antibiotics, whether the probiotic intervention was safe, and if a probiotic intervention was cost effective. Nineteen total studies were examined and critiqued for their credibility and quality. Several concepts emerged within the literature review including flaws in study design, high heterogeneity, presence of selection bias, and significant variability in intervention methodologies (concerning species, dosage, duration, and initiation of probiotic). Analysis of study findings suggest there is a low to moderate effect of a probiotic on CDI reduction, no evidence of adverse effects related to probiotic usage compared to placebo or no intervention, and data supporting institutional cost savings related to probiotic implementation. However, due to the lack of replicated studies and lack of data to support specific prescribing practices, more research is warranted. Until then prescribing practices should be left to the discretion of the prescribing provider, who should consider patient preference, and weigh benefits and risks with use as on a case to case basis.

Conclusions

Overall, the literature contained within this review supported the use of a Lactobacillus containing probiotic when initiated within three days of antibiotic start, as a measure to reduce CDI incidence within a hospital setting. This can only be stated with low to moderate certainty due to the high heterogeneity seen within most of the systematic reviews and poor methodology and study design seen within individual studies.

The evidence supported probiotics as an effective measure to reduce *Clostridium difficile* incidence within the hospital setting. Despite many studies excluding high-risk patients, the articles which did include high risk patients did not find any significant evidence of an increased risk for adverse events. The concept of excluding high risk patients may be an outdated theory based on a small volume of case studies suggesting septicemia related to probiotic usage. This topic should be further addressed with more research.

The cost-benefit analysis of probiotics and the savings to an institution seemed promising. When adding in a patient's quality of life measures, support for the use of probiotics was further increased. There is hope that the potential financial savings from this intervention will be appealing to many institutions. Ideally as a result, support for further research within the institutions should occur and be funded.

During the literature review process and analysis of the current evidence, links to implications for nursing and advanced nursing practice were addressed, probiotics may be a safe and inexpensive way to further decrease incidence of CDI. As antibiotic resistance becomes more prominent within the world, , further treatment and preventative

aspects of care need to be considered. Further research is needed on dosage, length of treatment. And the use of probiotics in high risk patient populations. The practice of including high risk patients in current studies is relatively new and studies that have been performed lack a-strong design and quality.

Implications and Recommendations

Studies focused on probiotics will continue to emerge with new evidence in the coming years. As advance healthcare providers, keeping up to date on the emerging evidence will be important. As bacteria and viruses continue to evolve and become more resistant, the increased risk of hospital acquired CDI needs to be evaluated and measures to combat infection prevalence need to be taken.

For now, a full institutional change to support routinely prescribing probiotics to patients on antibiotics is not supported. However, prescribing of a Lactobacillus probiotic to an average risk patient who is taking antibiotics would not be against the current evidence. Recommendations for the optimal probiotic prescription: the frequency, dosing, and duration of the prophylactic treatment is not clear in the evidence. At this time, providers should practice their critical thinking skills as well as right to autonomy and prescribe probiotics on a case to case basis. Consideration of patient preference should be included. Patients that are offered a probiotic supplement should be educated on the risks of taking a probiotic and the risks associated with not taking a probiotic. Again, the risk versus benefits, would be based on each patient's clinical presentation and state of health. Providers and all healthcare workers should continue to use accepted strategies to prevent CDI infection in the hospital setting including proper hand hygiene, antibiotic stewardship, and contact isolation measure for patients diagnosed with CDI.

To advance the current evidence, advanced practice nurses and providers should provide the current research findings and flaws to hospital stakeholders with hopes that funding for more rigorous research will occur. Further research should be based off strengths of previous studies. Future studies should have a strong control on variables and detailed explanation of the research process. Ideally, a double-blind randomized control trial utilizing multiple hospital institutions should be performed. Within all of these institutions. the same brand, dosage, and frequency of administration, and initiation of the probiotic or placebo should be completed. Study expectations should be clear on prescribing goals and probiotics should be initiated within three days of antibiotic start. The method and practice for testing CDI should be uniform, and current institutional standard of practice for infection prevention, pre-intervention should be similar. A universal reporting protocol should be in place to report adverse events with the probiotic use.

Once further research is completed, if the evidence supports the use of probiotics with high confidence, hospital stakeholders should be re-engaged to determine if an intuitional change will be supported. If change is supported guideline development and education to prescribing providers should be performed. Guideline development and clinical decision support tools which could flag a provider that a probiotic should be considered when high risk antibiotics are prescribed, would be helpful. Once again, these would only be indicated once more rigorous and precise research is performed and if the research obtained supports the use of probiotics.

At this time, providers are recommended to remain current on emerging evidence related to the use of probiotics. Critical thinking skills and autonomy should be utilized to

weigh the benefits versus risk of using probiotics on case to case basis. As always, patient preference should be determined, and patients should be educated on the benefits versus risk of using a probiotic supplement.

Summary

Research contained within this review of literature supports the use of probiotics administered concurrently with antibiotics as a prophylactic measure to prevent CDI in the hospital setting with moderate certainty. Evidence supports that probiotics have low associated risk with usage for those who are not immunocompromised. Cost savings is apparent within the studies analyzed. However, due to high heterogeneity seen between each individual study and lack of study replication, confidence in these study findings is low to moderate.

At this time providers should engage in reviewing emerging evidenced based research that emerges. Consideration for the use of a probiotic supplement should be gauged on a patient to patient basis and risk versus benefit of probiotic usage should be analyzed. As with any care provided, patient preference should be analyzed. Patients should be educated on the benefit and risks associated with the usage of a probiotic supplement, as well as, the risk associated with not utilizing the supplement.

Advanced practice providers should continue to be at the forefront of pursuing research. Once further high-quality research with high rigor is performed, data found within those studies can be used to support or not support an institutional change. Until then, all healthcare providers should continue to practice universal infection control measures and CDI prevention methods specified by his/her individual institution and

providers should use critical thinking and autonomy to determine the benefits versus risk of prescribing a probiotic to patients on a case to case basis.

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Table A1.

Clinical Definition and Recommended Treatment for Clostridium difficile Infection in Adults

Clinical Definition	Signs/Symptoms	Recommended Treatment Methods
Initial Episode- Mild	Leukocytosis less than 15,000. Serum creatinine less than 1.5mg/dL	First line treatment: Vancomycin 125mg every six hours for ten days. Or Fidaxomicin 200mg twice per day for ten days If neither Vancomycin or Fidaxomicin are available: Metronidazole 500mg three times per day for ten days.
Initial Episode Moderate	Leukocytosis greater than 15,000 Creatinine greater than 1.5mg/dL	First line treatment: Vancomycin 125mg every six hours for ten days. Or Fidaxomicin 200mg twice per day for ten days
Initial Episode Severe	Leukocytosis greater than 15,000 Creatinine greater than 1.5mg/dL Hypotension, shock, ileus, mega colon	Vancomycin 500mg every six hours via mouth or nasogastric tube. If ileus is present add rectal instillation of Vancomycin 500mg every six hours AND Intravenous Metronidazole 500mg every eight hours
First Recurrence		If Metronidazole was used for first episode: Vancomycin 125mg every six hours for ten days Or Prolonged taper of Vancomycin 125mg every six hours for 10-14 days then 125mg twice per day for seven days, then once per day for seven days, Lastly once every three days for two to eight weeks
Second Recurrence		Prolonged taper of Vancomycin (see above) Or Vancomycin 125mg every six hours for 10 days followed by Rifaximin 400mg three times daily for twenty days Or Fidaxomicin 200 mg twice per day for ten days Or Fecal microbiota transplantation

Referenced from: McDonald et al. (2018)

Table B1.
Database Search

Date of search	Key Words Used	Database used	Listed	Reviewed	Used
1/29/19	Prophylactic Probiotic and *Clostridium difficile* and Antibiotics	CINAHL	18	14	1
2/6/19	*Clostridium difficile*, Probiotics, Hospital	PubMed	44	15	2
2/20/19	Patient Experience and *Clostridium difficile*	CINAHL	36	3	1
3/1/19	Probiotic, *Clostridium difficile*	Cochrane	23	1	1
3/10/19	Probiotic	OVID	2	2	0
3/10/19	Economic Burden, *Clostridium difficile*	PubMed	112	4	1
3/12/19	Probiotics, Reduce, *Clostridium difficile*	Google Scholar	1989	2	0
3/15/19	Cost Analysis, Probiotics, Reduce *Clostridium difficile*	Cochrane	2	1	1
3/19/19	Cost, Probiotics, *Clostridium difficile*	PubMed	14	3	1
10/23/19	Probiotics and *Clostridium difficile*	EBSCOhost	214	9	3
11/1/19	Cost Effectiveness, Probiotics	PubMed	36	4	2
11/15/19	Safety, Probiotic	CINAHL	194	20	3
11/27/19	Probiotic, Immunosuppression	PubMed	2	1	1

Table C1.

Level of Evidence Key

Level of evidence (LOE)	Description
Level I	Evidence from a systematic review or meta-analysis of all relevant RCTs (randomized controlled trial) or evidence-based clinical practice guidelines based on systematic reviews of RCTs or three or more RCTs of good quality that have similar results.
Level II	Evidence obtained from at least one well-designed RCT (e.g. large multi-site RCT).
Level III	Evidence obtained from well-designed controlled trials without randomization (i.e. quasi-experimental).
Level IV	Evidence from well-designed case-control or cohort studies.
Level V	Evidence from systematic reviews of descriptive and qualitative studies (meta-synthesis).
Level VI	Evidence from a single descriptive or qualitative study.
Level VII	Evidence from the opinion of authorities and/or reports of expert committees.

Note. The level of evidence scheme is based on a studies quality in design, validity, and applicability to care. The higher the level of the evidence, the greater the strength in the study. This level of evidence key is based on literature by: B. J., Swan, B. A., Ladwig, G., & Tucker, S. (2008). *Evidence-based nursing care guidelines: Medical-surgical interventions.* (p. 7). St. Louis, MO: Mosby Elsevier.

Table D1.
Literature Review

Citation/ Search Engine Used	Purpose/ Objectives	Study population/ Sample/ Setting	Study Design/ Methods/ Major Variables/ Instruments and Measures	Results/ Major Findings	Implications/ Critiques	Comments/ Themes	L O E
Box et al. (2018) OVID	Evaluate the effectiveness of administering "Bio- K+", a Lactobacillus probiotic in patients receiving antibiotics with the goal of lowering healthcare associated *Clostridium difficile*.	-*N* = 1576 -Received antibiotics and probiotics:*n* = 649. -Received antibiotics only: *n* = 927. -Setting: 400 bed community hospital in La Jolla, CA., March 29th 2016- Sept 30th 2016. -Inclusion: Patients >18 years of age, receiving >1 dosage of antibiotics, and had a hospital stay >3 days. -Exclusion: CDI diagnosis within 3 days of admission.	Retrospective cohort study -Scripps Institutional review board approved -Probiotic prescribing left to providers discretion. -Not randomized: all patients on antibiotic included in study. Any patients who received probiotics were in the intervention group. -Demographic data analyzed: length of stay, number of antibiotics used, ICU, mortality rates, and co-morbidity index -Analysis performed using ALESC version3.0.1 2 tailed students T-tests, and fishers exact tests.	-Each cohort was not demographically similar (statistical difference in ICU stay and severity of disease). -11/649 patients receiving antibiotics and probiotics developed CDI -8/927 patients receiving antibiotics alone developed CDI CDI difference- not statistically significant (*p* = 0.16).	Patients in the probiotic group had a longer length of stay, higher "Charlson co-morbidity index", and higher amount of antibiotics given. Thus, results are likely skewed There was high variability on when the probiotics were initiated from the start of antibiotics. Did not analyze type of antibiotic prescribed	Authors do not recommend the use of probiotics due to insufficient evidence Prescribing of probiotics was not a required practice, it was at the discretion of the provider. This may lead to skewed results as the physician may have prescribing bias- higher risk patients Flaw of study was they did not analyze the type of antibiotics prescribed with each group to assess for heterogeneity. Some antibiotics carry a higher risk in association to CDI rates. Authors note their methods of leaving prescribing practices to the physicians is more real-world applicable. However, this variable allows for high bias.	IV

Note. LOE = level of evidence, N = total sample population, n = subset population, CDI = *Clostridium difficile* infection, ALESC = A Language and Environment for Statistical Computing,

Table D2.
Literature Review

Citation/ Search Engine Used	Purpose/ Objectives	Study population/ Sample/ Setting	Study Design/ Methods/ Major Variables/ Instruments and Measures	Results/ Major Findings	Implications/ Critiques	Comments/ Themes	LOE
Carvour et al. (2019) -EBSCO host	Identify predictors that might be modified at a hospital level with the goal of decreasing CDI rates.	-*N* = 5029, patients tested for CDI. -Sample: hospitalized adult >18 years old. -Setting: University of New Mexico Hospital May 1st, 2011-September 21st 2016. -Clients were chosen if clinician suspected CDI may be present.	-Poorly designed case control cohort study. -Retrospective chart analysis from 2011-2016 used the clinical identifying factor of CDI assay test from data warehouse. -Those who were tested for CDI assay negative or positive were included in the review. -Utilized predictive logistic regression modeling and multivariable models utilizing SAS version 9.4. -Variables searched against: location of diagnosis or initial test, probiotic use, current steroid use, diabetes, current proton pump inhibitor medication use, and month of diagnosis	Significant difference in age of diagnosis. Patients who are greater than 65 years of age = higher risk (p = 0.08). Diagnosis in ED more prevalent than any other patient care area (p = 0.0001). Patients on statin medication had higher association with having CDI (p = .01). Probiotic usage in last 180 days (p = .0001).	Utilizing retrospective data chart analysis has many flaws. Analyzing previous probiotic usage prior to admission, these findings are highly biased as clients may have initiated probiotics due to symptoms associated with CDI such as diarrhea. Due to the retrospective aspect of the study, this factor cannot be clarified therefore is not a clear link of a risk of probiotic use.	Due to information regarding when probiotics were started and for what purpose, stating probiotics may be unsafe and may cause CDI cannot be fully inferred. Randomization was lacking as any patient suspected of CDI was included in study. -There was a high degree of selection bias. The study provides good insight of possible factors that may be related to CDI rates, however due to the design and quality of the study, no true inferences can be made.	IV

Note. LOE = level of evidence CDI = *Clostridium difficile* infection, *N* = total sample population

Table D3.
Literature Review

Citation/ Search Engine Used	Purpose/ Objectives	Study population/ Sample/ Setting	Study Design/ Methods/ Major Variables/ Instruments and Measures	Results/ Major Findings	Implications/ Critiques	Comments/ Themes	LOE
Dudzicz et al. (2018) -CINAHL	Analyze the incidence of CDI among immunosuppressed patients hospitalized in the nephrology and transplant ward in the period before, during, and after stopping LP299v probiotic -Determine if there are benefits to prophylactic probiotic use in patients receiving immunosuppression therapy	-*N* = 5341 -*n* = 24 (total patients on immunosuppressive therapy and antibiotics over 3-year period who developed CDI). -12-month pre - intervention: *n* = 10 -12-month during intervention: *n* = 2 -12-month post intervention: *n* =12 -Sample: Patients in nephrology and transplant wards receiving immunosuppressive therapy and antibiotics (any), age greater than 18 years old -Medical University of Silesia in Katowice, Poland.	Retrospective, single-center study. All patients in ward during 12-month intervention period receiving immunosuppression and antibiotic were given prophylactic probiotic- LP299v, orally once per day Data was compared to 12-month pre-intervention of no probiotic intervention and 12-month post intervention period of no probiotic. Data analyzed with STATISTICA 12.0PL, Chi² tests, and an alpha 0.05	After initiation of LP299v prophylaxis, incidence rate of CDI significantly declined-10.3 to 1.1 per 1000 patients (RR 0.11; 95 % CI [0.03–0.47], *p* = 0.0003). -After cessation of probiotic, CDI significantly increased from 1.1 to 7.7 per 1000 hospitalized patients (RR 6.93; 95% CI [1.58–30.47], *p* = 0.0028 -Average prophylaxis duration was 14 ± 7 days. - The cost of CDI was 17.5 PLN (4.1 €) per one patient (converted to USD = 4.5 dollars). cost of prevention for one case of CDI is 262.5 PLN (61.5 €) (Converted to USD = 68.9 USD)	This is the first study found to include a high-risk population group. n = was above power which was 20 however, this is a very small sub-sample population. May be biased due to lack of same size groups in pre-intra-post intervention groups	Interesting the study was done in Poland as this likely would not be approved by IRB board in United States as administration of probiotics to immunocompromised patients is **theorized** to be dangerous. -This study may in the future be considered a landmark study supporting use for patients who are immunocompromised -H2 blockers was noted to be used in 82% of patients who were positive for CDI -Included cost savings and cost needed to benefit one patient. -Supports the use of probiotics and does not find any adverse events related to probiotic usage.	IV

Note: LOE = level of evidence, CDI = *Clostridium difficile* infection, LP299V = Lactobacillus plantarum 299v, *N* = total sample population, *n* = RR = relative risk, CI = confidence interval, PLN = Polish -Zloty- (form of currency), USD = United States dolla

Table D4.
Literature Review

Citation/ Search Engine Used	Purpose/ Objectives	Study population/ Sample/ Setting	Study Design/ Methods/ Major Variables/ Instruments and Measures	Results/ Major Findings	Implications/ Critiques	Comments/ Themes	LOE
Goldenberg et al. (2018) -PubMed	To analyze the efficacy and safety of probiotics in preventing *Clostridium difficile* in adults and children by analyzing *Clostridium difficile* infection rates and adverse outcomes of probiotic usage	-39 RCT studies analyzed. -*N* = 9,955 -Adults and children hospitalized and those in the outpatient, setting who receive antibiotics of any route and received probiotics of any species or concentration. - Setting: 13 countries mostly all 1st world countries except: Turkey, Chile, and Bulgaria	-Systematic review with meta- analysis -4 search engines utilized (PubMed, Embase, Central, and Cochrane). -Included studies from 1966-2017 -Two trained reviewers screened abstracts. -Selection bias controlled by use of *Cochrane Handbook for Systematic Review of Interventions* -Each study scored for quality by GRADE criteria -Statistical analysis by RevMann Software - Reported RR with 95% CI, and NNT -Analyzed heterogeneity with funnel plot for both CDI incidence and adverse events -Baseline risk percentages in relation to risk reduction rate	-Heterogeneity analysis for CDI incidence = (p = 0.79) (low risk of bias - Heterogeneity analysis for adverse events (p = 0.05) (moderate risk of bias) - CDI incidence in intervention group versus control: intervention group = 1.5% (70/4525), CDI incidence in control = 4% (164/4147), RR = .40, 95% CI [0.30-0.52], NNT = 42, 95% CI [32-58] 60% risk reduction, GRADE score = moderate. -Adverse effects in intervention group versus control: -Intervention: 170/1000 = 1.7% versus control: 141/1000 = 1.4%, RR= .83, 95% CI [0.71-0.97] GRADE score = low -Baseline risk of 0-2% not significant reduction in CDI with probiotics (p = 0.34) -Baseline risk of 3-5% not significant reduction of CDI with probiotics (p =0.70) -Baseline risk > 5% significant risk reduction with use of probiotics: RR = .30 (risk reduction of 70%), 95% CI [0.21-0.42] , p = 0 .001	-Wide data search range 1966-2017 -Moderate bias for analysis of adverse events -Low quality of evidence for adverse events group - High publication bias for adverse events - Wide population sample: adults and children included. -Setting has a few countries that may be considered not 1st world.	"Recent clinical practice guidelines do not recommend probiotic prophylaxis, even though probiotics have the highest quality evidence among cited prophylactic therapies." -Writer notes American hospital's average CDI baseline risk is 3%	I

Note. LOE = level of evidence, RCT = randomized control trial, *N* = total sample population, CDAD = *Clostridium difficile* infection, RR = relative risk, CI = confidence interval, NNT = number needed to treat

Table D5.
Literature Review

Citation/ Search Engine	Purpose/ Objectives	Study population/ Sample/ Setting	Study Design/Methods/ Major Variables/ Instruments and Measures	Results/ Major Findings	Implications/ Critiques	Comments/ Themes	LOE
Guillemin, et al. (2014) -CINAHL	Explore the perceived burden from a patient's perspective on the lived experience of in hospital treatment of CDI. The study aimed to assess the impact and burden of CDI from time of initial symptoms, through hospitalization and post discharge.	-*N* = 24 -*n* = 12 French patients (9 men, 3 women). - Age range: 41-91 years old. -Average hospital length of stay 30 days. -*n* = 12 -USA patients (10 women and 2 men). Age range: 50-78 years old. -Average length of stay 8 days. -All patients had CDI within the 14 months of interview -USA and France -Interviews conducted November 2011- July 2012.	-Qualitative (phenomenological) -Purposive and some convenience sampling used. (a research company found participants but a doctor at a single hospital also enrolled a few of his own patients). -Semi-structured interviews -Open ended questions used -4 researchers used (2 from each country) -Interviews conducted via 1-hour phone call that was recorded -Interview guide was utilized by researchers -Data coding performed with Atlas.ti software. -Data saturation was predetermined to be when less than 5% of new concepts were emerging with each interview. Data saturation began to occur at 15th patient interviewed. -Data was grouped into three stages: prior to hospitalization, during hospitalization, discharge	-Negative effects seen in psychological and emotional health on patient and family -Subsequently patients reported change in diet and health habits post discharge and through time of interview -Negative effects on cognitive abilities (experienced pre and during hospitalization) -Negative effects on physical health, experienced throughout pre diagnosis, and post treatment -Negative effect on sleep seen during and post hospitalization -Negative effects on professional life experienced diagnosis, treatment and post treatment -Financial burden experienced throughout diagnosis, treatment and post treatment	-Interesting article in the terms of the emotions, embarrassment, and fear patients experienced during CDI. -Motivating on the precaution's healthcare workers can take to prevent this infection. -Brings to light the other aspects of burden to CDI other than increased mortality rated and increased health care costs. -Explores the psychologic repercussions of the infection. -Supports need for further patient education and support during diagnosis	-Sample bias likely occurred with the physicians who recruited patients. -No interrater reliability or formal education for interviewers was stated which may skew the participants reports. -Interview was conducted over the phone which leaves the patient's non-verbal ques out for examination.	VI

Note. LOE = level of evidence, CDI = *Clostridium difficile* infection, *N* = total sample population, *n* = sub population

Table D6.
Literature Review

Citation/ Search Engine	Purpose/ Objectives	Study population/ Sample/ Setting	Study Design/Methods/ Major Variables/ Instruments and Measures	Results/ Major Findings	Implications/ Critiques	Comments/ Themes	LOE
Hassan et al. (2018) -PubMed	Determine efficacy and safety of probiotics in adult and pediatric cancer patients	-25 studies included -Pooled *N*- 2242 -Cancer patients receiving chemotherapy, radio therapy or surgery whom received probiotics as an intervention- Outcomes assessed: antibiotic associated diarrhea, gastrointestinal infections and any adverse events. -Setting- inpatient -Japan, Italy, Canada, Australia, Greece, China, Slovakia, Brazil, Thailand, Spain, Finland, India, Hungary. -1995-2018	-Systematic review and meta-analysis -Focused on obtaining RCTs, non-randomized studies and case reports were included in safety analysis. - Databases searched: Medline Embase, AMED. -Selection- 2 reviewers 1 separate party for discrepancies -Cochrane risk of bias tool used to minimalize selection risk -Loke Method used to assess quality of studies -Data analyzed by Mantel-Haenszel method - 16 studies used probiotics with >1 strain of bacteria, 11 studies include >3 strains, 18 studies included Lactobacillus strains, 15 included Bifodobacterum -Outcomes assessed: antibiotic associated diarrhea, gastrointestinal infections and any adverse events	-Pooled analysis- reduced incidence of AAD: OR=0 .52, 95% CI = [0.34-0.78] -Results concerning severe diarrhea, septicemia, and central line infections had poor confidence intervals due to high heterogeneity reported in studies -Severe diarrhea: OR = 0.67, 95% CI = [0.15-2.98] -Septicemia: OR = 0.39 95% CI = [0.13-1.17] -Adverse events in intervention group = 237 Adverse events in control group = 314 -Author states no conclusions of probiotic efficacy nor safety can be determined due to the vast heterogeneity between each study	-Sub group analysis of age, cancer treatment type and strain of probiotic not able to be completed due to significant heterogenicity -Performance bias high 29% -Author reports it is unclear if adverse events were recorded with each incidence or per person	-No studies from America. Possibly due to high risk patient population and strict research requirements. -Focused on safety aspect on a high-risk population	I

Note. LOE= level of evidence, *N*- total sample population, RCT- randomized control trial, AAD = antibiotic associated diarrhea, OR = odds ratio, CI = confidence interval

Table D7.
Literature Review

Citation/ Search Engine Used	Purpose/ Objectives	Study population/ Sample/ Setting	Study Design/ Methods/ Major Variables/ Instruments and Measures	Results/ Major Findings	Implications/ Critiques	Comments/ Themes	LOE
Johnston et al. (2012) -PubMed	Determine the efficacy and safety of probiotics (any strain or dose), for the prevention of CDAD in adults and children receiving antibiotics	-*N* = 3,818 adult or pediatric patients in randomized control trials treated with antibiotics and received probiotics of any strain or dosage that were tested for CDI/stool analysis -Duration of patient follow up ranged from 1 week to 3 months -Study's initiation and duration of probiotic treatment varied -Setting: Inpatient and outpatient. -Date of studies ranged from 1989-2010 -Sample size was not large enough to meet power. Needed 5,676 samples, only obtained 3,818	-Systematic Review of literature and meta-analysis -6 credible databases utilized for search -2 independent reviewers analyzed studies meeting criteria for involvement. - Each individual article was assessed for quality using GRADE approach - 20 RCTs were included in analysis. -Used relative risks and 95% CI, used alpha of (0.05) and Beta of (.20) with a relative risk reduction of 30% using the DerSimoninan-Laird Random effects model	-Risk bias was low in 7 studies and high/unclear in 13 studies - Overall quality of evidence moderate. Baseline risk of CDI ranged from 0-40% - Findings: patients receiving probiotics showed risk reduction. RR = 0 .34, 95% CI = [0.24-0.49], Chi squared = 0%, and heterogeneity = (p = 0.79) bias low. - Control risk = 50 cases per 1000 persons - Intervention group 17 cases per 1000 persons 95% CI [12-25] -Writer notes effect size for CDI reduction is moderate but no statistics are given - Studies using multiple species probiotic versus single strain showed relative risk reduction of CDI however not statistically significant Multi-strain: RR= 0.25, 95% CI = [0.15-.41] Single species: RR = 0.50, 95% CI [0.29-0.84]	-Date of literature reviewed included studies > 10 years old - Low heterogeneity between studies is good. -Too small of sample size / high risk of type 2 error. Did not meet power analysis - Overall significance was rated as "moderate" effect, no statistical number given. -13 of the 20 studies data for CDAD were missing for 5-45% of patients.	-Assessed which stain appears to be most effective. - Supported use of probiotics/ risk reduction -Inadequate sample size -Safety analyzed -High variation in initiation of probiotic and follow up length -Supports use of probiotics	I

Note. LOE = level of evidence, CDAD = *Clostridium difficile*-associated diarrhea, CDI = *Clostridium difficile* infection, RCT = randomized control trials, CI = confidence interval, RR = relative risk

Table D8.
Literature Review

Citation/ Search Engine Used	Purpose/ Objectives	Study population/ Sample/ Setting	Study Design/ Methods/ Major Variables/ Instruments and Measures	Results/ Major Findings	Implications/ Critiques	Comments/ Themes	LOE
Kamdeu Fansi, et al. (2012) -PubMed	Perform a cost-benefit analysis utilizing previous study findings to estimate the direct medical costs that might result from the use of a Bio K+ (Lactobacillus containing probiotic), formula in two different doses to reduce the risk of AAD and CDI in hospitalized patients on antibiotics translated into costs based in North American healthcare	*Based on study analyzed for cost analysis-* *N* = 255 -Placebo: *n* = 84, cohort 1 (one capsule dosage): *n* = 85, cohort 2 (two capsule dosage): *n* = 86 - Study data obtained from Gao et al (2010) RCT performed in China in 2008-2009. Inclusion> 18 years of age, hospitalized >3 days <14 days.	-Probiotic administered within 36 hours of antibiotic -Cost were determined based on the 2009 United states dollar, using the Consumer Price Index. -Only direct costs determined- no adjusts for quality of life -Hospital costs determined by the median cost of hospitalization in relation to diagnosis of CDI which was obtained from a USA study in 2009 -Authors utilize a decision tree to formulate 5 assumption models. -Utilized Crystal Ball software for all the analysis data	Study found decreased incidence of CDI with probiotics versus placebo: Placebo= 23.8%, Cohort 1= 9.4%, Cohort 2 = 1.2% -Cost of CDI related hospitalization per patient, per day= 1,424.16 - Findings supported cost effectiveness of probiotics: -Due to reduced risk reduction and reduced incidence of CDI, by implementing dosage of 1 probiotic per day for all patients at risk, results in a savings of 981 dollars per patient. -Implementing dosage of 2 probiotics per day results in savings of 833/patient. -For a hospital comparable to the one in the Gao study, this results in 1.68million dollars savings for an institution	-Very thorough cost analysis. Provided numerous scenarios/assumptions -Strong quality study. -The Gao study which was analyzed, has higher rates of CDI baseline than most American hospitals do.	Must keep in mind, these figures are based off of values from one study. However, it is beneficial to see the cost savings that occurs when few cases of CDI are prevented.	I

Note. LOE = level of evidence, AAD = antibiotic associated diarrhea, CDI = *Clostridium difficile*, *N* = total sample population, *n* = sub-sample population, RCT = randomized control trial.

Table D9.
Literature Review

Citation/ Search Engine Used	Purpose/ Objectives	Study population/ Sample/ Setting	Study Design/ Methods/ Major Variables/ Instruments and Measures	Results/ Major Findings	Implications/ Critiques	Comments/ Themes	LOE
Kujawa-Szewieczek et al. (2015) -PubMed	Retrospectively analyze CDI rates among patients whom are hospitalized and receiving antibiotics before the start of routine administration of LP299V to all patient receiving antibiotics as hospital protocol for patients in the nephrology and transplantation wards.	-*N* = 3533 -CDI preintervention: *n* = 21 -CDI post intervention: *n* = 2 -Setting: nephrology and transplantation ward at a medical university in Silesia, Poland. -Data analyzed for 2 years -October 2012-October 2013 (prior to hospital protocol initiation) -November 2013-November 2014, data analyzed after hospital protocol initiated to start LP299V with all antibiotics.	-Retrospective quasi-experimental single center study (case-control) -In the period between 2012-2013 the unit's routine was to administer probiotics of any variation to reduce incidence of CDI -2013-2014 LP299V was the only probiotic administered concurrently with the start of any antibiotic -CDI diagnosis made by 2 step immunoassays. Any patient with diarrhea was tested. -Statistical analysis performed by STATISTICA 7.0 -alpha set as: 0 .05	-Decreased incidence of CDI post intervention from 1.21% to 0.11%, $p = 0.0001$ -Total analysis of both groups identified urinary tract infection was the main diagnosis and reason for treatment with antibiotics which led to CDI -Fluoroquinolones 34.8% and carbapenems-34.8% had the highest association with CDI.	-No mention if control versus intervention group were similar-(heterogeneity) no *p* values provided. -Demographics of total population not provided. Study methods not clear Retrospective, but unclear if staff was blinded or knew study was being performed -Total amount of patients who had CDI was low-24/3533 -Power for study was not specified	-In the intervention time frame, less antibiotics were prescribed. Thus, results may be skewed due to less high-risk antibiotics being used. -PPI use was noted in 86% of patients who had CDI. In the intervention group less patients took PPIs -This patient population is considered a higher risk patient population; these findings may support that probiotics may be safe in immunocompromised patients	IV

Note. LOE = level of evidence, CDI = *Clostridium difficile* infection, LP299V = Lactobacillus plantarum strain 229v, *N* = total sample population, *n* = total sub-sample population

Table D10.
Literature Review

Citation/ Search Engine Used	Purpose/ Objectives	Study population/ Sample/ Setting	Study Design/ Methods/ Major Variables/ Instruments and Measures	Results/ Major Findings	Implications/ Critiques	Comments/ Themes	LOE
Lau & Chamb-erlain (2016). PubMed	Analyze the incidence of CDI in randomized clinical trials which assess the use of probiotics for adult and pediatric patients in the inpatient and outpatient setting who are receiving antibiotics.	26 RCTs *N* = 7,957 Received probiotics: *n* = 4,124, No intervention: *n* = 3,833 -Inclusion: RCT comparing the use of any strain probiotic, articles in English, probiotics instituted within 3 days of antibiotic start, and continued for the entire duration of the antibiotic treatment. Exclusion: most studies excluded patients that were severely immunocompromised, and who had gastrointestinal surgery.	-Systematic Review and Meta-Analysis -Comprehensive Meta-Analysis software version 3. -Cochrane's Q and I^2 to assess study heterogeneity -Two tailed T-test used for data sets. -Sub-group analysis performed on type of probiotic used, age, and patient setting (inpatient vs outpatient) -Funnel plot utilized to rule out selection bias. -Search engines used: PubMed, Cochrane, and Google Scholar -Diagnosis of CDI made by presence of diarrhea and positive stool culture -Measured CDI rates, patient length of stay, patient age, and hospital versus outpatient setting	-No publication bias present: Eggers test (p = 0.748) -No significant heterogeneity between trails (p = 0.751). -Probiotic group had significant decreased risk in developing CDI: RR= 0.63, 95% CI = [0.294-0.531], p = 0.001 -Hospitalized patients were likely to benefit from probiotic use compared to outpatients -Inpatient: (RR = 0.390, 95% CI [0.283-0.538], p = 0.001) -Outpatients (RR = 0.306, 95% CI [0.013-7.470], p = 0.468)	- Flaw is that the review includes seven studies that were greater than 10 years old. - Limitations in differences in strain, dosage, and duration of probiotics used. -Heterogeneity present in patient age, co-morbidities, and healthcare setting. -Wide sample range- inpatient and outpatient included as well as adults versus children. - no mention on how studies were measured for quality or how many reviewers were included.	- Overall thorough meta-analysis - Many of the studies included in the analysis do not note the side effects of probiotics. However, four studies did report no significant difference in side effects from probiotic group to placebo. - Supports the use of probiotics -Author addresses there are a few case reports noting sepsis believed to be related to probiotic use. They discern this evidence as being inconsistent, and not statistically significant.	I

Note. LOE = level of evidence, CDI = *Clostridium difficile* infection, RCT = randomized control trial, N = total population sample, n = sub-population sample, p = measure of statistical significance, RR= relative risk, CI= confidence interval

Table D11.
Literature Review

Citation/ Search Engine	Purpose/ Objectives	Study population/ Sample/Setting	Study Design/Methods/ Major Variables/ Instruments and Measures	Results/ Major Findings	Implications/ Critiques	Comments/ Themes	LOE
Leal et al. (2016) CINAHL	Performed a cost-effectiveness analysis to evaluate the risk of CDI and the costs of receiving oral probiotics versus no probiotics over the course of 30 days.	-23 RCT studies examined and published by the Cochrane Review -Studies included in the systematic review: Adult inpatients receiving antibiotics regardless of route of administration and received an intervention of probiotic of any species or concentration. - Studies utilized; continued probiotics for at least 5 days post antibiotic completion.	-Systematic review -Data from Cochrane review was utilized to form a cost analysis. -Relative risk rates of CDI and increased length of hospital stay was derived from systematic reviews -Length of treatment for CDI, length of probiotics, cost for stool analysis, special room cleaning, additional supply cost, and contact precaution costs all included in analysis and obtained from Alberta Health Services records (public funded healthcare system). - Cost per day of contact precautions was used from a study performed in 2012. -Utilized 1-way sensitivity analysis for assessing cost savings per relative risk rates. - Did not directly assess quality of life indicators into cost versus savings	-Reduced risk of CDI in intervention group 5.05% versus 2% - Cost of probiotics per patient if administered during course of antibiotic therapy and 5 days post completion = 24 dollars. - Cost per patient treated for CDI if relative risk is 5% in intervention group = 327 dollars versus non-intervention group = 845 dollars. Cost savings of 518 dollars per patient. -Cost savings per patient if relative risk is 1% (low) is 73 dollars per patient treated. - Cost savings per patient if relative risk is 25% (high) is 3,098 dollars per treated patient - Writer expresses the high likelihood of increased patient satisfaction/ quality of life with reduced risk of CDI with the probiotic intervention due to reduced risk for lengthened hospital stay, the emotions related to being in isolation, and the physical complications that arise from CDI (p.1082). -Theoretically for a hospital with 380,000 admissions the cost for probiotics would be 2.2 million dollars but may result in a 44-million-dollar savings (p. 1085).	-On average patients with CDI spend 1-3 weeks longer in the hospital (p.1079). - Funding provided by Alberta Sepsis Networks and National Collaborating Centre for Infectious Disease, and Baxter. - American hospital average risk for CDI is about 3% - Flaws: No *p*-values, effect sizes, nor confidence intervals stated in article.	-Cost savings -CDI reduction Discusses possible quality of life implications for use of probiotics. - Sampling bias unclear - Statistical significance not provided	I

Note. LOE = level of evidence, CDI = *Clostridium difficile*, RCT = randomized control tria

Table D12.
Literature Review

Citation/ Search Engine	Purpose/ Objectives	Study population/ Sample/ Setting	Study Design/Methods/ Variables/Instruments and Measures	Results/ Major Findings	Implications/ Critiques	Comments/ Themes	LOE
Lewis et al. (2017) PubMed	Evaluate the outcome of a hospital wide initiative to decrease proton pump inhibitor prescribing and increase prescribing and administration of Florajen- a multi-strain Lactobacillus containing probiotic with an analysis goal of determining the impact on hospital acquired *Clostridium difficile* rates.	-*N* = 43,206 -Cohort one: *n* = 21,166 -Cohort two: *n* = 22040 -Cohort/phase one: July 1st 2013-June 30th 2014 -Cohort two: July 1st 2014-June 30th 2015 -Exclusion- Age less than 18 and pregnancy, patients with central venous catheter lines, immunosuppressed patients, intensive care unit patients. -Setting: Johnson City Medical Center (488 bed institution)	-Single center retrospective cohort study All patients admitted to hospital included in study. Standard infection control measures maintained for all patients. -Methods: during phase one, physicians were educated on risks of PPI prescribing in relation to increased CDI rates. -A probiotic bundle was included in order sets for all patients receiving antibiotics Florajen was ordered as a once per day dosage. -Hospital associated CDI was defined as diagnosis after 3 days since admission and diagnosis was made using a polymerase chain reaction test Cohort comparison tests were made using a Mann-Whitney test. To analyze a cohort's impact on CDI rates a Fischer's exact test with an alpha of 0.05 was used.	-Statistically significantly decreases from cohort one to cohort two: PPI usage- 677 to 581, (p = 0.0002). Health care associated CDI rates (number of CDI rates per 1000 patient days) 0 .49 to 0.39 (p = 0.04). This represents a relative risk reduction of 20% -Probiotic usage increased significantly from cohort one to cohort two: 97 to 223 (p = 0.0006.) -Cost savings: the average additional costs associated with hospital acquired CDI for this institution is 11,000 dollars per patient. A reduction in 12 cases over the year (which was seen in this study), results in a savings to the institution of 130,000 dollars per year.	-Flaw is that the study does not include randomization and is retrospective -Complete effectiveness of probiotics cannot be truly determined due to additional variable of reduced prescribing of PPIs - Overall, good quality of a small institutional change Adding probiotics to an antibiotic prescribing order set is a good method to increase usage. This also allows prescriber autonomy as they can elect to not use the probiotics as well	The protocol for administration of the Lactobacillus probiotic contained safe handling instructions to prevent probiotic related infection: Administered in capsule route. If patient has a nasogastric tube, the probiotic cannot be administered. Nurse administers medication wearing gloves and performs hand hygiene after administration.	IV

Note. LOE = level of evidence, *N* = total sample population, *n* = sub-sample population, PPI = proton pump inhibitor, CDI = *Clostridium difficile* infection, *p* = measure of statistical significance

Table D13.
Literature Review

Citation/ Search Engine Used	Purpose/ Objectives	Study population/ Sample/ Setting	Study Design/ Methods/ Major Variables/ Instruments and Measures	Results/ Major Findings	Implications/ Critiques	Comments/ Themes	LOE
Li et al. (2018) - CINAHL	Cost analysis to assess the benefits financially for the institution and also assessing quality of life via length of hospital stay in relation to the use of prophylactic probiotics for the prevention of *Clostridium difficile* in adolescents and children.	- Four randomized control trials analyzed with measured outcomes being incidence of CDI and direct medical costs related to treatment of the incidences of CDI. -Hospitalized patients less than 18 years of age receiving antibiotics intravenously or orally and probiotics -The 4 studies were not described in depth, no setting was provided.	-Systematic review and meta-analysis -Studies searched via online sources: PubMed, EMBASE, and Cochrane Library. - 2 independent reviewers assessed literature. Cochrane handbook was used to prevent selection bias - Cost analysis was based off of United States hospital costs. - Univariate sensitivity analysis was used along with a decision tree model to analyze data	- Oral probiotics lowered risk of CDI 4.6% to 0.45%. No confidence interval or *p* value given. - Cost of probiotics per day averaged 2.83 dollars. - For institution with the probiotic strategy total cost per patient treated for was 16,668.70 dollars compared to 20,355 dollars per patient treated in the non- intervention hospital due to risk reduction - Cost savings of 3,686 dollars per patient treated. - No data on selection bias/ heterogeneity of studies was provided	-Small number or studies analyzed (4) -Vague information on the 4 studies analyzed - Information posted in medical journal, likely there was page limit constraints. - Statistical process not well explained. - Statistical data not supported with confidence levels or *p* values.	-Use of probiotics appear to reduce incidence of CDI and have cost savings for a hospital Overall, poor quality systematic review due to lack of detail and	I

Note. LOE = level of evidence, CDI = *Clostridium difficile* infection

Table D14.
Literature Review

Citation/ Search Engine Used	Purpose/ Objectives	Population/ Sample/ Setting	Study Design/Methods/ Major Variables/ Instruments and Measures	Results/ Major Findings	Implications/ Critiques	Comments/ Themes	LOE
Maziade et al. (2013) -PubMed	Determine the effect of adding a probiotic called Bio-K+ (*Lacto acidophilus* and *L. casei*) to an existing *Clostridium difficile* standard precaution measure protocol (proper handwashing, modified contact precautions for current patients with CDI and antibiotic stewardship), in patients receiving any antibiotics. The primary outcome to be measured was CDI rate/occurrence and secondary measurement of severity of CDI symptoms	-*N*- 31,832 -Phase one: *n* = 1,580 -Phase two and three: *n* = 4,968 -Phase 4: *n* = 25,284 -Phase one: August 2003-January 2004 -Phase two: February and March 2004 -Phase three: May 2004-August 2005 -Setting: community hospital in Quebec, Canada. -Inclusion criteria: age >18 years old -No exclusion criteria disclosed	-Open prospective quasi-experimental cohort study -Methods- Probiotic administered within 2-12 hours of any antibiotic. Probiotic continued for 30 days or until antibiotic completion. -Consisted of four phases: 1- Standard precautions 2. Implementation of liquid probiotic for all patients on antibiotics 3. Hospital relocated/new built hospital 4. Data comparison with regional hospitals near Quebec -Instruments- SPSS data analysis Measures: level of significance, alpha- 0.05 Incidence rates between phases compared with 2-sided chi-square tests and student's T- tests	-Phase 1: Mean of 18.4 cases per 1000. 5.1 severe cases per 1000 people. -Phase 2: Severe cases of CDI decreased from 5.1 cases per 1000 to 1.3 cases per 1000, (p = 0.03). -Phase 3: Cases of CDI dropped from Phase one mean of 18.4/1000 to 3.8/1000. (p = 0.003). -Severe cases decreased from 5.1/1000 patient to 0.21/1000 patients (p = 0.001) When comparing phase 1 with phase 2 and 3 combined, (pre-intervention with post intervention), rates of CDI decreased 73% (p = 0.001) Severe cases of CDI rates decreased 27.5% (p = 0.001) -No adverse events found	-In phase three, the hospital re-located and double rooms were less available. -Patient demographics were not presented for each phase therefore similarity between the two groups cannot be determined. - apache scores had no significant difference between the two groups. -Study was of good quality Study supported the use of probiotics	-The authors note, no approval was needed from the ethical review board. This is a common theme in studies performed outside of the USA. -Unique in no exclusion criteria- allowed high risk patients to be involved central venous lines, intensive care unit patients, cardiac valve replacement	IV

Note. LOE = level of evidence, CDI = *Clostridium difficile* infection, *N* = total sample population, *n* = subset population, *p* = measure of statistical significance

Table D15.
Literature Review

Citation/ Search Engine Used	Purpose/ Objectives	Study population/ Sample/ Setting	Study Design/ Methods/ Major Variables/ Instruments and Measures	Results/ Major Findings	Implications/ Critiques	Comments/ Themes	LOE
Pattani et al. (2013) -PubMed	Systematic review and meta-analysis of evidence to determine the efficacy of probiotic administration concurrently with antibiotic administration in adult hospitalized patients to prevent CDI and/or AAD, incidence and in return decrease mortality and decrease health care costs.	-16 studies included focusing on hospitalized adults receiving antibiotics and probiotics containing one or more of the following: Lactobacillus, Saccharomyces boulardii and or Enterococcus with the end point assessing CDI, and/or AAD rates, -Inclusion: studies in English, designed as RCTs. -Exclusion: probiotics used for reoccurring CDI treatment of *H.pylori.* -Only 5/16 studies were multicenter - Studies were conducted in USA, UK, China, Canada, Italy, Norway, Turkey, and Switzerland. -Mean ages: 33-79.9	-Systematic Review & Meta-Analysis Search engines used: Medline, Embase, Cochrane. -3 reviewers analyzed each article to limit inclusion bias -Each article was reviewed by 2 independent reviewers using the global quality rating scale (good, fair, or poor). Disagreement on an article was resolved by 3rd reviewer. -Data synthesis tool used for meta-analysis: RevMan 5.0 a Cochrane collaboration tool. - RR, RD, NNT, & 95% CI, calculated by DerSimonian Laird Method. -Clinical heterogeneity was assessed for population type, probiotic type, and quality of study. -Funnel plot used to assess for publication bias.	-Rates of CDI = 3% or 18/572 intervention and 55/527 in placebo yielding a RR = 0.37, 95% CI [0.22-0.61], RD = 0.07, 95% CI [0.11-.0.02]. NNT 14, 95% CI [9-50] -Meta analysis of type of probiotic in relation to reduction of rates of AAD and CDI all showed reduction. However, only the combined Lactobacillus probiotics showed a significant reduction in CDI & AAD. -No effect size noted	-Moderate degree of publication bias present -There may be differences in styles of nursing practice to prevent CDI or antibiotic prescribing practices may differ between the various studies leading to different/skewed results in each individual study.	-Although article sounds promising, the NNT in relation to reduction of CDI, (4, 95% CI [9-50]), is a large CI this is concerning as cost vs benefit may not be there if NNT is closer to 50. -Probiotics containing Lactobacillus seem to be the most efficacious choice -Article supports the use of probiotics to reduce risk of CDI and AAD	I

Note. LOE = level of evidence CDI = *Clostridium difficile* infection, AAD = antibiotic associated diarrhea, RCT = randomized control trials, *H. pylori* = *Helicobacter pylori*, RR = relative risk, RD = risk difference, NNT = number needed to treat, CI = confidence interval

Table D16.
Literature Review

Citation/ Search Engine Used	Purpose/ Objectives	Study Population, Sample/ Setting	Study Design/Methods/ Major Variables/Instruments and Measures	Results/ Major Findings	Implications/ Critiques	Comment Themes	LOE
Redman et al. (2014) PubMed	Perform a systematic review and meta-analysis of literature to collect data regarding the safety and efficacy of probiotic usage in people with cancer	- *N* = 1530 -Control: *n* = 756 -Treatment: *n* = group- 774 - Adult cancer patients -Inclusion criteria- enrolled in RCT, diagnosed with cancer, receiving probiotics, and studies with secondary analysis of safety. -Setting: RCT in Finland, Brazil, India, Thailand, Hungary, Italy, China, Japan, Canada, and Spain -17 studies analyzed safety -11 studies analyzed efficacy.	-Systematic Review with Meta-analysis Data collected from 17 different search engines. A 40-step search strategy was performed using Medline, Embase, and Amed Data collection took place from 2010- 2012. -2 independent reviewers for study selection, 1 separate review used for disputes. Studies were reviewed utilizing Cochrane collaboration risk for bias assessment tool -Data analyzed using Rev Man 5.2 system. -Variables- decreased incidence of diarrhea utilizing the common toxicity criteria for analyzing degree and severity of diarrhea and adverse outcomes Clinical heterogeneity was assessed for selection criteria, performance, detection bias, attrition bias, and reporting bias. Bias detected by $I^2 > 50\%$	-Efficacy: probiotics may be beneficial in reducing frequency of diarrhea: OR = 0.32, 95% CI [0.13-0.79] *p* = 0 .01 -Data to support probiotics may reduce frequency of bowel movements appears promising, however only two studies were included in this analysis and bias was high in studies. Therefore, full conclusions cannot be drawn (mean bowel movements per day decreased by 9.6 movements, 95% CI [10.45- 8.75], *p* = 0.00001 -Safety**:** pooled adverse events in probiotics = 103 versus placebo =145 -No statistical analysis for significance noted for adverse events. -Author note: due to the significant heterogeneity of treatment options and variation of standard of cares and numerous variables, determining which adverse effects are related to probiotic consumption is fairly impossible	-Study does not provide in depth pooled demographics of population. -Case reports were included in statistics for safety -Effect size not noted for statistic results -Inclusion and exclusion criteria explanation was brief - No statistical evidence to determine if adverse events are significant	-Article seems to support use of probiotics and infers that cancer patients are immunocompromised and likely to have the highest risk of adverse events, yet appear to not have a significant difference in adverse events. -The authors do describe the case studies that note connection to probiotics to severe adverse events. In some cases, the adverse events are proven to not be related to probiotic usage.	I

Note. LOE = level of evidence, RCT = randomized control trial, *N* = total sample population, *n* = sub sample population, OR = odds ratio, CI = confidence interval, p = measure of statistical significanc

Table D17
Literature Review

Citation/Search Engine Used	Purpose/ Objectives	Study population/ Sample/ Setting	Study Design/ Methods/ Major Variables/ Instruments and Measures	Results/ Major Findings	Implications/ Critiques	Comments/ Themes	LOE
Sadanand et al. (2019) PubMed	Evaluate the safety of Lactobacillus rhamnosus probiotic as a treatment method in the pediatric patient population who are experiencing graft versus host disease (GVHD) and/or who have recently undergone HSCT many of whom have CDI or other GI ailments. The aim specifically was to assess for probiotic associated bacteremia.	*N* = 15 Median age = 7 60% of population had an unmatched/unrelated donor. Pediatric allogenic HSCT recipients 2011-2016	-Single-center retrospective study -Probiotic doses varied from one capsule or packet daily to two packets four times daily. -Primary analysis of bacteremia -Secondary analysis of what immunosuppressive medicine the patients are on. occurrence rates of GVHD and presence of CDI	-5/15 patients experienced blood stream infections within the first 100 days of transplant. None of these cases occurred while a patient was on the Lactobacillus rhamnoses probiotic. None of the 5 cases of bacteremia were related to the Lactobacillus species. 70% of the patients had CDI or GI GVHD by day 100 and were subsequentially started on probiotics after symptoms started	-No statistical data provided. -Large variation in the population characteristics -No rigor in study due to prospective nature. - Low power as only had 15 patients -Fair study. Most shows the safety of probiotics in a very high-risk population.	Study evaluates safety of probiotics in a high risk-immune suppressed group. This study does not analyze the efficacy of probiotics as a prophylactic method. Large variation in the dosage of probiotics administered.	IV

Note. LOE = level of evidence, GVHD = graft versus host disease, HSCT = hemopoietic stem cell transplant, CDI = *Clostridium difficile*

Table D18.
Literature Review

Citation/ Search Engine Used	Purpose/ Objectives	Study Population, Sample/ Setting	Study Design/Methods/ Major Variables/Instruments and Measures	Results/ Major Findings	Implications/ Critiques	Comment Themes	L O E
Selinger et al. (2013) CINAHL	To determine if a probiotic containing: Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus delbrueckii subsp. bulgaricus, Streptococcus thermophilus, reduces the risk of CDI and antibiotic associated diarrhea as well as analyze adverse events	-*N* = 122 -Placebo: *n* = 61 -Intervention: *n* = 61 -Adult hospitalized patients receiving systemic antibiotics -Exclusion criteria: severe nausea and vomiting, no oral access, ICU admission, had diarrhea prior to study initiation, acute pancreatitis, previous use of probiotics 1 week before study initiation, severely immunocompromised , (not specified). -Four hospitals: Albert Edward Infirmary, North Bristol, Hull Royal Infirmary, and Weston General Hospital -April 2010-Feb 2012.	-RCT (stated in article) reviewer feels it is Quasi- experimental due to sampling technique -Double Blind -Stratified cluster sampling used -Patients were assessed for eligibility, if consent approved, were administered probiotic or placebo within 48 hours of first antibiotic. -Probiotic and placebo administered twice per day for the duration of antibiotic treatment and 7 days after. -Patient diary: reported if medication was taken, symptoms, number of stools, and stool characteristics. -Daily Bristol stool charts. If stool was categorized as type 6 or 7 twice in one day, a stool sample was sent for CDI testing. -CDI testing performed using Premier Toxin A+B at Hull and Bristol site. Quick Check complete test was used at Weston and Wigan sites -	-No determination could be made on reduction of CDI rates as neither group had an incidence of CDI. -Significant reduction of AAD was noted (p = 0.006) -There was no significant difference in length of hospital stay. - Adverse side effects were not significant between the control and interventional group (p = 0.63) In fact, the placebo group had higher rate of side effects 8.9% vs 6.8% supporting the minimal risk/side effects of probiotics	-Low *N*, Power analysis for 90%, 5% LOS, *N* needed to be >389 -Poor retention during study: initial enrollment- *N* = 231. end point- *N* = 122. - Poor retention -Study used two different instruments depending on site to test stool samples for CDI. Imposes high risk of error -The “average risk” and “severely immunocompromised patient not defined. - Study funded by pharmaceutical company	Cannot determine if CDI is reduced as no cases were noted. -Poor sampling -Does state that adverse effects were not significant vs placebo	III

Note. LOE = level of evidence, CDI = *Clostridium difficile* infection, N = total sample population, ICU = intensive care unit, RCT = randomized control trial, AAD = antibiotic associated diarrhea

Table D19.
Literature Review

Citation/ Engine	Purpose/ Objectives	Study Population, Sample/ Setting	Study Design/Methods/	Results/ Major Findings	Implications/ Critiques	Comment Themes	LOE
Shen et al. (2017) PubMed	-Primary purpose: review RCT studies and analyze if the use of probiotics reduces incidence of CDI. Secondary purpose was to determine if there was a correlation to type of probiotic administered, dosing of probiotics, timing of initiation, duration of treatment and quality of studies analyzed.	-19 RCTs analyzed -Total sample: *N* = 6,261 -Probiotic: *n* = 3,277 -Placebo: *n* = 2,984 -Mean age: 68 -Inclusion criteria: hospitalized patients, age 18 years or older on antibiotics IV or oral, receiving probiotics as a primary prevention method. -Excluded patients: pregnant, neutropenia, HIV, malignant cancer, transplant patients receiving immunosuppression, and preexisting GI disorders. -Probiotics used in studies= 12 formulations all containing Lactobacillus, Saccharomyces, Bifidobacterium, & Streptococcus either alone or in combination. -Studies conducted in 8 countries: USA, UK, Turkey, Canada, Norway, Italy, China, & Germany.	-Systematic review & meta- analysis -Search engines: Medline, Cochrane Library, Ovid, and ProQuest. -2 reviewers -Disagreements settled by 3rd reviewer. - Bias controlled by use of *Cochrane Handbook for Systematic Review or Interventions* -Quality of studies analyzed using standardized GRADE system - Publication bias was assessed by use of funnel plot and Egger's regression - Meta-regression performed by STATA program	-No significant heterogeneity across the 19 studies ($p = 0.56$) -Meta- analysis supports probiotic to prevent CDI vs placebo or no intervention Risk of CDI in control group: 0-40% Risk of CDI in intervention group: 0-11% RR= 0.42, 95% CI [0.30-0.57] $p = 0.001$ -NNT= 43, 95% CI [36-58] - Probiotic initiation: more effective if started within 2 days of antibiotic administration: RR = 0.32, 95% CI [0.22-.48] versus greater than 2 days from antibiotic start time: RR = 0.70, 95% CI [0.40-1.23] - No significant difference in probiotic formulation effectiveness ($p = 0.34$) -Writer does argue use of Lactobacillus due to heavily studied formula -Analysis of adverse effects from placebo to intervention not statistically different ($p = 0.35$) -Quality of evidence measured by GRADE system = high quality -No effect size noted	-Supports use of probiotics as primary prevention of CDI, most effective if started within 2 days of antibiotic initiation. -Writer theoretically notes: if a hospital's baseline CDI rate is 1.5%-7.4% the research suggests 1 case of CDI would be prevented by every 23-144 patients on probiotics.	-No financial funding conflictions -Credible researchers -Very strong article	I

Note. LOE = level of evidence, CDI = *Clostridium difficile*, RCTs = randomized control trials, USA = United States of America, UK = United Kingdom, IV = intravenous, HIV = human immunodeficiency virus, GI = gastrointestinal, RR = relative risk, CI = confidence interval, NNT = number needed to treat, *p* = measure of statistical significant

Table E1.

Theme Matrix

Item	Methods/backgrounds		Interventional Methodology		Findings		
	Heterogeneity/Selection bias/Poor methods of sampling	**Excluded high risk patients**	**Lactobacillus containing probiotic**	**Timing of probiotic effects CDI reduction**	**Decrease in CDI rates**	**Cost effective**	**Notes side effects of probiotic**
Box et al. (2018)	Y	NS	Y	NS	N	NS	NS
Carvour et al. (2019)	Y	NS	NS	NS	N	NS	NS
Dudzicz et al. (2018)	Y	N	Y	Y	Y	Y	NS
Goldenberg et al. (2018)	N-rates of CDI Y-Safety	NS	Y	NS	Y	NS	Y,
Guillemin et al. (2014)	Y	N/A	N/A	N/A	N/A	N/A	N/A
Hassan et al. (2018)	Y	N	NS	NS	N/A	Y	Y
Johnston et al. (2012)	N	NS	Y	NS	Y	NS	Y
Kamdeu Fansi et al. (2012)	Y	NS	Y	Y	Y	Y	NS
Kujawa-Szewieczek et al. (2015)	Y	N	Y	Y	Y	NS	Y
Lau et al. (2016)	Y	Y	Y	NS	Y	NS	Y

Table E1. (*continued)*
Theme Matrix

Item		Methods/backgrounds		Interventional Methodology		Findings	
	Heterogeneity/Selection bias/Poor methods of sampling	**Excluded high risk patients**	**Lactobacillus containing probiotic**	**Timing of probiotic effects CDI reduction**	**Decrease in CDI rates**	**Cost effective**	**Notes side effects of probiotic**
Leal et al. (2016)	Y	NS	Y	NS	Y	Y	NS
Lewis et al. (2017)	Y	Y	Y	Y	Y	Y	NS
Li et al. (2018)	Y	NS	Y	NS	Y	Y	NS
Mazaide et al. (2013)	Y	N	Y	Y	Y	NS	Y
Pattani et al. (2013)	Y	Y	Y	NS	Y	NS	NS
Reman et al. (2014)	Y	N	Y	NS	NS	NS	Y
Sadanand et al. (2019)	Y	N	Y	NS	NS	NS	Y
Selinger et al. (2013)	Y	Y	Y	NS	NS	N	NS
Shen et al. (2017)	N	Y	Y	Y	Y	Y	NS

Note. N= no, Y = yes, NA = not applicable NS = not specified

Table F1.

Concept Analysis Process Elements

Identified Concept of Interest	Theoretical Definition	Operational Definition	Antecedents	Consequences	Type of Research Design
Probiotic	None Stated	-Lactobacillus containing probiotic administered within three days of antibiotic start. -Continued for the duration of antibiotic treatment	-Patients 18 years or older, hospitalized, receiving antibiotics. -Exclusion criteria: none	-12/16 studies report reduced incidence of CDI -Cost effective/ substantial cost savings to institutions - No major differences in side effects from probiotic intervention. One study reported significantly less adverse events in probiotic group than placebo/control versus placebo/control group.	Ranged from systematic reviews with meta-analysis to small case cohort quasi-experimental studies.

Note. CDI = *Clostridium difficile* infection