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Inpatient Rehabilitation, Diabetes, and the Risk of Clostridium Difficile Infection

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This is to certify that the doctoral dissertation by

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Abstract

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by

Kerry A. Flint

MSN, University of New Mexico, 2009

BSN, University of Phoenix, 2005

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

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Abstract

Clostridium difficile is a frequent cause of healthcare-associated infections (HAI) and is associated with increased risk of morbidity and mortality. Studies suggest environmental and host characteristics increase patient's susceptibility to *C. difficile* infection (CDI). However, few studies have examined the risk of CDI among those with diabetes or patients in the acute rehabilitation (AR) setting. A case-control study, using secondary data (n = 473), evaluated the relationship between CDI and diabetes and identified modifiable environmental exposures. An ecosocial framework was used to examine the relationship between these two complex diseases among hospitalized patients in an AR setting. Results of the multiple logistic regression showed that patients with diabetes experienced 2.5 times the risk for CDI (p = 0.03) compared to non-diabetic patients. Multiple logistic regression was also used to assess for modifiable exposures among AR patients with diabetes only. Findings from this sub-analysis found the significant exposures in this population were antibiotics (OR = 3.9; p = 0.01) and insulin use (OR = 2.6; p = 0.015), suggesting an effect on the intestinal microbiome. Understanding the relationship between CDI and diabetes among the AR population promotes positive social change through the reduction of CDI associated morbidity and mortality among diabetic patients. Findings from this study support antibiotic stewardship efforts across the spectrum of healthcare delivery and the development of new strategies to decrease the economic burden associated with CDI for individuals, healthcare facilities, and at the national level.

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Chapter 1: Introduction to the Study

Introduction

A key public health issue is healthcare-associated infections (HAI) and the prevention of these infections as a measure of healthcare quality. This research study proposes to investigate the relationship between diabetes and *Clostridium difficile* infection (CDI) in a healthcare setting. *C. difficile* is a spore forming bacteria found in the environment that affects a range of outcomes in those infected. Outcomes range from mild or moderate diarrhea, to severe life-threatening inflammation of the colon, and death (Cohen et al., 2010). Increasing prevalence of CDI in the United States in recent years has resulted in a multiple level approach to prevention (The White House, 2015). This study will evaluate the relationship between diabetes and CDI to support efforts to reduce the incidence of CDI among hospitalized patients. People with diabetes are a population group with frequent healthcare exposure across the continuum of healthcare delivery (Booth & Hux, 2003). Understanding the relationship between different population groups can promote positive social change by identifying and targeting infection prevention measures in a population group with high healthcare utilization and exposure. Prevention efforts, in turn can improve healthcare outcomes and reduce the costs of healthcare delivery. Information gained from this research has the potential to inform and support healthcare professionals and public health policy makers' efforts to implement clinically relevant and effective decisions related to CDI prevention.

This first chapter presents background information regarding the burden of diabetes and CDI, describes the purpose of the study, the research questions and

hypotheses this study will address. The theoretical framework, methodology, definitions, assumptions, scope, limitations, and significance of the study are also described in this chapter.

Background

C. difficile is a leading cause of healthcare-associated infections in the United States, associated with increased morbidity and mortality among infected patients (Magill et al., 2015; Lessa et al., 2015). The economic burden is also significant, with estimated costs in the billions of dollars annually (Desai et al., 2016). The Centers for Disease Control and Prevention (CDC) has identified CDI as an immediate public health threat requiring urgent and aggressive prevention and control measures (Centers for Disease Control and Prevention [CDC], 2013). Efforts to understand the burden of CDI in healthcare settings has resulted in national surveillance and reporting of CDI incidence. Exposure to antimicrobial agents has been strongly associated with the development of CDI, in part due to alterations in host intestinal microbiota (Loo et al., 2011; Owens, Donskey, Gaynes, Loo, & Muto, 2008). Other important factors associated with an increased risk of CDI include age and underlying disease, for example, diabetes (Kyne, Sougioultzis, McFarland, & Kelly, 2002; Wenisch et al., 2012).

Diabetes disease presents a significant health burden, affecting a sizable proportion of the U. S. population (CDC, 2017). Evidence that those with diabetes could be at increased risk for CDI is unclear and often conflicting (Qu & Jiang, 2014). In some studies diabetes was associated with increased risk for CDI (Shakov, Salazar, Kaqunye, Buddora, & DeBan, 2011; Wenisch et al., 2013; Zilberberg, Reske, Olsen, Yan, &

Dubberke, 2014), while others report finding no significant association (Daneman et al., 2014; Freedberg, Salmasian, Friedman, & Abrams, 2013; Henrich, Krakower, Bitton, & Yokoe, 2009). Researchers have also reported lower a risk of severe CDI disease (Rao et al., 2013) and CDI mortality among patients with diabetes (Stewart & Hollenbeak, 2011), In addition, studies examining CDI risk factors have not specifically included diabetes as a variable (Loo et al., 2011; Morrison et al., 2011).

The relationship between diabetes and CDI is plausible (Qu & Jiang, 2014). It has been suggested that the presence of diabetes increases susceptibility to infectious agents through alterations in immune function (Bertoni, Saydah & Brancati, 2001; Muller et al., 2005; Shah & Hux, 2003). Such susceptibility to infections may lead to increased exposure to antibiotics. Changes in the gut microbiota following exposure to antimicrobials could explain the increased risk for CDI associated with recent antibiotic use (Theriot et al., 2014), by providing an opportunity for *C. difficile* to germinate and grow. There is also evidence demonstrating that *C. difficile* growth is aided by elevated sialic acid levels (Ng et al., 2013). Sialic acid, a protein bound carbohydrate, is found in higher concentrations among diabetics compared to non-diabetics (Varghese, Asha, Celine, & Prasanna, 2015). Differences in the ratios of gut microbiota utilizing sialic acid as an energy source exist between those with and without diabetes disease (Larsen et al., 2010). Differences and alterations to the gut microbiota of diabetic patient's due to host-derived sialic acid levels (Jandhyala et al., 2015) and increased exposure to antimicrobials would suggest an increased risk for CDI among diabetics not consistently supported in the literature (Qu, & Jiang, 2014).

Purpose of Study

The primary purpose of this quantitative case-control study is to assess the association between diabetes and CDI while controlling for selected environmental and host characteristics. The independent variable is a diagnosis of diabetes disease, and the dependent variable, a laboratory confirmed test for *C. difficile*. A second aim of this study is to identify modifiable environmental and host characteristics that increase the risk of CDI among hospitalized diabetics. The independent variables of interest are antibiotic use, gastric acid suppressants, and body mass index(BMI). The dependent variable is CDI. Control variables include age, ethnicity/race, gender, admission diagnosis, comorbidities, functional status, and diabetes disease severity.

Research Questions and Hypothesis

Research Question 1: Is there any relationship between diabetes and CDI among hospitalized patients in the acute rehabilitation (AR) setting?

H_o1: There is no relationship between diabetes disease and CDI among patients in the AR setting.

$H_1 1$: There is a significant relationship between diabetes and CDI among patients in the AR setting.

Research Question 2: Are modifiable environmental (antimicrobial and medication exposures) and host characteristics (behaviors, BMI, diabetes management) associated with CDI among hospitalized diabetics in AR settings?

H_o2: There is no relationship between selected modifiable variables and CDI among diabetic patients in the AR setting.

$H_1$2: There is a relationship between modifiable variables and CDI among diabetic patients in the AR setting.

Theoretical Framework

An ecological theoretical model is used to frame and guide this research study. The ecological perspective uses a system- based approach; examining patterns of health within the context of dynamic interrelationships between the biological, physical, social, cultural, and historical contexts existing at the local and global level, as well as individual attitudes and behaviors (McLaren & Hawe, 2005; Satariano, 2006). Ecological theory is grounded in the assumption that demographic and socioeconomic differences influence susceptibility and resilience to health risks (Satariano, 2006). Krieger (2011) further developed this theory in the field of epidemiology, considering the multiple pathways affecting the distribution of health and disease in populations. The key construct of Krieger's ecosocial theory is embodiment. Embodiment describes the biological integration of social and ecological context through socially patterned and exposure-induced pathogenic pathways. These pathways are mediated by physiology, behavior, and gene expression that affect the development of health and disease states (Krieger, 2012). Krieger's (2008) ecosocial theory provides a framework to examine relationships and distribution of disease at the individual and population level (Figure 1).

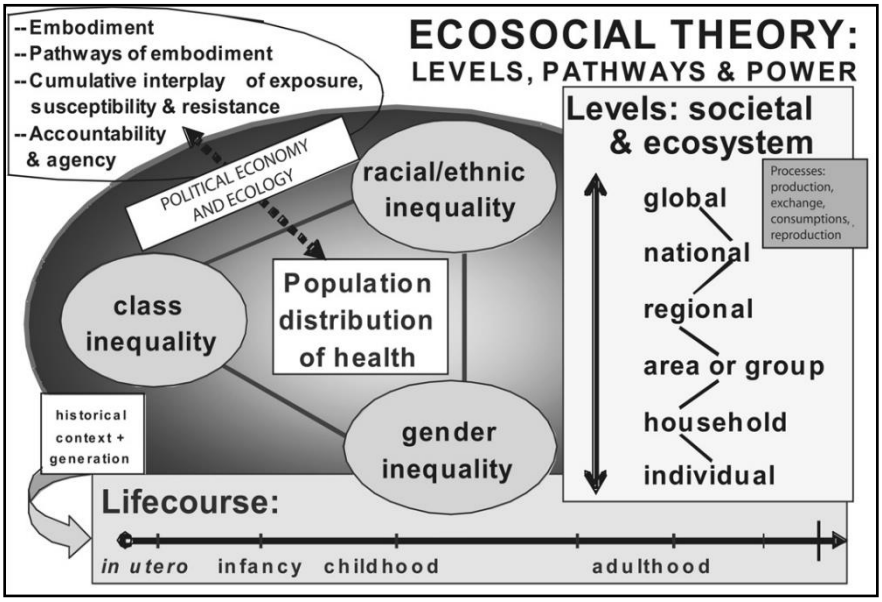

Figure 1. The ecological and ecosocial concepts used as the theoretical framework to examine the association between diabetes and CDI (Krieger, 2008, p. 224). Reprinted with permission[1].

Both diabetes and CDI are diseases associated with multiple risk factors contributing to disease onset. Ecological and ecosocial theory provides a framework to examine the complex connections that frequently exist between disease and health. Diabetes, a chronic disease, has multiple pathways contributing to disease onset and complications of disease (Hill et al., 2013a). CDI is also complex, in terms of exposure risks associated with health care utilization (Burke & Lamont, 2014). An ecological perspective expands on the agent, host, and environment concepts associated with infectious disease epidemiology by acknowledging the broader context in which infectious diseases occur and transmit among susceptible hosts (Satariano, 2006; Smith et al., 2005). The ecological perspective also expands the biomedical perspective of infectious disease causation and treatment (Armstrong, 2000), often present in healthcare

settings. Identifying effective prevention measures requires an understanding of the multiple pathways contributing to disease. Satariano (2006) suggests the ecological approach examines the context in which individual's function and respond, and provides the opportunity for public health intervention when considering health through an integrated and multilevel lens. Hill, Nielsen, and Fox (2013) also suggest the use of an ecosocial perspective to frame prevention efforts. Especially, as this perspective considers the environmental factors, social determinants, and the influence of public policy on individual and population health and related behaviors (Hill, Nielsen, & Fox, 2013).

Nature of the Study

This study is observational in nature, using a case-control design to examine the association between diabetes (independent variable), and CDI (dependent variable) among adult patients in the AR setting. A case-control design allows the investigation of associations between exposure and outcome. In case-control designs, cases, those known to have the outcome of interest (dependent variable), are compared to a similar group in which the outcome is absent (Szklo & Nieto, 2014). Comparison data regarding exposure histories (independent variables) between the groups are analyzed to identify factors associated with an increased risk of developing the disease or outcome of interest (Szklo & Nieto, 2014). The decision to use a case-control design lies in its suitability to investigate rare or infrequent outcomes, less than 20% (Aschengrau & Seage, 2008). Previously published CDI estimates in the AR, indicate a prevalence of 15% (Mylotte, Graham, Kahler, & Goodnough, 2000). Cases, defined as AR patients with a diagnosis

of CDI, and controls, AR patients without a diagnosis of CDI, were drawn from the same hospital population during the defined study period. Covariates of interest include sex, race/ethnicity, BMI, and admission diagnosis. Other covariates include exposure to medications (antibiotics, gastric acid suppressants, insulin, and oral antihyperglycemics) environmental exposures (feeding tubes, prior locations), and comorbidity indices which include cardiovascular disease, chronic kidney disease, hypertension, liver disease, and dementia.

AR facility administrative data using International Classification of Diseases – 9th Revision (ICD-9) diagnostic codes was used to identify cases and controls. Information on independent variables for study participants was extracted from the AR facilities medical records. Analysis methods included descriptive statistics and logistic regression modeling.

Definitions

Acute Rehabilitation (AR) Hospital: A specialized inpatient setting for improving a person's health, function, mobility and independence following injury or illness, so they may successfully return to home, work, and community activities (American Medical Rehabilitation Providers Association [AAPM&R], 2016). Admission to acute medical rehabilitation is based on the functional and/or cognitive deficits of the patient, the need for medical supervision, the patient's ability to participate in therapies, and realistic outcome goals (American Academy of Physical Medicine & Rehabilitation, 2012). Participation requirements include the ability to participate in at least three hours of

therapy a day or 15 hours per week (Centers for Medicare & Medicaid Services [CMS], 2012.).

Binary Toxin: A toxin consisting of two separate components. Select strains of *C. difficile* bacteria can produce binary toxins composed of an enzymatic activator and a receptor-mediated binding component (Barth, Aktories, Popoff, & Stiles, 2004; Gerding, Johnson, Rupnik, & Aktories, 2014).

Chronic Kidney Disease (CKD): describes the loss of kidney function, which may result in end-stage renal disease requiring dialysis therapy. The assessment of the presence of chronic kidney disease in study participants was based on documentation in the medical record at time of admission.

Clostridium difficile: A spore-forming, gram-positive anaerobic bacillus that produces two exotoxins, toxin A and toxin B, causing symptomatic infection (Carrico, 2013; Goudarzi, Seyedjavadi, Goudarzi, Aghdam, & Nazeri, 2014).

Clostridium difficile infection (CDI): A disease caused by the toxins produced by the organism *Clostridium difficile* (Carrico, 2013).

Comorbidity: The presence of additional diseases in relation to an index disease in a single individual. The term is used to measure the overall impact of multiple diseases in an individual (Valderas, Starfield, Sibbald, Salisbury & Roland, 2009, p. 3.59).

Exotoxin: A "protein produced by a bacterium and released into its environment causing damage to the host by destroying other cells or disrupting cellular metabolism" (Carrico et al., 2013).

Healthcare associated infection (HAI): Infections that occur while patients are receiving treatment for medical or surgical conditions.

Microbiota: "ecological community of commensal, symbiotic, and pathogenic microorganisms that literally share our body space" (Lederberg & McCray, 2001, para. 8). Intestinal microbiota describes the resident microorganisms in the intestine.

Proton pump inhibitors (PPI): A class of medications which inhibit gastric acid secretion by the inhibition of the H+/K+ ATPase, in the parietal cells of the stomach. PPI are used for the treatment of gastric and duodenal ulcers, gastroesophageal reflux disease, and other excessive gastrointestinal acid secretory disorders (Drugs.com).

Social determinates of health: "the circumstances, in which people are born, grow up, live, work and age, and the systems put in place to deal with illness. These circumstances are in turn shaped by a wider set of forces: economics, social policies, and politics" (World Health Organization, 2008).

Assumptions

The nature of this study assumes both cases and controls are from a dynamic population, and that the control group is representative of the base population that produced the cases (Aschengrau & Seage, 2008). Therefore, it is assumed that should a member of the control group develop CDI, they would meet the case criteria. The selection of cases and controls impacts the internal validity of the data (Szklo & Nieto, 2014). The assumption that both cases and controls are representative of the population from which the sample is drawn relates to the external validity of the results (Creswell, 2009; Szklo & Nieto, 2014). In this study, cases and control subjects are drawn from a

post-acute inpatient population. Admission to post-acute inpatient medical rehabilitation is based on functional deficits, medical needs, and ability to participate in therapies (AAPM&R, 2012; CMS, 2016). It is assumed that patients admitted to this setting meet the criteria for inpatient rehabilitation as defined by the Centers for Medicare and Medicaid (CMS, 2016). It is also assumed that documentation of diabetes and other health and demographic related information represents accurate reporting of information by the patient and healthcare providers. Another assumption of this study is that laboratory tests positive for *C. difficile* toxin reflect an infective process, leading to the clinical decision to test for a causative agent based on clinical guidelines (Cohen et al., 2010). A final assumption is that susceptibility to disease encompasses the historical, cultural, environmental, and socioeconomic factors and exposures across the life course of individuals.

Scope and Delimitations

The scope of this study includes adult patients, over 18 years of age, admitted to an acute medical rehabilitation hospital in New Mexico between January 1, 2009, and September 30, 2015. Case finding used ICD-9 discharge diagnosis code 008.45 and a positive laboratory confirmed test for *C. difficile* toxin. Positive test results included the detection of toxins A or B, detection of *C. difficile* cytotoxin by PCR, or positive culture for *C. difficile*. Controls included patients over 18 years of age admitted to the same facility without a diagnosis of CDI during their hospitalization. Diabetic patients were persons with a preexisting diagnosis of diabetes at the time of admission. Due to the inability to accurately differentiate between T1D and T2D, all diabetic patients were

included. Exclusions included patients 18 years of age or younger, and those admitted to the facility with a diagnosis of CDI and receiving treatment on admission.

Limitations

Design and methodology limitations include the observational nature of the study, which allows conclusions of association between variables but prevents establishing cause and effect. Use of medical records to collect information on variables equates a secondary data source. Secondary data sources are a recognized limitation as data was originally collected as part of the routine care of patients and not the purposes of this study. This limitation can affect the quality of the data due to missing or incomplete data, inconsistencies in documentation between healthcare professionals, errors in transcription, and misclassification of information during abstraction and coding. In addition, self-reported information regarding race and ethnicity, and behaviors' such as smoking are subject to recall bias. Measures to address this limitation include the exclusion of cases with missing variables from the analysis. Selection bias is a concern in case-control designed studies when differences exist in the selection of cases and controls. This bias can occur when cases and controls are selected using different source populations and different selection criteria. The use of a convenience, non-probability sampling method also increases the potential for selection bias. Measures to overcome this limitation include selecting both cases and controls from the same hospital population, during the same time-period. Due to the infrequency of cases randomized sampling techniques were not utilized.

Generalizability to all healthcare facilities is another limitation. The study population is limited to those admitted to an inpatient rehabilitation setting and findings may not transfer to other healthcare or community settings. Population differences resulting from a single state in the Southwest region of the United States may also limit generalization of findings to other geographical regions.

Significance

This study, assessing the association between diabetes and risk for CDI has the potential to effect positive social change in several ways. The effects of positive social change could be measured through the reduction of CDI associated morbidity and mortality among diabetic patients, and through reductions in the economic burden associated with this infection. Results of this research could also contribute to the current body of knowledge regarding risk factors associated with CDI in hospitalized patients by identifying modifiable risk factors in this population. Determining the effect of environmental and patient level characteristics is important to prevent the onset of primary or recurrent infection. In addition, investigating the relationship between diabetes and CDI within an ecosocial context could advance the theory that diabetics develop unique intestinal microbiota and disruptions to this microbiota that contribute to an increased risk for CDI.

CDI can negatively affect quality of life related to physical and social functioning, and fear of recurrent disease (Guillemin et al., 2014; Weaver et al., 2017). Patients with CDI may require readmission to the acute care setting. Readmission to acute care not only affects the patient's rehabilitation progress but also can have financial

consequences for AR facilities (Ottenbacher et al., 2015). Identifying modifiable risk factors among diabetic patients has implications for patient education and patient participation in activities to reduce their risk for CDI. Clinical implications from this research include identification and mitigation of risk among AR patients related to differences in disease characteristics, and decisions regarding CDI prevention and treatment options. Identification of risk factors in the AR population also has the potential to support future research including clinical trials for medical interventions such as fecal transplants, as well as antibiotic and vaccine research.

Summary

CDI presents a significant risk to hospitalized patients and the public's health as a leading cause of HAI. The emergence more virulent and resistant bacterial strains of *C. difficile* highlights the need for concern among healthcare providers and consumers (Carrico, 2013). Studies examining the prevalence of CDI in the United States have focused on acute care settings (Magill et al., 2014) and risk factors associated with such settings, limiting assessment of disease risks in post-acute settings (DePestel & Aronoff, 2013). In addition to the burden of CDI, the prevalence of diabetes in U.S. is estimated at 14% of the population (Menke, Casagrande, Geiss, & Cowie, 2015), with more than one million new cases diagnosed each year (CDC, 2015, 2017). Patients with diabetes experience high exposure to healthcare and subsequent risk for HAI (ADA, 2014).

Diabetes has been identified as a potential risk factor in the development and severity of CDI (Wenisch et al., 2012). However, associations between the two variables are not clearly established in the literature, and few studies have specifically investigated

diabetes and risk for CDI (Eliakim-Raz et al.,2015). Assessing the relationship between diabetes and CDI plays an important role in limiting morbidity and mortality in the diabetic population, and identifying variables that could reduce exposure and subsequent development of CDI

Chapter 2 will present a review of the published literature related to the independent and dependent variables, providing support for the inconclusive findings regarding an association between diabetes and CDI. Chapter 2 will critically review studies to support the research problem, the research questions, and the significance of the study. This review of the literature will also present research establishing the theoretical framework used to identify selected variables and guide the analysis and the interpretation of the study results.

Chapter 2: Literature Review

Introduction

The purpose of this study is to evaluate the association between diabetes and the risk of *Clostridium difficile* infection (CDI) among hospitalized patients in post-acute settings and to identify modifiable environmental and host characteristics. Diabetes is a chronic metabolic condition affecting more than 12% of the U. S. population (CDC, 2015, 2017). Persons with diabetes experience increased morbidity and mortality from disease-related complications (ADA 2014, CDC, 2017), resulting in a greater need for healthcare services. Frequent exposure to healthcare services and the healthcare environment may place patients at increased risk for HAI (ADA, 2014). The elevated risk for HAI is also supported by Gan (2013) who suggests host characteristics associated with diabetes can increase susceptibility to infection.

Clostridium difficile has become a leading cause of HAI in the United States (Magill et al., 2014). CDI is also associated with increased morbidity and mortality, especially as resistant and increasingly virulent strains of *C. difficile*, such as genotype 027/BI/NAP1 emerge (He et al., 2013; Hensgens, Goorhuis, Dekkers, Van Benthem, & Kuijper, 2013; Lessa et al., 2015). The increasing burden of CDI in healthcare settings also has economic implications related to both in direct costs and indirect societal costs. Total direct and indirect costs associated with healthcare-acquired CDI are estimated to cost the U. S. 4.7 billion dollars annually (Desai et al., 2016). A marked increase over previously reported estimates of almost 800 million dollars using 2008 data (McGlone et

al., 2012). Review of the literature regarding CDI suggests environmental, and host characteristics increase susceptibility to CDI across a variety of healthcare settings.

The purpose of this review is to present an overview of the literature significant to this research topic. In addition, this literature review will show how the interplay between environmental and host characteristics supports the plausibility of a relationship between diabetes and CDI. An expansive body of literature exists across disciplines and populations related to diabetes and *C. difficile*. However, research examining the relationship between diabetes and CDI is limited, leaving a void in our understanding of the risk and impact of CDI in diabetic patients in healthcare settings.

The first section of this chapter begins with a description of the methods and key terms used to search the literature relevant to this research issue. This is followed by a description of the theoretical foundation and the relevance in addressing this research issue, a comprehensive review of the literature related to the key variables, and conclusions based on the information presented.

Literature Search Strategy

A search of the literature was conducted to evaluate the current body of knowledge regarding the relationship between diabetes and CDI. The following search engines and databases, accessed through Walden University Library services were utilized: EBSCOhost, CINAHL & Medline, ProQuest, and Science Direct. Internet searches using the search engine Google Scholar were also conducted. The Walden University Library location service requested difficult to obtain peer-reviewed articles.

Bibliographies of published studies and review articles were also used to identify relevant studies.

Key search words and terms were employed to identify pertinent articles related to the research questions. Keywords were linked by Boolean search terms and included the following:

- *Clostridium difficile*, or *C. difficile*, or CDI, and diabetes, *C. difficile* and risk factors, *C. difficile* and rehabilitation.
- Diabetes and infection, and inflammation
- Gut motility, gut microbiota
- Ecosocial theory, ecosocial theory and diabetes, ecosocial theory and diabetes, diabetes and health disparities

Scope of Literature Review

The scope of the literature review included an extensive search of published materials in the past five years, extending into the past 20 years. Much research examining risk factors for CDI occurred in the late eighties and early nineties. As concerns regarding the prevalence of CDI have grown, there appears a resurgence of research building on prior findings, particularly in genomic research. A variety of literature was reviewed and includes various methodologies, ranging from experimental in vitro studies, observational studies, meta-analysis, and reviews. Literature sources included published peer-reviewed journal articles, published dissertations, and infectious disease and disease prevention texts.

Current Research Issues

A large body of current literature exists related to *C. difficile* and diabetes as independent topics. A search of the ProQuest Dissertations and Theses database identified several dissertations investigating CDI in both human and animal populations. However, limited literature regarding *C. difficile* in diabetic or AR populations was identified. The overall increase in publications over recent years, suggests unknown factors contribute to CDI disease, including identification of high-risk groups, and effective prevention measures across healthcare settings.

Theoretical Foundation

Ecosocial theory describes an epidemiology theory of disease distribution. Nancy Krieger proposed this theory 1994 to address the limitations of traditional causal relationships between specific agents and diseases to explain patterns and process of disease (Krieger, 1994; Krieger, 2011). Ecosocial theory is one of several multilevel social-ecological approaches identified in the literature, where health outcomes are studied within the broader social and environmental systems in which people operate (Susser & Susser, 1996). Krieger's Ecosocial theory expands previous works in epidemiological theory to include multiple system levels and tempo-spatial factors, such as place of residence or community setting, and history to provide greater context when describing factors contributing to health status and outcomes (Krieger, 2011).

Major Theoretical Propositions

Several core propositions underpin Ecosocial theory. These propositions have application in understanding the relationship between diabetes and CDI. The premise of

Krieger's (2011) ecosocial theory is that peoples' states of health, and disease, are shaped by the literal embodiment of the lived experience in both social and ecologic contexts. Thus, the way in which people live and interact within the world around them is determined by current and changing societal arrangements of power, property, production, and reproduction of social and biological life. Krieger defines embodiment as the biological manifestation of cumulative exposures to the material and social world in which we live, across the life course from utero to death (Krieger, 2005). Societal arrangements and patterns influence the distribution of disease at various levels and along different spatiotemporal scales in response to capacity and resources. For example, multiple socioeconomic and environmental exposures during one's life have been identified as contributing to the biological embodiment of both diabetes and CDI (Eze et al., 2014; Kivimäki et al., 2015; Stringhini, Zaninotto, Kumari, Kivimäki, & Batty, 2016). Krieger (2011) also suggests that understanding the distribution of disease exclusively from a disease process perspective fails to adequately explain why and how disease patterns change over time and space (p. 215). Rather, ecosocial theory allows one to consider how exposure, susceptibility, and resilience to social and biological phenomena over time create causal pathways leading to a state of embodiment.

Analysis of the Literature

Ecosocial theory provides a framework to examine the social and ecological factors contributing to health and health outcomes in epidemiologic and social research. Previous works incorporating ecosocial theory include position papers examining the role of ecosocial theory in public health research and public health policy (Bisung & Elliot,

2014) and research studies across a broad range of health issues (Krieger et al., 2013; Phillips et al., 2013; Shavers, Klein, & Fagan, 2012; Yamada & Palmer, 2007). Studies using an ecosocial perspective address health outcomes across a variety of population groups, with Krieger, frequently noted as the principal author. The variables most often examined within the ecosocial framework are gender, race, ethnicity, and socioeconomic disparities in health outcomes across a range of chronic and infectious diseases. Ecosocial theory has also provided the theoretical framework in recently published doctoral dissertations using qualitative and quantitative designs (Alford, 2014; Eke, 2013; Marley, 2013). Although several social-ecological theories have been proposed in recent years (Krieger, 2011; McLaren & Hawe, 2005), the increasing use of ecosocial theory in dissertations (Alford, 2014; Eke, 2013; Marley, 2013) likely reflects increased recognition of the complexities surrounding health behaviors' and outcomes. Despite the potential of ecosocial theory to frame complex health issues, application of ecosocial theory in understanding CDI is limited. The concepts of multiple pathways of exposure that people experience across their life-course could influence their susceptibility or resistance to this infection and may help identify disparities in disease distribution

Ecosocial Theory and Diabetes

Research into complex public health issues such as diabetes often uses an ecological or multifaceted approach (Trickett & Bheeler, 2013). Krieger (2005) suggests an ecosocial approach is well-suited to understanding the multiple factors contributing to disease onset and related outcomes through the connection of biological and social constructs. Despite the potential of ecosocial theory in diabetic research, researchers

examining diabetes within this framework is limited, with dissertation research predominating. Marley (2013) conducted a qualitative study examining the association between the place where people live and the associated cultural, political, and social context, and diabetes among White Mountain Apache. In this study, diabetes represented the biological expression of embodiment, through cumulative exposure to environmental, social, political, historical, and natural factors. Crocker (2013) also used ecosocial theory to frame a quantitative analysis describing the health characteristics and social determinants of Aboriginal peoples living outside tribal reservation with and without diabetes in Canada.

Multiple causal pathways can lead to the onset of disease, and the ecosocial concept of embodiment includes social, economic, environmental, political exposures. The term social determinates of health describing the conditions in which people live, learn, and work is one such pathway. Diabetes disease is strongly linked to social and economic conditions (Clark & Utz, 2012). Hill et al. (2013) note factors contributing to diabetes incidence and effective diabetic management are multi-level and impacted by social, environmental, political, and historical context. They also discuss the responsibility of public health agencies in reducing health disparities through data collection and research. These research responsibilities align with the ecosocial concept of agency, which refers to the need to monitor, address and explain disparities in health outcomes. Krieger (2011) describes the concept of agency as a responsibility of epidemiologic researchers. Although Hill et al. (2013) did not explicitly discuss

ecosocial theory or the concept of embodiment, their article did detail the conceptual pathways that can lead to disease.

Other multilevel theories incorporating social and ecological aspects similar to ecosocial theory occur in diabetic population research. Chang and colleagues (2013) examined characteristics associated with diabetes in a Hispanic population living in a U.S. border town, using a socio-ecological framework. Findings from their multivariate analysis showed dietary and biological factors most strongly associated with diabetes. The authors used a multilevel socio-ecological framework which incorporated the complexity and interrelatedness that exists between individual, relationship, community, and societal factors. There are similarities between socio-ecological models and the ecosocial theory proposed by Krieger. Both theories examine the interrelationships between exposure and societal and ecosystem levels, but ecosocial theory also considers how different temporal and spatial scales influence current and changing patterns of health inequalities (Krieger, 2011, p.223).

Rationale for Theory Selection

Ecosocial theory provides a dynamic and multilevel theoretical framework for research evaluating the association between diabetes and CDI in an AR setting. This framework offers a way to explain how the accumulation and interaction of different environmental conditions and experiences of hospitalized patients across the continuum of care may impact susceptibility or resilience to disease (Krieger, 2001; Schneiderman, Ironson, & Siegel, 2005). The concept of embodiment and the multifactorial pathways of disease causation are applicable to understanding the complexities associated with CDI

and diabetes. For example, ecosocial theory provides a bridge connecting the physical and social environments in which people live and interact and the complex ecological structure of the intestinal microbiome. The intestinal microbiota forms unique ecosystems which develop in response to various environmental and biological exposures over an individual's life-course (Rajilić-Stojanović, 2013). Krieger's ecosocial theory focuses on factors contributing to the distribution of disease not only from a life-course perspective but also via multilevel processes and ecosystems. Such multilevel processes and ecosystems can range from the individual micro level to global scale considerations (Krieger, 2011). Using the ecosocial theory of distribution to view the issue of CDI among the diabetic population supports examining the issue at the individual, organizational, and population level. It also acknowledges host and environmental factors that may contribute to an increased susceptibility or resilience based on previous exposures and life course events. In addition, consideration of the ecosocial pathways leading to CDI disease could identify opportunities for disease prevention

Literature Review Related to Key Variables and Concepts

Clostridium difficile Infection

C. difficile is a recognized pathogen in healthcare settings and a leading cause of pseudomembranous colitis (Carrico, 2013). Today, *C. difficile* is a leading cause of HAI (Magill et al., 2014). Lessa et al. (2015) reported an estimated 66% of CDI cases are healthcare related compared to community acquisition. Similar estimates are also reported by Olsen and colleagues (2016) across three national administrative databases. The CDC considers *C. difficile* a high-level and urgent threat to public health. This basis

for this assessment by the CDC comes from the organism's natural resistance to multiple antibiotics and the social and economic costs associated with this infection (CDC, 2013).

Researchers have consistently identified increased morbidity and mortality related to CDI across a variety of patient populations. Bartlett and colleagues (1978) first reported *C. difficile* as the causative agent in pseudomembranous colitis, refuting previous assumptions that it was non-pathogenic (Bartlett, 2008). Experimental studies investigating the action of *C. difficile* toxins suggest there are several mechanisms by which both toxins damage and destroy cells, resulting in increased permeability and inflammation of the intestine (Pruitt & Lacey, 2012), and systemic disease (Steele et al., 2012). Complications from CDI can result in prolonged hospitalization, the need for post-discharge care, and death. Tabak, Zilberberg, Johannes, Sun, and McDonald (2013) estimated CDI attributable risk of death at 4.5%. However, a recent study by Desai et al. (2016) using a broader population base estimated attributable mortality at 10%.

The ability of *C. difficile* to cause disease comes from the production of toxins (Kelly & LaMont 1998; Kuehne et al., 2010). Primary exotoxins associated with CDI are toxin A (TcdA) and toxin B (TcdB). A third binary toxin, *C. difficile* toxin (CDT), has been identified in hyper-virulent *C. difficile* strains (Gerding et al., 2014). Advances in molecular and genomic analyses are enabling researchers to identify the presence of specific bacterial strains and toxins (Eckert et al., 2014; Janezic, Marín, Martín & Rupink, 2015; Monot et al., 2015). Experimental studies investigating the action of toxins in CDI indicate there are several mechanisms by which both toxins damage and destroy cells, resulting in increased permeability and inflammation of the intestine (Pruitt

& Lacey, 2012) and systemic disease (Steele et al., 2012). The presence of toxins not only has significance for causing disease but is an essential marker in diagnostic tests. Risk factors strongly associated with the onset of CDI are based on disruptions to the microbiota of the host and include environmental exposure to antibiotics and gastric acid suppressants. Other environmental factors include exposure to hospital environments. Host risk factors identified in the literature include age, gender, race and the presence of commodities, including diabetes disease.

Diabetes

Diabetes mellitus (DM), describes a chronic condition which results from the inadequate production, or the inability to effectively utilize the hormone insulin, causing blood glucose levels to increase (International Federation of Diabetes [IFD], 2014). There are two main types of diabetes. The determination as to the type of diabetes diagnosed depends on when the presentation of disease occurs and the cause of disease onset. Type 1 diabetes (TD1) typically presents with acute metabolic imbalance associated with autoimmune response and non-insulin production in children and young adults (Forouhi & Wareham, 2014). Type 2 diabetes (T2D), the more prevalent of the two categories, occurs because of alternations in insulin secretion, and or insulin resistance. T2D is associated with increasing age, obesity, family history of diabetes, gestational diabetes, physical inactivity, and race/ethnicity (ADA, 2014; CDC, 2015). Dietary risk factors also exist for T2D and which include diets high in red or processed meats, sugar-sweetened beverages, and limited intake of fruits and vegetables (Forouhi & Wareham, 2014).

Diabetes affects an estimated 23 million adults in the U. S, with T2D accounting for 95% of all cases (CDC, 2017). Disparities in diabetes outcomes occur across a variety of population groups, locations, and socioeconomic status. Fraze, Jiang, & Burgess, (2010) found diabetes associated with frequent hospitalizations either as a direct cause or from related complications, especially among those of low income. Education, income, and neighborhood environment are consistent predictors of diabetes disease (Garcia et al., 2015; Krishnan, Cozier, Rosenberg, & Palmer, 2010; Lee et al., 2011) especially with cumulative exposure (Stringhini et al., 2016). Exposure to risk factors can have a direct and indirect influence on physiological stress and inflammatory responses within the body and are thought to explain the differences in disease risk within populations (Garcia et al., 2010).

Untreated diabetes of any type can result in complications that lead to debilitating systemic damage (Fowler, 2011). Complications affecting the gastrointestinal system include gastroesophageal reflux, gastroparesis, and diabetes-related neuropathy which increase susceptibility to enteric disease (Krishnan, Babu, Walker, Walker, & Pappachan, 2013). Mechanisms contributing to an increased risk of infection among those with diabetes, include the impact of hyperglycemia and oxidative stress on immune system function, the required immune response, and the unique attributes of the infective organism including tissue tropism (Gan, 2013). For example, both Gan (2013) and Peleg, Weerarathna, McCarthy, and Davis, (2007) suggested that defects in innate and adaptive immunity resulting from impaired neutrophil and T-cell functions increase susceptibility to infection among diabetic patients. Growing evidence also suggests a critical

relationship between immune regulation and the intestinal microbiome (Gilbert et al., 2016; Molloy, Bouladoux & Belkaid, 2012).

Intestinal Microbiota

The intestinal microbiota represents a diverse and dynamic ecosystem performing essential mechanical and biochemical functions (Gilbert et al., 2016). Changes or disruptions to the composition of this ecosystem can create dysbiosis and subsequent illness (Gilbert et al., 2016; Rajilić-Stojanović, 2013). Within the bacterial ecosystem of the intestine, select phyla have been identified as having specific metabolic functions (Patterson et al., 2014). These functions include the breakdown and metabolism of indigestible foods, the synthesis of vitamins, and the production of metabolites that promote states of health and disease (Patterson et al., 2014; Rajilić-Stojanović, 2013). For example, *Clostridia* species have an essential role in the fermentative digestion process and are part of the normal intestinal flora. However, they also can cause disease through the production of toxins. *C. difficile*, although a member of the Clostridia species, is not commonly found within the normal intestinal flora of humans, due to the bacteria's inability to successfully compete for nutrients in the healthy microbial ecosystem of the gut (Voth & Ballard, 2005). However, disruptions to the microbiota can provide an opportunity for organisms such as *C. difficile* to establish a viable niche (Theriot et al., 2013). The diversity of organisms is an indicator of a healthy microbial ecosystem within the gut (D'Argenio, & Salvatore, 2015). Differences in the distribution and diversity of the intestinal microbiota are found to exist among different population groups (Escobar, Klotz, Valdes, & Agudelo, 2014; Mueller et al., 2006; Rajilić-

Stojanović, 2013). Differences in diet, health behaviors', genetic characteristics, and disease states likely explain these variations within the intestinal ecosystem. Buonomo and Petri (2016) suggest that hospitalized patients are at risk for disturbances to the diversity and health of the microbiota due to changes in diet, exposure to medications and medical interventions. Hospitalized patients may also have an increased risk of exposure to *C. difficile* spores due to the prevalence of CDI in hospital settings.

Scientific and technological advances are providing researchers with a greater understanding as to the composition and function of the intestinal microbiota (Gilbert et al., 2016). This knowledge includes the role of microbiota in the development and maintenance of the immune system. There is also evidence suggesting that the diversity and distribution of the host microbiota within the gut plays a role in the onset of non-infectious diseases including diabetes (Biedermann & Rogler, 2015). Diabetes can negatively impact immune function and inflammatory responses through several pathways including the composition and selective activity of commensal bacteria within the gastrointestinal system (Brestoff, & Artis, 2013). Research into the microbiota suggests people with diabetes have differences in both the diversity and the distribution of organisms (Larsen et al., 2010; Qin et al., 2012a). Larsen and colleagues (2010) describe differences in the distribution of common intestinal bacteria phylum between persons with T2D and non-T2D persons. In this study, researchers found diabetic subjects had a higher abundance of Bacteroidetes (M = 50.4% vs. M = 35.1%) and significantly fewer Firmicute bacterial groups

> (M=36.8% vs. M = 56.4%), such as Clostridia, compared to controls. Studies comparing diversity suggest Firmicutes account for 60 to 70% of colonic bacterial species and Bacteroidetes 28 to 30% (Yang, Xie, Li, & Wei, 2009; Wang, Ahrné, Jeppsson, & Molin, 2005). Qin et al. (2012a) conducted a complex case-control metagenome-wide association study among a Chinese cohort, reporting the functional composition of bacteria differed between T2D and controls at the genus level. In this study population, those with T2D were found to have fewer butyrate-producing bacteria, which includes Clostridia species, and more pathogenic bacteria when compared to non-diabetic controls. Of the 37 butyrate-producing bacteria identified from the sample, only 21% were present in the T2D group, none of which were among previously isolated species of butyrate-producing bacteria located in the human colon (Qin et al., 2012b, p.30).

In a similarly designed study comparing European women, Karlsson et al. (2013) identified differences in the composition and structure of fecal microbiota between diabetics and non-diabetics. Karlsson and colleagues used their bioinformatics methodology to compare their findings with the Chinese cohort data (Qin et al., 2012a), observing similar differences in bacterial functional composition and metabolic pathways existed between cohorts. However, differences in species diversity and abundance were noted between the two cohorts perhaps reflecting differences between populations. Differences in the distribution of select bacterial groups between those with diabetes and non-diabetics could provide an opportunity for *C. difficile* to proliferate should favorable conditions develop. Favorable conditions include disruptions to established intestinal

bacteria, providing an opportunity for *C. difficile* bacteria to access nutrient sources not otherwise available but necessary for replication and growth.

Sialic Acid

In the human intestine, sialic acids (Sias), perform several functional roles. Sias are protein-bound monosaccharides characterized by a nine-carbon backbone and have an essential role in the regulation of cellular function (Varki & Schauer, 2009). The most abundant Sias in humans is N-acetylneuraminic acid (Varki & Schauer, 2009). Within the mucous layer of the intestine, Sias provide a source of energy and nutrition for both commensal and pathogenic bacteria (Vimr, Kalivoda, Deszo, & Steenbergen, 2004). Sias also have a role in regulating host immune function (Varki & Gagneux, 2012).

Recent studies demonstrate that Sias are utilized by *C. difficile* as an energy source. Ng and colleagues (2013) showed that *C. difficile* has the genetic ability to catabolize mucosal mucin. Mucin, a glycoprotein found in intestinal mucous contain Sias which bind to the terminal, non-reducing ends of oligosaccharide chains (Vimr et al., 2004). However, for *C. difficile* to expand, the bacteria require an available source of free sialic acid (Ng et al., 2013). This new understanding supports the hypothesis that competition for nutrients and disruption to commensal bacteria provides an opportunity for *C. difficile* to develop a niche in an otherwise limiting environment (Britton & Young, 2014).

Sialic Acid and Diabetes

Research into sialic acid (Sias) indicates people with diabetes have higher amounts of circulating Sias compared to non-diabetics (Khalili et al., 2013; Schmidt et

al., 1999: Varghese, Asha, Celine, & Prasanna, 2015). Schmidt and colleagues (1999) identified an association between increased serum levels of Sias and orosomucoids, a glycoprotein to which sialic acid binds, and incident diabetes among a large U. S. cohort. A later study by Khalili et al. (2013) analyzing health data from a large Swedish cohort also observed a positive relationship between serum Sias and increased risk for diabetes and diabetic complications. Despite limitations for comparison due to differences in population groups and the variables included in the analyses, both longitudinal studies suggested that people with diabetes have elevated circulating concentrations of Sias. Elevated levels of Sias in those with diabetes suggest a potential pathway by which people with diabetes could become susceptible to CDI. For example, disruptions within the microbiota, especially to commensal bacteria utilizing Sias as an energy source, could increase availability for *C. difficile* bacteria and the potential for bacterial expansion (Huang, Chassard, Hausmann, von Itzstein, & Hennet, 2015; Ng et al., 2013). The association between Sias levels and diabetes are further supported by findings from Varghese, Asha, Celine, and Prasanna (2015) who conducted a case-control study evaluating the serum concentration of inflammatory markers, including Sias in patients with T2D. Varghese and colleagues found participants with T2D had significantly higher levels of serum Sias compared to non-diabetic controls.

Factors Associated with Disruptions to the Intestinal Microbiota

Antimicrobial therapy

A well-established relationship exists between exposure to antibiotic therapy and an increased risk for CDI (Bartlett, Moon, Chang, Taylor & Onderdonk, 1978). The

initial link between CDI and antibiotics was established by Bartlett, Moon, Chang, Taylor and Onderdonk (1978) with the identification of *C. difficile* as a causative agent in antibiotic-associated colitis. Over the past several decades' researchers have shown most classes of antibiotics related to an increased risk for CDI in hospitalized patients (Owens et al., 2008). Variation in reported findings between classes of antibiotic reflects differences in the susceptibility patterns and virulence among different strains of *C. difficile*. For example, Vardakas, Konstantelias, Loizidis, Rafailidis, and Falagas (2012) conducted a meta-analysis comparing risk characteristics for BI/NAP1/027 and non-BI/NAP1/027 *C. difficile* strains. Results from their analysis indicate different susceptibility and resistance patterns exist between strains. BI/NAP1/027 strains were associated with prior exposure to fluoroquinolones a class of antibiotics previously not associated with an increased risk for CDI (Freeman & Wilcox, 1999). However, Clindamycin, a predisposing factor in non-BI/NAP1/027, did not pose a significant threat. These differences support increasing concerns regarding emerging antibiotic resistance among select strains of CDI. Stevens, Dumyati, Fine, Fisher, & Van Wijngaarden (2011) found evidence from a large prospective cohort study suggesting cumulative exposure to antibiotics over time increases the risk for CDI, making links to specific antibiotics challenging. The mechanism by which antibiotics predispose the host to CDI results from the disruption to the host's normal intestinal microbiota. This disruption enables colonization and expansion of other microorganisms into previously occupied niches. It is also suspected that antimicrobials are not the only medications to have a disruptive effect on the microbiome.

Proton pump inhibitors

Proton pump inhibitors (PPI) are a frequently utilized medication in hospitalized patients and associated with an increased odd of developing CDI (Barletta & Sclar, 2014; Buendgens et al., 2014; Dial, Alrasadi, Manoukian, Huang, & Menzies, 2004). Exposure to PPI medications are thought to contribute to the risk for CDI by altering the diversity of the intestinal microbiota (Bavishi, & DuPont, 2011; Imhann et al., 2015; Seto, Jeraldo, Orenstein, Chia, & DiBaise, 2014). Although findings from several meta-analyses (Arriola et al., 2015; Deshpande et al., 2015; Janarthanan, Ditah, Phil, Adler, & Ehrinpreis, 2012) support an association between PPI exposure and CDI, the role of gastric acid suppression in increasing susceptibility to CDI is not entirely understood. Some researchers hypothesize that high gastric acidity destroys harmful pathogens (Clooney et al., 2016; Janarthanan, Ditah, Phil, Adler, & Ehrinpreis, 2012; Jump, Pultz, & Donskey, 2007). Suppression of gastric acid production then raises the gastric pH and increases the bacterial load of pathogens within the gut environment. An early study by Dial, Alrasadi, Manoukian, Huang, and Menzies (2004), found that patients receiving PPI medication had an increased risk of CDI compared to those not exposed. Similar findings from a case-control study were reported by the same research team (Dial et al., 2004), investigating CDI risk while controlling for comorbidities and severity of disease. More recently, both Barletta and Sclar (2014) and Buendgens et al. (2014) reported an increased risk for CDI associated with PPI exposure among intensive care unit (ICU)

patients. Links between PPI exposure and CDI onset are reported in several meta-analyses (Deshpande et al., 2015; Kwok et al., 2012; Tleyjeh et al., 2012). However, substantial heterogeneity between these studies was noted as a limiting factor in the analysis. Several studies found increased risk associated with PPI use and concurrent antibiotic exposure when compared to PPI use alone (Gordon, Young, Reddy, Bergman, & Young, 2016; Kwok et al., 2012). Recent evidence also suggests that long-term PPI use may affect the microbiome. Clooney and colleagues (2016) reported different ratios of Bacteroidetes and Firmicutes between PPI and non-PPI users. Such differences may increase host susceptibility allowing *C. difficile* bacteria to grow and expand outside of the stomach. This hypothesis is supported by findings from in vivo and cohort studies (Imhann et al., 2015; Nerandzic, Pultz, & Donskey, 2009). Nevertheless, not all studies have reported increased risk for CDI associated with PPI use. Novack and colleagues (2014) found no statistically significant risk between PPI exposure and CDI when comparing similar levels of disease severity, arguing that previously reported associations are the result of differences between comparison groups. The findings by Novack et al. (2014) mirror prior findings by Shah, Lewis, Leopold, Dunstan, & Woodhouse (2000) who also found no association between risk for CDI and PPI use when comparing samples testing positive for *C. difficile* toxin, and those that test toxin negative. Furthermore, Faleck and colleagues (2016) examined the risks of PPI exposure in patients in 14 ICU and found that PPI use did not to increase the risk for CDI nor was it found to effect adverse outcomes following CDI infection.

Although there is some discrepancy regarding exposure to PPI in hospitalized patients, their use has relevance for the diabetic population experiencing gastrointestinal complications of altered intestinal motility and gastroesophageal reflux disease. Such complications may place diabetic patients at increased risk for CDI due frequent and longer-term usage of gastric acid suppressing medications (Huang & Wang, 2009). The frequent utilization of PPI among hospitalized patients, including those with diabetes is important as PPI may confound the relationship between diabetes and CDI, similar to antibiotic exposure.

Diabetic medications

Medications used in the management of diabetes, are thought to have some impact on the microbiome. Metformin, an oral antihyperglycemic used in T2D, has been found to reduce the risk of CDI in diabetic populations (Eliakim-Raz et al., 2014). Eliakim-Raz and colleagues (2014) evaluated the risk of CDI among a sample of hospitalized patients, using a case-control design. The researchers found patients on metformin therapy were 42% less likely to develop CDI compared to patients on other treatment modalities, such as insulin. The therapeutic effect of drugs, like metformin are thought to come from metabolic alterations within the intestinal microbiome (Forslund et al., 2015; Wu et al., 2017). Forslund et al. (2015) note that medication modalities influencing the microbiome could have a confounding effect, and should be controlled for in data analysis. The authors (Forslund et al., 2015) hypothesis was supported with differences found in the intestinal microbiome of those taking metformin and those not on metformin therapy. Specific differences included a decreased abundance of butyrate-

producing organisms in patients with T2D not on metformin, compared to those receiving metformin. Butyrate-producing bacteria are thought to play a protective antimicrobial role and depletion of these organisms is associated with an increased risk for CDI (Antharam et al., 2013; Schubert et al., 2014). Studies examining cardiovascular risk in T2D have also found patients taking metformin have lower levels of serum sialic acid than those on alternative oral antiglycemics (Rahman, Malik, Bashir, Khan & Idrees, 2010).

Enteral feeding tubes

Patients receiving enteral nutrition via feeding tubes have been identified as having an increased risk for CDI (Bliss et al., 1998; O'Keefe, 2010). In a study specifically evaluating CDI in tube feed patients, Bliss et al. (1998) found patients receiving tube feedings were nine times more likely to acquire CDI than non-tube feed patients. Brown and colleagues (1990) also reported an association between nasogastric (NG) tubes and increased risk for CDI in a case-control study. Although Brown, Talbot, Axelrod, Provencher & Hoegg (1990), found patients with NG tubes to have 28 times greater risk for CDI, the small sample size, and differences noted between case and control patients makes these finding less reliable. For example, more than 25% of controls came from the obstetrics and gynecology services which likely have healthier, and younger female patients. Recent studies (van Werkhoven et al., 2015; Wijarnpreecha et al., 2016) have continued to report an increased risk for CDI associated with the use of gastric and nasogastric feeding tubes. However, smaller effect sizes are reported compared to earlier studies (Brown, et al., 1990; Bliss et al., 1998). In contrast, Lin et al.

(2015) conducted a prospective cohort study examining risk factors for CDI in a Taiwanese population and found tube feeds were not a statistically significant risk factor for developing CDI in both bivariate and multivariate analyses. Larentis, Rosa, De Santos, and Goldani (2015) found no association between tube feeds and CDI in bivariate analysis, but the authors did find tube feeding an independent risk factor associated with poor outcomes in CDI.

Several mechanisms for the increased risk for CDI with the use of feeding tubes have been proposed. These include the transfer of *C. difficile* bacteria by healthcare workers during routine manipulation of the tubes (Best, 2008; Bliss et al.,1990; Brown et al., 1990), and the potential contamination of enteral formula from the environment (Bliss et al., 1998; Mutters et al., 2008). There are also some indications that the type of enteral formula can alter the gut microbiota, promoting the expansion of bacteria, including *C. difficile* in the gut (Iizuka et al., 2004). O'Keefe (2010) notes that elemental and low-residual formulas, while readily absorbed in the small intestine lack the complex carbohydrates and fiber that support a diverse and protective microbiota within the colon. Disruptions to the microbiota from these types of formula can also provide an opportunity for *C. difficile* to proliferate within the colon and cause disease (O'Keefe, 2010).

Prior healthcare location

The risk of CDI among the AR population could be affected by previous exposure to healthcare settings, with patients exposed to risk factors, such as antibiotics and contaminated environments. Information regarding the prevalence of CDI or

colonization in the AR environment is limited. Marciniak and colleagues (2006) investigated the prevalence of *C. difficile* colonization among rehabilitation patients admitted from an acute care setting. Findings from this case-control study found 16% of patients were colonized with *C. difficile*. However, evidence indicating prior colonization as predictive of developing CDI was inconclusive. Other studies examining the transmission of CDI among different hospital settings, reported higher estimated rates of transmission among residents in long-term care (LTC) settings compared to the acute hospital or the community (Durham, Olsen, Dubberke, Galvani & Townsend, 2016). Ricciardi, Nelson, Griffith, and Concannon, (2012) also suggest that higher rates of CDI among LTC residents result in an increase burden of CDI in acute care hospitals. However, a recent study by Ziakas et al. (2016) among a national sample of LTC residents, found that almost two-thirds of those diagnosed with CDI had a been hospitalized within the previous 30 days or had a hospital discharge within the last 90 days. Similar findings were reported by Zarowitz, Allen, O'Shea, and Strauss (2015), who evaluated a large national sample of nursing home residents. Results from this research found only 21% of CDI cases were nursing-home acquired, and the majority, 85%, of cases were admissions from acute care hospitals. Although patients often move between healthcare settings, most admissions to post-acute settings are from acute care hospitals (Hunter et al.,2016; Zarowitz et al., 2015; Ziakas et al., 2016). In addition, characteristics among cases, such as exposure to antimicrobials, underlying health conditions, and older age are consistently identified across various healthcare settings (Hunter et al.,2016; Zarowitz et al., 2015; Ziakas et al., 2016). Different healthcare

settings could impact the exposure burden of CDI. However, limitations noted in previous research regarding an absence of data from prior hospitalizations, time from exposure to infection, and sample size (Marciniak, Chen, Stein, & Semik, 2006; Mylotte, Russell, Sackett, Vallone, & Antalek, 2013) reduces the value of adjusting for location in the analysis.

Individual Host Factors

Age

Evidence of a correlation between advanced age and an increased risk of CDI have been published both in the U.S. and globally. Lessa et al. (2015) reported population estimates of incidence HAI-CDI in the U.S. among those 65 years of age and older of 481.5 per 100,000 persons compared to only 83.1 per 100,000 persons aged 45 to 64 years. Similarly, an European population-based surveillance study of HAI- CDI found persons over 65 years incurred three times the risk of CDI compared to those of younger age (Bauer et al., 2011). Smaller studies have also reported older adults experience higher risk for CDI and increased disease severity. Patel, Wieczorkiewicz, and Tuazon (2016) found advanced age, defined as over 70 years, associated with a 2-fold increased risk of developing severe CDI disease. Lee et al. (2016) also reported more severe illness among hospitalized Korean patients 65 years and older compared to those under 65. Using a prospective study design, Kurti et al. (2015) described CDI incidence in an Eastern European hospital population. Although they reported 83% of CDI cases were over 60 years of age, age alone was not a significant risk factor. Instead, an association with disease severity and mortality was identified. The severity of illness among those

with CDI is likely affected by multiple factors, including different bacterial strains. Miller et al. (2010) found select *C. difficile* strain associated with worse outcomes. Disease severity and *C. difficile* attributable mortality did increase with age, particularly in those over 60 years. However, the very old experienced poor outcomes regardless of *C. difficile* strain.

Race and ethnicity

Disease and health-related outcomes are frequently examined within the context of race and ethnicity in the U.S. Understanding the role of race and ethnicity and social determinants in health distribution is complex (Ichiro, Daniels, & Robinson, 2005). Reports of racial and ethnic differences in CDI incidence and outcome measures suggest that some level of health disparity may exist. Differences include higher rates of CDI in White compared to non-Whites population groups. Lessa et al. (2015) analyzed surveillance data from ten States across the U. S. and found rates for both incidence and recurrent CDI higher in Whites compared to non-Whites. Also, Mao, Kelly, and Machan (2015) and Olanipekun, Salemi, de Grubb, Gonzalez, and Zoorob (2016) examined the effect of race on CDI. Using secondary data from the Healthcare Cost and Utilization Project Nationwide Inpatient Sample (NIS), both studies reported higher rates of infection among Whites compared to other racial and ethnic groups. Additionally, Mao and colleagues found Whites more likely exposed to antibiotics than other races. Findings from a study by Bakullari et al. (2014) suggest HAI occurs more frequently among Asian and Hispanic populations. Asian populations also experienced a higher occurrence rate of CDI, compared to White, non-Hispanic groups (0.5% vs. 1.1%) in a

Medicare population. Murphy, Avery, Dubberke, & Huang (2012) also reported an increased probability of healthcare-onset CDI among Asians compared to Whites. However, non-Hispanic Whites were more likely to experience CDI following discharge. Although not evaluated, such findings may reflect differences in access to care in the outpatient setting (Murphy et al., 2012). In contrast to other studies, Freedberg et al. (2013) found Black race associated with an increased risk for recurrent CDI when evaluating PPI exposure. In this hospital-based cohort, the multivariate analysis found Black race associated with increased risk for CDI compared to Whites. Differences in CDI outcomes related to race and ethnicity indicate multiple factors and pathways contribute to risk. Bakullari et al. (2014) suggested that language barriers could adversely impact some population groups when hospitalized. Other variables such as socioeconomic, environmental and social factors may also contribute increased risk for CDI (Freedberg et al., 2013; Lessa et al., 2015). The increased risk for Caucasians found in large inpatient population datasets, may reflect greater access and exposure to healthcare settings and antibiotics compared to other minority groups.

Obesity

High BMI has been linked to both the risk of developing diabetes and CDI (Bishara et al., 2013; Leung, et al., 2013; Leung, Carlsson, Colditz & Chang, 2016; Nguyen, Nguyen, Lane, & Wang, 2011). The CDC (2016) classifies a normal or healthy BMI between 18.5 and 24.9 and obese, as a BMI equal or greater than 30. Nguyen and colleagues (2011), using data from the National Health and Nutrition Examination Survey found 49% of diabetics were also obese based on their BMI. Ganz et al. (2014)

conducted a case-control study using data from a large U.S. health system and found the risk for T2D between 2.5 and 5 times greater among those within the obese BMI categories. Leung, Carlsson, Colditz, and Chang (2016) also reported a strong association between obesity and risk for diabetes using population-based health utilization data. There is also evidence suggesting a link between obesity and the risk of developing CDI. Bishara et al. (2013) conducted a case-control study testing the hypothesis that obese persons may have increased susceptibility to CDI compared to lean persons, based on potential differences in the gut microtia between the groups. Findings from their multiple regression analysis found obesity an independent risk factor in CDI among this study population. Leung and colleagues (2013) also investigated the relationship between obesity and the risk for CDI among hospitalized patients. Results from their retrospective analysis suggest an association between obesity and CDI, among those without prior exposure to healthcare facilities after controlling for antibiotic use. No significant relationship was found between obesity and healthcare-associated CDI. However, the small sample size suggests the study may not have had adequate power to detect a statistically significant association.

Disease severity

A potential confounder in the relationship between diabetes and CDI is the severity of diabetes. Diabetes can adversely affect the body's vascular systems (Fowler, 2011). The resulting damage to the macro and microvascular systems contribute to complications such as cardiovascular disease, peripheral vascular disease, stroke, nephropathy and retinopathy (Fowler, 2011). Complications of diabetes are also

associated with increased morbidity and mortality (Steiner & Friedman, 2013). Steiner and Friedman (2013) examined comorbidities among hospitalized patients using data from the NIS. The analysis found diabetes was a frequent discharge comorbidity among those with three or fewer underlying conditions across all age groups. Of interest, the proportion of adults with four or more chronic diseases was highest for Whites, while Hispanics had the least. The number of presenting complications and risk for CDI could reflect the overall health status of patients, measured as the number or the type of health complications on admission. Wenisch et al., (2012) investigated risk factors for severe CDI in a small sample of hospitalized patients, noting more than 60% of the sample had moderate to severe underlying diseases based on the Charlson commodity index. Multivariate analysis found only diabetes, chronic kidney disease and chronic pulmonary disease associated with increased risk of severe CDI, and diabetes associated with higher odds of infection. The authors reported no association between disease severity and increased age. A limiting factor in the interpretation of these results is the potential for inadequate power due to the small sample size, especially when correlations between increasing age and disease severity have been identified (Kyne, Sougioultzis, McFarland, & Kelly, 2002; Murphy et al., 2012). Murphy et al. (2012) identified individual characteristics predictive for CDI included age and diabetes in both bivariate and multivariate analysis. Tartof and colleagues (2014) also reported higher proportions of CDI cases among those with diabetes and severe diabetes in addition to 14 additional underlying conditions.

Most studies examining CDI address the potential confounding of underlying conditions on the outcome. However, few studies differentiate between the diabetes severity as was done in the study by Tartof et al. (2014). Interestingly, there is evidence suggesting that diabetes may be protective against CDI. Stewart and Hollenbeak (2011) analyzed NIS data from 2007, evaluating risk factors associated with excess attributable costs and mortality between those with and without CDI. In their analysis, both diabetes and diabetes with complications resulted in lower odds of dying compared to those without CDI. This unexpected finding may reflect less virulent strains circulating in hospitals during the sampling period or less precise testing methods than currently available. In addition, the use of administrative databases poses limitations related to the availability of clinical data such as diagnostic results and medications specific to individual patients.

Clostridium difficile Infection and Diabetes

Few studies have examined the association between diabetes and CDI despite the increasing prevalence of both diseases. A recently published population-based study examining CDI among patients with T2D reported an overall prevalence of CDI among hospitalized patients with T2D of 6.8 per 1000 acute care discharges (Olanipekun et al., 2016). Thus, people with diabetes could account for a large number of cases when compared to national estimates of 13.8 CDI cases per 1000 discharges (Jarvis, Schlosser, Jarvis, & Chinn, 2009). Olanipekun et al. also reported a positive correlation between CDI and increased mortality, duration of hospitalization, and cost. Although Olanipekun et al. reported on findings from a large randomized cohort of hospitalized patients, the

sample excludes post-acute patients in rehabilitation and long-term acute care hospitals. However, with an estimated 76% of hospitalized patients discharged to post-acute settings (Burke et al., 2015), the prevalence of CDI in the diabetic population was likely underestimated. Shakov, Salazar, Kaqunye, Buddora, & DeBan (2011), found people with diabetes had an increased for recurrent CDI. Since the outcome of interest was recurrent disease, no association between incident CDI risk and diabetes was evaluated. Limited evidence suggests diabetic patients who develop CDI may have unique characteristics. For example, Hassan, Rahman, Huda, Wan Bebakar and Lee (2013) found diabetic patients with CDI were younger and diagnosed with sepsis, thus more likely to have received antibiotics. However, the validity of their results is limited by the small number of CDI cases included in the analysis. More recently, Olanipekun et al. (2016) analyzed data from a large U. S. national sample, and found differences in race and income when comparing those with diabetes and CDI and diabetics without a diagnosis of CDI. Similar to other reported studies (Mao, Kelly, and Machan, 2015), the Olanipekun et al. (2016) study found a higher proportion of CDI occurring in Whites. Differences associated with income were also noted, with a larger proportion of those with CDI having higher household incomes while lower income was positively related to an increased length of stay, associated costs, and risk for mortality. The differences noted by Olanipekun et al. may reflect the impact socioeconomic status and overall health status have on those with diabetes.

Summary and Conclusions

Investigations into the relationship between diabetes and CDI have been observational and most often using historical data. The inability to infer causation is an inherent weakness of observational studies (Rothman, Greenland, Poole, & Lash, 2008), as even well-designed observational studies remain vulnerable to unexpected or unknown confounding variables. Within the reviewed literature, differences in sample populations and sample size were frequent, and likely explained the variation in reported outcomes. For example, sample sizes ranged from 159 patients in a single hospital setting (Hassan et al., 2014) to over 3,000,000 patients included in a national inpatient database over a ten-year period (Olanipekun et al., 2016). Differences in geographical locations and healthcare settings also existed, although the majority of studies included hospitalized patients from acute care settings. Some researchers used large population-based samples to examine CDI outcomes providing a nationally representative population from which to interpret and extrapolate findings. Population-based samples drawn from national data sources often provide access to large samples which strengthen the credibility of the results. However, such samples have limitations. For example, the NIS database contains data from a large number of participating community hospitals yet, excludes data from post-acute hospital settings such as rehabilitation and long-term care facilities (Healthcare Cost and Utilization Project [HCUP], 2016). Other limitations of administrative databases are the accuracy and availability of data extracted from medical records. Differences between studies also existed regarding the measurement of variables, in particular, comorbidities. The most frequently used measure of disease

severity identified in the literature was the Charlson Comorbidity Index, although variation in the presentation of included variables was noted. Other strengths identified from this review include consistencies in the diagnosis of CDI, with studies using similar testing processes and definitions**.**

Conclusion

This review of the literature addressed several major themes related to diabetes and CDI. The role of the intestinal microbiota is shown to have a strong influence in regulating the immune system, as well as limit available niches for pathogenic bacteria. The development of commensal flora and balanced ecosystem within the intestinal environment depends on the availability of essential nutrients and the organism's ability to access and utilize them. Research into the role of Sias as a nutrient source for *C. difficile* bacteria and as an indicator of inflammatory processes in persons with diabetes raises the question as to whether diabetes poses an increased risk for CDI. Few studies have specifically examined the relationship between diabetes and CDI. Most research into CDI outcomes include diabetes as a comorbidity measure related to disease severity, rather than a primary risk factor. Exposure to antibiotics adversely affects the risk for CDI through organism resistance and disruption to the commensal bacteria of the gut. Such disturbances, in turn, support the opportunistic expansion of *C. difficile* bacteria. Exposure to PPI medications may also contribute to CDI, although the mechanisms for this association are not well understood. Host characteristics such as age, race, underlying disease states and disease severity also appear to contribute to CDI. Despite the myriad of research related to CDI, understanding the determinants contributing to

disease onset remains unclear. In addition, little research appears to focus on the impact of CDI among hospitalized patients with diabetes. This literature review has identified possible mechanisms unique to diabetic patients contributing to an increased risk for CDI in this population.

My study evaluating the relationship between diabetes and CDI addresses the need for data regarding CDI in the diabetic population. This study also fills a gap in the literature regarding CDI risk factors in the post-acute setting. Addressing the deficits identified in the literature is an important step for CDI prevention. The following chapter discusses the design and methodology elements of this study, including a description of the population, sampling, and analysis strategies

Chapter 3: Research Method

Introduction

A case-control research design was used to answer the research questions regarding the relationship between diabetes and CDI, and the presence of modifiable risk factors among diabetic patients. The main purpose of this study was to assess the association between diabetes and CDI among the acute-rehabilitation population. Evaluation of this relationship included controlling for select environmental and host characteristics. For this study, the outcome variable was the presence of CDI and the independent variable diabetes. Control variables include age, ethnicity/race, gender, admission diagnosis, health status, functional independence, and diabetes disease severity. The second aim of this study was the identification of environmental and host characteristics sensitive to modification in the diabetic population. Other independent variables of interest include antibiotic use, gastric acid suppressants, diabetic management, BMI, and the presence of gastric feeding tubes.

Chapter three presents the proposed methodology to answer the aforementioned research questions. This chapter describes the research design and supporting rationale. Variables included in the analysis are presented and operationalized. This chapter also describes the sampling plan, the data collection methods, the ethical considerations pertinent to this research study, and a discussion regarding potential threats to the external and internal validity of the proposed study. Finally, the methods for the statistical analysis and testing of hypotheses are described.

Research Design and Rationale

Independent and dependent variables of interest are diabetes and CDI, respectively. Variables acting as potential confounders include antibiotics, obesity and PPI. Persons with diabetes may experience greater exposure to antibiotics, thereby increasing their risk for CDI. Likewise, diabetics may also have increased exposure to PPI medications resulting from disease-related complications, and there is evidence suggesting PPI may increase the risk of CDI. Potential confounders include patient comorbidities which could influence the strength of the relationship between the independent and dependent variable, including obesity. Age is a potential confounding variable associated with both increased risk of diabetes and CDI. Covariates include ethnicity/race, gender, admission diagnosis, duration of hospital stay, diabetes disease severity, obesity, and underlying co-morbidities.

Case-control designs support the evaluation of exposure-disease associations and allows for retrospective comparison of factors which may contribute to the risk of disease (Szklo & Nieto, 2014). The comparison between cases and controls can generate estimates of exposure prevalence and risk factors in the source population (Rothman, Greenland & Lash, 2008, p.112). Case-control studies support the use of secondary data and for use in diverse and dynamic populations such as those found in hospital settings (Carlson & Morrison, 2009; Vandenbroucke & Pearce, 2012). A defining characteristic of case-control studies is the selection of cases based on the outcome of interest, which for this study is CDI. The case-control design is also useful when studying infrequent or rare outcome events. Although CDI is an HAI of concern, the estimated incidence of

CDI among the acute care settings is less than 20% (Magill et al., 2014) with an estimated frequency of 15 % among the AR population (Mylotte, Graham, Kahler, Young, & Goodnough, 2000).

Methodology

Population

A total of 7953 discharge records were identified for the study period, August 01, 2009, and September 30, 2015, with 217 records having an ICD-9 code for CDI. The final number of cases meeting the inclusion criteria was 102. Both cases and controls came from the same source population. The source population included all patients discharged from a New Mexico free-standing urban AR hospital during the defined study period. This acute inpatient rehabilitation hospital accepts patients from throughout the State with an estimated 1200 discharges per year. The average length of stay at this hospital is 14 days. Patients access the AR setting to improve their functional independence while still receiving inpatient hospital care, allowing patients to return to their homes and communities.

Sampling and Sampling Procedures

Participant selection

The following plan outlines the strategies used to increase the representativeness of the participants in this study and reduce sampling errors. For this study, all available cases, and a sample of eligible controls was drawn from the same target population. A positive laboratory test for *C. difficile* toxin during an episode of hospitalization was needed to meet the criterion as a case. Randomly selected patients discharged during the

study time frame without a positive test for *C. difficile* toxin were eligible for inclusion in the control group. The exclusion criterion for both cases and controls were discharged patients under the age of 18, and those patients receiving treatment for CDI at the time of admission as noted in the admission history and physical.

The target population consisted of all discharged patients from the research site during specified study period. The following procedures describe the selection of both cases and control samples. A query of the facility administrative data was used to generate a list of all patients discharged during the study period. Information requested for this query was limited to discharge date, ICD-9 code discharge diagnoses, and medical record number. ICD-9 code 089.45 provided the initial screen to identify cases of CDI. The medical record number was necessary to locate the correct medical record for review in the absence of an electronic medical record. Use of ICD-9 codes to query nosocomial CDI has been used previously with good sensitivity, but limited specificity when compared to laboratory results (Scheurer, Hicks, Cook, & Schnipper, 2007). To limit the potential for misclassification, laboratory results were reviewed to confirm the CDI diagnosis. All verified CDI cases meeting the inclusion criteria were included in the case group. For each case, two controls were selected from the list of discharged patients. The discharge list was organized by date and controls selected using the medical record number located above and below the case subject. In the event, consecutive cases were identified, the next available units above and below the cases were selected, maintaining the 1:2 ratio. This method of control selection reduced potential sampling bias by increasing the likelihood that controls were from the same

population that produced the cases.

A priori power analysis

This research study used a fixed sample capturing all eligible CDI cases identified during the study period. An estimated 25 cases of hospital-associated CDI were reported at the facility each year. This estimate was based on historical infection control surveillance reports. Prior to data collection, a priori analysis of the expected power was conducted. Information from the power analysis provided an estimation of type 2 error associated with a sample of this size. OpenEpi software (Dean, Sullivan, & Soe, 2002) was used to generate the power analysis for a two-tailed test with the estimated sample size of 125cases during the originally proposed 57-month study period of January 1, 2011 through September 30, 2015. The level of significance was set at 5%, with a 95% confidence interval. An odds ratio of 2 was estimated from the proportion of diabetes exposure among cases and controls obtained from previously reported data (Weeks, 2009, Meng, Pickett, Babey, Davis, & Goldstein, 2014). Review of the literature suggested the estimated proportion of hospitalized patients with diabetes ranges from 18% in the rehabilitation setting (Weeks, 2009), to almost 20% in the acute care settings (Fraze, Jiang, & Burgess, 2010), although estimates of 30% have also been reported (Meng et al., 2014). Additional selected studies reported that 24 to 38 % of CDI cases also had a history of diabetes (Abdelsattar et al., 2015; Hunter et al., 2016; Tartof et al., 2014; Zilberberg et al., 2014). Based on this reported data, the percent of exposure among cases was estimated at 30%. The power analysis calculation indicated that the estimated sample size is unlikely to achieve the desired 80% power (Table 1).

Table 1

Results of A priori Power Analysis

Input Options	Input Data
Two-sided confidence interval (%)	95
Number of cases	125
Percent of exposure among cases (%)	30
Number of controls	250
Percent of exposure among controls (%)	18
Odds Ratio	2
Power: Normal approximation	74.28%

Note. Power analysis generated for unmatched case-control study using OpenEpi statistical software (Dean, Sullivan, & Soe, 2002). Number of cases is estimated from an estimated number of CDI cases occurring each year at facility.

Data Collection Methodology

The initial data collection study period from January 1, 2011, through September 2015 found 140 records coded for CDI. However, 71 did not meet the inclusion criteria. Exclusion criteria included receiving treatment for CDI at time of admission (n = 40), or laboratory test results negative for *C. difficile* toxin. Twenty-four records coded for CDI were negative for toxin, although positive for antigen, and seven records were miscoded with either negative results reported or no documented test result. The number of actual cases (n = 69) was unable to provide adequate power, increasing the risk of a Type II

error. Thus, the study period was extended to include an additional 24 months, following approval from the Walden University IRB. The second set of data found a total of 77 potential cases. Unfortunately, access to discharged records was restricted to patients discharged after August 1, 2009, resulting in the removal of 31 cases and 50 controls. Of the remaining available CDI coded records (n = 46), one was excluded due as unable to locate scanned chart, and 11 were excluded due to CDI treatment at the time of admission.

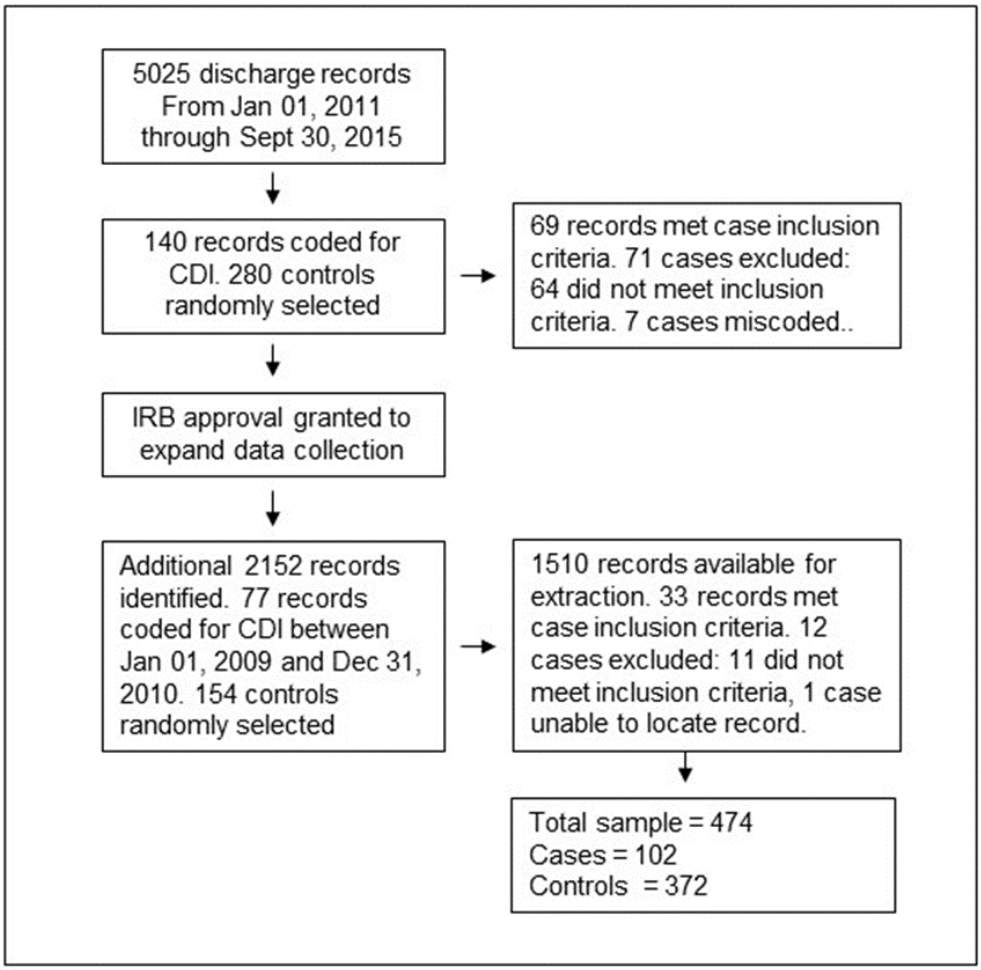

Figure 2. Flowchart

Data Extraction Procedures

The analysis dataset for this case-control study was constructed utilizing a secondary data source. Permissions to build a data set from information documented in the hospital medical record was granted by the Chief Executive Officer at the study site. The permission process included review of the dissertation proposal by the facility's leadership and risk management department. In addition to permissions obtained from the healthcare facility, Walden University Institutional Review Board (IRB) approval was obtained prior to commencing data collection.

Once the study participants were selected, the medical record for each subject was reviewed for study eligibility. The medical record provided documentation regarding the medical history, and clinical care of patients, by trained healthcare providers. A manual chart review of each eligible record was conducted, and data for each study variable extracted and recorded on a standardized data collection form. A new data collection form was completed for each subject and identified using a unique study code. Demographic variables collected included age, sex, ethnicity, and length of stay. Care was taken to extract only that data necessary to answer the research questions and avoided the collection of any patient identifying information. Use of a data collection tool supports a standardized approach to data abstraction and increases the internal validity and reproducibility of the study (Gregory & Radovinsky, 2012). Data from the collection tool was inputted into an Excel spreadsheet (www.microsoft.com), creating the data set for statistical analysis. A manual process for review and data extraction was necessary as the research site used a paper-based medical record.

Instrumentation and Operationalization of Constructs

Instrumentation

Patient co-morbidities and disease complications in this sample were measured using the modified Cumulative Illness Rating Scale (CIRS). The CIRS as a measure of comorbidity has been used previously in rehabilitation related research, including orthopedic, stroke and burn patient populations (Bejor, Ramella, Toffola, Comelli, & Chiappedi, 2013; Giaquinto et al., 2001). It combines two indexes, a cumulative index and a severity index (Linn, Linn & Gurel, 1968; Salvi et al., 2008). Researchers have also found the CIRS a valid and reliable tool for research use (de Groot, Beckerman, Lankhorst, & Bouter, 2003). The CIRS rates 13 items organized by body system, and uses a 5-point severity rating, ranging from no impairment (0) to extremely severe impairment (4). Summing of all items provides an overall impairment measure. Limitations with this scale include the element of clinical judgment in assigning severity scores. However, having defined parameters can improve the reliability of severity scoring.

The severity of diabetes disease was measured using the Diabetes Complications Severity Index (DCSI) (Young et al., 2008). This 13-point complication index provides a measure of risk for adverse diabetes outcomes using the type and number of complications present (Young et al., 2008). Complications included in the DCSI are cardiovascular disease, metabolic, nephropathy, neuropathy, peripheral vascular disease, retinopathy, and stroke. The DCSI was developed using laboratory data and ICD-9

codes, with each complication group categorized into three levels (no abnormality = 0, some abnormality = 1, severe abnormality = 2) depending on the presence and severity of the complication. The DCSI was developed and validated using 4229 participants enrolled in a larger longitudinal prospective population-based cohort in the U. S. (Young et al., 2008). The DCSI was selected for this study as it specifically measures the severity of complications in a diabetic population and addresses a broad range of complications associated with the disease.

A third instrument used to evaluate the functional independence of patients admitted to AR was the Functional Independence Measure (FIM). In the U.S., the FIM provides both a measure of disability at admission and the functional gains following inpatient medical rehabilitation. Developed in the 1980's, the FIM is a product of the American Academy of Physical Medicine and Rehabilitation and the American Congress of Rehabilitation Medicine. The FIM software is available and licensed through Uniform Data System (UDS) for Medical Rehabilitation (www.udsmr.org). The extensive use of the FIM in the U.S. is in part due to the quality reporting requirements for inpatient rehabilitation facilities receiving reimbursement through CMS (Granger, 2013). Documentation of the admission and discharge FIM is recorded in the medical record for later extraction and upload to the UDS database.

The FIM instrument consists of 18 items; thirteen items measure motor tasks and five items address cognition (Rehabilitation Institute of Chicago [RIC], 2013). The patient's level of independence is evaluated by certified clinicians. The measure of independence is, based on an individual's ability to complete defined tasks. Tasks are

rated on a 7-point ordinal scale, where 1 is complete dependence requiring total assistance and 7 is complete independence. The level of function is calculated from the total score which ranges from a minimum score of 18 to maximum score of 126 (RIC, 2013). The FIM assessment is conducted at admission and repeated at discharge.

The FIM has been shown to have high internal consistency and validity across a range of rehabilitation diagnoses, with strong construct validity (RIC, 2013). Dodds and Colleagues (1998) evaluated internal consistency for a general rehabilitation population, reporting an admission FIM using Cronbach's α of .93, and a discharge FIM of α = .95. More recent evaluation of relatability and validity of the FIM in rehabilitation burn patients reported overall Cronbach's α of .96 for motor scales and .97 for cognitive scales, and strong construct validity scalability coefficients > 0.5 (Gerrard et al., 2013). Although studies indicate strong internal consistency, variability in routine use among personal, and the potential for missing data may reduce the internal validity.

Operationalization of Variables

The following table (Table 2) describes each of the variables, the level of measurement, and how each variable is operationalized.

Table 2

Operationalization of Study Variables

Variable	Type of Variable	Operational Definition	Values
CDI	DV	Positive assay or PCR for *C. difficile* toxin laboratory results	1 = Yes 0 = No
Diabetes	IV	Documentation of diabetes in the admission H & P	1 = Yes 0 = No
Admission diagnosis	IV	Rehabilitation admission diagnosis group as defined by CMS	1 = stroke, 2 = spinal cord injury, 3 = multiple trauma, 4 = brain injury, 5 = amputation, 6 = burns, 7 = lower limb fractures, 8 = complex orthopedic conditions, 9 = musculoskeletal, 10 = neurological disorders, 11 = debilitation
Age	IV	Age of participant at the time of admission.	Minimum value =19
Sex	IV	Documented sex	1 = Female 2 = Male
Ethnicity	IV	Documented ethnicity	1 = Caucasian 2 = Hispanic 3 = Black/African American 4 = Asian 5 = Native Hawaiian or Other Pacific Islander 6= American Indian, 7 =Other Blank = unknown; Missing
Antibiotics	IV	Documentation of antibiotics received by participants in prior 30 days before discharge	1 = Yes 0 = No
Height	IV	Documented height on admission (Used to calculate BMI variable)	Continuous variable in inches

Variable	Type of Variable	Operational Definition	Values
Weight	IV	Documented weight at time of admission (Used to calculate BMI variable)	Continuous variable in pounds
BMI	IV	Body mass index, calculated from documented height (inches) and weight (pounds)	1 = Underweight = <18.5 2 = Normal weight = 18.5–24.9 3 = Overweight = 25–29.9 4 = Obesity = BMI of 30 or greater
Comorbidities	IV	Other disease states documented in the admission record	Nominal
Cumulative Illness Rating Scale (CIRS)	IV	Comorbidities assessed by body system to Provides a measure of whole person impairment based on the sum of 13 system items	Score range from 0 to 52
Diabetes Complication Severity Index score (DCSI)	IV	Evaluates presence and severity of diabetes related complications: Retinopathy, Nephropathy, Neuropathy, Cerebrovascular, Cardiovascular, Peripheral vascular disease, Metabolic	Score range 0 to 13
Diabetes Control	IV	Prescribed method of controlling blood glucose levels	1 = diet 2 = oral 3 = insulin 4 = both insulin and oral
Tube feeding	IV	Presence of a feeding tube	0 = No 1 = Yes
FIM	IV	Functional Independence Measure assessed on admission	Scored18 to 126
PPI	IV	Documentation of Proton pump inhibitor drug administered in prior 30 days before discharge	0 = No 1 = Yes

Note. DV = dependent variable; IV = independent variable

Data Analysis Plan

IBM SPSS Statistics [Version 23.] software was used to conduct all analysis of the data. The data was cleaned and frequencies examined to identify outliers. For variables with outlying values, the associated data collection form was reviewed for errors in data entry and corrected. Distribution of continuous variables was examined for assumptions of a normal distribution. Data cleaning techniques to limit the effect of potential errors included replacing outlying values with the next highest score that is not an outlier (Field, 2013). This method avoided deletion of data from the analysis and thereby reduction of the sample size. One record was removed from the dataset due to the substantial number of variables with missing data.

Research Questions

Research Question 1: Is there any relationship between diabetes and CDI among hospitalized patients in the acute rehabilitation (AR) setting?

Research Question 2: Are modifiable environmental (antimicrobial and medication exposures) and host characteristics (behaviors, BMI, diabetes management) associated with CDI among hospitalized diabetics in the AR setting?

Statistical Tests and Procedures

Descriptive statistics were measured and examined to describe characteristics of the sample. The distribution of continuous variables was assessed using measures of central tendency and dispersion including the mean and standard deviation. Categorical data was presented as proportions. Differences between groups were tested using the independent t-test. Had data not followed a normal distribution, non-parametric tests

such as the Mann-Whitney U or Wilcoxon Rank Sum test would have been employed. Categorical variables were analyzed using Person's Chi-square ($\chi 2$) to measure the association between two groups.

Exploratory analysis of the data included evaluating variable frequencies, assessment of interactions between the exposure variable and covariates, and assessment of potential confounders. Continuous independent variables were assessed for linearity and multicollinearity. In response to the small fixed sample size, independent variables were transformed into dichotomous variables. This decision was made following review of the cross-tabulated frequencies to ensure the assumption of expected frequencies was not violated with all cells having a minimum frequency of five. Assessment of effect modifiers and confounders was based on analysis of the literature presented in chapter 2.

Research Question 1

To test the relationship between diabetes and CDI Pearson's chi-square test was conducted. To adjust for potential confounding variables, hierarchical multiple logistic regression modeling was used to test the study hypotheses. Hierarchical backward elimination was used (Kleinbaum & Klein, 2010) to determine the best estimate of the relationship. The initial model (Table 5) included all potential confounding variables and the effect modifying term to create a baseline model for comparison from which to assess which variables could be eliminated from the final model. To determine the best fitting model variables were excluded in turn from the model and model refitted. Initial models included all covariates. Only those risk factors found significant ($p \leq 0.05$) or deemed relevant based on previous research were retained in the final models. Results of both

bivariate and multivariate regression models are reported as odds ratios. Changes to the exposure variable, diabetes, were assessed for change in odds ratio and precision as noted by 95% confidence interval. Null hypothesis testing was set at the 5% probability level (p-value ≤ 0.05), two-tailed. Estimates of population parameters had a 5% margin of error, and are reported as 95% confidence intervals.

Research Question 2

Multivariate logistic regression was used to examine the second research question. The total sample was split to include only those with diabetes in the regression analysis. Variables excluded from the analysis include age, sex and ethnicity as these are non-modifiable host characteristics. Also eliminated were exposures such as having a feeding tube, having had gastric surgery. The health-status variable FIM score was also excluded, as deficits in functional status are justification for admission to an AR facility. Variables retained for inclusion were antibiotic, and PPI exposure, BMI as a potential indicator of nutritional status, CIRS as this instrument included host behaviors related to alcohol, substance and tobacco abuse in scoring criteria. Variables specific to the diabetic population, diabetic severity index and diabetic medications were included as these are reflective of disease management and monitoring.

Backward hierarchal logistic regression was conducted assess for potential confounders. Because no primary exposure was identified, and evidence of potential confounding present, all variables were inputted into the final model for analysis. Null hypothesis testing was also set at the 5% probability level (p-value ≤ 0.05), two-tailed

and estimates of population parameters had a 5% margin of error, and reported as 95% confidence intervals.

Threats to Validity

External Threats

Potential threats to validity included both external and internal sources (Frankfort-Nachmias & Nachmias, 2008). External sources of bias include unknown differences between cases and the controls. Such differences can limit the generalizability of findings to other population groups beyond the study sample. Unrecognized threats impacting external validity can lead to incorrect conclusions and inferences from the sample data to different population groups, settings, or temporal situations (Creswell, 2008). For this study, potential threats limiting the generalizability of the results include selection bias due to the type and location of the healthcare facility, and the study period (Creswell, 2008; Burns & Grove, 2005). Efforts to minimize these potential threats included avoiding inferences beyond those groups included in the sample and within the specific healthcare setting. For example, extending claims beyond the AR hospital setting. Also, endemic strains of *C. difficile* or the emergence of new strains may limit generalizations to other geographic regions or time frames.

Internal Threats

Internal validity describes the exclusion of rival explanations for the identified association between variables (Frankfort-Nachmias & Nachmias, 2008). Factors that pose a threat to the internal validity of this study come from errors introduced during the study design, conduct, or analysis process (Rothman, Greenland, & Lash, 2008). Specific

internal validity threats include uncontrollable differences between the cases and controls during the sample selection process. Measures used to reduce this risk included drawing the control group from the same population as cases during the same time frame. Other threats include historical events occurring during the study period (Frankfort-Nachmias & Nachmias, 2008) such as changes in *C. difficile* testing methods, or testing recommendations, which can impact the effect of the relationship between variables. Additionally, the presence of confounding variables can distort the association between diabetes, the independent variable, on the outcome of interest. Unknown or extraneous variables not captured in the analysis dataset could have a confounding effect, leading to over or underestimation of the effect size (Rothman, Greenland & Lash, 2008). Information bias is another internal validity threat resulting from the misclassification of exposure or diagnosis (Rothman, Greenland, and Lash, 2008; Szklo & Nieto, 2014). The use of secondary data can increase this threat due to unknown errors in documentation, administrative coding, or missing information.

Additional threats to validity include drawing inaccurate conclusions about the data (Creswell, 2009). Threats associated with statistical validity include inadequate sample size, where the available sample size, does not provide adequate power to detect an effect, increasing the risk of a type 2 error (Ellis, 2010). Calculating the study power a priori can mitigate this risk by adjusting other associated parameters such as increasing the sample size or the effect size. Imprecise variable definitions and measures can also pose a validity threat (Creswell, 2008). Careful consideration and documentation of

variables, including variable definitions, scales of measurement, and appropriate selection of statistical tests reduce the risk of erroneous conclusions.

Ethical Procedures

Protecting the anonymity and confidentiality of personal health information was of paramount concern in this case-control study. Ethical considerations specific to this research study included the type of personal health information collected and the safeguarding of sensitive health information during the data collection process. These concerns included determining how best to protect the privacy and dignity of discharged patients (Frankfort-Nachmias-Nachmias, 2008; Santelli, 2013). Formal approval to conduct this research study was granted by the Walden University IRB (Approval number 04-25-17-0379668). The IRB application included a signed Data Use Agreement from the research site authorizing the collection and analysis of their data.

This study utilized archival data located in the hospital medical record. Risk of patient harm associated with the collection of data for this study was minimal. This risk assessment was based on the retrospective nature of the study, with data originally collected during routine patient care. No intervention or contact with patients or clinical personal was required for data collection. In addition, no patient identifying information, such as patient name, date of birth, social security number, medical record number, or residence data was included in the final dataset. Regardless of the risk, protecting the privacy rights and respect for the patient were recognized, and measures aimed at preserving the anonymity and confidentiality of the individual's health information implemented (Frankfort-Nachmias & Nachmias, 2008). Methods employed to protect the

privacy of patient information located within the medical record included exclusion from the dataset any data that could potentially identify patients and the collection of de-identified data only. De-identification includes the removal of any personal and geographical information possibly resulting in disclosure of the patient's identity and includes administrative data such as hospital episode numbers. Other measures to protect patients included reducing the risk of data linking by separating the initial list of discharged patients which contained hospital episode numbers and the final dataset. Limiting the collection of information to only that necessary to answer the research question and aggregating the data for analysis also increased adherence to the ethical use of health information.

Professional and ethical conduct across all aspects of the research process is essential to protect the privacy of patients and the organizations in which research is conducted. Ethical behavior is a direct concern when research is done in one's professional workplace. Conducting research in such settings can introduce issues related to bias, perceived coercion, and breaches of confidentiality. Measures to limit these risks in this study included the use of a secondary data source, and maintaining a clear separation of clinical/professional and investigator roles. Separation of roles included collecting data outside of scheduled work hours. To avoid potential and actual breaches of confidentiality, all chart review was conducted in a private area and limited to only those sections of the record relevant to the variables of interest.

Protecting confidential data and maintaining its integrity requires measures to securely manage and store the collected data both electronically and in hard copy. The

dataset is stored electronically on a password-protected portable hard drive. A single backup copy of the dataset is stored in a locked cabinet. Both the hard drive and backup storage devices will be maintained for at least five years as required by Walden University. The dataset does not contain identifying information. Each study record was assigned a unique identifier code. Once the dataset was completed, the master list which included hospital encounter numbers was destroyed. The use of a master list containing the encounter number was necessary to generate the list of discharged patients and to locate the medical charts of the sample for manual review. This master list was critical as the research site did not have an electronic medical record, instead, the facility used a paper documentation system. Following patient discharge, the medical record is electronically scanned for archival storage. During active data collection, the master list provided the only linkage to the dataset, with access limited to the researcher.

Summary

A case-control study design was selected to evaluate an association between diabetes and CDI among AR patients. In this study, the dependent variable is CDI and the independent variable, diabetes. The data analysis plan was based on a fixed number of available cases, with two controls identified for each case. Although the selection of cases was drawn from all available CDI discharges during the study period, the controls were randomly selected from non-CDI discharges within the same time-period. The medical record of discharged patients meeting the inclusion criteria provided the secondary data for the study. Data collection activities included a review of the medical

record and subsequent extraction of select information necessary to measure the variables, and construction of a de-identified dataset.

The use of a case-control design poses a risk for selection and information bias. Both forms of bias can threaten the internal validity of the study. Efforts to minimize selection bias included the random sampling of controls, and selecting controls from the same population that produced the CDI cases. Use of a standardized data collection tool and a documented process for addressing missing data also helped control for information bias. Another potential risk to validity is the effect of confounding variables. Use of multivariate logistic regression allowed for controlling of covariates within the analysis, as a means of addressing the threat of confounding variables.

This third chapter describes the data analysis plan used to answer each one of the research questions and test the study hypothesis. This plan included a description of the study sample and the statistics used to compare cases and controls. Bivariate and multivariate logistic regression models were used to evaluate the relationship between diabetes and CDI and to identify modifiable risk factors. Charts, tables, and narrative are used to summarize the results of this study.

Ethical considerations are a critical element of any research study. For this dissertation research, permission was granted by Walden University IRB. In addition, authorization to access the medical records of discharged patients at the proposed research site was given by the facility CEO. Measures to protect the privacy of patient information included the purposeful extraction of data to exclude any patient identifying data, the secure storage of the dataset, and the aggregate analysis of data.

Chapter 4: Results

Introduction

The purpose of this research study was to evaluate the association between diabetes and CDI. Specifically, to assess if there is a relationship between diabetes and CDI among hospitalized patients in the acute rehabilitation (AR) setting and if are there any modifiable environmental and host characteristics associated with CDI among hospitalized diabetics in this select setting. This chapter describes the sample population, and present results of the multiple logistic regression analysis used to answer the aforementioned research questions.

Results

Sample Characteristics

Participants age ranged from 21 to 97 years with a negatively skewed distribution (Figure 3.). BMI values fell between 13.7 to 59.9, with positive skew and leptokurtic distribution (Figure 4.). Both CIRS and FIM showed normal distribution. Among those with diabetes, the DCSI score ranged from 0 with no complications to a score of 13; distribution had a positive skew and negative kurtosis. The majority of those with diabetes managed their disease with insulin (16%) or a combination of oral and insulin therapies (13%).

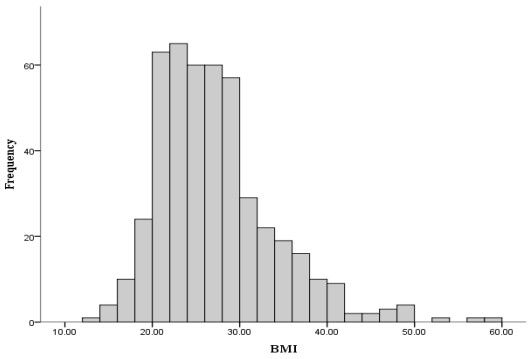

Figure 3. Age distribution and frequency of age by years.

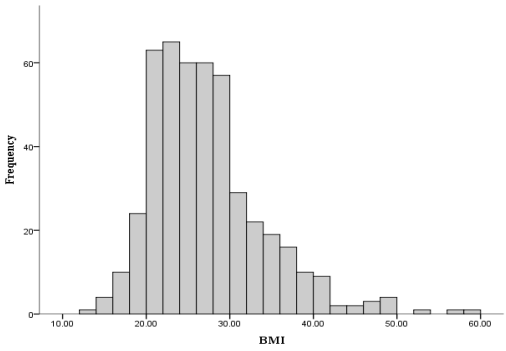

Figure 4. Distribution and frequency of sample BMI.

The sample available for analysis was predominately female (51.8%) with a mean age of 68 years (Table 3). Across both cases and controls, most participants were Caucasian (59.4%), Hispanic/ Latino (28.3%), Native Americans (9.5%). Black/African Americans (1.9%) and Asian (0.8%) were in the minority. The most frequent diagnosis among patients admitted to the AR facility was orthopedic conditions (28.3%), followed by stroke and debilitation, with each accounting for 17% of the sample. Those categorized as other (10.6%) included patients admitted with arthritis, cardiac or pain syndrome diagnoses. Among those with CDI, debilitation was the most frequent diagnosis (29.1%), while for controls, orthopedic conditions (30.5%) the most common.

Table 3

Characteristics of Sample Population by Outcome Variable

Characteristics	Total Sample (N = 473)	Cases (n = 102)	Controls (n = 371)	p-value (95% CI)
Age, years, mean (SD)	68.17 (14.21)	68.06 (13.94)	68.20 (14.30)	.931 (-2.99, 3.26)
Sex (%)				.219
Female	245 (51.8)	47 (46.1)	198 (53.4)	
Male	228 (48.2)	55 (53.9)	173 (46.6)	
Race/ Ethnicity (%)				.756
Caucasian	281 (59.4)	66 (64.7)	215 (58.0)	
Hispanic	134 (28.3)	27 (26.5)	107 (28.8)	
African American	9 (1.9)	1(1.0)	8 (2.2)	
Asian	4 (.8)		4 (1.1)	
AI/AN	45 (9.5)	8 (7.8)	37 (10.0)	
BMI, mean (SD)	27.20 (6.75)	26.32 (5.84)	27.45 (6.97)	.136(-.36, 2.61)
Diabetes, yes (%)	176 (37.2)	46 (44.7)	131 (35.3)	.107
Admit Diagnosis (%)				.001*
Stroke	81 (17.1)	11 (10.8)	70 (18.9)	
Spinal Cord	31 (6.6)	6 (5.9)	25 (6.7)	
Multiple Trauma	6 (1.3)	2 (2.0)	4 (1.1)	
Brain Dysfunction	38 (8.0)	6 (5.9)	32 (8.6)	
Amputation	28 (5.9)	11(10.8)	17 (4.6)	
Burns	1 (.2)		1 (.3)	
LE Fracture	1 (.2)	1 (1.0)		
Orthopedic Cond.	134 (28.3)	20 (19.6)	114 (30.7)	
Neurological	22 (4.7)	3 (2.9)	19 (5.1)	
Debilitation	81 (17.1)	30 (29.4)	51 (13.7)	
Other	50 (10.6)	12 (11.8)	38 (10.2)	
Prior Location (%)				<.001*
Acute Care	426 (90.1)	82 (80.4)	344 (92.7)	
Home	7 (1.5)		7 (1.9)	
Long-term Acute	33 (7.0)	16 (15.7)	17 (4.6)	
Nursing Home	7 (1.5)	4 (3.9)	3 (.8)	
CIRS, mean (SD)ǂ	17.97 (5.32)	19.83 (4.81)	17.46 (5.35)	<.001* (-3.47, -1.30)

Characteristics	Total Sample (N = 473)	Cases (n = 102)	Controls (n = 371)	p-value (95% CI)
DCSI, mean (SD) †	3.64 (3.17)	3.84 (3.12)	3.57 (3.19)	.621 (-.136, .811)
FIM, mean (SD)	82.61 (21.84)	76.73 (21.47)	84.23 (21.69)	.002* (2.75, 12.26)
Antibiotics, yes (%)	315 (66.6)	84 (82.4)	231(62.3)	<.001*
PPI, yes (%)	205 (43.3)	60 (58.8)	145 (39.1)	<.001*
Tube Feeding, yes (%)	39 (8.2)	15 (14.7)	24 (6.5)	.013*
GI Surgery, yes (%)	11 (2.3)	7(6.9)	4 (1.1)	.003*
Diabetes Therapy (%)†				.047*
Diet	18 (10.3)	4 (8.9)	14 (10.8)	
Insulin	78(44.6)	27 (60.0)	51 (39.2)	
Oral	62 (35.4)	9 (20.0)	53 (40.8)	
Oral & Insulin	17 (9.7)	5 (11.1)	12 (9.2)	

Note. *Statistically significant at p-value ≤ 0.05, two-tail; CI = confidence interval
† Variable includes only those with a diagnosis of diabetes at time of admission to AR facility.
ǂ Levene's Test for Equality of variance significant (p-value < 0.05) values reported do not assume equal variance.

Differences between groups were tested using the independent t-test for continuous variables and Fisher's exact test for categorical variables. Ninety percent (p-value < 0.001) of patients transferred from acute care settings, and seven percent from long-term acute care facilities (LTAC). Comparisons between acute care and other healthcare settings for CDI frequency, found statistically significant differences between both LTAC (X^2 (1) = 15.59, p = <0.001) and nursing home settings (X^2 (1) = 6.21, p = 0.03) as prior locations. Notable differences (p-value ≤ 0.05) were also found among variables related to exposure and health status. Comparison of means between cases and controls found differences between CIRS and FIM scores with CDI cases having a higher average CIRS score (m = 19.83) compared to those who were not diagnosed with CDI (m

= 17.46). Patients with CDI (n = 102) were found to have lower mean FIM scores (m = 76.73) indicating less functional independence, compared to the control group (m = 84.23). Fisher's exact test was used to evaluate differences in categorical variables between cases and controls, with differences (p-value <0.05) noted for prior exposure to antibiotics, protein pump inhibitors (PPI), the presence of a feeding tube, GI surgery within 30 days of admission, admission diagnosis, and prior location. Similar frequencies between the two groups were found among host characteristics of age, gender, and ethnicity. No statistically significant differences were also noted among the health status variables body mass index (BMI), and diagnosis of diabetes.

For continuous variables, all interactions tested were found non-significant (p-value > 0.05) indicating that the assumption for linearity was met. Assessment of collinearity found tolerance values less than 0.1 and variance inflation factor (VIF) less than 10, suggesting no violation of this assumption. An interaction between age and diabetes, with differences in effect size, was found to exist between those aged 65 and younger and those older than 65 years (Table 4).

Table 4

Observation of Age as an Effect Modifier

	≤ 65 Yrs.			>65 Yrs.		
Variable	*OR*	*p*-value	95% CI	*OR*	*p*-value	95% CI
Diabetes	2.20	.032	1.07, 4.52	1.12	.708	.631, 1.97

Note. Statistically significant at p value ≤ 0.05, two-tail; CI = confidence interval

Research Question 1 and Hypothesis

Research Question: Is there any relationship between diabetes and CDI among hospitalized patients in the acute rehabilitation (AR) setting?

H_o1: There is no relationship between diabetes disease and CDI among patients in the AR setting.

$H_1 1$: There is a significant relationship between diabetes and CDI among patients in the AR setting.

Thirty-six percent of the sample was admitted to the AR hospital with a diagnosis of diabetes. Results of the Pearson's chi-square test found no association (X^2 (1) = 2.66, p = 0.10) between diabetes and CDI. The crude odds ratio (OR = 1.45), as a measure of effect, suggested those with diabetes were 45% more likely to develop CDI than non-diabetics. However, this finding was not statistically significant (p = 0.10; 95% CI [0.93, 2.26]). Evaluation for the presence of effect modifiers influencing the relationship between diabetes and covariates found age to modify the relationship between diabetes and CDI, evidenced by increasing both the odds ratio and the statistical significance of the association (table 4).

To determine the effect of potential confounding on the relationship multivariate logistic regression modeling was conducted. Variables selected for inclusion were those identified from bivariate logistic regression to have a statistically significant (p-value ≤ 0.05) association with CDI, and those considered relevant risk factors were included: age, gender, ethnicity, BM, CIRS, FIM, admission diagnosis group, prior location, antibiotics, PPI, feeding tube, GI surgery, and age x diabetes interaction (Table 5).

Table 5

Full Logistic Regression Model Containing All Potential Confounding and Interaction Variables

							95% CI	
Variable	*B*	*SE*	Wald	*df*	*p*-value	*OR*	Lower	Upper
Diabetes	1.075	.473	6.047	1	.014*	2.930	1.244	6.902
Age >65	.409	.348	1.380	1	.240	1.505	.761	2.976
Male	.776	2.53	1.189	1	.275	1.318	.802	1.166
Caucasian	.452	.266	2.878	1	.090	1.571	.932	2.648
BMI >25	-.571	.257	4.034	1	.045*	.596	.360	.988
CIRS	.018	.029	.37 1	1	.542	1.018	.962	1.077
FIM	-.015	.006	5.543	1	.019*	.986	.974	.998
Admit Group: Debility	.383	.330	1.348	1	.246	1.467	.768	2.802
Acute Care Loc:	.858	.398	4.645	1	.031*	2.358	1.081	5.143
Antibiotic	.987	.306	10.44 4	1	.001*	2.684	1.475	4.886
PPI	.416	.255	2.655	1	.103	1.515	.919	2.498
Feeding Tube	.273	.425	.413	1	.521	1.314	.571	.3024
GI Surgery	1.664	.687	5.869	1	.015*	5.280	1.374	20.293
AGE*Diabetes	-.930	.521	3.191	1	.174	.394	.142	1.095
Constant	-1.739	.849	4.196	1	.041	.176		

Note. Statistically significant t at *p*-value ≤ 0.05, two-tail; CI = confidence interval

A hierarchical backward elimination modelling assessment found the variables gender and having a feeding tube to have negligible effect as potential confounders and were removed from the final model. Although, the CIRS variable had the least significance, having this variable in the model provided a narrower confidence interval and was retained in the final model (Table 6). In the final model, having had GI surgery

in the 30 days before admission was excluded due to the imprecise confidence interval, 95% CI [1.37, 20.29], likely resulting from the small number of patients.

Table 6

Final Hierarchical Multiple Logistic Regression Model Controlling for Confounding and Interaction Variables

							95% CI	
Variable	*B*	*SE*	Wald	*df*	*p*-value	Exp(*B*)	Lower	Upper
Diabetes	.929	.428	4.703	1	.030*	2.531	1.093	5.858
Age: >65	.327	.340	.924	1	.366	1.387	.712	2.700
Caucasian	.389	.261	2.214	1	.137	1.475	.884	2.461
BMI: ≥ 25	-.494	.252	3.841	1	.050*	.610	.373	1.000
CIRC	.031	.028	1.268	1	.260	1.032	.977	1.090
FIM	-.015	.006	6.570	1	.010*	.985	.973	.996
Acute Care Loc.	.799	.383	4.351	1	.037*	2.223	1.049	4.709
Admit Group: Debility	.420	.322	1.696	1	.193	1.522	.809	2.863
Antibiotic	1.046	.299	12.207	1	<.001*	2.846	1.583	5.116
PPI	.493	.250	3.879	1	.049*	1.637	1.002	2.672
MD*Age	-.855	.513	2.776	1	.096	.425	.155	1.163
Constant	-2.099	.832	6.369	1	.012	.123		

Note. Nagelkerke R Square =.181. * statistical significance *p*-value ≤ 0.05, two-tail; CI = confidence interval

After controlling for potential confounders, the sample of acute rehabilitation patients with diabetes had 2.53 greater odds of developing CDI compared to those without diabetes ($p = 0.03$, 95% CI [1.09, 5.86]). Including the variable GI surgery in the

past 30 days prior to admission increased the odds ratio but reduced estimate precision (*OR* = 2.8, Wald = 5.689, $p = 0.017$, 95% CI [1.20, 6.61]). Based on these findings, the null hypothesis that there is no association between diabetes and CDI was rejected in favor of the alternate hypothesis that there is an association between diabetes and CDI after controlling for race, BMI, CIRC, FIM, coming from an acute care location, debility admitting diagnosis group, and exposure to antibiotic and PPI medications.

Research Question 2 and Hypothesis

Research Question 2: Are modifiable environmental (antimicrobial and medication exposures) and host characteristics (behaviors, BMI, diabetes management) associated with CDI among hospitalized diabetics in AR settings?

H_o2: There is no relationship between selected modifiable variables and CDI among diabetic patients in the AR setting.

H_12: There is a relationship between modifiable variables and CDI among diabetic patients in the AR setting.

Descriptive statistics to explore differences between those with diabetes and non-diabetics are presented in Table 7. Several statistically significant differences were noted with a higher percentage of Native Americans (15.9% vs. 5.7%, $p = 0.003$) having a diagnosis of diabetes. Differences were also noted amongst Hispanics who also had a higher proportion of diabetes (34.1% vs. 24.9%, $p = 0.032$) and Caucasians who had higher numbers of non-diabetics (67.7% vs. 45.5%, $p < 0.001$). No differences were found for African Americans or Asian ethnicities. Differences between groups were also

found for BMI, admission diagnosis, CIRS. No differences were found between groups for antibiotic or PPI exposure, FIM score, prior location, feeding up or GI surgery.

Table 7

Characteristics of Sample by Exploratory Independent Variable

Characteristics	Total Sample (N = 473)	Diabetes (n =176)	No Diabetes (n = 297)	p-value (95% CI)
Age, years, mean (SD)	68.17 (14.21)	68.35 (12.33)	68.06(15.24)	.833 (-2.94, 2.37)
Sex (%)ǂ				.634
Female	245 (51.8)	94 (53.4)	151 (50.8)	
Male	228 (48.2)	82 (46.6)	146 (49.2)	
Race Ethnicity (%)				< .001*
Caucasian	281 (59.4)	80 (45.5)	201 (67.7)	
Hispanic	134 (28.3)	60 (4.1)	74 (24.9)	
Black/AA	9 (1.9)	5 (2.8)	4 (1.3)	
Asian	4 (.8)	3 (1.7)	1 (0.3)	
AI/AN	45 (9.5)	28 (15.9)	17 (5.7)	
BMI, mean (SD)	27.20 (6.75)	29.40 (7.4)	25.92 (5.9)	<.001 (-4.71, -2.24) *
CDI, yes (%)ǂ	176 (37.2)	45 (25.6)	57 (19.2)	.107
Admit Diagnosis (%)				< .001*
Stroke	81 (17.1)	27 (15.3)	54 (18.2)	
Spinal Cord	31 (6.6)	9 (5.1)	22 (7.4)	
Multiple Trauma	6 (1.3)	3 (1.7)	3 (1.0)	
Brain Dysfunction	38 (8.0)	16 (9.1)	22 (7.4)	
Amputation	28 (5.9)	20 (11.4)	8 (2.7)	
Burns	1 (.2)		1 (0.3)	
LE Fracture	1 (.2)		1 (0.3)	
Orthopedic Cond.	134 (28.3)	32 (18.2)	102 (34.3)	
Neurological	22 (4.7)	8 (4.5)	14 (4.7)	
Debilitation	81 (17.1)	40 (22.7)	41(13.8)	
Other	50 (10.6)	21 (11.9)	29 (9.8)	
Prior Location (%)				.201

Characteristics	Total Sample (N = 473)	Diabetes (n =176)	No Diabetes (n = 297)	p-value (95% CI)
Acute Care	426 (90.1)	159 (90.3)	267 (89.9)	
Home	7 (1.5)		7 (2.4)	
Long-term Acute	33 (7.0)	14 (8.0)	19 (6.4)	
Nursing Home	7 (1.5)	3 (1.5)	4 (1.13)	
CIRS, mean (SD)ǂ	17.97 (5.32)	20.03 (4.87)	16.74 (5.20)	<.001 (-4.21, -2.34) *
DCSI, mean (SD) †		3.64 (3.17)		
FIM, mean (SD)	82.61 (21.84)	82.65 (21.30)	82.59 (22.19)	.977 (-4.15, 4.03)
Antibiotics, yes (%)ǂ	315 (66.6)	126 (71.6)	189 (36.4)	.087
PPI, yes (%)ǂ	205 (43.3)	80 (45.5)	125 (42.1)	.502
Tube Feeding, yes (%)ǂ	39 (8.2)	10 (5.7)	29 (9.8)	.166
GI Surgery, yes (%)ǂ	11 (2.3)	4 (2.3)	7 (2.4)	1.00
Diabetes Therapy (%)†				
Diet		18 (10.3)		
Insulin		78(44.6)		
Oral		62 (35.4)		
Oral & Insulin		17 (9.7)		

Note: *Statistical significant at p-value ≤ 0.05, two-tail; CI = confidence interval
† Variable includes only those with a diagnosis of diabetes at time of admission to AR facility.
ǂ Fishers Exact test

The final model (Table 8), indicate those with diabetes, when exposed to antibiotics have 4.2 times greater odds of acquiring CDI compared to those who did not receive antimicrobial therapy (OR = 4.24, p = 0.005). For patients receiving insulin the odds of diabetes were 2.6 (p = 0.015). Exposure to PPI medication increased the odds of CDI compared to diabetic patients who did not receive PPI. CIRS appeared to have a confounding effect on PPI exposure (Table 9). Overweight and obese persons had a lower risk of CDI compared to normal and underweight with each unit decrease in BMI the odds of CDI were reduced by 0.43. However, neither the relationship between PPI

and CDI or between BMI and CDI were statistically significant. Diabetes severity, measured using the Diabetes Complication Index Score was also not a significant risk factor, although less severe disease did lower the odds of CDI. However, a wide confidence interval was noted across all these variables. The analysis found antibiotic exposure (*OR* = 3.86, *p* = 0.010) and insulin therapy (*OR* = 2.56, *p* = 0.015) as modifiable risk factors for CDI. Therefore, the null hypothesis that there are no modifying factors in this population was rejected in favor of the alternate hypothesis that modifying factors are present among diabetic AR patients after controlling for BMI, DCIS, CIRS, and PPI.

Table 8

Multiple Logistic Regression Examining Modifiable Risk Factor Among Diabetics

							95% CI	
Risk Factor	*B*	*SE*	Wald	*df*	*p*-value	Exp(*B*)	Lower	Upper
Antibiotic	1.352	.527	6.579	1	.010*	3.867	1.376	10.869
PPI	.612	.400	2.338	1	.126	1.844	.842	4.041
BMI ≥ 25	-.561	.405	1.922	1	.166	.570	.258	1.262
CIRS	.037	.045	.678	1	.410	1.038	.950	1.135
Insulin	.941	.385	5.961	1	.015*	2.563	1.204	5.456
DCIS	-.041	.066	.376	1	.540	.960	.843	1.093
Constant	--3.079	1.046	8.655	1	.003	.046		

Note. Hosmer and Lemeshow Test: X^2 (8) = 7.524 (*p*-value = 0.481); Nagelkerke R square = .174; * statistically significant at *p*-value ≤ 0.05, two-tail; CI = confidence interval.

Table 9

Observed Effect of CIRC on Logistic Regression Model Examining Modifiable Risk Factor Among Diabetics

	Adjusted Model with CIRS				Adjusted Model without CIRS			
			95% CI				95%CI	
Risk Factors	*OR*	*p*-value	Lower	Upper	*OR*	*p*-value	Lower	Upper
Antibiotics	3.867	.010	1.376	10.869	3.748	.012	1.342	10.469
PPI	1.844	.126	.842	4.041	2.076	.051	.997	4.325
BMI >25	.570	.166	.258	1.262	.553	.141	.251	1.218
Insulin	2.563	.015	1.204	5.456	.382	.012	.180	.830
DCSI	.960	.540	.843	1.093	.382	.730	.867	1.105
CIRS	1.038	.410	.950	1.135	3.748	.012		
Constant	.046	.003			.234	.036		

Note. Adjusted model without CIRS: Hosmer and Lemeshow Test: $X^2(8) = 3.83$ ($p = 0.871$); Nagelkerke R square = .169; * statistically significant at p-value ≤ 0.05, two-tail; CI = confidence interval.

Summary

The purpose of this study was to examine the relationship between diabetes and CDI and to identify any modifiable risk factors associated with CDI in the acute inpatient rehabilitation setting. This chapter presented the results of the data analysis conducted to address the two research questions related to above-noted purpose. Of the initial 7593 records identified during the study period, a total of 473 records met the inclusion criteria for analysis. Comparisons between cases and controls found differences related to admission diagnosis with cases having a higher frequency of amputation and debility, and having come from a post-acute setting. The control group had a higher frequency of antibiotic exposure. Among those with a diagnosis of diabetics, a higher percentage of

cases were prescribed insulin to manage their disease compared to oral or combination regimes. Hierarchical multivariate logistic regression conducted to evaluate the relationship between diabetes and CDI, suggested that diabetes is associated with CDI after controlling for potential confounding variables in this population. Age was identified as an effect modifier in the relationship. Results from this analysis should be interpreted with caution due to the small number of cases, the small effect size, and presence of interacting variables.

Findings from the analysis examining modifiable risk factors among this acute rehabilitation population with diabetes found only exposure to antibiotics and insulin to have an association with CDI of statistical significance. Interpretation of these findings, including both significant and non-significant results, implications for positive social change, and future recommendations will be discussed in Chapter 5.

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction

Clostridium difficile is a leading cause of healthcare associated infection in the United States (Magill et al., 2014) and is associated with a significant health and economic burden (Desai et al., 2016; McGlone et al., 2012). Diabetes is a highly prevalent disease associated with increased healthcare utilization from disease-related complications (Zhuo et al., 2014). The purpose of this research was to evaluate the association between diabetes and the risk for CDI and to identify any modifiable risk factors specific to patients with diabetes. The study used an ecosocial theory of disease distribution as the theoretical framework. The knowledge gained from this research will increase the understanding of CDI in select healthcare populations and settings.

Our case-control study examined the relationship between diabetes and CDI among patients discharged from an acute medical rehabilitation facility. Multiple logistic regression was used to test for the association between the dependent variable CDI and the exposure variable, diabetes. Results indicated a statistically significant association between diabetes and increased odds for CDI. The study also sought to identify the presence of modifiable risk factors for CDI among diabetic patients in this healthcare setting. The results found antibiotic exposure and insulin therapy associated with an increased odds ratio for CDI in this population sample.

Interpretation of Findings

Research Question 1

Results of the analysis testing the association between diabetes and CDI found patients with diabetes had increased odds of developing CDI after controlling for confounding variables. Identifying an association between diabetes and CDI in this sample population supports previous research examining alterations and differences in the intestinal flora of persons with diabetes (Karlsson et al., 2013; Larsen et al., 2010; Qin et al, 2012a). Such differences are permissive with intestinal microbiota diversity shown among population groups attributed to variation in diet, genetic characteristics, exposures and disease states (Escobar et al., 2014). Admissions to healthcare settings, altered nutritional status, and medications have also been cited as impacting the intestinal biome (Buonomo & Petri, 2016). These factors and cumulative exposures among persons with diabetes may explain the increased odds for CDI and support previous studies suggesting susceptibility to CDI is increased among those with diabetes (Shakov et al., 2011; Tartof et al., 2014; Wenisch et al, 2012).

Exposure to antibiotic therapy in the previous 30 days at time of admission had the strongest relationship for with CDI (*OR* 2.8, $p = <0.001$, 95% CI [1.6, 5.1]). A result concurring with findings reported in the literature suggesting disruption to the intestinal microbiota leads to expansion of *C. difficile* bacteria (Becattini, Taur, & Pamer, 2016; Theriot et al., 2014). In my study, differences in the frequency of antibiotic exposure were noted in the diabetic population. Antibiotic exposures were more common among those with CDI. However, when comparing persons with diabetes to non-diabetics

(Table 7) no difference in exposure was found. Frequently of exposure to antibiotics may be related to disease states. Patients admitted to the AR setting from acute care facilities may have greater exposure to antibiotic therapy based on their state of health, medical intervention, and standard antibiotic utilization. Admission to the AR hospital setting from acute care and LTAC locations was found to increase the odds of CDI in this sample. This differs from opposite findings in the acute care literature where admission from long-term care or nursing homes is considered a risk factor (Durham et al., 2016). Possible explanations for the discrepancy in my study may indicate that a prior exposure to any healthcare setting, acute or long-term, may increase the risk for CDI, or that the duration of exposure to other healthcare settings, including the facilities underlying burden of CDI increases the risk of infection.

Antibiotic exposure could be related to the admission diagnosis, with a greater proportion of non-diabetic patients admitted following orthopedic surgery in which a single prophylactic dose of antibiotics is routinely given as part of surgical site prevention (Berríos-Torres et al., 2017; Bratzler et al., 2013). Also, patients with diabetes may have experienced longer duration or cumulative exposure to antibiotics with debilitation, the most frequent reason for admission.

Study participants older than 65 years of age were found to have an increased risk for CDI, however this finding was not statistically significant. Although, age did not have a confounding effect on the relationship between diabetes and CDI, the variable was an effect modifier of this relationship. Previous studies have found higher incidence of CDI among those of older age (Lessa, 2015; Pechal, Lin, Allen, & Reveles,2016). Non-

significant findings in this study may reflect the differences in patients admitted to the AR setting compared to acute care facilities or other geographical locations.

Research Question 2

The second research question examined modifiable risk factors associated with CDI among diabetics only. In this sub-sample of patients with diabetes, recent exposure to antibiotics (within prior 30 days) and glucose control medication (insulin therapy) were found associated with an increased risk for CDI. Exposure to antibiotics increased the odds of CDI by more than three-fold. Although there was no significant difference in the frequency of antibiotic exposure between diabetics and non-diabetics in this study, studies examining antibiotic utilization indicate that those with diabetes are more likely to receive broad spectrum antibiotics (Jenkins et al., 2014; Jääskeläinen, Hagberg, Forsblom & Järvinen, 2017) and for a longer duration of time (Jääskeläinen et al., 2017). More aggressive treatment of infection and prophylaxis use in surgical patients is likely based on previous studies linking diabetes disease to an increased risk of infection and infection related mortality (Martin et al., 2016; Magliano et al., 2015). However, such prescribing practices can lead to unnecessary exposure to antibiotics and increased risk for CDI (Stevens, 2011). Thus, efforts to reduce exposure including antibiotic selection, and minimal duration of therapy have strong potential in CDI prevention activities.

Among those on medications for glucose control, insulin therapy was associated with an increased risk for CDI. Recent studies have also found insulin to increase the risk of infection in hospitalized patients with diabetes, while oral antiglycemics have been found to lower the risk for CDI (Eliakim-Raz et al., 2014). The protective quality of

oral antiglycemics, has been linked to increased microbial diversity within the gut. Oral antiglycemics increase butyrate-producing organisms (Antharam et al., 2013; Zhang et al., 2017), which in turn is thought to limit available energy sources for *C. difficile* expansion. However, the overall role of oral therapies and insulin is likely confounded by factors such as therapeutic dosing, combination therapies, and the role of long-acting insulins and glucose control. It is worth considering the impact of increased monitoring and tighter control of blood glucose levels in hospitalized patients. In addition, insulin is recommended over other antihyperglycemic agents in hospitalized patients for blood glucose management (ADA, 2016), which may account for the higher insulin utilization. The CIRS index includes elements of diabetes control within the score allocation, using hemoglobin A1c results. The CIRS index provided a measure of comorbidity and included measures of behavior such as tobacco, alcohol, or other dependent behaviors. CIRS index was found to be significantly higher when compared to non-diabetic patients. However, this variable was not found to offer significant value to the model. Early evaluation of patients for resuming home regimes or appropriateness of antihyperglycemic agent could reduce insulin exposure and limit risk for CDI.

Limitations of the Study

This study is subject to several limitations including the use of a case-control design. Inherent limitations within the case-control design increase the potential for bias. Informational bias could result from differences in the quality of information within the medical record and misdiagnosis. Efforts to mitigate this risk included the use of a standardized collection tool and confirmatory review of test results for inclusion as a

case. Laboratory conformation of *C. difficile* toxin did eliminate a sizeable proportion of cases (53%) originally identified using the ICD-10 codes. It is also possible that not all cases of CDI occurred during the AR admission. Marjolein and colleagues (2012) reported the highest risk for CDI occurring within the 30 days following antibiotic exposure. Thus, cases of CDI occurring after discharge from the AR hospital but within the 30-day window were not captured for analysis.

Adherence to the inclusion criteria also impacted the final sample size available for analysis and the ability to generate adequate power to confidently accept observed differences between groups. There was also the possibility of underrepresentation of cases if patients experienced onset of symptoms post discharge. This study focused on a specific healthcare population. Therefore, findings from this study may not transfer to other healthcare settings. In addition, characteristics of the sample may reflect unique characteristics of the geographical location and patient population within the U. S., particularly characteristics related to age and ethnicity. The inability to control for all possible risk factors also limits the interpretation of the findings. Although, patient comorbidities were measured and included as covariates, the use of index scores prevented further drill down into specific behaviors or conditions, and a consideration for future studies

Recommendations

Recommendations for future research include expanding study populations to other geographical locations and healthcare settings. Using a broader population offers the potential to obtain larger samples and to compare findings between different

healthcare settings. Other recommendations based on the methodology of the current study and theoretical framework is the further exploration of the multiple pathways related to both susceptibility and resistance to CDI among patients with diabetes. Pathways related to social economic status and environmental exposures, as well as a more detailed approach in controlling for comorbidities and health-related behaviors.

Implications for Positive Social Change

There are several implications for positive social change because this study focuses on a topic important for local and national efforts in HAI prevention. The high morbidity and mortality associated with healthcare-associated CDI have led to prevention efforts becoming a public health priority at the national level (Centers for Disease Control and Prevention, 2013; Office of Disease Prevention and Health Promotion, 2016). Findings from this research have the potential to identify select population groups at risk CDI, and more importantly to identify modifiable risk factors for CDI. Understanding associations between at-risk populations, such as those with diabetes, and CDI expand what is currently known about this infection and may offer insights and opportunities for clinicians and researchers to develop targeted prevention strategies and interventions. Findings from this research have the potential improve health outcomes among those with diabetes in the post-acute healthcare settings by improving the quality and safety of healthcare delivery. Insights from this research could also impact health outcomes of diabetics by improving the quality and safety of healthcare delivery, through reinforcing the role of antibiotic stewardship programs and appropriate prescribing practices by clinicians in post-acute settings. Addressing the burden of CDI through

effective prevention efforts also has economic implications for reducing healthcare costs, both direct and indirect for the individual and healthcare facilities. In addition, improving health outcomes among those with diabetes disease also offers economic benefits for all levels of society.

Conclusion

Healthcare associated infections place a considerable burden on individuals, healthcare systems and society as a whole. HAI reduction is increasingly becoming a measure of quality care and linked to national healthcare policy. CDI has been identified as a leading cause of HAI and associated with increased morbidity and mortality. Efforts to understand the mechanisms contributing to CDI suggest disruptions to the intestinal microbiome have a key role. Increasingly research on the intestinal microbiome indicates a number of pathways or exposures over time create unique ecosystems. Differences have also been found among those with diabetes when compared to non-diabetics. Yet little research has been conducted to address CDI in the diabetic population. There is also limited research regarding CDI in the AR setting.

To my knowledge, this is the first study to examine the relationship between diabetes and CDI in the AR hospital setting. Findings from this study showed that those with diabetes in an AR hospital were more likely to develop CDI compared to non-diabetics. Risk factors sensitive to intervention were found for antibiotic and insulin exposure. The role of antibiotics as a risk factor reinforces the need for judicious use of antibiotics across the healthcare spectrum. The role of insulin as a risk factor remains unclear; however increased awareness among clinicians of the potential risk supports a

proactive approach to diabetes management in the AR setting. Additional research is needed to further our understanding of the relationship between diabetes and CDI and the factors which increase CDI susceptibility and resilience. This study advances what is currently known regarding the relationship between diabetes and CDI and moves us closer to improving healthcare outcomes.

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Footnotes

[1] From “Proximal, distal, and the politics for causation: What’s level got to do with it?” by N. Krieger, 2008, *American Journal of Public Health, 98,* p.224.

Appendix A: Permission Letter

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March 8, 2016

Kerry Flint
PO Box 2153
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Dear Kerry Flint,

This letter shall grant you worldwide non-exclusive rights and non-transferable permission to use the figure from the article indicated below in your upcoming dissertation entitled *Diabetes and Clostridium difficile Infection*. Such permission is for one-time print and electronic use only and does not include future editions/dissertations, additional printings, updates, ancillaries, derivatives, customized forms, translations, or promotional pieces. Sheridan Content Solutions must be contacted each time such new use is planned. The figure must be used as originally published with no revisions or modifications.

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Figure 1 – page 224

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Appendix B: Instrument Permissions

Fabio Salvi <f.salvi@univpm.it> Feb 3 (1 day ago)

to me

Dear Kerry,
the CIRS is free of charge and/or permission.
You can use it without further authorization.
Good luck!

Fabio Salvi, M.D.

----Messaggio originale----
Da: "Kerry Flint" <kerry.flint@waldenu.edu>
Data: 22/01/2017 23.59
A: <f.salvi@univpm.it>
Ogg: Letter requesting permission to utilize the Modified Cumulative Illness Rating Scale

Fabio Salvi, MD,
S.O.D. Clinica di Medicina Interna,
Azienda Ospedaliero-Universitaria "Ospedali Riuniti," Via Conca n. 71,
60131 Ancona, Italy.
f.salvi@univpm.it

January 22, 2017

Dear Dr. Salvi

I am a Ph.D. student in the Public Health Program at Walden University, currently working on my dissertation. I read your article "A Manual of Guidelines to Score the Modified Cumulative Illness Rating Scale and Its Validation in Acute Hospitalized Elderly Patients" published the Journal of the American Geriatric Society, in 2008. The instrument you used to measure heath status looks appropriate to measure comorbidity for my dissertation research. Therefore, I would like to request permission to utilize the Modified Cumulative Illness Rating Scale described in the article. I would appreciate if you can provide a written authorization to utilize this instrument and provide guidance on the steps to gain this permission.

Thank you for your time and consideration.

Kerry Flint

PhD Student
School Public Health
Walden University
Email: kerry.flint@waldenu.edu

To: youngb@u.washington.edu

Bessie A. Young, MD

Veterans Affairs Puget Sound Heath Care System (152E),

Epidemiologic Research and Information Center,

Seattle, WA 98108, USA

youngb@uw.edu

February 15, 2017

Bessie Ann Young

Feb 15

to me

Hi Kerry, you don't need my permission to use the DCSI-it is in the public domain. I don't have access to any of the codes for it. What we did should be listed in the paper. If you still need permission, you definitely have it. best, Bessie ----------

Bessie A. Young, MD, MPH Professor, Division of Nephrology, Dept of Medicine Section Head VA Nephrology VA Puget Sound Health Care System 1660 S. Columbian Way, RDU 111A Seattle WA, 98108 phone: (206) 277-3586 fax: (206) 764-2563

Kerry Flint <kerry.flint@waldenu.edu>

Feb 15

Kerry Flint <kerry.flint@waldenu.edu>

Jan 22

to youngb

Bessie A. Young, MD

Veterans Affairs Puget Sound Heath Care System (152E),

Epidemiologic Research and Information Center,

Seattle, WA 98108, USA

youngb@u.washington.edu

January 22, 2017

Dear Dr. Young

I am a Ph.D. student in the Public Health Program at Walden University, currently working on my dissertation. I read your article "Diabetes Complications Severity Index and Risk of Mortality, Hospitalization, and Healthcare Utilization" published in the American Journal of Managed Care in 2008. The instrument you used to measure diabetes severity looks appropriate to measure the disease for my dissertation research. Therefore, I would like to request permission to utilize the Diabetes Complications and Severity Index (DCSI) described in the article. I would appreciate if you can provide a written authorization to utilize this instrument and provide guidance on the steps to gain this permission.

Thank you for your time and consideration.

Kerry Flint

Ph.D. Student

School of Public Health

Walden University

Email: kerry.flint@waldenu.edu