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Effectiveness Of Probiotics In Preventing Antibiotic Associated Diarrhea And Clostridium Difficile In Long Term Care

Marva Edwards-Marshall
University of Central Florida

EFFECTIVENESS OF PROBIOTICS IN PREVENTING ANTIBIOTIC ASSOCIATED DIARRHEA AND C*LOSTRIDIUM DIFFICILE* IN LONG TERM CARE

by

MARVA EDWARDS-MARSHALL
B.S.N. University of Central Florida 2002
M.S.N. University of Central Florida 2004

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ABSTRACT

Problem/Purpose: Antibiotic associated diarrhea (AAD) and *clostridium-difficile* diarrhea (CDAD) are the most common forms of infectious diarrhea in long-term care facilities. The purpose of this study was to determine the effectiveness of probiotics in preventing AAD and CDAD in the long term care geriatric population, and to identify interventions that can be used to improve clinical practice.

Background/Significance: Prophylactic use of probiotics have been purported to decrease the incidences of AAD and CDAD. Previous studies have yielded contradictory results on the efficacy of probiotics. The objective of this study was to evaluate the impact of administration of probiotics on the rate of infectious diarrhea in the Long Term Care (LTC) population

Method: This was a retrospective cohort study. The charts of residents of a LTC facility who were 65 years of age and older, and were administered antibiotic therapies, with or without co-administration of probiotics were reviewed. A data collection instrument was created for this study and piloted prior to its utilization. A chi-square test of independence was calculated to obtain the results.

Results: Forty-four residents received probiotics with antibiotics, five cases of diarrhea were reported; no cases of CDAD were reported. In 39 residents who received antibiotics without probiotics, two cases of diarrhea and one case of CDAD were reported.

Conclusion: The study showed no statistically significant evidence to support the effectiveness of probiotic use in the prevention of AAD and CDAD in a long term care facility. The incidence of AAD was higher in the group with probiotics

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CHAPTER ONE

Probiotics are living organisms, which when ingested have the beneficial therapeutic effect of reestablishing normal intestinal flora. Each probiotic has its own unique characteristic and effects. Probiotics belong to several species such as *lactobacillus, bifidobacterum, streptococcus*, and yeasts and molds. The probiotics *Saccharomyces boulardii, lactobacillus rhamnosus GG, Lactobacillus plus acidophilus, Lactobacillus bulgaricus, lactobacillus casi* and *bifidobacterum bifidium* are some of the most frequently used probiotics (Bergogne-Berezin, 2000). Several studies have been conducted over the past 20 years on their effectiveness in the prevention of antibiotic-associated diarrhea (AAD) and *clostridium-difficile* diarrhea (CDAD) with varied results about their effectiveness.

The prevention of AAD and CDAD, or extent of these infections, might assist in the reduction of morbidity and mortality in the vulnerable geriatric population of long term care (LTC) facilities. This population is at greater risk of acquiring these infections because of frequent administration of antibiotics. Other risk factors include comorbid conditions, frailty, cross infection, age, or congregate living (Schroeder, 2005). CDAD is the most common infectious cause of diarrhea in LTC residents (Laffan, Greenough, & Zenilman, 2006)

Probiotics are used despite a lack of definitive evidence of their effectiveness in the prevention of AAD and CDAD in the LTC population. Studies conducted on adult subjects found that probiotics were effective in the prevention of AAD (Can, BeÅŸirbellioglu, Avci, Beker, & Pahsa 2006; Gotz, Romankiewicz, Moss, & Murray, 1979; McFarland et al., 1995; Surawicz et al., 1989). However, two studies found there was no significant benefit of probiotics

in the prevention of AAD and CDAD (Lewis, Potts, & Barry, 1998; Thomas et al., 2001) . Five meta-analyses on the use of probiotics for the prevention of ADD have been published. These contained studies that included children. McFarland's (2006) landmark meta-analysis of 25 randomized controlled trials found that a variety of different types of probiotics have some therapeutic effect on AAD and CDAD. However, the analysis showed that only three types of probiotics significantly reduced the development of AAD, and only one was effective for CDAD. However, none of these study reports provided sufficient data on dosing and duration of therapy.

Problem/Significance

The widespread use of antibiotics promotes occurrences of diarrheal infections. Antibiotics disrupt the intestinal microflora which is a protective barrier against the colonization of intestinal pathogens (Marteau, Vrese, Cellier, & Schrezenmeir, 2001). With the interruption of this protective barrier, patients become susceptible to opportunistic infections such as AAD and CDAD (Bergogne-Berezin, 2000; Surawicz, 2003).

AAD can occur during or shortly after antibiotic administration. Even a single dose of antibiotic can produce an episode of AAD (Katz, 2006). Diagnosis of AAD is made in the absence of other known causes of diarrhea. Frequency of AAD varies with the type of antibiotic used and can occur within a day of starting antibiotics or up to six weeks after completion of antibiotics (Katz, 2006). AAD occurs in 25% of adults receiving antibiotics with rates as high as 26-60% in hospital outbreaks (Katz, 2006; McFarland, 2006).

The World Health Organization defines diarrhea as watery or unformed stools, occurring more than 3 times a day for at least 2 days. AAD occurs within two months of

antibiotic therapy. Risk factors associated with AAD include the use of broad spectrum antibiotics, such as amoxicillin, second and third-generation cephalosporin, and clindamycin. Other risk factors include long courses of antibiotic therapy, or repeated courses of antibiotic therapy, and extremes of age, less than 6 and greater than 65 years (Bergogne-Berezin, 2000). Additionally, predisposing factors such as history of AAD, serious concomitant disease, chronic digestive diseases, co-morbidity, and immunodeficiency can precipitate AAD. Prolonged hospitals stay, surgery, gastrointestinal procedures, nasogastric alimentation and residing in a nursing home, are all risk factors associated with AAD (Bouhnik, 2006).

CDAD is diagnosed by a positive stool culture for toxin (A or B), stool cytotoxicity assay positive for Toxin B, or endoscopy for colonic pseudomembranes. CDAD the most severe form of AAD, accounts for 15% to 25% of AAD and can be very difficult to treat (Doron, Hibberd, & Gorbach, 2008).

The prevalence of c*lostridium difficile* can range from 2.1% to 8% in LTC facilities during a one year period (Simor, Yake & Tsimidis, 1993). *C-difficile* is present in 2-3% of typically healthy adults and in as many as 70% of normally healthy infants, and is the most common infectious cause of acute diarrhea in nursing homes (Simor, Yake & Tsimidis, 1993). Eighty percent of CDAD onset occurs during antibiotic therapy and 8% to 33% of long term care residents treated with antibiotic therapy acquires infection with CDAD (Simor 2002). Laffan, Greenough, and Zenilman (2006) in their study found that the incidence of CDAD ranged from 0 to 2.62 cases per 1,000 resident days, with a recurrent rate of 21.7% of patients. Current

treatment for AAD and CDAD is with the administration of specific antibiotics, metronidazole and vancomycin.

Probiotics are living organisms (yeast or bacteria) which, when administered in adequate amounts, have a potentially beneficial therapeutic effect. Some of these are the prevention of antibiotic-associated diarrhea, decreasing the frequency of recurrent *Clostridium-difficile* infection, and preventative and curative activity against acute infectious diarrhea (McFarland, 1998; Bouhnik, 2006). Several studies found that prophylactic probiotics are not widely used, although they have been extensively studied (Kopp-Hoolihan, 2001; Sazawal, 2006). There are over 800 publications on probiotics completed to date (Piche, & Rampal, 2006). However, these research studies conducted on the efficacy of probiotics provide contradictory results. This may be due to the study designs, type of probiotic, differing dosage and length of treatment.

There are currently no studies on the effectiveness of prophylactic probiotic administration, specifically in the LTC geriatric population. Therefore, it is the intent of this study to obtain information which can direct clinical practice for the use of probiotics as prophylactic therapy for AAD and CDAD in LTC geriatric population. Overall clinical practice may be enhanced through the development of evidence to support the use of probiotics in the LTC geriatric population.

Objectives

The objective of this study is to evaluate the effectiveness of probiotics when administered with antibiotics for the treatment of a variety of infectious diseases with the goal of preventing of AAD and CDAD. The assumption is that probiotics are effective in the prevention of AAD and CDAD (Surawicz et al. 1989; McFarland et al., 1995; Bergogne-Berezin, 2000; Bouhnik, 2006; Can et al. 2006). The incidences and prevalence of AAD and CDAD in the LTC setting presents a challenge to the health care system as CDAD is the most commonly identified cause of diarrhea in LTC. Furthermore, as the population ages, concern of infections and diseases are expected to rise in the LTC population (Laffan et al., 2006). Additionally, there is sufficient evidence through randomized control trials (RCT) to suggest effectiveness of probiotics in prevention of these infections. (Gotz et al., 1979; Surawicz et al., 1989; McFarland et al., 1995; Can et al., 2006).

The design is a retrospective cohort study of a geriatric population in the LTC setting. The overall aim is to direct clinical practice in the management of AAD and CDAD infections in this patient population. The geriatric population of LTC facilities includes individuals with many comorbid conditions, depressed immune systems. Polypharmacy and frequent use of antibiotics place them at a higher risk of acquiring diarrheal infections.

The research questions to be addressed are:

1. Are probiotics effective in preventing AAD and CDAD in the LTC population?
2. Which probiotic dosing is effective in preventing AAD and CDAD?
3. What is the most effective duration of probiotic administered in preventing AAD and CDAD?

CHAPTER TWO

This chapter presents a review of past and current literature on the efficacy of probiotics in the prevention of AAD and CDAD. Studies included randomized control trials (RCT), meta-analysis and systematic reviews. Eleven studies met the inclusion criteria and are explored in this chapter.

Antibiotic-associated diarrhea (AAD) is a common problem found in up to 25% of patients, following the use of antibiotics. Up to 25% of these cases progress to *clostridium-difficile* diarrhea (CDAD) (Katz, 2006). The mechanisms underlying AAD include the proliferation of pathogenic microbes and reduction of fermentative activity on the part of the microflora (Rambaud, Buts, Corthier & Flourié 2006). The frequent use of antibiotics in the geriatric population in the long term care (LTC) setting puts them at risk for acquiring these infections because of age, multiple co-morbidities and immunocompromised state.

Probiotics are purported to be suitable for use in the prevention of these infections (McFarland 2006) although, several studies have been conducted on the therapeutic benefit of probiotics without conclusive results (Dunkduri 2005). Currently, use of probiotics is at the discretion of the prescriber as there are no current guidelines for its use.

Review of Literature

A review of literature was conducted to determine whether the administration of probiotics along with antibiotic therapy would decrease the incidences of ADD and CDAD in the geriatric population based on studies conducted to this date. The search terms used were probiotics, diarrhea, antibiotic *clostridium-difficile*, evidence based practice, 65+ years, practice

protocol, clinical trials, humans, and English language. Databases searched included CINAHL, MEDLINE, PubMed, Cochrane Systemic Review, and Cochrane Central Register of Controlled Trials. Trials in which probiotics were given for prevention of AAD and CDA were utilized as the major inclusion criterion for the study. Exclusion criteria for studies were use of probiotics for treatment of AAD and CDAD, children only studies, and reviews. The articles which met inclusion criteria included six original studies, four meta-analysis and one systemic review which provided data on over 5,000 treated patients.

The literature search yielded 302 studies. After limiting the search to studies in which probiotic were used for prophylaxis of AAD, CDAD, and which were randomized control trials (RCT), 51 studies were identified and screened for further inclusion. Eleven studies were selected based on predefined inclusion criteria of studies in which probiotic were used for prophylaxis of AAD and CDAD, and were randomized control trials (RCT). (see Figure1for flow diagram of included and excluded studies).

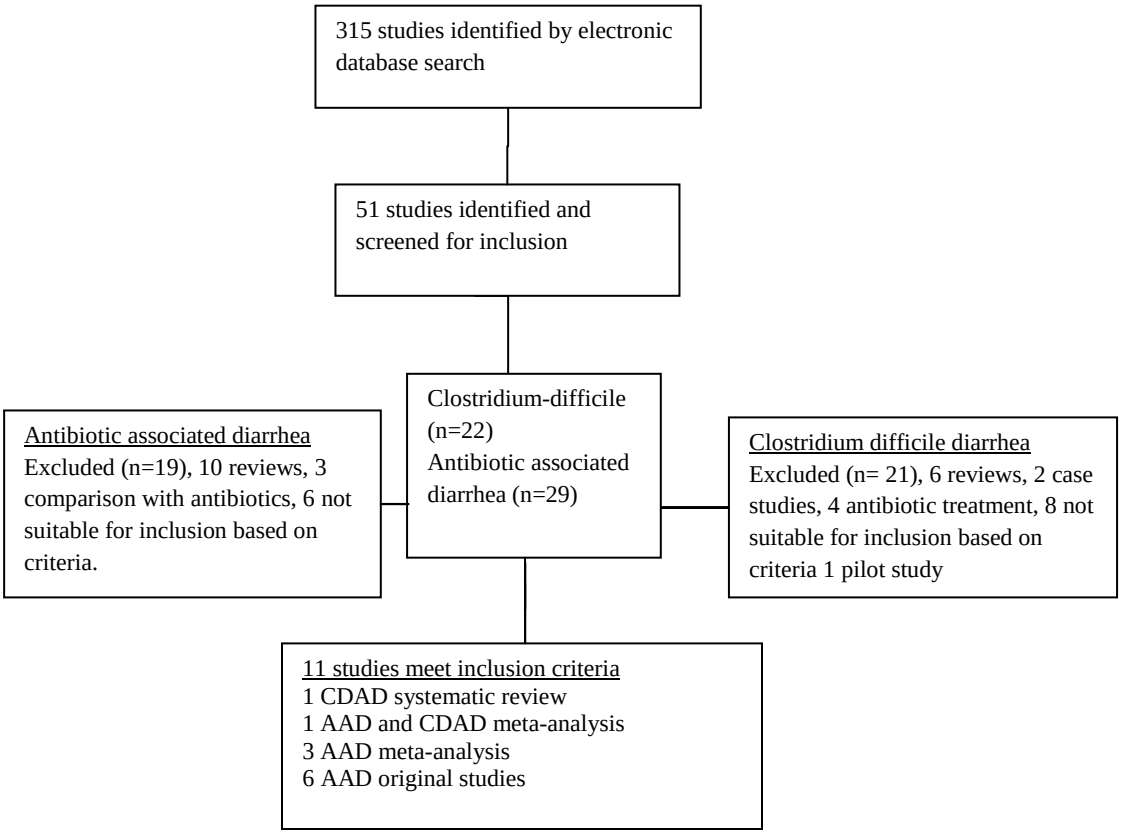

Figure 1 Flow diagram of included and excluded studies.

Note: AAD indicate antibiotic associated diarrhea. CDAD indicate *clostridium-difficile* diarrhea.

Gotz and colleagues (1979) conducted a randomized controlled placebo trial of 98 hospitalized patients' with ages ranging from 18 to 88 who were treated with Ampicillin and were also administered *Lactobacillus acidophilus* and *Lactobacillus bulgaricus* to determine the efficacy of these probiotics in the prevention of AAD and CDAD. The patients were treated with one packet of either *Lactobacillus acidophilus, Lactobacillus bulgaricus* or placebo four times a day for the first five days of ampicillin therapy. Data from 79 patients were collected and reviewed, the results showed that the patients in the ampicillin and placebo group had ampicillin-

induced diarrhea at a rate of 14% (p=0.03) and those in the ampicillin and probiotics group experienced no diarrhea. This result suggests that prophylactic use of probiotics appears to be effective in the prevention of AAD.

Surawicz et al. (1989) conducted a randomized controlled placebo trial of 180 hospitalized patients receiving the antibiotics clindamycin, cephalosporins, or trimthoprim-sulfamethazole. Subjects were randomized to receive either a placebo or *Saccharomyces boulardii.* The study was conducted over a period of 23 months during which time the duration of antibiotic therapy administration varied. The results showed that 22% of patients receiving antibiotic and placebo acquired AAD compared to 9.5% of those receiving antibiotic and probiotic (p=0.038). This result suggests that prophylactic probiotics appear to be effective in the prevention of AAD.

Another study which showed efficacy of probiotics in the prevention of AAD and CDAD was conducted by McFarland et al. (1995). In this randomized controlled placebo trial 193 patients were treated with the B-lactam, tetracycline, and the probiotic *Saccharomyces boulardii* (1g/day) within 72 hours of the start of antibiotic through to 3 days after completion of the antibiotic therapy. The patients were followed up for seven weeks after antibiotic therapy. Fourteen point six percent (14/96) of patients receiving antibiotic and placebo developed AAD (p=0.02). Whereas 7.2% (7/97) of patients receiving antibiotic and probiotics developed AAD, with the efficacy of *Saccharomyces boulardii* in the prevention of AAD being 51%. Suggesting that *Saccharomyces boulardii* a probiotic has demonstrated effectiveness in preventing AAD.

Can et al. (2006) recently conducted a randomized controlled placebo trial of 151 hospitalized patients receiving antibiotics. Subjects were randomized to receive either the

probiotic *Saccharomyces boulardii* or a placebo with the antibiotic therapy. The results of this study showed that 9% (7/78) patients in the antibiotic and placebo group developed AAD and 1.4% (1/73) patients in the antibiotic and probiotics group developed AAD ($p=<0.05$). On further evaluation two of seven stool samples collected from the placebo group with AAD tested positive for CDAD, however, no stool from the probiotic group tested positive for CDAD, which provides evidence that probiotics is effective in preventing AAD and CDAD when compared with placebo.

Studies conducted by both Lewis et al., 1998 and Thomas et al., 2001 found no significant efficacy in the administration of probiotics for the prevention of AAD. Lewis, et al.(1998) conducted a randomized controlled placebo trial of 69 hospitalized patients who were prescribed antibiotics and were randomized to receive the probiotic *Saccharomyces boulardii* (113 mg) twice a day or placebo during the course of the antibiotic therapy. Their results showed 17% (5/33) of patients receiving antibiotic and placebo developed CDAD and 21% (3/36) in the antibiotic and probiotic group developed CDAD. The conclusion of the study was that efficacy was not shown in favor of probiotics in preventing AAD and CDAD when compared with placebo.

Thomas et al. (2001) conducted a randomized controlled placebo trial of 267 hospitalized patients who were administered either *Lactobacillus GG* ($20x10^9$ CFU) one capsule two times a day and a placebo one two times a day over a 14 day period and monitored for seven days after completion of the treatment. The results showed that 29.3% (39/133) patients receiving antibiotic and the probiotic *Lactobacillus GG* had diarrhea, whereas, 29.9% (40/134) participants receiving

placebo developed diarrhea. The conclusion of the study was that efficacy was not shown in favor of probiotics in preventing AAD when compared with placebo.

Three meta-analyses and one systematic review were examined to evaluate the effects of probiotics in the prevention of diarrhea associated when used in combination with antibiotic. D'Souza, Rajkumar, Cooke, & Bulpitt (2002) conducted a meta-analysis of nine randomized placebo-controlled trials covering over 1,300 subjects. The results supported the conclusion that probiotics can be used in the prevention of AAD, that S*accharomyces boulardii* and lactobacilli have the potential to be used for this infection.

Cremonini, et al. (2002) conducted a meta-analysis of seven randomized placebo-controlled trials covering over 800 subjects. The results supported the conclusion that probiotics were more effective than placebo in the prevention of AAD. Suggesting administration of probiotic can have benefit on AAD. However, they concluded that the evidence of beneficial effects is not very definitive as published studies are flawed by a lack of placebo design and peculiar population features.

Sazawal, et al. (2006) in their meta-analysis of 19 masked randomized placebo-controlled trials involving over 2, 000 subjects found that six of the studies on prophylactic probiotic use had statistical significance with an overall reduction of 52% of AAD.

A systematic review of eight randomized controlled trials conducted by Dendukuri, Costa, McGregor & Brophy (2005) was conducted to identify studies in which the prevention or treatment of CDAD with probiotic therapy was the primary or secondary outcome. The results showed that there was insufficient evidence in studies conducted to date to for routine use of probiotics for the prevention of CDAD.

The major meta-analysis of probiotics for the prevention of AAD and treatment of CDAD was conducted by McFarland (2006). This study examined 31 randomized control trials which studied the use of probiotics for the prevention of AAD and treatment of CDAD. Twenty-five of these studies reviewed were for the prevention of AAD and involved over 2500 subjects. The results showed a 44% reduction of AAD in adults, 52% of the studies showed a reduction in the incidences of AAD compared to placebo, with higher dosing associated with positive efficacy. Moreover, a variety of probiotics Lactobacillus rhamnosus GG, Saccharomyces boulardii and probiotic mixtures showed significant efficacy and promise as effective therapies for the reduction of AAD. The study also found that Saccharomyces boulardii was an effective treatment for CDAD.

Discussion

Antibiotic-associated diarrhea and CDAD infections are common; but potentially serious health problems Prevention of these infections is justified as they can be costly for this population in morbidity and mortality as well as the price of treatment. The restoration or maintenance of the gut microflora in the presence of antibiotic use is necessary to prevent the occurrences of these infections. The main original studies on the use of probiotics were not definitive in the efficacy of probiotics in the prevention of AAD and CDAD. This may be due to the study's design, the length of therapy, duration of therapy, follow up period and dosing of probiotic administered. It is of note however, that the majority of studies did provide evidence of efficacy. The meta-analysis or systematic review did show that efficacy was evident in the majority of studies. These studies included children studies and pilot studies.

Limitations of these studies are that all they were conducted either with hospitalized patients or outpatient adults or children (specifically the meta-analysis or systematic reviews), not principally elderly residents in LTC facilities. In conclusion, the studies of the benefits reported do not adequately include the geriatric population of LTC facilities; therefore, there is a need to obtain this information. Consequently, the intent is to conduct future studies to investigate the effectiveness of administering probiotics in this specific population for the prevention of AAD and CDAD. The results of such a study can contribute knowledge of best clinical practice in the care of this population.

CHAPTER THREE

In this chapter, the research design to address the three research questions is discussed. The three research questions are: 1.Are probiotics effective in preventing AAD and CDAD in the LTC population? 2. Which probiotic dosing is effective in preventing AAD and CDAD? 3. What is the most effective duration of probiotic administered in preventing AAD and CDAD? The setting, participants, sampling, human subjects, data collection tool and procedure are also presented. Data analysis, strengths and limitations of the research design and plans for future studies are explored.

Research Design

This was a retrospective descriptive cohort study of the effectiveness of probiotics administration among LTC residents' ages 65 years and over who were administered antibiotics with or without probiotics within the past 12 months. The intent of this study was to determine if the prophylactic use of probiotics was effective in preventing AAD and CDAD.

Strengths

The strengths of retrospective cohort studies are that naturally occurring events can be studied and the measurement predictor cannot be biased by knowledge of which participants have the outcome of interest (Hulley, Cummings, Browner, Grady & Newman 2001). Retrospective cohort studies are less expensive and time consuming than RCTs. The resources are mainly directed at collection of data only. Additionally, participants have already been identified, baseline measurements have been made and the follow-up period has already taken place.

Limitations

The main limitation of retrospective cohort studies is the restricted control the researcher has over the design of the approach of sampling the population and the nature and quality of the predictor variables. The existing data may not include information that is important to answering the research questions. Data may be incomplete, inaccurate, or measured in ways that are not ideal for answering the research question (Hulley et al. 2001).

Setting/Participants/Sampling

The study setting was at a LTC facility in Melbourne Florida which has 160 beds, and various occupancy rates. The participants were a convenience sample of geriatric patients, aged 65 years and older who were residing in the facility for more than six months and were treated with antibiotics for a period of one day or more, between January 2009 and December 2009. Data was obtained from a chart review. If a participant received probiotics at the same time as an antibiotic in any of the commercially available species, *lactobacillus*, *bifidobacterum*, *streptococcus* and yeasts and molds, in pill, capsule, granule or suspension form, during the 12 month period they were included in the treatment group. The participants who received antibiotics without probiotics during the 12 month period comprised the control group. The data on subjects meeting inclusion criteria was obtained from the participants' facility medical records. Exclusion criteria included age less than 65 years; reside in the facility less than six months, i.e. patients who have transitioned from rehabilitation care, and those having a past medical history of inflammatory bowel disease, such as Chron's disease, ulcerative colitis or irritable bowel syndrome.

Human Subjects

The researcher received permission from the LTC facility to conduct the study. Because of the retrospective record review design of the study no risk to humans was expected. Approval to conduct the study was received from the institutional review board (IRB) at the University of Central Florida prior to the data collection process. The protected health information (PHI) was kept separate from the patients' chart identification number.

In order to maintain confidentiality and meet the health insurance portability and accountability act (HIPAA) requirements, all protected health information (PHI) was de-identified. Elements that can be used to identify a specific person, or the person's relative, employer or household members were not collected. Charts were tracked and deidentified by assigning random numbers to each chart; these numbers were kept in the facility's medical record file. A data use agreement between researcher and facility was obtained. (Appendix A). An approval of exempt human research was obtained from IRB prior to the initiation of the study (Appendix B).

Data Collection Tool

The data collection tool used to summarize information from the chart review was a demographic and clinical profile form which captured information about the participants' age, gender, length of residency in the LTC facility, chronic medical conditions, and antibiotic therapy within the period from January 2009 through December 2009. (Appendix C). Probiotic data collection consists of type of probiotic received, form of probiotic, number of doses per day and duration of therapy. AAD and CDAD data was defined as three or more loose stool within

two months after antibiotic therapy, new episode of diarrhea associated with positive culture or toxin (A or B), positive culture of any other bacteria or virus. Prior to the study a pilot of the data collection instrument was completed. The principal researcher reviewed a sample of five charts using the data collection tool. Adjustments were made to the form for easier data recording.

Procedure

Data was collected by the principal investigator. The data was be reviewed to assess for content validity to determine if the data collected covered a representation of the element to be measured or if there was additional information pertinent to the study that needed to be examined.

Data Analysis

Statistical analysis was performed using SPSS software version 17.0 (Statistical Package for the Social Sciences). The chi-square test of independence analysis was used to test for statistical significance of the relationship between probiotic use and non probiotic use in the prevention of AAD and CDAD. The null hypothesis states that there is no difference in prevention of AAD and CDAD with administration of antibiotics with or without probiotics. The Cochran's Q was used to determine if there is a difference in AAD and CDAD rates in subjects who were administered probiotics in various doses of 1, 2, 4, or 6 doses per day. The null hypothesis states there is no difference in the dose of probiotics administered and the prevention of AAD and CDAD.

CHAPTER FOUR

This chapter provides the results of the study. The demographics and clinical profile of the participants are provided. This includes age, gender, chronic conditions, and conditions treated with antibiotics. The types of antibiotics and probiotics used in this population within the 12 month period are specified.

Results

Data was obtained from electronic computer charting in a single LTC facility. Data was obtained from the resident's profile, physician's orders, nursing notes and eMAR (electronic medication administration record). Laboratory test results were obtained from archived paper medical records as they were not available from the electronic computer charts. Data was analyzed with SPSS 17, analysis included frequencies, crosstabs and Chi-square analysis. One hundred and ninety-two charts were identified for review. Seventy charts failed to meet inclusion criteria for one or more reasons. Reasons charts were excluded were that residents had lived at the facility less than six months (n=54), ages less than 65 (n=15), or the resident had a pre-existing condition of irritable bowel syndrome (n=1). Other charts which were excluded were of patients who did not receive either antibiotics or probiotics (n=39) therefore, 83 charts met inclusion criteria.

Sample

Ages of the residents in the final sample ranged from 65 to 106 years, with a mean age of 82 years. There were 56 female (67.5%) and 27 males (32.5%) as illustrated in Table 1. The most common chronic diseases found in this sample were dementia, chronic pain, constipation, dysphagia and diabetes mellitus (See Table 2 for common chronic conditions). Sixty-nine of the

83 subjects had two or more of these chronic conditions. Infections treated with antibiotic therapy over the 12 month period were often recurrent. These included urinary tract infection (UTI), upper respiratory infection (URI), skin and soft tissue infection (SSTI), pneumonia and a variety of other infectious diseases, with urinary tract infection as the most frequently treated condition (See Table 3 for common conditions treated with antibiotics). Forty-two of the 83 were treated with antibiotics for two or more infections.

Table 1 Age and Gender Distribution

Characteristics	Number	%
Age		
Mean	82 years	
Gender		
Male	27	32.5
Female	56	67.5

Table 2 Common Chronic Conditions

Chronic conditions	n	%
Diabetes	26	31.3
Constipation	44	52
Chronic pain	47	56.6
Dementia	48	57.8
Dysphasia	38	45.8

Table 3 Common Conditions Treated with Antibiotics

Conditions	n	%
Urinary tract infection	48	57.8
Pneumonia	11	13.3
Upper respiratory infection	25	30.1
Cellulitis	8	9.6
Skin and Soft tissue infection (SSTI)	17	20.5
Other conditions	24	28.9

Eighty-three residents were administered antibiotics of various classes during the 12 month period of January 1, 2009 to December 31, 2009. Forty-four residents (53%) were administered probiotic along with antibiotic therapy, whereas 39 (47%) received antibiotics only. Antibiotics were prescribed and administered a total of 234 times to the 83 residents. While 36 individuals received only one course of antibiotic, many received more than that. In some cases participants received four or five courses of antibiotics. In one case antibiotic was administered 18 times to a single resident for various infections over the 12 month period. See Table 4 for summary of frequency of antibiotics prescribed and administered for the full study group. Various classes of antibiotics were administered. These included quinolones, cephalosporins, penicillins, macrolides, sulfonamides, tetracyclines and a combination or other classes within the 12 month period. This is illustrated in Table 5.

Table 4 Frequency of Courses of Antibiotics Prescribed During 12 Month Period of Study

Number of Courses of Antibiotics Prescribed	Number of Patients who Received Indicated Courses of Antibiotic
1	36
2	14
3	11
4	10
5	6
6	1
7	1
8	1
10	1
14	1
18	1

Table 5 Class of Antibiotics Administered to Patients in the Study

Classification	Name	Number of Times Prescribed and Administered	Route of Administration
Cephalosporin			
1st Generation	cefalaxin	15	PO
	cefadroxil	1	PO
2nd Generation	cefotetan	1	PO
	cefprozil	1	PO
	cefuroxime	13	PO
3rd Generation	ceftriaxone	19	IM
4th Generation	cefepime	1	IV
Sulfonamides	trimethoprim-sulfamethoxazole	11	PO
Tetracycline	trimethoprim-sulfamethoxazole DS	8	PO
Quinolones	doxycycline	16	PO
	tetracycline	1	PO
Aminoglycoside	levofloxacin	48	PO
Penicillin	ciprofloxacin	36	PO
	gentamycin	2	IM
	amoxicillin	14	PO
	ampicillin	5	PO
Macrolide	amoxicillin/clavlanate	7	PO
	pen-V-K	1	PO
Other	azythromycin	19	PO
	erythromycin	1	PO
	primaxin	1	IV
	nitrofurantoin	11	PO
	linezolid	1	PO
	clindamycin	1	PO

Note: PO indicates by mouth. IM indicates intramuscular. IV indicated intravenous.

Probiotic was administered with antibiotic 78 times of the 234 courses of antibiotics prescribed within the 12 month period. Probiotic was given in various frequencies, forms and dosing and duration. Duration did not always match duration of the antibiotics. Seventy-six doses were of various forms of *acidophilus*, and two were of Saccharomyces *boulardii*. The most common forms of probiotics administered were capsules (n=59) and caplets (n=18) Dose of

probiotic was not noted on many of the records. Frequency of probiotic administration varied. This is illustrated in Table 6. The duration of probiotic therapy varied. The most frequent duration of 10 days illustrated in Table 7. The most frequent dosing was one, two times a day (See Table 8 for frequency of probiotic dosing).

Table 6 Types of Probiotic Used

Type of Probiotics	Number of Times Rx	Form of Probiotics	Doses of Probiotics	Duration of Therapy	Prescribed Amount
Acidophilus	45	Capsules	Unknown	<7 days to 16 days	1 Daily; 1 BID; 1 TID; 2 BID
Acidophilus	18	Caplets	Unknown	< 7 days to 14 days	1BID to 2 BID
Acidophilus	06	Capsules	16 mg	10 to 14 days	1 BID
Acidophilus Pectin	02	Capsule	Unknown	10-14 days	1 BID
Acidophilus	03	Capsule	175 mg	10-14 days	1 BID
Saccharomyces boulardii	02	Capsule	250 mg	<7days-10 days	1 BID
Acidophilus	01	Wafer	Unknown	10 days	1 BID
Acidophilus	01	Capsule	1 mg	10 days	1BID

Note: BID indicates two times a day. TID indicates three times a day.

Table 7 Duration of Probiotic Therapy

Duration of Probiotic	Number of Times Prescribed
<7 days	5
7 days	10
10 days	52
14 days	10
21 days	0
>21 days	0
Other (16 days)	1

Table 8 Frequency of Probiotic Administered

Prescribed Amount	Frequency Prescribed
1 Daily	04
1 BID	62
2 BID	08
1 TID	04
2 TID	0

Note: BID indicates two times a day. TID indicates three times a day.

Findings

The occurrence rate of diarrhea episodes found in the 83 residents was 8 (9.6%). There were five cases of diarrhea in the 44 residents who were administered both antibiotics and probiotics (11.4%). None of these records had documentation of positive cultures for clostridium-difficile or other organisms. There were two cases of diarrhea in the 39 residents who were administered antibiotic without probiotic (5.2%). One subject was positive for *clostridium-difficile* toxin A/B (2.6%), after administration of antibiotic without probiotic. The ages of the residents who had diarrhea ranged from 69 to 97 years. Not all the residents who had episodes of diarrhea had been administered antibiotic by mouth. Four of the eight residents had a diagnosis of dysphagia and one had a percutaneous gastrostomy tube (PEG) with which all medications were administered.

Research Questions

Question One

Are probiotics effective in preventing AAD and CDAD in the LTC population?

Data was analyzed with SPSS 17. Analysis was completed using the chi-square test to compare the relationship of diarrhea rate within two months of antibiotic administration with probiotics and without probiotics. Antibiotic with probiotic administration had an 11.4% (n=5) occurrence rate for AAD, whereas antibiotic administered without probiotic had a 5.2% (n=2) occurrence rate ($X^2(1) = 1.041$, $p > .308$). No statistically significant difference was found between the numbers of cases of AAD in those who were administered both antibiotics and probiotics and those who were administered antibiotic without a probiotic. Antibiotic with probiotic administration had no occurrence of CDAD, whereas antibiotics without probiotics administration had 2.6% (n=1) occurrence ($X^2(1) = 1.142$, $p > .285$). No statistically significant difference was found between the number of cases of CDAD in those who were administered antibiotics and probiotics and those who were administered antibiotic without probiotic (See Table 9 for results on the effectiveness of prophylactic probiotic use). Therefore, the null hypothesis which states that there is no difference in prevention of AAD and CDAD with administration of antibiotics with or without probiotics is supported.

Question Two

Which probiotic dosing is effective in preventing AAD and CDAD?

Data was analyzed with SPSS 17. Analysis was calculated using Cochran's Q statistical test to answer this question, however, the variables were not dichotomous, and therefore, the test could not be performed. Moreover, no effective dosing is found in the study as there were only two types of probiotics given, one only twice and the other in various forms and dosing; furthermore, no significant effectiveness of probiotics administration with antibiotic was shown in preventing AAD and CDAD.

Question Three

What is the most effective duration of probiotic administered in preventing AAD and CDAD?

Data was analyzed with SPSS 17. Analysis was calculated using Cochran's Q statistical test to answer this question, however, the variables were not dichotomous, and therefore, the test could not be performed.

Table 9 Results on the Effectiveness of Prophylactic Probiotic Use

Drug Administration	n (% AAD)	n (% CDAD)	Conclusion
Antibiotic with Probiotic	5 (11.4%)	0	No statistically significant evidence found to conclude relationship between probiotic use and prevention of AAD and CDAD
Antibiotic without Probiotic	2 (5.2%)	1 (2.6%)	No statistically significant evidence found to conclude relationship between probiotic use and prevention of AAD and CDAD
P-Value	.308	.285	

CHAPTER FIVE

This chapter explores and discusses the study's findings. The chapter includes limitations of the study conducted, conclusions and suggestions for further studies to be conducted in the population of LTC; also, nursing implications are suggested.

Discussion

The findings of this study do not provide evidence to support a relationship between probiotic use in the prevention of AAD and CDAD. The incidence of AAD was higher in the group with probiotics by four events.

The results of this study showed no statistically significant evidence to support the effectiveness of probiotic use in the prevention of AAD or CDAD. Previous randomized control trial conducted by Gotz et al (1979) found that *Lactobacillus acidophilus* and *Lactobacillus bulgaricus* were effective in preventing AAD in hospitalized patients who were administered ampicillin therapy versus placebo. Also, Surawicz et al. (1989) in a randomized controlled placebo study showed efficacy of *Saccharomyces boulardii* versus placebo in preventing AAD in patients taking various antibiotics. McFarland et al. (1995) in a randomized controlled placebo trial and Can et al. (2006) in a randomized controlled placebo study with *Saccharomyces boulardii* versus placebo also showed efficacy of probiotic in the prevention of AAD. However, these studies were conducted in hospitalized patients in a controlled environment with a limited number of antibiotics and probiotics administered. In this study however, *Saccharomyces boulardii* was prescribed and administered on two separate occasions with no occurrences of AAD or CDAD.

The results showed that some of the inconstancies found in previous studies were observed in this study, such as; there were a variety of antibiotics administered at various frequencies with probiotics administered inconsistently with antibiotic administration. For example a resident was prescribed antibiotics five separate times during the 12 month period for various infections and was prescribed probiotics two of the five times an antibiotic was prescribed. Some of the treatment durations of probiotics were the same as the antibiotic duration while others were either less than or more than the duration of the antibiotic. This is shown by the disproportionate number of antibiotics administered (n=234) when compared to the number of probiotics administered (n=78) illustrated in Figure 4. Therefore there was an overlap in the treatment group (those who received antibiotic and probiotic) and the control group (those who received antibiotic only) which may impact the results. The highest number of times a probiotic was prescribed to an individual resident was three; however, antibiotics were prescribed from one to 18 times to an individual resident for a variety of infections on different occasions.

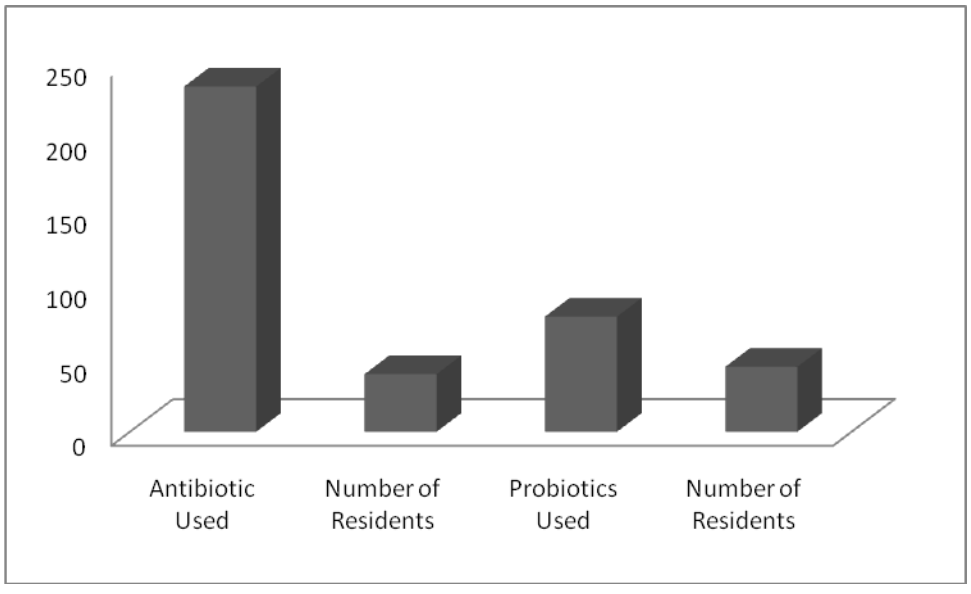

Figure 2 Frequencies of Antibiotics and Probiotics Used

The comparison of earlier studies with this study is complex, as this study is a retrospective review on the outcome of the administration of prophylactic probiotics to geriatric patients in a LTC facility. This population has multiple comorbid conditions and frequent use or administration of antibiotics. This is evident by findings that the study population received antibiotics on 234 different occasions in a 12 month period, with a range of one to 18 courses of antibiotic administered per resident.

Various classes of antibiotics were administered over the 12 month period. There were no controls on the duration, frequency or dosing of probiotic or antibiotic used, as shown by the various forms and doses of probiotics and antibiotics. Earlier studies were conducted in hospitalized patients of varying ages from 18 to 88 years of age, whereas, the age range of this population is 65 to 106 years old, the age difference of the hospitalized patients vary significantly from those of this study and does not reflect a crucial representation of the LTC population. Consistent with this study's findings Lewis et al. (1998) and Thomas et al. (2001), in their randomized placebo controlled studies also found no significant efficacy of probiotics in the prevention of AAD.

Limitations

The major limitation of this study is the restricted ability to control the administered elements (probiotics and antibiotics) to the participants, as this study was a retrospective chart review. Laboratory tests were not available through the electronic medical record, which necessitated reviewing the results with archived paper medical records which were not filed by category. The data presented may be incomplete or inaccurate and not closely monitored for accuracy. For example the reporting or documenting episodes of diarrhea, or missed doses of

either antibiotic or probiotic may not have been adequately documented, which can have significant importance to the results.

In making comparison with earlier studies, the form and duration of probiotics, as well as the number of times antibiotics were administrated to the participants, ranged from one to 18 courses of antibiotics per resident over the 12-month period. Whereas, earlier studies were conducted in hospital settings, the route of administration and frequency of administration may have been more controlled which could produce different results. Some studies reported use of oral antibiotics and the use of more than one antibiotic during the study. Other factors to be considered are the chronic conditions of the population with 45.8% of the residents having a diagnosis of dysphagia; the forms of probiotics were mainly capsule or caplet. This necessitated modifications prior to administration which may have altered absorption or bioavailability of antibiotics. This can change the outcome on the effectiveness of the drugs.

Conclusion

This study showed no benefit of probiotic in preventing diarrhea associated with antibiotic or clostridium-difficile. The assumption is that all available data was accurate and complete. This study also did not provide answers to the questions:

1. Which probiotic dosing is effective in preventing AAD and CDAD?
2. What is the most effective duration of probiotic administered in preventing AAD and CDAD?

This study demonstrated that the answers to the questions are difficult or even impossible to be obtained through retrospective studies if there are inconsistencies in the prescribing of doses

and duration of therapies. A more tightly controlled prospective study or changes in procedure related to the documentation of dosing and the consistency of their use may be able to produce answers to these questions. Additionally, even a longer duration of study may provide answers to these questions.

The inconsistencies found in this study in which prophylactic probiotics were prescribed suggest a lack of knowledge on the most effective probiotic dose, frequency or duration and, possibly, effectiveness of the therapy. Also, the lack of a consensus on the efficacy of probiotic as shown by previous studies' contradictory results, may also contribute to these inconsistencies. There are no current guidelines to direct these practices. There is a lack of research reported in literature to guide the clinical practice of prophylactic probiotic administration in LTC; therefore there is a need to conduct ongoing studies in this area so that healthcare providers can base their treatment decisions on established evidence. Providers in LTC must be more proactive in observing effectiveness of therapies administered to their patients to ensure that therapeutic effects are achieved, which can be done through outcomes research studies and establishment of practice guidelines.

The use of prophylactic probiotics has been studied for over 20 years, some of the studies were presented in this study, however, there still remain questions that are unanswered, with regard to LTC population and effectiveness of this therapy. It may be another 20 years before an answer to the study's question is determined, hopefully, this will not occur and more studies in the LTC populations will be conducted to obtain sufficient evidence to establish appropriate

guidelines. This population is plagued by pill burden and polypharmacy, therefore, safety and effectiveness of therapies need to be established prior to routine use.

The results of this study did not show effectiveness in the prevention of AAD and CDAD with the use of prophylactic probiotics co-administered with antibiotics for infectious diseases in LTC patients. This study is an initial review conducted retrospectively on the effectiveness of probiotics in preventing AAD and CDAD in the geriatric population. Currently no other studies were conducted in this area with which to make comparisons. Although, there are several randomized placebo controlled trials completed in the hospitalized setting with adult patients which have shown efficacy, these RCTs do not provide adequate representation of the LTC population.

Implications for Nursing

The results of this study may have provided some evidence to guide the practice of the administration of prophylactic probiotics in LTC, however, this is an initial study and further retrospective and prospective studies are needed to provide sufficient evidence on the administration of probiotics for prevention of AAD and CDAD. The lack of well designed studies in this population and studies about the efficacy of therapies may be a reason why probiotics are prescribes inconsistently. There is a need to demonstrate efficacy of a drug prior to use in these and all other patients. Although studies shows that AAD occurs in 25% of adults receiving antibiotics and the prevalence of CDAD ranges from 2.1% to 8% in long term care facilities during a one year period (Katz, 2006: Simor, Yake & Tsimidis, 1993), other proven measures of prevention and control need to be considered.

Previous studies found that higher dosing and longer duration of probiotic therapy resulted in treatment efficacy. As observed in this study the lack of standardization of probiotics preparations may also contribute to ineffectiveness as dosing may be subtherapeutic. The form of probiotics may have been altered for administration as 45.8% of the patients had a diagnosis of dysphagia, which may also have contributed to subtherapeutic dosing. Therefore, it is of great importance for nurse practitioners and other prescribers to specifically order types, forms, dosings, and frequencies of drugs, to consider the abilities of the patient to swallow the drugs.

Given that this study is limited to one LTC facility and the sample size is a small representation of the geriatric population, it would be of great importance to conduct further studies which can add to an evidenced based clinical practice.

The LTC population is at risk for infectious diarrhea based on the widespread use of antibiotic therapy as shown in this study. A few previous studies support the use of prophylactic probiotic therapy to decrease incidences of infectious diarrhea. However, this study found no evidence which supports these findings. This is an initial study to review the effectiveness of probiotics in the LTC geriatric population, it is recommended that further studies are conducted in the geriatric population of LTC facilities before recommendation for use of probiotics prophylactic for AAD and CDAD is specified.

APPENDIX A
LETTER OF APPROVAL FOR STUDY

Appendix C: letter of approval for study.

WEST MELBOURNE HEALTH AND REHABILITATION
2125 West New Haven Avenue
West Melbourne, Florida 32904
Phone (321) 725-7360
Fax (321) 727-8006

October 6, 2009

To whom it may concern:

As the Administrator of West Melbourne Health and Rehabilitation Center, I am writing this letter giving Marva Edwards- Marshall, ARNP full disclosure and permission to conduct a study at our skilled nursing facility. This study is on the topic of effectiveness of probiotics in conjunction with antibiotic therapy. I trust this study will be beneficial to my residents and nursing staff alike. If I may provide more information, please don't hesitate to contact me. Thank you in advance for your consideration in this matter.

Sincerely,

Julie Morris

Julie D. Morris, NHA
Administrator
West Melbourne Health & Rehabilitation Center

APPENDIX B
IRB LETTER OF APROVAL FOR STUDY

University of Central Florida Institutional Review Board
Office of Research & Commercialization
12201 Research Parkway, Suite 501
Orlando, Florida 32826-3246
Telephone: 407-823-2901 or 407-882-2276
www.research.ucf.edu/compliance/irb.html

Approval of Exempt Human Research

From: **UCF Institutional Review Board #1**
FWA00000351, IRB00001138

To: **Marva Edwards-Marshall**

Date: **March 31, 2010**

Dear Researcher:

On 3/31/2010, the IRB approved the following activity as human participant research that is exempt from regulation:

Type of Review:	Exempt Determination
Project Title:	EFFECTIVENESS OF PROBIOTICS IN PREVENTING ANTIBIOTIC ASSOCIATED DIARRHEA AND CLOSTRIDIUM DIFFICILE IN LONG TERM CARE
Investigator:	Marva Edwards-Marshall
IRB Number:	SBE-10-06855
Funding Agency:	
Grant Title:	
Research ID:	N/A

This determination applies only to the activities described in the IRB submission and does not apply should any changes be made. If changes are made and there are questions about whether these changes affect the exempt status of the human research, please contact the IRB. When you have completed your research, please submit a Study Closure request in iRIS so that IRB records will be accurate.

In the conduct of this research, you are responsible to follow the requirements of the Investigator Manual.

On behalf of Joseph Bielitzki, DVM, UCF IRB Chair, this letter is signed by:

Signature applied by Joanne Muratori on 03/31/2010 09:20:24 AM EST

Joanne Muratori

IRB Coordinator

APPENDIX C
DATA COLLECTION TABLE

Participant number _____ Date _____ Age _____

B. **Gender**: □ Male □ Female

C. **Date of admission _____** D. **Unit _____**

E. **Chronic medical conditions:**

1. 8.
2. 9.
3. 10.
4. 11.
5. 12.
6. 13.
7. 14.

15. Irritable bowel syndrome □ Yes □ No 16. Colitis □ Yes □ No

17. Chron's Disease □ Yes □ No

F. **Antibiotic administration:** □ Yes □ No G. **Class of antibiotic_____**

H. **Name of Antibiotic _____** I. **Duration of Therapy _____**

J. **Diagnosis for Antibiotic Therapy: Circle all that apply**

1. Urinary Tract I infection
2. Pneumonia
3. Upper Respiratory Infection
4. Cellulitis/Soft Tissue Infection
5. Other/list:

K. **Probiotic Administered □Yes □ No**

L. **List all Probiotic Used**

1. 5.

2. 6.

3. 7.

4. 8.

M. **Duration Probiotic** **Form of probiotic**

< 7 days Pill

7 days Granule

10 days Capsule

14 days Suspension

21 days

> 21 days

Other list:↑

N. **Dose of probiotic**

1/day 2/day

4/day 6/day

Other:

Diarrhea ≥ 3 loose stools/day within 2 months of antibiotic therapy: □ Yes □ No

C-diff new episode of diarrhea associated with positive culture or toxin (A or B): □ Yes □ No

Positive Culture of other stool: □ Yes □ No O. **Results** _____

Comments:

APPENDIX D
REQUEST TO CONDUCT STUDY

To: Administrator of West Melbourne Health and Rehab Center

Subject: Request for permission to conduct research study at your facility

Proposal Title: **Efficacy of probiotics in decreasing the incidences of antibiotic associated diarrhea and *clostridium difficile.***

Introduction:

Prophylactic use of probiotics have been purported to decrease the incidences of Antibiotic associated diarrhea (AAD) and *clostridium-difficile* diarrhea (CDAD). The purpose of this review is to evaluate the efficacy of probiotics in preventing AAD and CDAD. There is sufficient data presented from previous studies to support the use of probiotics for prevention of AAD and CDAD.

Nature and Purpose:

The study will involves chart review of LTC residents specifically to determine the effectiveness of probiotics in decreasing or preventing antibiotic associated diarrhea and *clostridium-difficile* associated diarrhea. The information on the effect of probiotics will provide information on the current practice patterns for prescribing probiotics to LTC residents, the most effective therapeutic dosing regimen, the most successful therapy duration. It will provide information which will contribute to implementation of an evidenced based clinical practice to support improving the quality of life in the LTC population.

Methodology and Expected Results

A review of charts of the residents of the facility would be conducted. The number of charts to be reviewed would be the number of residents residing in the facility during the period of January 2009 through December 2009. Only chart of residents' ages sixty five and older, which were treated with antibiotic therapy, with or without administration of probiotics would be reviewed. Instruments to be employed include LTC facility charts and medical records and a data collection form.

Timeline for study:

January-April 2010: Collect and compile data

May-July 2010: Write formal paper on the results of study.

Thank you for considering my application. I believe that the results of this study will benefit both the residents and staff of your facility.

Marva Edwards-Marshall ARNP ANP-BC

Table 10 Synthesis of Literature Review on Efficacy of Probiotics.

Authors	Probiotics	Patients	Number of patients	Antibiotic	Duration of treatment	Findings (% diarrhea)	P value	Conclusion
Gotz et al (1979)	*Lactobacillus acidophilus Lactobacillus bulgaricus*	Hospitalized	98	Ampicillin	Variable	8.3% vs., 21% placebo	P=0.03	Probiotics effective in prevention of AAD.
Surawicz et al. (1989)	*Saccharomyces boulardii*	Hospitalized	180	Clindamycin Cephalosporins, trimthoprim-sulfamethazole	Variable	9.4% vs. 31% placebo	P=0.07	Probiotics effective in prevention of AAD.
Lewis et al (1998)	*Saccharomyces boulardii*	Hospitalized	69	Various	14 days	21% vs. 17% placebo	Not Stated	Probiotics show no effect in prevention of AAD
McFarland et al. (1995)	*Saccharomyces boulardii*	Hospitalized	193	B-lactam tetracycline	Variable	7.2 %vs. 14.6 % placebo	P=0.02	Probiotics effective in prevention of AAD.
Thomas et al. (2001)	*Lactobacillus GG*	Hospitalized	302	Various	Variable	29.3% vs. 29.9% placebo	P=0.93	Probiotics show no effect in prevention of AAD.
Can et al (2006)	*Saccharomyces boulardii*	Hospitalized	151	Various	Variable	1.4% vs. 9% placebo	P=<0.05	Probiotics effective in prevention of AAD.

Table 11 Synthesis of Meta-Analysis and Systematic Reviews on Efficacy of Probiotics.

Authors	Pub Yr	Purpose	Findings	Conclusion
McFarland	2006	• 31 RCT studies were used to evaluate the prevention of AAD and treatment of CDAD. • Sample size for AAD studies (n=25) with >2,800 subjects.	• Adults with 44% reduction in AAD in probiotic group. • 52% studies showed a significant reduction in the incidences of AAD compared to placebo group.	• Probiotics were effective in the prevention of AAD.
D'Souza et.al	2002	• Randomized placebo-controlled meta-analysis study on the prevention of AAD with probiotic use. • Sample size (n=9) studies, with >1300 subjects.	• Probiotics more effective at preventing incidences of AAD than placebo.	• In all nine trials, probiotics were given in combination with antibiotics. Results of this study suggest that probiotics were effective in preventing antibiotic diarrhea. With significance of P<.001.
Sazawal, et. al.	2006	• Randomized, placebo-controlled trials were used to evaluate the effectiveness of probiotics in the prevention of AAD • Sample size (n=6) using > 2000 subjects	• Overall reduction of 52% in AAD in the probiotic group.	• Overall the risk ratios was 0.65, which is significant and suggests that probiotics is effective in preventing AAD. • Some of the studies the results were more significant than others, however overall efficacy was significant.
Dendukuri et. al.	2005	• 4RCT studies were used to evaluate the effectiveness of probiotics in the prevention of CDAD • Sample size (n=4) involving	• Insufficient evidence on the effectiveness of probiotics in preventing CDAD.	• Probiotics were not shown to be effective in preventing CDAD.
Cremonini et. al.	2002	• Randomized placebo-control studies were used to determine the efficacy of probiotics in prevention of AAD. • Sample size (n=7) with > 800 subjects.	• 52% overall reduction in the probiotics group for AAD.	• The RR of 0.3966 indicates a strong benefit of probiotics for prevention of AAD. • Studies not exclusive to geriatrics.

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