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Risk Factors and Outcomes for Bloodstream Infections Among Patients with Skin Infections

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Abstract

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PharmD, Wayne State University, 1981

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Dissertation Submitted in Partial Fulfillment

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Doctor of Philosophy

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Abstract

Acute bacterial skin and skin structure infections (ABSSSI) are common infections within the local community, and they result in higher morbidity and health care costs. While risk factors for skin and soft tissue infections have been previously evaluated, risk factors associated with secondary bloodstream infections (BSI) has not been investigated, especially in an intercity patient population with limited health care resources. In this case control investigation, 392 patients consisting of 196 cases (ABSSSI + BSI) and 196 controls (ABSSSI) were investigated to determine risk for BSI. Both sociodemographic and underlying conditions were evaluated. According to bivariate analysis of cases and controls, individuals with ABSSSI + BSI were significantly older ($p < 0.001$), more often male ($p = 0.008$), and had a higher percentage of abnormal symptoms, such as elevated temperature, white blood cell count, and acute renal failure on hospital admission ($p < 0.001$). Individuals with ABSSSI + BSI also had a higher percentage of chronic renal failure ($p = 0.002$), diabetes ($p = 0.005$), congestive heart failure ($p = 0.012$), intravenous drug use ($p = 0.012$), and a history of prior hospitalization ($p < 0.001$). Several of these factors remained statistically significant by logistic regression analysis, such as male gender *aOR* of 1.85, 95% CI 1.11-3.66; acute renal failure *aOR* 2.08, 95% CI 1.18-3.67; intravenous drug use *aOR* 4.38, 2.22-8.62; and prior hospitalization *aOR* 2.41, 95% CI 1.24-4.93. This study contributes to positive social change by identifying patient characteristics that are associated with ABSSSI-related BSI, thus providing health care providers the ability to improve patient outcomes in this underserved patient population.

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Dedication

This dissertation is dedicated to my family for their unwavering support over the last 5 years. I would like to thank them for all of the time I needed to work on this degree program including the late evenings, early mornings, and time spent away from family outings and vacations. This was especially true in the case of my wife who despite these hardships was always encouraging and supportive of me. I will always be grateful to them for allowing me to achieve this personal goal.

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Chapter 1: Introduction to the Study

Introduction

Acute bacterial skin and skin structure infections (ABSSSI) are complicated skin and soft tissue infections that are caused by bacterial pathogens including resistant bacterial organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA) that were previously susceptible to a variety of common antibiotics. The Food and Drug Administration (FDA, 2013) issued new nomenclature in an effort to define complicated skin and skin structures infections. ABSSSI are complicated skin and skin structure infections that generally require hospitalization and parenteral antibiotics and include the diagnosis of cellulitis/erysipelas, wound infection, major cutaneous abscess with an accompanying redness, or an induration or edema that extends to a minimum lesion surface area of $75cm^2$ (Moran, Abrahamian, Lovecchio, & Talan, 2013). ABSSSI are one of the most common infections in both the community and hospital settings (Amin et al., 2014; Pallin et al., 2008; Pollack et al., 2015). There are a variety of complications that can occur secondary to ABSSSI. One of the most severe complications is bloodstream infection (BSI; Lipsky, Kollef, et al., 2010; Suaya, Eisenberg, Fang, & Miller, 2013; Tattevin et al., 2012). While risk factors for ABSSSI have been well documented, there is limited information regarding risk for BSI in patients with ABSSSI.

The purpose of this study was to evaluate the risk factors associated with BSI in patients with ABSSSI who reside in intercity Detroit. Individuals living in the intercity with low socioeconomic status are likely to have poor access to health care resources and may be at a higher risk for BSI secondary to ABSSSI; this population has not been well-

studied. Evaluating this patient population for risk factors for BSI may lead to improvement in patient outcomes and potentially reduce the risk for BSI. This study may lead to positive social change because the population that was evaluated has been previously shown to be at high risk for complications and increased infection severity.

The background for the study, along with supporting evidence from the literature, is reviewed in Chapter 1. The background section is followed by the problem statement, the purpose of the study, the dependent and independent variables, and the research hypotheses. Next, the theoretical and conceptual framework is discussed followed by the nature of the study. Definitions of the primary outcome variables, study assumptions, and the scope and delimitations are also provided in this chapter. Lastly, in this chapter, I discuss the study limitations, significance of the study, and potential implications for social change consistent with the scope of the study.

Background

Skin and skin structure infection (SSSI) is a disease of the skin and is defined as an infection of the epidermis, dermis, and/or deeper subcutaneous tissues (Dryden, 2010). The Infectious Diseases Society of America classify SSSI into a mild infection consisting of cellulitis/erysipelas without a purulent focus; moderate infection consisting of cellulitis/erysipelas and systemic signs of infection; and severe infections that includes failure to respond to previous antibiotic therapy, systemic signs of infection, infection in immunocompromised patients and deeper infections involving bullae, necrotizing fasciitis, and evidence of organ dysfunction (as cited in Stevens et al., 2014). The most common SSSIs types are cellulitis and erysipelas, which are the diffuse spreading skin

infections that are not associated with a suppurative focus. Abscesses are also common and consist of a collection of pus within the dermis and deeper fascia and are often associated with inflammation and purulent discharge (Amin et al., 2014).

The number of patients diagnosed with SSSIs has been steadily increasing in the United States over the last decade (Amin et al., 2014; Itani et al., 2011; Tattevin et al., 2012). This increase in SSSIs has coincided with rising hospital admissions and complications including secondary bone and joint infections, amputations, and BSI (Ray, Suaya, & Baxter, 2013a; Suaya et al., 2013). BSIs are considered one of the most severe complications of ABSSSI as BSI carries a significant risk for morbidity and mortality (Lipsky, Kollef, et al., 2010; van Hal et al., 2012). The most common bacterial pathogen associated with BSI secondary to ABSSSI is *Staphylococcus aureus (S. aureus)*. *S. aureus* are now commonly resistant to penicillin and other beta-lactam antibiotics making it more challenging for clinicians to appropriately treat these infections. These organisms are collectively referred to as methicillin-resistant *S. aureus* (MRSA) and make up more than 50% of all *S. aureus* strains associated with infections encountered in the community (Ray, Suaya, & Baxter, 2012).

Community-associated MRSA infections (CAMRSA) are associated with ABSSSI, and the prevalence of these infections has increased over the last decade in the United States (Moran et al., 2006; Pallin et al., 2008). In a retrospective study of 133,450, Ray et al. (2012) evaluated *S. aureus* isolates obtained from patients with infections from a large U.S. integrated health care organization over the years 1998-2009. During this time period, the prevalence of MRSA infections increased from 9% to 49%

between the years of 1998 until 2005 and decreased slightly from 49 to 43% between 2006 and 2009 (Ray et al., 2012). This overall increase in MRSA was most often seen in BSI specimens and was most pronounced in individuals who were 18-49 years of age and African Americans (Ray et al., 2012). The largest increase in MRSA was observed from community-associated infections, and the increase in MRSA was disproportionately higher in African American and Hispanic American patients compared to European American patients (Ray et al., 2012). In addition, after adjusting for other demographic factors, Ray et al. found that that African Americans and individuals of low socioeconomic status were at increased risk of MRSA infection (Ray et al., 2012). The rise in MRSA infections over the last 10-15 years was largely due to the increase in CAMRSA across the United States (Moran et al., 2013). While the relationship between CAMRSA as and ABSSSI has been described, the relationship between CAMRSA and BSI has not been well characterized. In an effort to evaluate this relationship, Tattevin et al. (2012) evaluated risk factors and outcomes for 549 patients with BSI caused by epidemic MRSA strains of which 55% were CAMRSA. Although the rates of mortality between MRSA and CAMRSA strains were similar, two risk factors for CAMRSA BSI were identified: concurrent SSTI and the use of antibiotics within the previous 30 days (Tattevin et al., 2012). Interventions that could reduce SSTI caused by CAMRSA could help to reduce the prevalence and severity of CAMRSA BSI (Tattevin et al., 2012).

A gap in knowledge exists and further characterization of patients who have ABSSSI is warranted to determine the risk factors associated with BSI. In addition, there is limited to no information on the relationship of ABSSSI, BSI, and socioeconomic

status. Information derived from this study may lead to improved outcomes in a patient population at a higher risk for complications secondary to ABSSSI associated BSI.

Problem Statement

ABSSSI are one of the most common infections encountered in community and health care settings (Dryden, 2010; Edelsberg et al., 2009). These infections are associated with many complications including bloodstream infections (Bassetti et al., 2012; Klevens et al., 2007). Patients with serious ABSSSI require hospitalization. Of those hospitalized, cellulitis and abscess are the most common types of ABSSSI and accounted for as many as 597,000 admissions or 1.5% of all hospitalizations in the United States in 2006 (Itani et al., 2011). *S. aureus* is one of the most common bacterial pathogens that cause ABSSSI (Dryden, 2009). The rate of CAMRSA as a cause of increased ABSSSI has increased, accounting for over 3 million annual emergency department visits and a prevalence of over 80% in some areas of the United States (Mistry et al., 2014; Pallin et al., 2008).

Certain patient populations may be at higher risk for infectious disease complications and poor treatment outcomes (Holman et al., 2011; Khabbaz, Moseley, Steiner, Levitt, & Bell, 2014; Moore, Keruly, & Bartlett, 2012). For example, the rates of invasive community-associated MRSA infections are higher among African Americans compared to European Americans and in individuals with lower socioeconomic status in the United States (Klevens et al., 2007). In addition, investigators evaluating African Americans of low socioeconomic status have reported a higher rate of persistent infection burden, higher hospital readmission rates, and increased risk of infection complications

including sepsis severity (Acosta et al., 2013; Morris et al., 2014; Zajacova, Dowd, & Aiello, 2009).

One of the worst worrisome complications of ABSSSI is bacteremia (Bassetti et al., 2012; Lipsky, Tabak, et al., 2010). Bacteremia secondary to ABSSSI was previously reported as infrequent. However, bacteremia can occur in up to 20% of patients with severe ABSSSI (Lipsky, Tabak, et al., 2010). Because bacteremia is associated with higher rates of mortality, several investigators have attempted to identify patient characteristics that are associated with bacteremia in patients with ABSSSI (Bassetti et al., 2012; Lipsky, Kollef, et al., 2010; Shurland, Zhan, Bradham, & Roghmann, 2007). However, risk factors for bacteremia, including measures of severity of infection, have not been evaluated in African American patients with ABSSSI and low socioeconomic status in an urban setting. Therefore, this study was useful in addressing a gap in knowledge in the current literature regarding this patient population.

Purpose of the Study

The purpose of this study was to evaluate the health outcomes of patients with low socioeconomic status in an urban city environment who had ABSSSI-related *S. aureus* BSI infection. The primary aim of this investigation was to characterize and determine the risk factors for patients with ABSSSI with concomitant BSI compared to patients with ABSSSI alone admitted to the Detroit Medical Center and Henry Ford Hospital in Detroit, Michigan. A secondary aim was to determine whether race/ethnicity impacted severity of disease in patients with ABSSSI-associated BSI. While limited information is available regarding the risk for ABSSSI among minority patients, there is

no information regarding the risk for ABSSSI with concomitant BSI in this patient population (Lipsky, Kollef, et al., 2010; Ray, Suaya, & Baxter, 2013b; Suaya et al., 2013; Tattevin et al., 2012). To address this gap, a quantitative methods approach was employed. Assessments were carried out via a case-control study design. The cases consisted of patients admitted to the hospital and diagnosed with ABSSSI and *S. aureus* BSI. The controls were comparable to cases that were admitted to the hospital for the diagnosis of ABSSSI, but did not have associated BSI. The dependent variable was ABSSSI with BSI. Additional dependent variables consisted of rates of mortality, length of hospital stay, and secondary complications. The independent variables that were believed to have an impact on whether a patient had ABSSSI or ABSSSI with bacteremia included age, race/ethnicity, diabetes, cardiovascular disease, renal failure, recent hospitalization, recent MRSA infection, socioeconomic status, alteration in temperature and white blood cell count, and receipt of antibiotics in the past 30 days (Lipsky, Kollef, et al., 2010; Tattevin et al., 2012). It was anticipated that characteristics identified by this investigation would assist health care providers in improving patient outcomes in this underserved population. The secondary outcome variable was the degree of disease severity among patients with ABSSSI associated BSI. Disease severity was based on number and type of surgical interventions. Covariate variables were the level of income and education. Identifications of these factors can lead to recommendations and prevention interventions to improve the health outcomes of patients with ABSSSI in an urban environmental setting.

Research Questions and Hypothesis

This study was designed to answer the following research questions:

RQ1. Are there significant differences in clinical and socioeconomic factors between patients with ABSSSI and ABSSSI with BSI in intercity Detroit?

Subquestions for RQ1 were the following:

1. Are there significant differences in the distribution of race/ethnicity between patients with ABSSSI and patients with ABSSSI- associated BSI?
2. Are there significant differences in age between patients with ABSSSI and patients with ABSSSI-associated BSI?
3. Are there significant differences in the distribution of gender between patients with ABSSSI and patients with ABSSSI-associated BSI?
4. Are there significant differences in education between patients with ABSSSI and patients with ABSSSI-associated BSI?
5. Are there significant differences in income levels between patients with ABSSSI and patients with ABSSSI-associated BSI?
6. Are there significant differences in insurance status between patients with ABSSSI and ABSSSI-associated BSI?
7. Is the presence of a comorbid condition, namely diabetes, renal failure, or cardiovascular disease, hepatic diseases, intravenous drug use (IVDU), paraplegia, HIV/AIDS, immunosuppression (steroids, radiation, chemotherapy) associated with ABSSSI-associated BSI?

8. Is alteration of temperature and white blood cell count at baseline associated with ABSSSI-related BSI?
9. Is a recent hospitalization (i.e., within the last 180 days of the present hospitalization) associated with ABSSSI-related BSI?
10. Is a recent hospitalization for MRSA or MSSA infection (i.e., within the last 60 days of the present hospitalization) associated with ABSSSI-associated BSI?
11. Is receipt of an antibiotic within the last 30 days associated with ABSSSI-related BSI?

H_o1: There are no differences in sociodemographic and clinical factors between patients with ABSSSI and ABSSSI-associated BSI.

H_a1: Patients with ABSSSI have different sociodemographic and clinical factors compared to patients with ABSSSI-associated BSI.

RQ2. Is race/ethnicity associated with disease severity (based upon surgical interventions [e.g., incision and drainage, wound debridement, amputation]) among patients with ABSSSI-related BSI?

H_o2: Race/ethnicity associated with disease severity (based upon surgical interventions, e.g., incision and drainage, wound debridement, amputation, shock or admission to the intensive care unit [ICU]) is not different between patients with ABSSSI and ABSSSI-associated BSI.

H_a2: Race/ethnicity associated with disease severity (based upon surgical interventions [e.g., incision and drainage, wound debridement, amputation, shock, or

admission to the ICU]) is different between patients with ABSSSI and ABSSSI-associated BSI.

Theoretical and Conceptual Framework

The theoretical framework for this study was the web of causation (Krieger, 1994). The web of causation conceptual framework is used to explain the association between events, the causal agent, and the affected entity. The web of causation includes a link between a preceding event and a subsequent outcome. The web of causation theorists focus on the etiology and provide a process and an explanation for the outcome of interest (Aschengrau, 2008; Krieger, 1994). The cause is a factor that plays a role in the disease development. A disease that develops within a population can be related to many different factors including genetic defects, disease causing pathogens, and social and behavioral differences or environmental factors (Aschengrau, 2008; Center for Disease Control and Prevention [CDC], 2012; Schneider, 2011). The web of causation was used in this investigation to explore the relationship between the patient characteristics and the targeted outcome variables between individuals with ABSSSI and ABSSSI-associated BSI. This framework formed the basis for evaluating the differences and similarities between patients with ABSSSI and ABSSSI-associated BSI for characteristics including race/ethnicity; age; gender; medical insurance status; and comorbidities, such as diabetes, renal failure, and cardiovascular diseases. In addition, I measured the severity of illness by surgical intervention and complications. I explain the web of causation and its relationship to this study further in Chapter 2.

Nature of the Study

A quantitative, case-control study design was chosen to address the primary research questions in this study. Case-control designs are retrospective investigations (Hebel, 2006) that are appropriate study designs for evaluating risk factors for patients with ABSSSI versus those with ABSSSI with BSI. Risk factors for BSI in patients with ABSSSI hospitalized for skin and soft tissue infections have been previously identified (Lipsky, Kollef, et al., 2010; Suaya et al., 2013). Although identifying social and personal factors that could act as potential treatment barriers are suggested to ensure a successful patient outcome, risk factors for patients with ABSSSI-associated BSI with low socioeconomic status have not been evaluated (Bagger, Zindrou, & Taylor, 2004; Itani et al., 2011; Klevens et al., 2007; Pollack et al., 2015; Ray et al., 2012).

The patient population included in this study was recruited from the Detroit Medical Center and Henry Ford Hospital. The Detroit Medical Center is made up of nine hospitals of which five are located in midtown Detroit Michigan. These hospitals service a large group of individuals residing in intercity Detroit Michigan. The Henry Ford Hospital is a major medical center that services a large portion of the population of Detroit.

The primary outcome variable was ABSSSI-associated BSI. The secondary outcome variable was disease severity, which was measured on number and type of surgical interventions. The independent variables evaluated included age; gender; race/ethnicity; educational level; income; medical insurance status; comorbid conditions including diabetes, renal failure, and cardiovascular disease, and recent hospitalization

defined as hospital contact within the last 180 days; and MRSA infection within the last 60 days. Descriptive statistics were used to characterize controls and cases. Continuous variables were compared by a student *t* test if normally distributed and Mann-Whitney U test if the normality assumption is not met. Categorical variables were evaluated using chi-square or, as necessary, a two-tailed Fisher's exact test. Multivariable analysis was performed using multiple logistic regression models.

Definition of Terms

Acute bacterial skin and skin structure infections (ABSSSI): ABSSSIs are skin infections that include cellulitis/erysipelas, wound infection, and major cutaneous abscess. The lesion is also defined by size with a minimum surface area of 75 cm^2. ABSSSI excludes burn and diabetic foot infections. ABSSSI are caused by bacterial pathogens and are commonly caused by *Staphylococcus aureus* including methicillin-resistant strains and *Streptococcus pyogenes.* Less common bacterial strains include other *Streptococcus* species, *Enterococcus faecalis,* and gram-negative bacteria (Pollack et al., 2015).

Bloodstream infection (BSI): Viable bacteria in the bloodstream with the presence of clinical symptoms that are associated with a high degree of morbidity and mortality (del Rio, Cervera, Moreno, Moreillon, & Miro, 2009). Complicated bloodstream infection is defined as persistent positive blood cultures obtained 48-96 hours after initial blood cultures, persistent fever at 72 h, and skin lesions suggestive of systemic infection (Corey, 2009). Uncomplicated bloodstream infection is defined as a negative blood culture secondary to removal of an intravenous catheter, defervescence within 72 hours,

no signs of infective endocarditis, absences of prosthetic medical devices, and no symptoms of metastatic infection (Fowler et al., 2003).

Community-associated methicillin-resistant Staphylococcus aureus (CAMRSA): CAMRSA strains are *S. aureus* strains isolated from patients in the community that are susceptible to most antibiotics but resistant to the beta-lactam antibiotics. CAMRSA strains are associated with skin and soft tissue infections. By definition, CAMRSA infections occur in patients from the community with no known health care risk factors (Klevens et al., 2007; Maree, Daum, Boyle-Vavra, Matayoshi, & Miller, 2007; Pallin et al., 2008).

Complicated skin and soft tissue infections: The most extreme form of skin and soft tissue infection that often requires surgical intervention and encompasses a number of complications and comorbidities including neutropenia, tissue necrosis, skin ischemia burns, and insect and animal bites (Dryden, 2010).

Methicillin-resistant Staphylococcus aureus (MRSA): MRSA are *S. aureus* bacterial strains that are resistant to beta-lactam antibiotics and have been shown to be associated with a higher rate of morbidity and mortality than methicillin-susceptible strains. These strains are often referred to multidrug resistant *S. aureus* because besides beta-lactams, these organisms are typically resistant to a variety of nonbeta lactam antibiotics. MRSA infections are usually associated with a variety of health care risk factors (Gordon & Lowy, 2008; Klevens et al., 2007).

Methicillin-susceptible Staphylococcus aureus (MSSA): MSSA are *S. aureus* bacterial strains that are susceptible to beta-lactam antibiotics and typically susceptible to a wide variety of nonbeta lactam antibiotics (Dryden, 2009).

Secondary bloodstream infection: The CDC (2015) stated that the primary site of infection may have seeded the bloodstream secondarily. The patient has a recognized pathogen cultured from one or more blood cultures and has at least one of the following signs or symptoms: fever (> 38.0^0 C), chills, or hypotension and the organism cultured from the blood is not related to an infection at another site (CDC, 2015).

Skin and skin structure infections (SSSI): SSSIs are described as both uncomplicated and complicated infections. Uncomplicated SSSIs include superficial infections, such as cellulitis, simple abscesses, furnucles, and impetigo. Uncomplicated SSSIs can often be treated with surgical intervention or antibiotics. Complicated SSSIs are infections involving deeper soft tissues that require significant surgical intervention. These patients usually have concomitant underlying comorbidities that may complicate the response to therapy (Itani et al., 2011).

Skin and soft tissue infections (SSTIs): SSTIs are microbial invasions of the epidermidis, dermis, and subcutaneous tissues resulting in inflammatory response and infection (Dryden, 2009).

A more detailed description of the variables and how they will be analyzed can be found in Chapter 3.

Assumptions

One of the primary assumptions of this investigation was that the prevalence of individuals with ABSSSI with BSI who reside in urban Detroit will be adequate enough after exclusions criteria are applied to complete the required sample size needed for the study. In addition, I assumed that the subject controls of patients with ABSSSI without BSI were representative of the same urban Detroit population from which patients with ABSSSI and BSI were collected. Previous BSI investigations from the Detroit Medical Center have identified skin as the infection source in 15.9-35% of MRSA BSI (Kullar, Davis, Levine, & Rybak, 2011; Kullar, Rybak, & Kaye, 2013; Murray et al., 2013). Therefore, I was comfortable that there was enough ABSSSI-associated BSI to meet the study sample size requirements. With respect to the study controls, although this was not a matched case-controlled study, every effort was made to ensure that patients with similar demographic and underlying comorbid conditions were collected for both ABSSSI and ABSSSI with BSI. Lastly, I assumed that the data collected from the Detroit Medical Center and Henry Ford Hospital electronic patient charts were accurately reported and contained all of the information required to carry out the investigation and there was no differences in the quality and completeness of the data between cases and controls.

Limitations and Scope of the Study

The primary objective of this study was to evaluate and characterize the risk factors for BSI in individuals with ABSSSI who reside in urban Detroit and have low socioeconomic status. Data were collected on patients who were diagnosed and treated

for ABSSSI at the Detroit Medical Center and Henry Ford Hospital. Limitations for this case-control investigation included the retrospective study design, which can introduce potential bias. Because of the potential for bias, case-control studies are not well suited for detecting weak associations (odds ratio ≤ 1.5). The retrospective design of case-control studies also make it more difficult to establish a clear temporal relationship between the exposure and the outcome (Aschengrau, 2008). In addition, because of the retrospective design of this study, the observations made during this investigation could be constrained by the ability to capture accurate and complete information from the database maintained by the Medical Center and Henry Ford Hospital. Another potential limitation for this study was the fact that the patients in Detroit treated by the Detroit Medical Center and Henry Ford Hospital may not be representative or generalizable to the general population or to other urban centers throughout the United States. The epidemiology of MRSA BSI may be dependent on the population (e.g., poor, uninsured, etc.) that the Detroit Medical Center and Henry Ford Hospital serves (Tattevin et al., 2012). It was also possible that patients may be treated differently (treatment bias) depending upon their socioeconomic status (insured versus uninsured, education, income levels) , which may impact the severity and overall outcome of the patients included in this study (Lipsky, Kollef, et al., 2010). Specific organisms characteristics may have also played a role as some strains of MRSA are more virulent (e.g., CAMRSA) or more drug resistant then others, and these organisms maybe more common in the community surrounding the Detroit Medical Center and Henry Ford Hospital compared to other centers throughout the United States (Tattevin et al., 2012). The incorporation of

inclusion and exclusion criteria and multivariable regression analysis in this investigation should have helped control for some of the potential confounder variables that have been encountered while conducting this study.

Significance of the Study

ABSSSI are one of the most common infections treated in both hospital and community settings. These infections are not only common, but they are increasing in prevalence (Amin et al., 2014; Pallin et al., 2008). Complications secondary to skin and soft tissue infections can be severe and include infection of deep tissues and infections of the bone (Moran et al., 2013). BSI represent one of the most severe complications secondary to ABSSSI (Suaya et al., 2013). Although some limited information on BSI secondary to ABSSSI exists, this study provided new insights on the risk of BSI in patients with ABSSSI who reside in urban Detroit with low socioeconomic status. This research contributed to positive social change by providing information on patient characteristics and risk factors that can be used to improve the health outcomes of this patient population.

Summary

ABSSSI are common infections that are increasing in prevalence and are associated with the rapid increase in invasive CAMRSA (Moran et al., 2013; Pallin et al., 2008). Although patients with ABSSSI are commonly treated in the community, patients with severe ABSSSI often require hospitalization. These patients usually have a variety of complications that can include deeper tissue abscesses and infection of the bone and underlying comorbidities, such as diabetes and renal failure (Lipsky, Kollef, et al., 2010;

Suaya et al., 2013). BSIs are associated with a high degree of morbidity and mortality (van Hal et al., 2012; Yaw, Robinson, & Ho, 2014). While there are a limited number of studies on BSI in patients with ABSSSI, scholars have not focused on a specific patient population. This aim of this investigation was to evaluate the characteristics and risk factors associated with ABSSSI-related BSI in patients residing in urban Detroit Michigan. I also evaluated the impact of race/ethnicity on the severity of ABSSSI-associated BSI. The results of this investigation may increase the knowledge, prevention, and treatment of ABSSSI-associated BSI in this patient population. In the next chapter, a discussion of the literature regarding this gap in the collective knowledge base, along with the theoretical frameworks, for this study, will be discussed.

Chapter 2: Literature Review

Introduction

ABSSSIs are one of the most common infections encountered in both community and health care settings (Pollack et al., 2015; Rajan, 2012). The overall prevalence of ABSSSI is increasing. For example, the number of emergency department visits for skin and soft tissue infections increased from 1.2 million to 3.4 million (a 3-fold increase, *P* for trend < 0.001) from 1993 to 2005 (Pallin et al., 2008). ABSSSI are most commonly treated on an outpatient basis; however, individuals with more severe infections require hospitalization. ABSSSI can be associated with many complications. These include deeper dermis infections requiring significant surgical interventions, infections of the bone, gangrene, and amputation. One of the most severe complications of ABSSSI is BSIs (Lipsky, Kollef, et al., 2010; Suaya et al., 2013). BSIs are associated with a high degree of mortality (Lipsky, Kollef, et al., 2010; Suaya et al., 2013). Mortality secondary to BSI has been linked to a number of risk factors, such as old age; immunosuppression; comorbid underlying conditions such as diabetes, peripheral vascular disease, liver, and kidney failure; and inadequate or inappropriate therapy (Bassetti et al., 2012; Itani et al., 2011). Although there are a number of studies on the risk factors for mortality associated with bloodstream infections, few scholars have evaluated evaluated skin and soft tissue infection as a risk factor for BSI. Further, these researchers have not focused on ABSSSI as a risk for BSI caused by the bacterial pathogen *Staphylococcus aureus,* and the risk of BSI was not evaluated in an urban population with low socioeconomic status.

In this chapter, the literature search strategy for this study, the theoretical foundation, the literature review related to the key variables and concepts for the study, and the overall summary and conclusions are reviewed.

Literature Search Strategy

The literature search strategy that was used for this review included multiple databases, journals, and online resources. The review was central to identifying the research gap, as well as previous investigations on skin and skin structure infections and the secondary complication of BSI. Walden Library databases (PubMed, MEDLINE, ProQuest Health & Medical Complete, Sage Premier, Google Scholar, and Web of Science from 2008 – 2015) were explored using search terms such as *ABSSSI*, *SSSI*, *complicated skin and skin structure infections (cSSSI)*, *CAMRSA*, *BSI*, and *risk factors associated with SSSI BSI*, *socioeconomic status*, *health care access*, *race/ethnicity, socioecological and ecological framework*, *chain of infection,* and *Web of Causation*. Additional resources that were explored included the CDC as well as the Medicare and Medicaid websites for literature and information on risk factors, complications, treatment guidelines, and medical insurance coverage policies with respect to ABSSSIs.

Articles relevant to the research topic were reviewed and selected for the literature review if they met study inclusion criteria including the study date parameters, were not redundant with previously selected papers, and supported the literature and research gaps. Some select articles from prior to 2008 were included because of their pertinent contribution to the study topic and their historical importance because CAMRSA is associated with ABSSSI, and the prevalence of this organism was first reported during

the later 1990s and early 2000-2005. The prevalence of this organism and its association with ABSSSI continues to increase in the community.

Theoretical Foundation

The theoretical framework chosen for this study was selected after exploring several theory constructs that were related to behavioral risk, patient risk factors or the relationship of events, the causal agent, and the subsequent outcome of interest, which was BSIs. The socioecological model was investigated as a possible framework for this study because of the interrelationships between the individual and their community (Burke, Joseph, Pasick, & Barker, 2009). Further, this model included a focus on the importance of individual beliefs and behaviors in the context of the social environment and its impact on health promotion(Glanz & Bishop, 2010). Ultimately, individuals are responsible for their own health. However, the social determinants of health and the social context in which they live contribute to the individual's health (CDC, 2014b). This fact is most apparent with minorities (e.g., African Americans, Hispanic Americans/Latinos, Native Americans) whose health is more often disproportionately affected compared to nonminority populations (European Americans) because of lower levels of education, lower socioeconomic status, inadequate housing, and living in proximity to unsafe environments (Thomas, 2014). While the socioecological model can be used to establish the link between health behavior and social environmental influence, it does not include an examination of patient characteristics that contribute to the risk of disease. In addition, health behavior factors are typically collected prospectively via surveys and are not documented in the electronic medical charts. This would make

assessments of health behaviors difficult to analyze as contributors to individual risk of BSI. Therefore, this model was not selected as the theoretical framework for this study.

Another potential theoretical framework that was evaluated was the chain of infection. This theory includes a description of infection transmission as a chain of events. Breaking any link of the chain could stop the transmission of infection (Schneider, 2011). The components of the chain consist of the pathogen (virus, bacterium, fungus, or parasite) causing disease, the reservoir or place in which the microorganism resides and thrives and the portal of exit where the infecting organisms leaves the reservoir and is then transmitted (mode of transmission) through the portal of entry (mucous membrane, wound, etc.) to the susceptible individual (CDC, 2012). Although the chain of infection theory is important to understanding the infectious process, the focus of this theory is based primarily on breaking the chain of events through prevention, epidemiologic surveillance, and interrupting transmission through infection control practices. Infection risk as it relates to patient characteristics including underlying disease states that contributes to infection acquisition, complications, and patient outcomes is not accounted for with this theory; therefore, this framework was not selected for this study.

The theoretical framework chosen for this study was the web of causation(Krieger, 1994). Causation is explained by the relationship between events and the connection between the causal agent and the affected entity. It links a preceding event with a subsequent outcome, emphasizes the mechanism of action, and provides a process that leads to the event of interest (Aschengrau, 2008). The cause can be defined

as a condition that plays a role in the development of disease. The occurrence of a disease within a population can be related to genetic abnormalities, microorganisms, social structural and behavioral differences, environmental factors, and other associated characteristics (Norton, 2015). The web of causation applied to my research because it was not clearly known why patients with ABSSSI went on to develop the complication of BSI. The underlying assumption was that there was a causal pathway that differs from patients with ABSSSI versus those with ABSSSI with BSI. Some of these characteristics may have been related to race/ethnicity and access to health care. In this investigation, I determined the underlying characteristics in patients with ABSSSI that were associated with BSI in urban Detroit.

Skin and Soft Tissue Infections

ABSSSIs are one of the most common infections treated in the community and the hospital environment (Edelsberg et al., 2009; Pallin et al., 2008). The National Hospital Ambulatory Medical Care Survey (NHAMCS, 2011) indicated that diseases of the skin and subcutaneous tissue accounted for 3.9% of emergency department visits. Further, skin and soft tissue infections were one of the top 20 leading diagnosis accounting for 2.4% of all emergency department visits in 2011(CDC, 2011). Additionally, in data collected from U.S. emergency departments between the years 1997 and 2005, researchers indicated that the prevalence of ABSSSI has increased by as much as 50% and involving up to 14.2 million patients in 2005 (Hersh, Chambers, Maselli, & Gonzales, 2008; Pallin et al., 2008).

ABSSSIs result from an invasion of the epidermis, dermis, and subcutaneous tissues by microbial pathogens resulting in an inflammatory response leading to erythema, pain, swelling, and often a purulent discharge (Dryden, 2010). The skin is colonized with a variety of microbial flora that can act as an inhibitory barrier to pathogenic invading organisms. When this barrier is compromised via a break in the skin, ulcers, burns, traumatic or surgical wounds, or pathogenic organisms can gain access and cause infection (Dryden, 2009; Ray et al., 2013a). SSSIs can be classified as uncomplicated and complicated, which are terms that can be useful for describing the severity of these infections. However, SSSI descriptions are more useful to for understanding the pathogenesis and designing treatment strategies. In fact, the term ABSSSI was adopted by the Anti-Infective Drugs Advisory Committee in 2010 in an attempt to focus on bacterial infections for new antibiotic clinical trials, as well as to reduce the ambiguity associated with the term cSSSI that includes bacterial and nonbacterial causes, bite wounds, bone and joint infections, diabetic foot infections, and catheter-associated infections. Diagnoses under the term ABSSSI included cellulitis, erysipelas, major cutaneous abscess, and burn infections (Rajan, 2012). Cellulitis is an infection of the deep dermis and subcutaneous tissue. It is characterized by inflammation, induration, redness, and poorly demarcated borders. Erysipelas is a form of cellulitis affecting the superficial dermal lymphatic glands, and it differs from cellulitis by having raised borders that are sharply demarcated. Cutaneous abscesses are defined as a purulent collection of pus within the dermis of the skin that are often accompanied by inflammation, redness, induration, swollen lymph nodes, and fever. Overall, cellulitis

and cutaneous abscess appear to be the most common ABSSSIs encountered in community and hospital settings. In a study evaluating the epidemiology and outcomes of 1,096 patients with cSSSI in hospitalized patients, cellulitis was the most common accounting for 56.8% of all infections followed by cutaneous abscess (35.1%), skin ulcers (10.3%), surgical wounds (8.9%), and diabetic skin wounds at 6.6% (Zervos et al., 2012). This finding was further corroborated by Itani et al. (2011) who evaluated 43,201 patients hospitalized with cSSSI. Of those patients with Gram-positive bacterial cSSSI, 49.4% were diagnosed as cellulitis, abscess, or cellulitis with abscess (Itani et al., 2011). Further, in an evaluation of a large database from the Kaiser Permanente Medical Care Program between the years 2006 to 2009, Ray et al. (2013b) identified 648,699 patients with SSSI. Of these, 63% (405,798) were diagnosed as cellulitis and abscess (Ray et al., 2013b).

Pathogens Responsible for Acute Bacterial Skin and Skin Structure Infections

Although a variety of organisms are capable of causing ABSSSI, Gram-positive bacteria such as *Staphylococcus aureus* and Streptococci species are the most common bacterial pathogens. Under certain circumstances, Gram-negative and anaerobic bacteria may be involved, especially in polymicrobial skin and skin structure infections such as diabetic foot infections and chronic skin ulcers (Dryden, 2010; Moran et al., 2013). Streptococcus species such as *Streptococcus pyogenes* are the primary cause of cellulitis and erysipelas, whereas *Staphylococcus aureus* are most commonly involved in cutaneous skin abscesses. To evaluate the most common organisms involved in cSSSI, Sader et al. (2007) collected 4,674 nonduplicate bacterial isolates from 38 medical

centers in the United States over the years 2000-2005 from patients with documented cSSSI. Of these isolates, 48.1% (2,248) were identified as *Staphylococcus aureus* (*S. aureus*), and 4.2% were beta-hemolytic streptococci (Sader et al., 2007). The remaining bacterial pathogens primarily consisted of *Pseudomonas aeruginosa*, *E. coli,* and Enterococcal species (Sader et al., 2007). Of the *S. aureus*, 43.5% were resistant to the semisynthetic penicillin antibiotic methicillin, commonly referred to as MRSA, and 56.5% were MSSA (Sader et al., 2007). Infection due to MRSA is problematic because penicillins and cephalosporins (known collectively as beta-lactams antibiotics) are not effective leaving clinicians with fewer and often more toxic therapeutic choices to treat these infections (Rehm & Tice, 2010). In addition, patients infected with MRSA generally have more complicated treatment outcomes including longer hospital stays, increased failure rates, higher mortality rates for invasive infections, and increased health care costs (Klevens et al., 2007; Ray et al., 2013b). The overall prevalence of MRSA infections is increasing. In data from a national surveillance network composed of 300 clinical microbiology laboratories across the United States, Styers, Sheehan, Hogan, and Sahm (2006) revealed that MRSA infection rates have increased during the years 1998 to 2005. In data collected from a large U.S. health plan database, Ray et al. (2013b) reported that MRSA-associated SSSIs increased from 5% in 1998 to 42% in 2005 and 37% in 2009.

Community-Associated, Methicillin-Resistant *Staphylococcus Aureus*

The CDC (2014a) reported a total of 75,309 invasive MRSA infection cases for 2012 with an incidence rate of 24 cases (CI 20.64-28.10) per 100,000 population. This

increase in invasive MRSA infections can be contributed to the epidemic rise of CAMRSA (Pollack et al., 2015). Risk factors for hospital-associated MRSA (HAMRSA) have been well documented and include hospitalization, recent surgical procedures, antibiotic exposure, residence in long-term care facilities, catheters, and medical devices including patients with renal dysfunction/hemodialysis and diabetic patients (Pulia, Calderone, Meister, Santistevan, & May, 2014; Rehm & Tice, 2010). Individuals with CAMRSA infections, however, are not associated with these traditional risk factors (Rehm & Tice, 2010). Individuals with CAMRSA infections can present with a relatively healthy background, such as athletes via sports exposure, individuals associated with overcrowded living conditions, poor hygiene, homeless, children in day care, incarceration, intravenous drug users, men who have sex with men, individuals with advanced age, youth (including newborns), recent contact with an individual with a similar skin infection, recent antibiotic exposure in the community, skin abrasions, open wounds, lesions attributed to spider bites, diabetes, and peripheral vascular disease (Meddles-Torres, Hu, & Jurgens, 2013; Pulia et al., 2014). Prior to 2000, MRSA was considered a rare pathogen associated with community-acquired infections (Moran et al., 2013). However, the prevalence of MRSA acquired from the community increased after the year 2000. In a single center study in a Los Angeles emergency department, Moran, Amii, Abrahamian, and Talan (2005) revealed that between the years 2000 and 2005, the prevalence of MRSA infections derived in the community more than doubled from 29% to 64%. CAMRSA has now been described as the leading cause of SSSI in the United States (Hersh et al., 2008; Raygada & Levine, 2009). In a follow-up study with 422

patients evaluated for skin and soft tissue infections from 22 geographically diverse emergency departments across the United States, Moran et al. (2006) determined that CAMRSA accounted for 59% of SSSI. In the US Healthcare Cost and Utilization Project National Inpatient Sample from 2000-2004, researchers determined that total hospital admissions increased by as much as 29% (Edelsberg et al., 2009). The largest increase in CAMRSA infections was among younger patients (< 65 years of age) and for urban rather than rural patients (Edelsberg et al., 2009). During this time period, hospital admissions were greatest for patients with more superficial infections, such as cellulitis and cutaneous abscess, as opposed to health care-associated deeper infections (Edelsberg et al., 2009). CAMRSA-associated SSSI continues to increase in prevalence. Using ICD-9 codes from the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey, researchers determined that the incidence of SSSI increased 84.7% over the years 1997-2002 and 2003-2008 (Meddles-Torres et al., 2013). During this time period, the primary infection type was cutaneous abscess, which increased by 98.3% over a 5-year period (Meddles-Torres et al., 2013). The increase in CAMRSA infections over the last decade is considered a public health threat (CDC, 2014a; Edelsberg et al., 2009).

Compared to HAMRSA, CAMRSA are more virulent carrying a wide range of exotoxins that cause tissue necrosis leading to severe disease (Rehm & Tice, 2010). Genetically, CAMRSA carries a smaller gene type known as staphylococcal cassette chromosome mec (SCCmec) Type IV & V. This gene cassette is associated with the methicillin-resistant phenotype that defines MRSA, but is different from HAMRSA

strains carrying the much larger multidrug resistant SCCmec cassette Types I-III (Chua, Laurent, Coombs, Grayson, & Howden, 2011). The most common circulating CAMRSA types in the United States over the last 10 years are USA300 and USA400 (Klevens et al., 2007; Maree et al., 2007; Moran et al., 2013). These strains are defined on the basis of their pulse-field gel electrophoresis DNA fingerprint (Chua et al., 2011). CAMRSA strains were first identified and documented in children in the mid-1990s with USA400 being the predominant strain. Since that time, USA300 has become the epidemic clone strain that common in the United States and is the most common bacterial pathogen causing ABSSSI (Chua et al., 2011; David & Daum, 2010; Rehm & Tice, 2010).

The CDC (2010) defined CAMRSA infections as MRSA infections that occur in the outpatient settings where the culture of MRSA has been obtained within 48 hours of the hospital admission. In addition, patients who meet the definition of CAMRSA infection do not have a history of MRSA infection or colonization and have no history of hospitalization, admission to a nursing home, hemodialysis, or surgery within the past year. These patients also do not have permanent indwelling catheters or medical devices that are in contact with the skin (CDC, 2010). While not a part of the CAMRSA definition from the CDC, others have defined CAMRSA on the basis of antibiotic susceptibility because, in general, CAMRSAs are susceptible to all antibiotics except beta-lactams and are, therefore, methicillin-resistant. In addition, some researchers include the genotype as a part of the definition with CAMRSA containing the novel smaller SCCmec IV or V cassette and the *luk*SF-PV genes, which encodes for the Panton-Valentine leukocidin (PVL) toxin. The PVL toxin is a white blood cell exotoxin

and is responsible for some of the most severe CAMRSA infection presentations (Herold et al., 1998; Vandenesch et al., 2003).

Investigations Evaluating Acute Bacterial Skin and Skin Structure Infections

Since the epidemic of CAMRSA first erupted, a number of studies have been conducted to examine the prevalence, risk factors, and health outcomes of patients with ABSSSI. Moran et al. (2006) conducted a prospective prevalence study of adult patients with SSTIs who were treated in the emergency departments of the Emergency ID Net, which is a network of university-affiliated hospitals from 11 cities across the United States. Individuals who had a purulent SSTI that was less than less than 1 week in duration were eligible for enrollment into the study (Moran et al., 2006). A total of 422 patients were enrolled into the study (Moran et al., 2006). Overall, the patients tended to be younger in age (median age of 39), more commonly men (62%), and mostly non-Hispanic blacks (49%; Moran et al., 2006). Abscess was the most common type of infection accounting for 81% of the patients followed by wound at 11% and cellulitis with purulent exudate at 8% (Moran et al., 2006). *Staphylococcus aureus* was the most common pathogen associated with SSTI with MRSA accounting for 59% of patients (prevalence range 15-74%; Moran et al., 2006). The other predominant organisms identified were methicillin-susceptible *Staphylococcus* aureus accounting for 17% and streptococcus species (7%; Moran et al., 2006). Of the 218 MRSA isolates recovered, 99% were determined to be CAMRSA on the basis of the CDC pulse-field electrophoresis definitions (Moran et al., 2006). Infections with MRSA included recent antibiotic use, abscess associated with a spider bite, history of MRSA infections, or close

contact with an individual who had a similar SSTI (Moran et al., 2006). Presence of underlying comorbid conditions and race and ethnicity were not associated with MRSA skin infections (Moran et al., 2006). However, when these factors were applied to a multivariable logistic regression analysis, Black race and the presence of a skin abscess were independently associated with MRSA skin and skin structure infections (Moran et al., 2006). MRSA was the most common organism that was identified with ABSSSI across 11 diverse U.S. cities (Moran et al., 2006).

Maree et al. (2007) conducted a study on CAMRSA infections from 1999 to 2004 in Los Angeles at the Harbor-UCLA Medical Center. This hospital system is a tertiary-care urban, hospital in Los Angeles County. CAMRSA strains were defined as MRSA strains isolated $\leq$ 72 hours of hospitalization (Maree et al., 2007). During this time period, a total of 352 patients with MRSA cultures were identified. Of these, 229 (65%) were men with a median age of 50 years. Of these patients infecting organisms, 128 were identified as CAMRSA via SCCmec type IV phenotype (Maree et al., 2007). When compared to HAMRSA, patients tended to be younger (48 vs. 54 years; p =0.02) and were more likely to have MRSA cultured from wounds, a shorter length of hospital stay prior to MRSA culture, and an infection identified after the year 2003 (Maree et al., 2007). CAMRSA infections were becoming more commonly encountered, were more likely to cause skin and skin structure infections, and tended to be more aggressive causing an infection with a higher severity and associated with a longer hospital stay (Maree et al., 2007).

In a large retrospective study of skin and soft tissue infections, Ray et al. (2013a) evaluated the incidence, offending pathogens, and patient characteristics. Over the years 2009 to 2011, a total of 376,262 SSTIs were examined. Of the patients who provided cultures (58,794), *Staphylococcus aureus* was the most common pathogen isolated (81%) with 46% of these identified as MRSA (Ray et al., 2013a). The incidence of SSTI was 496 per 10,000 person-years and was highest in individuals ≥65, Native Americans, African Americans, individuals identified as multiracial, and individuals with diabetes (Ray et al., 2013a). Asian Americans and Hispanic Americans had a reduced rate of SSTIs while African Americans between 18 and 50 years of age were at a disproportionately high risk for SSTI compared to European Americans (Ray et al., 2013a). In addition, Hispanic American and African American patients were more likely to have MRSA identified as the causative pathogen for SSTI compared to European Americans (OR: 1.79; CI; 1.67-1.92, OR: 1.24, CI; 1.18-1.31), and Asian American patients were less likely to have MRSA (OR: 0.73, CI; 0.68-0.78). Further, individuals of lower income status were at an increased risk of MRSA SSSTI (Ray et al., 2013a). Patients with diabetes were found to have approximately twice the rate of SSTI (RR: 1.93, CI: 1.90 to 1.96) compared those without diabetes (Ray et al., 2013a). In a posthoc analysis evaluating race and ethnicity by age group, Asian Americans and Hispanic Americans were found to have lower rates of SSTI at every age group except for children less than 5 years of age (Ray et al., 2013a). When evaluating the age bracket of 18 to < 65, African Americans had SSTI rates substantially higher (RR: 1.27, CI; 1.23 to 1.31 compared to European Americans of the same age (Ray et al., 2013a). However, at all

other age brackets, African Americans had SSTI rates similar or lower than European Americans (Ray et al., 2013a). Overall, after adjusting for demographic characteristics, the investigators concluded that the risk of SSTI was greatest for individuals with diabetes, those of lower socioeconomic status, and children under 5 years of age while Asian Americans were of lower risk. In addition the rate of SSTI varied by both age and race/ethnicity and warranted further investigation (Ray et al., 2013a).

Skin- and Soft Tissue-Associated Complications

Complications from SSTIs can be severe and include necrotizing infections requiring extensive surgery, gangrene, amputation, bone and joint infections (including osteomyelitis), bloodstream infections, and sepsis (Dryden, 2010; Lipsky, Tabak, et al., 2010; Sreeramoju et al., 2011; Wilson et al., 2011). Using a large repository U.S. health care database, Suaya et al, 2013 evaluated 2,227,401 SSTI episodes and their complications diagnosed from 2005 to 2010. The most common SSTI type was abscess and cellulitis accounting for 50.5% and 54.4%, respectively, and 10% of these patients were diabetics (Suaya et al., 2013). Compared to diabetic patients, nondiabetic patients with SSTIs were more likely to be diagnosed in ambulatory settings (96.2 vs. 88.7%; $p<0.01$; Suaya et al., 2013). Complications secondary to SSTI were noted to occur more than five times higher in patients who had diabetes compared to nondiabetic patients (4.9% vs. 0.8%; $p<0.01$; Suaya et al., 2013). Osteomyelitis was the most common complication in patients with SSTIs diagnosed in ambulatory settings and was more commonly observed in patients with diabetes compared to nondiabetic patients (3.3 vs. 0.4%; $p< 0.01$; Suaya et al., 2013). Overall, complications were highest and more severe

among the hospitalized patients. In these patients, bloodstream infections, endocarditis, and sepsis were the most common complications occurring in 24.7 and 16.3% of patients with and without diabetes, respectfully (Suaya et al., 2013). The rate of subsequent rehospitalizations was nearly double for patients with diabetes compared to nondiabetics (15.1% compared to 7.8%, respectfully; Suaya et al., 2013). Overall, patients with diabetes had both higher rates of SSTI complications and subsequent hospitalizations (Suaya et al., 2013).

Lipsky et al. (2010) also evaluated complications in diabetic patients with SSTI. A total of 3,030 hospitalized patients with positive bacterial cultures from 97 U.S. hospitals over the years 2003 and 2007 were evaluated. Factors that were significantly associated with mortality included the severity of illness upon hospital admission ($p< 0.001$), the type of SSTI (cellulitis vs. ulcer vs. surgical infection; $p<0.001$) and a nonfoot SSTI location ($p< 0.05$; Lipsky et al., 2010). Patients with skin and soft tissue wound infections that had polymicrobial isolates including *Pseudomonas aeruginosa* or non-Pseudomonas gram-negative monomicrobial bacteria had a significantly increased mortality rate ($p< 0.01$ and $p< 0.001$, respectfully; Lipsky et al., 2010). Severity of illness, transfer from another acute care hospital, patients from nursing homes, or individuals with wound cultures who demonstrated gram-negative pathogens including *Pseudomonas aeruginosa* and polymicrobial infections including MRSA were associated with increased length of stay and hospital costs (Lipsky et al., 2010). Further, patients with SSTI wounds infected with MRSA tended to be more severely ill on clinical presentation (Lipsky et al., 2010). Overall, Lipsky et al. identified significant

independent risk factors for prolonged hospital stays: increased costs and mortality. In addition, patients with SSTI who had wounds with MRSA tended to have greater severity of illness at clinical presentation (Lipsky et al., 2010). Scholars identified MRSA, diabetes, polymicrobial infections that included gram-negative pathogens, and severity of illness on hospital presentation as risk factors for SSTI complications.

Infections Secondary to Acute Bacterial Skin and Skin Structure Infections

In the United States, BSI ranked as the 11th leading cause of death in 2008 (Minino, Murphy, Xu, & Kochanek, 2011). *Staphylococcus aureus* is one of the most common pathogens causing BSI in both community and health care settings (Sievert et al., 2013). *Staphylococcus aure*us BSIs are associated with a high degree of complications including metastatic spread causing septic arthritis, vertebral osteomyelitis, and infective endocarditis (Corey, 2009; del Rio et al., 2009). Mortality secondary to *Staphylococcus aure*us is significant and ranges from 20-40% (Gould, 2007; Kobayashi, Yokota, Takahashi, Arioka, & Fukui, 2014). There are a variety of risk factors that have been associated with the increased risk of mortality secondary to *Staphylococcus aureus* BSI. While conducting a systematic review of predictors of mortality secondary to *Staphylococcus aureus* BSI, van Hal et al. (2012) identified age (1.3 fold increase for every decade of life), ethnic origin (27.7/100,000 for European Americans compared to 66.5/100,000 population for African Americans), and underlying comorbid conditions (presence of alcoholism, immunosuppression, cirrhosis, congestive heart failure, cancer, chronic renal failure requiring dialysis, as well as the presence of multiple comorbid conditions as important factors that predicted mortality). In addition, the source of

infection, and whether *Staphylococcus aureus* BSI developed in the community versus in hospital settings, was also a factor. Of interest, MRSA BSI had a much higher rate of mortality compared to MSSA (van Hal et al., 2012).

The relationship between MRSA BSI and increased mortality was previously documented by Shurland et al. (2007) who evaluated 438 patients with MRSA infections at a Veterans Affairs medical center. Patients with MRSA BSI had a higher mortality risk compared to patients with MSSA BSI (RR, 1.7, 95% CI: 1.3-2.4, $p< 0.01$; Shurland et al., 2007). In addition, patients who died from MRSA infections tended to be older, have more underlying diseases, and were more likely to have severe sepsis compared those patients who survived (Shurland et al., 2007). SSTIs were listed as one of the most common sources of BSI with 29.3% listing MRSA as the causative pathogen versus 22.5% MSSA (Shurland et al., 2007).

Contributing to data impacting the outcome of patients with MRSA BSI, Yaw (2014), using an observational cohort study design, examined the long-term outcomes of patients with MRSA and MSSA bacteremia. Patients with *Staphylococcus aureus* BSI from July of 1997 to June of 2007 were evaluated for crude survival time. Although infection-related mortality was not statistically different between MRSA and MSSA BSI after adjusting for known predictors, such as comorbid conditions, severity of illness, cancer, and association with long-term care facilities, patients with MRSA BSI had much shorter survival time (14 months, [IQR 1-86] compared to MSSA BSI at 54 months [IQR 3-105]; hazard ratio 1.46, 95% CI; 1.8-79; $p = 0.01$; Yaw, 2014). Yaw et al. concluded

that the findings of worsening long-term outcomes had treatment implications for MRSA BSI.

ABSSSI is a common source of *Staphylococcus aureus* BSI (Lipsky, Kollef, et al., 2010). In data from the meta-analysis of predictors of mortality in *Staphylococcus aureus* BSI from 41 investigations, Van Hal et al. (2012) indicated that patients with BSI secondary to ABSSSI were at an intermediate to moderate risk (2-9 fold increased risk) of mortality compared to patients with urinary tract, intravenous catheters, ear, nose, and gynecological foci listed as the source of infection. Since the epidemic spread of CAMRSA starting in 2000, strain type USA 300 has become the predominant cause of ABSSSI in the United States (Zervos et al., 2012). The aggressive spread of this organism is of importance because CAMRSA is considered a highly invasive pathogen capable of infecting individuals without the traditional risk factors for MRSA infections. As part of a surveillance study evaluating the molecular characteristics and clinical characteristics of patients infected with *Staphylococcus aureus* strains from 2000 to 2008, Tattevin et al. (2012) identified that the USA 300 strain type accounted for 55% (304/549) of BSIs and that this strain type was the predominant MRSA clone causing community-associated infections. In addition, there was a strong correlation (Pearson $r = 0.953$) between USA 300 ABSSSI and USA 300 BSI, indicating that USA 300 (CAMRSA) ABSSSI was a primary source of BSI and that efforts to control USA 300 ABSSSI may decease subsequent BSIs and their patient outcome consequences (Tattevin et al., 2012). Further, Tattevin et al. claimed that USA 300 BSI was now predominantly a community infection

and had emerged as a consequence of USA 300 ABSSSI in the poor urban area of San Francisco.

In the only study to determine risk factors among patients with BSI hospitalized for SSTI, Lipsky, Kollef, et al. (2010) evaluated a large database of adult hospitalized patients from 97 hospitals in the United States from the years 2003 to 2007. Of the 8,747 patients evaluated, 1,021 (11.7%) were determined to have BSI (Lipsky, Kollef, et al., 2010). Independent predictors of BSI were old age, male sex, comorbidities such as coronary heart disease, presence of infected devices of prosthesis, health care-associated infections, abnormal vital signs such as respiratory rate, low or high pulse rate, temperature less than 35.6^0C, and abnormal white blood cell counts ($p< 0.001$; Lipsky, Kollef, et al., 2010). Lipsky, Kollef, et al. identified that risk factors for BSI were important for early recognition and to manage complications including morbidity and mortality associated with BSI. The limitations of this study were that (a) Lipsky, Kollef, et al. only concentrated on hospitalized patients and, therefore, the findings are not generalizable to patients with community infections and (b) patients selected were not specific to an urban city setting where access to health and other socioeconomic factors could have an influence on the risk factors associated with BSI secondary to ABSSSI (Lipsky, Kollef, et al., 2010).

Socioeconomic Factors Contributing to Infection

Socioeconomic factors affect individual health outcomes. The socioeconomic environment of the neighborhood can have both direct and indirect impact on health. Direct effects on health include injuries from crime, environmental hazards, and illness

from toxic exposures (Khabbaz et al., 2014; Lantz & Pritchard, 2010). Indirect influences on health include chronic exposure to social stressors such as poverty, unemployment, and discrimination. Additional mechanisms that link the socioeconomic environment to health include health risk behaviors such as poor diet, physical inactivity, and tobacco use and the lack of adequate housing and access to health care services (Lantz & Pritchard, 2010). Certain patient populations may be at higher risk for infectious disease complications and worse treatment outcomes (Holman et al., 2011; Khabbaz et al., 2014; Moore et al., 2012). Using data from the National Health and Nutrition Examination Survey (NHANES) from 1988 through 1994, Zajacova et al. (2009) evaluated socioeconomic status and its relationship to chronic and persistent infections including *Helicobacter pylori* infections, periodontal infections, herpes viruses, and hepatitis viruses in 19,275 individuals. Demographic variables included race/ethnicity, education, and income variables (Zajacova et al., 2009). Across all age and race/ethnic groups, the burden of infection was highest among those with the lowest education and income (Zajacova et al., 2009). Independent of education and income, non-Hispanic Black adults and Mexican Americans had a significantly higher burden of infection compared to non-Hispanic White adults (Zajacova et al., 2009). In addition, investigators evaluating race/ethnicity and low socioeconomic status have reported higher hospital readmission rates and increased risk of infection complications including sepsis severity highest among African Americans (Acosta et al., 2013; Morris et al., 2014). The rates of invasive CAMRSA infections are highest among Blacks compared to Whites and in individuals with lower socioeconomic status in the United States (Klevens et al.,

2007). In a study on trends in U.S. hospital admissions for SSTI between 1998 and 2004, the highest rates for SSTI admissions were among individuals younger than 65 years of age and for urban rather than rural hospitals (32% vs. 11%; Khabbaz et al., 2014; Lantz & Pritchard, 2010; Moore et al., 2012). The higher rates of SSTI among urban hospitals is of interest because inner city patient populations are more likely to be diverse, have higher rates of poverty, health risk behaviors, and poor access to health care resources (Khabbaz et al., 2014; Lantz & Pritchard, 2010; Moore et al., 2012). In order to make improvements in individual health outcomes, it is important to evaluate patients in urban settings who have low socioeconomic status and are at high risk for infections and complications.

Summary

The pertinent literature regarding ABSSSI, the pathogens responsible for causing this infection, and the relationship between ABSSSI and bloodstream infection was reviewed in this chapter. The theoretical framework for this study, web of causation, was used to describe the relationship between events and the causal agents producing the outcome of intent and identifying the risk factors associated with BSI. It was not clearly known why patients with ABSSSI develop BSI. However, individuals with ABSSSI who reside in urban environmental settings are at higher risk for complications secondary to ABSSSI including BSI because of socioeconomic status, race/ethnicity, high risk health behaviors, and poor access to health care resources. Methicillin-resistant *Staphylococcus aureus* is the primary pathogen involved in ABSSSI including patients with secondary BSI. CAMRSA is a highly virulent organism and the most common bacterial pathogen

causing infections including ABSSSI in the community. There have been a number of investigations on ABSSSI in recent years. These researchers have identified risk factors for ABSSSI including race, such as African Americans; age (< 65 years); and a number of comorbid conditions, such as diabetes. However, there is little to no information regarding patients with ABSSSI and their risk for BSI, and there are no studies on inner city adults of low socioeconomic status. In this chapter, I documented the knowledge gap regarding ABSSSI and the risk of BSI, which supported the need to evaluate these risk factors.

In the next chapter, the methods section for the investigation will be described. This section includes the research questions that were addressed, the rationale for the research design, ethical considerations, patient population, justification for the selected sample size, patient characteristics to be collected, and statistical approaches that were used to analyze the data.

Chapter 3: Research Method

Introduction

The purpose of this study was to evaluate the health outcomes of patients with low socioeconomic status in an urban city environment who had ABSSSI-related *S. aureus* BSI infection. The primary aim of this investigation was to characterize and determine the risk factors for patients with ABSSSI with concomitant BSI compared to patients with ABSSSI alone admitted to the Detroit Medical Center (DMC) and Henry Ford Hospital (HFH). The secondary aim was to determine whether race/ethnicity impacted the severity of ABSSSI-associated BSI.

A detailed description of the methodology that was used to carry out this investigation will be described in this chapter. In the first section of the chapter, I describe the research design and rationale. Included in this section is a description of the dependent and independent variables, the research design, and the research questions and their importance for advancing the knowledge about the subject area. Within this chapter, the target population is defined, and the estimated sample size, power and desired effect size, sampling procedures, time frame, and the inclusion and exclusion criteria are presented. The procedures that were used for gaining access to the data, data collection, and a description of the study participants' demographics and characteristics are also included. In addition, the research variables are defined and a description of how the variable was measured is provided. Procedures for data cleaning, as well as the software for statistical analysis that was used, are described. The planned statistical analysis, rationale for variable inclusion, and procedures for data interpretation are

discussed. Threats to internal and external validity and ethical concerns are also discussed. Lastly, this chapter will provide a summary of the design and methodology, as well as a transition statement for Chapter 4.

Research Design and Rationale

An observational, case-control study design was chosen to evaluate BSI associated with ABSSSI. This quantitative research design was selected because it is a preferred method for examining the type of research questions and hypotheses testing that was performed in this investigation, as detailed below (Aschengrau, 2008; Creswell, 2009; Song & Chung, 2010). The primary objective of this investigation was to evaluate the risk factors associated with BSI in patients residing in urban Detroit Michigan. A secondary purpose of this investigation was to explore the impact of socioeconomic status on the severity of BSI. Risk factors for BSI in patients who had been hospitalized for ABSSSI have been previously evaluated (Lipsky, Kollef, et al., 2010). However, risk factors in patient populations with low socioeconomic settings have not been identified. A case-control study design was selected because it is one of the most efficient methods to evaluate exposure and disease. Case-control studies start with the subjects who have outcome of interest at the outset of the investigation, and then the investigator looks back in time to examine potential causative factors. After the outcome has been identified, subjects with the outcome or disease are categorized as cases, and subjects without the outcome/disease are categorized as controls. By comparing subject characteristics including exposure factors between cases and controls, the potential cause and risk factors for disease development can be derived. Compared to cohort studies, case-control

studies are better suited for evaluating rare events, are more rapid and less expensive to complete, require fewer subjects, and accommodate the assessment of multiple risk factors for a single outcome (Song & Chung, 2010). This study design was considered a basic and valid epidemiologic approach to measure the relationship between an exposure and disease development(Aschengrau, 2008). Case-control studies have been routinely used to examine risk factors associated with ABSSSI, MRSA, and MRSA BSI (Bassetti et al., 2012; Davis et al., 2007; Shurland et al., 2007). The higher frequency of ABSSSI compared to other infections, retrospective design, and the availability of electronic medical case documentations limited any resource and time constraints for collecting and analyzing data. The primary dependent (outcome) variable for this investigation was the diagnosis of BSI. The independent variables were patient characteristics and factors that may determine whether patients with ABSSSI develop secondary BSI; they included age, gender, educational level, income, race/ethnicity, diabetes, cardiovascular disease, renal failure, cirrhosis, intravenous drug use, recent hospitalization, recent MRSA infection, alteration in body temperature, WBC, and receipt of antibiotics in the past 30 days (Lipsky, Kollef, et al., 2010; Tattevin et al., 2012).

The secondary purpose of this investigation was to evaluate the impact of social economic status and the degree of severity associated with ABSSSI-associated BSI. Social determinants of health and the social context in which individuals live are contributing factors to an individual's health (CDC, 2014b). The relationship between social determinants and its impact on health has been demonstrated most often in minorities such as African Americans, Hispanic Americans/Latinos, and Native

Americans. Individuals with lower socioeconomic status and minimal education levels who are living in inadequate housing all have been shown to contribute the individual health status (Thomas, 2014). To determine the impact of socioeconomic status on severity of disease, race/ethnicity, age, education level income, and insurance status was used as independent variables. Research questions and the variables that were evaluated in this investigation are listed in Table 1 and 2.

Summary of Variables by Research Question

1. Are there significant differences in clinical characteristics, risk factors, and socioeconomic factors between patients with ABSSSI and ABSSSI-associated BSI?

Table 1

Variables

Variable	Independent/Dependent	Variable Type	Statistical Test
Race/Ethnicity	Independent	Categorical; African-American will serve as the reference variable, Caucasian, Hispanic and Other will serve as the other variables	Chi-Square/Logistic Regression
Gender	Independent	Dichotomous; Male/Female	Chi-Square/Logistic Regression
Age	Independent	Categorical, 18-35, 36-50, 51-75, > 75	Chi-Square/Logistic Regression
Education	Independent	Categorical, hierarchy variables: < high school, H.S. graduate, college graduate, graduate school	Chi-Square/Logistic Regression
Income	Independent	Categorical; hierarchy variable as poverty < $24,250, $24,250-$32,500, low income, $32,501-$49,999, middle income $50,000-$100,000 or upper middle income > $100,000-$200,000 per household of 4	Chi-Square/Logistic Regression
Insurance Status	Independent	Dichotomous variable, present or absent	Chi-Square/Logistic Regression
Renal Failure, Diabetes, Cardiovascular Disease, hepatic disease, IVDU, paraplegia, HIV/AIDS, immunosuppression (steroids, radiation, chemotherapy)	Independent	Dichotomous variable, present or absent	Chi-Square/Logistic Regression
Temperature, White Blood Cell Count (WBC)	Independent	Categorical; < 35.6^0C or > 38.0^0C, WBC > 11 x 10^9 cells/L	Chi-Square/logistic Regression
Recent Hospitalization within the last 180 days	Independent	Dichotomous; present or absent	Chi-Square/Logistic Regression
Recent Hospitalization for MRSA or MSSA infection within the last 60 days	Independent	Dichotomous; present or absent	Chi-Square/Logistic Regression
Receipt of antibiotic within the last 30 days	Independent	Dichotomous; present or absent	Chi-Square/Logistic Regression
ABSSSI-associated BSI	Dependent	Dichotomous; present or absent	Chi-Square/Logistic Regression

2. Is race/ethnicity associated with disease severity (based upon surgical interventions [e.g., incision and drainage, wound debridement, amputation]), admission to the ICU, or shock between patients with ABSSSI and ABSSSI-associated BSI?

Table 2

Variables and Tests

Variable	Independent/Dependent	Variable Type	Statistical Test
Race/ethnicity	Independent	Categorical; African-American, will serve as the reference variable and Caucasian, Hispanic and other will be the other variables	Chi-Square/Logistic Regression
Surgical intervention, incision and drainage in OR, wound debridement and amputation, admission to ICU or shock	Dependent	Dichotomous; Incision and drainage present/absent, wound debridement present/absent, amputation present/absent	Chi-Square/Logistic Regression

Population

The population selected for this investigation was patients who were hospitalized with the diagnosis of ABSSSI with BSI who were admitted to one of the DMC hospitals or HFH located within the city of Detroit. The DMC and HFH were chosen to collect cases and controls for this investigation because this nine-hospital system has a centrally located campus located in midtown Detroit and, therefore, services a large section of the inner city Detroit patient population. Cases that were included in this study consisted of patients admitted to the DMC and HFH with BSI whom developed within 48 hours of admission and whom had ABSSSI identified as the primary infection source. Study controls consisted of patients who were admitted to the DMC and HFH with the diagnosis of ABSSSI without BSI. Patients were excluded if they had the diagnosis of burns, gangrene, animal or human bites, and osteomyelitis due to severe complications associated with these infections. Both cases and control patients were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] diagnostic codes via the DMC and HFH electronic medical records. The health care records were used to establish the exposure history for each study participant (Aschengrau, 2008). The DMC and HFH electronic medical records are detailed data files that describe the patient's characteristics, laboratory values, diagnosis, progress, and patient outcome including discharge status.

Sample Selection

Consecutive cases and controls were selected from January 2010-December 2015 from the electronic patient chart database of the DMC and HFH urban campuses on the

basis of ICD-9-CM diagnostic codes for ABSSSI and BSI. The time period of 2010-2015 to collect cases was selected because this period of time was consistent with the most recent guidelines for the diagnosis and treatment of SSTIs; therefore, medical practice with regards to ABSSSI would be current and consistent (Mistry et al., 2014; Moran et al., 2013; Pulia et al., 2014). Patients admitted to the hospital with the diagnosis of ABSSSI or ABSSSI with BSI within 48 hours of admission were considered community-associated ABSSSI or ABSSSI with BSI (Lark et al., 2001; Lipsky, Tabak, et al., 2010). Control cases were identified by ICD-9-CM diagnostic codes for SSTIs that met the definition of ABSSSI (abscess, cellulitis, abscess with cellulitis, and wound infection). Cases were identified by ICD-9-CM diagnostic codes for BSI for which ABSSSI had been identified as the source infection for BSI. Only community-associated ABSSSI was included in this investigation because the primary objective of this study was to evaluate the risk for BSI among individuals with ABSSSI from the urban community of Detroit. Therefore, chronic SSSI including decubitus ulcers, hospital-derived SSSI secondary to surgical wounds, gangrene, amputation, and medical devices were not included (Ray et al., 2013a). Community-associated infection was defined as ABSSSI on hospital admission. Community-associated ABSSSI with concomitant BSI was defined as individuals who had ABSSSI with BSI on admission or who developed BSI within 48 hours of hospital admission and for which the treating physicians had documented that ABSSSI was the source of the BSI (Lipsky, Kollef, et al., 2010; Tattevin et al., 2012). Patients with SSTIs with the diagnosis of necrotizing fasciitis, pyomyositis, burns, or ABSSSI secondary to recent surgery were excluded because these infections

required immediate surgical intervention or had a high likelihood of poor patient outcomes irrespective of concomitant BSI (Micek et al., 2010).

Procedures for Data Access

Access to the medical records of the DMC for the inclusion of cases and controls was obtained via an application to the DMC Research Committee. A separate application was made to the HFH Institutional Review Board (IRB). The application included the detailed study protocol, data collection forms, and a description of the number of patients as well as the specifics on patient data that were collected. Once the DMC research application was approved, an IRB application approval was obtained from Walden University and subsequently from Wayne State University, which served as the IRB for Wayne State University and the DMC. Upon receiving permission to collect data from the DMC and IRB approvals from Walden University, Wayne State University, and HFH, data collection began. All data were de-identified to protect the personal information of the participants. Participant data were collected via Internet password-protected data collection software.

Sample Size

The study population consisted of patients from the DMC urban campus hospitals Detroit Receiving Hospital, Harper University Hospital and Sinai-Grace Hospital, and HFH who were diagnosed with ABSSSI or ABSSSI with BSI. The minimum sample size for an unmatched case-control study was calculated using the statistical test for differences in proportions(Fleiss, 2003) as follows:

$$n = \left(\frac{r+1}{r}\right)\frac{(\bar{p})(1-\bar{p})(Z_{\beta}+Z_{\alpha/2})^2}{(p_1-p_2)^2}$$

n = sample size in the case group

r + 1/r = ratio of controls to cases

$(\bar{p})(1-\bar{p})$ = a measure of variability (similar to standard deviation)

Z_{β} = represents the desired power (typically 0.84 for 80% power)

$Z_{\alpha/2}$ = represents the desired level of statistical significance (typically 1.96)

$(p_1 - p_2)$ = effect size (the difference in proportions)

I used a sample size calculation OpenEpi with 1:1 for cases and controls to determine a sample size requirement of 187 cases and 187 controls (total sample of 374) to reach a power of 0.80 using a 2-sided significance level (1-α) of 0.05 to detect an adjusted odds ratio of 2.0 (least extreme OR to be detected) for a factor with a known prevalence of 10-20% (diabetes, renal failure, prior antibiotics, recurrent infection; Carratala et al., 2003; Lark et al., 2001; Micek et al., 2010; OpenEpi, 2015). Regarding my ability to meet the sample size requirement, I previously described the treatment of over 300 patients meeting the definition of ABSSSI infection from a single DMC hospital over a 2-year period (2012-2014; Claeys et al., 2015). Therefore, I was confident that I could meet the sample size requirement because I proposed to collect cases from multiple DMC hospital and HFH sites over an extended 5-year period.

Operationalization

Variable Definitions

1. Race/ethnicity was designated as listed in the patient's medical chart and was defined as categorical variables as the following: African American, referent group, was compared to European American, Hispanic American, and other racial/ethnic groups.
2. Gender was recorded as listed in the patient's medical chart and was defined as a categorical variable as male or female.
3. Age was measured in years (mean+/- standard deviation years) and was collected from the patient's medical chart and defined as a continuous variable.
4. Education was derived from the medical chart and was defined as a categorical variable as < high school, high school graduate, college graduate, and graduate school graduate.
5. Income was derived from the Census Bureau of Statistics by the patient's zip code (i.e., average yearly household income within zip code).
6. Insurance status was collected from the medical chart and was defined as a dichotomous variable as present or absent.
7. Comorbid conditions were derived from the medical chart and were defined as dichotomous variables: diabetes; with or without end organ damage; present or absent, chronic renal failure defined as creatinine clearance < 30 ml/min or receiving renal dialysis; present or absent,

cardiovascular disease; present or absent, intravenous drug use; present or absent, hepatic disease; present or absent, paraplegia; present or absent, HIV/AIDs; present or absent, use of steroids equivalent to prednisone 20 mg per day; present or absent and chemotherapy or radiation (within 30 days of hospital admission; present or absent.

8. Charlson comorbidity index score was derived from the patient's chart and was defined as a continuous variable.
9. Temperature and white blood cell count (WBC) was derived from the patient's medical chart and was defined as continuous variables as temperature $< 35.6^0$C or $> 38.0^0$ C, or 35.6-38.0^0C and WBC $\geq 11 \times 10^9$ cells/L.
10. History of recent hospitalization was collected from the medical chart and was defined within the last 180 days of the current hospitalization. These data were treated as a dichotomous variable (recent hospitalization present or absent).
11. History of recent hospitalization of MRSA or MSSA infection (within the last 60 days) was collected from the medical chart and was treated as a dichotomous variable (recent MRSA or MSSA infection present or absent).
12. History of ABSSSI within the last 60 days was defined as a categorical variable: present or absent.

13. Recent antibiotic exposure within the last 30 days was collected from the medical chart and was treated as a dichotomous variable (antibiotic exposure–present or absent).
14. Type of antibiotic exposure (antibiotic class) within the last 30 days was collected from the medical chart and was treated as a dichotomous variable: present or absent.
15. Location prior to hospital admission was derived from the patient's medical chart and was defined as community, other hospital, skilled nursing facility, rehabilitation center, or other long-term care facility and was treated as a categorical variable: present or absent.
16. Length of hospital stay (days) was defined as a continuous variable.
17. Surgical intervention an indicator of disease severity was collected from the medical chart and was defined as dichotomous variable as surgical intervention– incision and drainage, debridement, or amputation: present or absent.
18. Admission to the intensive care unit was defined as a dichotomous variable: present or absent.
19. Length of stay (days) in the intensive care unit was defined as a continuous variable.
20. Type of ABSSSI was defined as abscess, cellulitis, abscess and cellulitis, infected wounds, and infections related to medical devices; type of ABSSSI was defined as dichotomous variables: present or absent.

21. Presence of polymicrobial pathogens was defined as a dichotomous variable: present or absent.
22. Type of organism cultured from infected skin or wound was defined as dichotomous variables as MSSA, MRSA, Streptococcus pyogenes, other staphylococci species, other streptococci species, Corynebacterium, anaerobes (i.e., clostridium), or Gram-negative organisms: present or absent.
23. Date of onset and clearance of bloodstream infection (days) was defined as a continuous variable.
24. Date of source control including drainage, wound debridement, and medical device removal was defined as a continuous variable.
25. *Staphylococcus aureus* cultured from bloodstream was defined as a dichotomous variable: present or absent.
26. Empiric and definitive (based on culture results) antibiotic therapy was defined as dichotomous variables as empiric vancomycin, clindamycin IV or PO, ampicillin/sulbactam, trimethoprim/sulfamethoxazole PO, other definitive therapy vancomycin, daptomycin linezolid IV or PO, ceftaroline, trimethoprim/sulfamethoxazole, clindamycin IV or PO, or piperacillin/tazobactam or other: present or absent.
27. Duration of inpatient antibiotics (days) was defined as a continuous variable.

28. Clinical outcome at discharge was defined as a dichotomous variable as alive, on antibiotics, alive, off antibiotics, left against medical advice (AMA), or deceased: present or absent.
29. Development of complications secondary to ABSSSI infection was defined as a dichotomous variable: present or absent.
30. Development of complications secondary to ABSSSI infection was defined as dichotomous variables as endocarditis, nonvertebral osteomyelitis, vertebral osteomyelitis, or other metastatic sites of infection: present or absent.
31. Reinfection within 30 days was defined as a dichotomous variable: present or absent.
32. Thirty day follow-up status was defined as dichotomous variables as deceased, alive, no readmission, readmission, infection related, readmission, non-infection-related, or other: present or absent.
33. ABSSSI-associated BSI was the primary dependent outcome variable and was determined via diagnosis verified in the patient's medical chart. ABSSSI-associated BSI was defined as individuals who had ABSSSI with BSI on admission or who developed BSI within 48 hours of hospital admission and for which the treating physicians had documented ABSSSI as the source of the BSI.
34. Final clinical outcome was defined as dichotomous variables as success with all symptoms resolved and no need for further antibiotics, improved

with some symptoms remaining and requiring further antibiotics and failure, symptoms remaining or change in antibiotics, or need for further surgical intervention.

Data Analysis Plan

Patient characteristics for cases and control patients were collected using the password-protected RedCap® data collection software, which is a comprehensive research data management system created by Vanderbilt University and hosted by Wayne State University. The online data collection tool included the patient's coded identifier number, demographics such as age and gender, vital signs, patient underlying conditions including comorbidities, location prior to hospital admission, laboratory values, and ABSSSI and BSI diagnosis. Data analysis was conducted using SPSS Statistics (Version 23.0, Armonk, NY: IBM Corp.). Data entered into RedCap® can be downloaded directly into SPSS. Data cleaning consisted of routine data analysis of the database for a variety of potential errors including missing responses, typing and coding errors, removal of duplicate data, removing spaces, and fixing dates and times. Data checks also included evaluating the database for data that were out of range, inconsistent, or had extreme values. Any missing values were treated to minimize their impact by assigning a suitable value or discarding them using a methodically decision process (e.g., case or pair wise deletion). This study had the following research questions: Are there significant differences in clinical and socioeconomic factors between patients with ABSSSI and ABSSSI with BSI in intercity Detroit? Is race/ethnicity associated with disease severity

(based on surgical interventions [e.g., incision and drainage, wound debridement, amputation]) among patients with ABSSSI-related BSI?

With respect to data analysis, descriptive statistics was used to characterize cases and controls. Continuous variables were compared by Student *t* test if normally distributed and Mann-Whitney U test if the normality assumption is not met. Categorical variables were evaluated using Pearson's chi-square test or, as necessary, a two-tailed Fisher's exact test. Regarding Research Hypothesis 1, patients with ABSSSI had different sociodemographic and clinical factors compared to patients with ABSSSI-associated BSI, the relationship between sociodemographic and clinical factors and the development of BSI was first examined using bivariate tests such as chi-square for categorical variables with Yates' correction where appropriate and Student independent *t*-test for continuous variables. All variables with a p value of ≤ 0.1 in the unadjusted analyses were included in a multivariable logistic model, which controls for confounding variables (Bursac, Gauss, Williams, & Hosmer, 2008). A backwards-stepwise elimination approach was used to eliminate the variable with the largest p value at each step. The Hosmer-Lemeshow statistic was used to evaluate the predicted and observed probability to test for evidence of a lack of a model fit (Paul, Pennell, & Lemeshow, 2013). Relationships between the predictor variables (e.g., race/ethnicity; comorbid conditions such as renal failure, diabetes, and cardiovascular disease etc.) and BSI were evaluated using the odds ratio and corresponding 95% confidence interval.

Research Question 2 was designed to examine whether race/ethnicity is associated with disease severity (based upon surgical interventions [e.g., incision and drainage,

wound debridement, amputation]). The impact of race/ethnicity on severity was evaluated using multivariable logistic regression. Bivariate analysis was performed initially. All variables with a *p* value ≤ 0.1 from the unadjusted analyses were included in the logistic model. A backwards-stepwise elimination approach was used to eliminate the variable with the largest *p* value at each step(Bursac et al., 2008). The Hosmer-Lemeshow statistic was used to compare the predicted versus observed values to test the goodness of fit (Paul et al., 2013). The results for Research Question 2 were evaluated using the odds ratio and the 95% confidence interval. For all analyses, a *p* value of < 0.05 was considered to be statistically significant.

Threats to Validity

Both internal and external threats to validity may affect the study results. Internal threats include misclassification, which is also referred to as a measurement error, could be a threat to the study validity. Misclassification can occur in the classification of the exposure or the disease (Aschengrau, 2008). In this investigation, comorbid conditions and the severity of the conditions such as diabetes, renal failure, and cardiovascular disease (exposure) had the potential for misclassification as these conditions were often documented via patient history at the time of admission. In addition, misclassification of BSI (disease) was possible because BSI could develop shortly after hospital admission and not be recognized at baseline. In addition, it was possible that BSI could be recorded as attributed to ABSSSI when the actual infection source was not detected during hospital admission. With respect to BSI, the diagnosis of BSI was only considered when diagnosed within 48 hours of admission and directly attributed to ABSSSI with no other

likely source of infection. External validity threats included investigator interpretation of the data including generalization of the data across different populations (Creswell, 2009). It was possible that the findings from the population of Detroit were unique and not easily generalizable to different patient populations. It was also possible that advancement in technologies including diagnostic techniques may reduce the significance of these findings including the associations of patient risk and BSI. Every effort was made in this study to accurately document underlying patient conditions and the diagnosis of BSI to avoid exposure and disease misclassification.

Ethical Procedures

To ensure that the research met all human investigational compliance, the research proposal was submitted to the Walden University IRB (IRB# 2-17-16 0303767); Wayne State University's IRB (IRB # 010616MIE; 12/14/15), which served as the IRB for the DMC; and coordinating IRB for the Henry Ford Hospital IRB (IRB # 10245; 1-8-16). In addition, the research proposal was submitted to the DMC Research Committee (DMC # 13730; 12/16/15) in order to gain access to the electronic medical record database. An expedited approval was obtained with an informed consent waiver because the study was a retrospective design. All data were de-identified to ensure patient confidentiality, and HIPAA guidelines were followed to protect patient rights. Data were collected on an Internet password electronic data collection form (RedCap®) developed by Vanderbilt University and hosted by Wayne State University. The data will be maintained for a period of 5 years and then will be destroyed.

Summary

Research design, methods, plan for data access, sample size requirements, patient population, and the planned data analysis were discussed in this chapter. Access to the DMC electronic medical records was obtained through the DMC Research Committee. Access to electronic medical records for Henry Ford Hospital was obtained from Henry Ford Hospital's IRB. In addition, the ethical procedures to protect patient rights were described including IRB evaluation and approval and procedures for data protection. In Chapter 4, I will review the purpose, research questions, and the hypotheses for this investigation, along with a detailed description of the results including descriptive statistics and the results of the bivariate and conditional logistic regression analysis.

Chapter 4: Results

Introduction

The purpose of this case-control study was to identify the risk factors and health outcomes of patients with low socioeconomic status in urban Detroit who had ABSSSI-related *Staphylococcus aureus* BSI. The primary goal of this investigation was to identify characteristics in patients with ABSSSI that were associated with the secondary development of BSI. A secondary goal of this study was to evaluate the impact of race and ethnicity on the severity of ABSSSI and ABSSSI-associated BSI. In this chapter, the results are depicted starting with the study population descriptive analysis, followed by the bivariate and multivariable analysis of the study variables.

Data Collection

A total of 5,267 electronic medical records from the DMC and HFH were reviewed from January 2010 to December 2015. Patients with ABSSSI and ABSSSI with BSI had to be diagnosed and admitted within 48 hours of admission to be considered a community-acquired infection. Patients with necrotizing fasciitis, pyomysitis, burns, gangrene, recent surgery, secondary to animal or human bites, and osteomyelitis were excluded given that these infections can be life threatening, require immediate surgery, and/or have nothing to do with risk factors or severity secondary to BSI. After these exclusions, 392 patients met the study criteria for inclusion.

The study population of 392 patients consisted of 196 cases (ABSSSI + BSI) and 196 controls (ABSSSI) with a median age of 47 years (range 18-96 yrs.) and a male predominance of 59.2% (see Table 3). Based on the sample size of 392 collected in this

study, the minimum sample size of 374 was exceeded to reach a power of 0.8 for a 2-sided significance level of 0.05 to detect an adjusted OR of 2.0 for a risk factor with a known prevalence of 10-20% as stated in Chapter 3. With respect to race, African Americans made up the majority of the study population at 56.1% followed by European Americans at 37.2%, other race/ethnicities at 6.1%, and Asian Americans 0.5%. The most common type of ABSSSI was abscess plus cellulitis accounting for 39.8% of the subjects followed by abscess with 33.2% cases, cellulitis 19.4%, infected wound 7.1%, and ulcers contributing to 0.5% of cases. In terms of sociodemographic characteristics by zip code, 6.9% had less than a high school education, 35.7% were considered below the federal poverty level in terms of income, and 19.1% had no medical insurance. Figure 1 displays the cases and control distribution per zip code for Detroit and non-Detroit areas.

Table 3

Demographic and Clinical Characteristics of Study Population, n = 392

Variable	Population
Age (yr.), mean, +/- (SD)	48.7 (17.4)
Gender, n, (%)	
Male	232 (59.2)
Female	160 (40.8)
Race, n, (%)	
African-American	220 (56.1)
Asian	2 (0.5)
Caucasian	146 (37.2)
Other	24 (6.1)
Sociodemographics by zip code, n, (%)	
>30% < high school education	27 (6.9)
Below poverty level income	140 (35.7)
No Medical insurance, n, (%)	75 (19.1)
Type of ABSSSI, n, (%)	
ABSSSI	130 (33.2)
Cellulitis	76 (19.4
ABSSSI + Cellulitis	156 (39.8)
Infected Wound	28 (7.1)
Ulcer	2 (0.5)
BMI kg/m^2 > 30, n, (%)	170 (43.4)
Staphylococcus aureus BSI, n, (%)	
Methicillin-susceptible	70 (17.9)
Methicillin-resistant	126 (32.1)

Note. Sociodemographic data < 30% high school education and below poverty level income were derived per zip code from federal census data. Status of medical insurance was obtained from the individual patient medical chart.

Figure 1. Case and Control by Zip Code

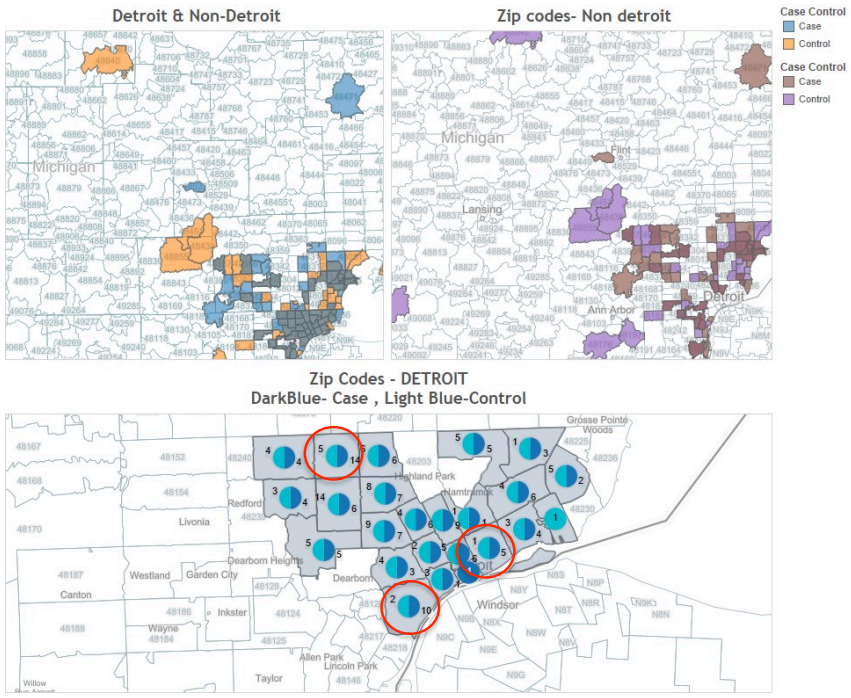

Figure 1. Case and control by zip code. Upper panels depict various zip codes from Detroit and non-Detroit areas from which cases and controls were derived. Bottom panel displays cases and controls per Detroit zip codes. Red circles indicate zip codes where higher rates of cases were observed

Results

Research Question 1 and Hypothesis

1. Are there significant differences in sociodemographic and clinical factors between patients with ABSSSI and patients with ABSSSI-associated bacteremia in intercity Detroit?

H_o1: There are no differences in sociodemographic and clinical factors between patients with ABSSSI and ABSSSI-associated BSI.

H_a1: Patients with ABSSSI have different sociodemographic and clinical factors compared to patients with ABSSSI-associated BSI

Data analysis by chi-square, Fisher's exact test, or Student independent *t*-test, or Mann Whitney U test—where appropriate—of demographic, sociodemographic, and clinical characteristics for patients with ABSSSI with BSI and ABSSSI are listed in Table 4. Individuals with ABSSSI + BSI were significantly older ($p< 0.001$) and were predominately male ($p = 0.008$) compared to those with ABSSSI. There were no significant differences observed with respect to race or sociodemographic characteristics by zip code such as education, median income levels including poverty, or the type or presence of medical insurance. Individuals with ABSSSI + BSI had a higher percentage of abnormal temperature, elevated WBC counts, and acute renal failure on hospital admission ($p< 0.001$). In addition, individuals with ABSSSI + BSI had a higher percentage of cellulitis and infected wounds or ulcers whereas individuals with ABSSSI had a higher percentage of abscess or abscess in combination with cellulitis ($p<0.001$). Figure 2 displays infection type for those with ABSSSI + BSI and ABSSSI. Although there was no difference in the infection site (e.g., upper versus lower extremity, $p = 0.930$), individuals with ABSSSI tended to have a higher rate of methicillin-resistant *S. aureus* ($p = 0.004$).

Table 4

Demographics, Sociodemographic, and Clinical Characteristics of Cases and Controls

Variables	ABSSSI + BSI *n* = 196	ABSSSI *n* = 196	*p* Value
Age (yr.), mean+/-(SD)	52.4 (18.4)	45.3 (15.5)	< 0.001
Gender, n, (%)			0.008
Male	129 (65.8)	103 (52.6)	
Female	67 (34)	93 (47.0	
Race, n, (%)			0.520
African-American	112 (57.1)	108 (55.1)	
Asian	1(0.5)	1 (0.5)	
Caucasian	68 (34.7)	78 (39.8)	
Other	15 (7.7)	9 (4.6)	
Sociodemographics by zip code, n, (%)			
Education >30% No High School	18 (9.2)	9 (9.6)	0.073
Median Income < poverty	78 (39.8)	62 (31.6)	0.092
Medical Insurance, n, (%)	39 (19.9)	36 (18.4)	0.399
BMI>30 kg/m^2, n, (%)	79 (41.6)	91 (46.4)	0.340
Abnormal Temperature, n, (%)	87 (44.4)	38 (19.4)	<0.001
Elevated WBC, n, (%)	138 (60.3)	91 (39.7)	<0.001
Acute Renal Failure, n (%)	98 (50)	48 (24.5)	<0.001
Type of ABSSSI, n (%)			<0.001
Abscess	56 (28.6)	74 (37.8)	
Cellulitis	56 (28.6)	20 (10.2)	
Abscess + Cellulitis	58 (29.6)	98 (50)	
Infected Wound	24 (12.2)	4 (2)	
Ulcer	2 (1)	0 (0)	
Infection Site, n, (%)			0.930
Upper Extremity	46 (23.5)	65 (33.2)	
Lower Extremity	84 (42.9)	83 (42.3)	
Head/Neck	31 (15.9)	20 (10.2)	
Torso/Trunk	35 (17.9)	28 (14.3)	
Methicillin-Resistant *S. aureus*, n, (%)	126 (64.3)	152 (77.7)	0.004
Polymicrobial, n, (%)	21 (10.8)	22 (11.2)	0.886

Note. Chi-square/Fisher's exact test was used for categorical variables, and Mann-Whitney U test for continuous variables.

Comorbid underlying conditions, patient characteristics, and clinical outcomes are listed in Table 5. As can be seen by the Charlson comorbidity index median and IQR, individuals with ABSSSI + BSI tended to have a higher number of underlying conditions such as chronic renal failure and diabetes that were associated with 1-year mortality compared to individuals with ABSSSI ($p< 0.001$). The distribution of comorbid conditions between ABSSSI + BSI and ABSSSI are depicted in Figure 3. The most common underlying conditions were diabetes, hypertension, and intravenous drug use. Of interest, these three conditions were significantly ($p = 0.003$, $p = 0.007$, $p = 0.012$, respectively) higher in patients with ABSSSI + BSI. In addition, there were significantly more patients with ABSSSI + BSI who had previous hospitalization within 180 days of hospital admission ($p < 0.001$) and who had a prior infection with methicillin-susceptible *S. aureus* within 60 days of hospital admission ($p = 0.014$). There were also a higher percentage of patients with ABSSSI + BSI who had an infectious diseases consult, were admitted to the intensive care unit, and experienced a longer hospital stay ($p < 0.001$). In addition, patients with ABSSSI + BSI had an increased hospital mortality ($p < 0.001$), a higher clinical failure rate at discharge ($p = 0.003$), more surgical complications such as incision and drainage at bedside ($p < 0.001$), and a higher amount of reinfection within 30 days of hospital discharge ($p = 0.006$). Antibiotic treatment for ABSSSI and BSI and ABSSSI is depicted in Figure 4. Vancomycin was the most commonly used antibiotic overall. Of interest, a significantly ($p = 0.001$) higher percentage of patients with ABSSSI + BSI were treated with vancomycin compared to those with ABSSSI (79.1 versus 64.3%). Clindamycin was the second most common antibiotic administered.

Although the use of clindamycin was higher in patients with ABSSSI (27 versus 18.9%), this difference was not statistically significant ($p = 0.055$). While cephalexin use was significantly ($p = 0.030$) higher in patients with ABSSSI, the overall use was low (6 versus 0, respectively).

Table 5

Comorbid Conditions, Patient Characteristics, and Clinical Outcomes

Variable	ABSSSI + BSI	ABSSSI	*p* Value
Comorbid Conditions			
Chronic Renal Failure, n, (%)	25 (12.9)	8 (4.1)	0.002
Hepatic Disease, n, (%)	18 (9.2)	4 (2.6)	0.005
Diabetes, n, (%)	76 (38.8)	49 (25.0)	0.003
Paraplegia, n, (%)	4 (2)	0 (0)	0.440
Hypertension, n, (%)	88 (44.9)	62 (31.6)	0.007
Congestive Heart Failure, n, (%)	19 (9.7)	7 (3.6)	0.015
IV Drug Use, n, (%)	44 (22.4)	25 (12.8)	0.012
Charlson Comorbidity Index, median, (IQR)	2 (1-5)	1 (0-3)	<0.001
Corticosteroids, n, (%)	2 (1)	1 (0.5)	0.562
Prior hospitalization 180 days, n, (%)	63 (32.1)	25 (12.8)	<0.001
Prior antibiotic use past 30 days, n (%)	18 (9.2)	16 (8.2)	0.720
Prior MSSA infection 60 days, n, (%)	6 (3.1)	0 (0)	0.014
Prior MRSA infection 60 days, n, (%)	11 (5.6)	7 (3.6)	0.334
History of ABSSSI past 60 days, n, (%)	22 (11.2)	14 (7.1)	0.162
Clinical Outcomes			
ID Consult	115 (5.7)	54 (27.7)	<0.001
Admission to ICU, n, (%)	25 (12.8)	5 (2.6)	<0.001
Length of hospital stay, (d), mean, (SD)	7.4 (5.7)	2.7 (2.2)	<0.001
Clinical failure at discharge, n, (%)	22 (11.3)	7 (3.6)	0.003
In hospital mortality, n (%)	8 (4.1)	0 (0)	<0.001
Complications, n (%)	7 (3.6)	1 (0.5)	0.034
Surgery, n, (%)	106 (54.1)	118 (60.5)	0.199
Incision and drainage at bedside, n, (%)	37 (18.9)	88 (44.9)	<0.001
Incision and drainage at OR, n (%)	68 (34.7)	76 (38.8)	0.402
Wound debridement, n (%)	9 (4.6)	6 (3.1)	0.300
Re-infection within 30 days, n, (%)	22 (11.2)	8 (4.1)	0.006

Note. The Charlson Comorbidity Index predicts the one-year mortality for a patient with a range of comorbid conditions. Chi-square or Fisher's Exact test was used for categorical variables and Mann-Whitney U test was used to analyze continuous variables.

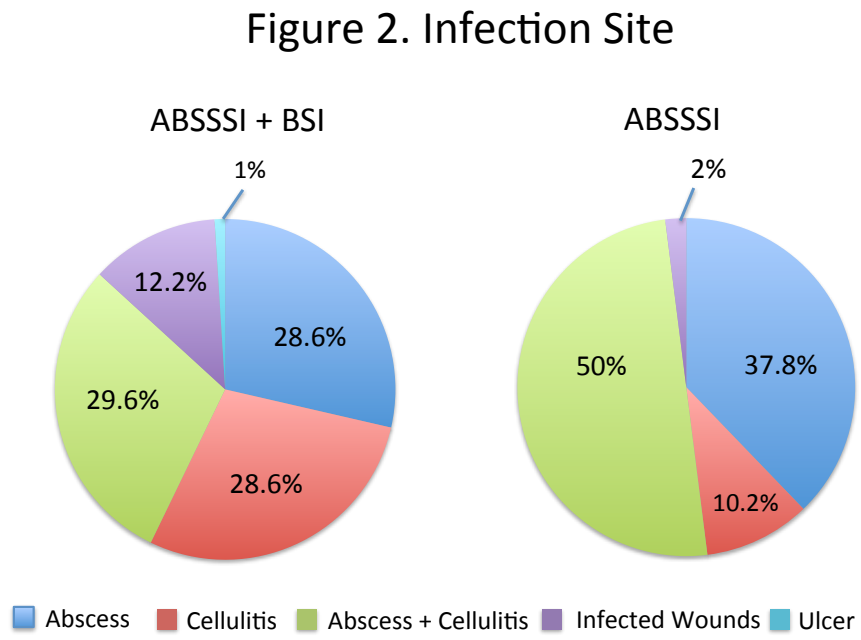

Figure 2. Infection type comparisons between ABSSSI + BSI and ABSSSI.

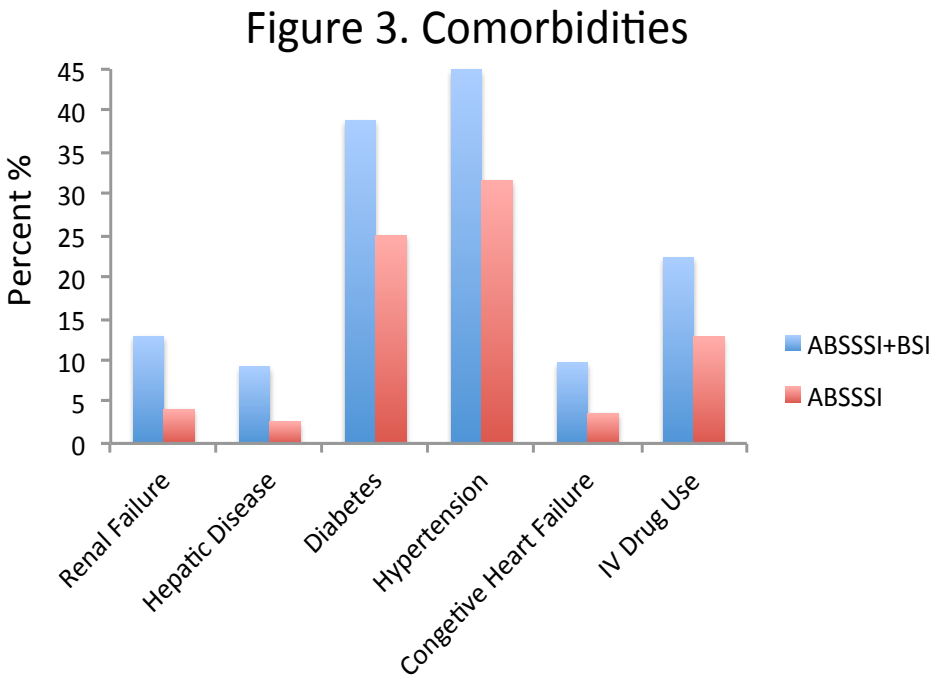

Figure 3. Comparison of comorbidities for ABSSSI + BSI and ABSSSI patients.

Figure 4. Antibiotic Treatment

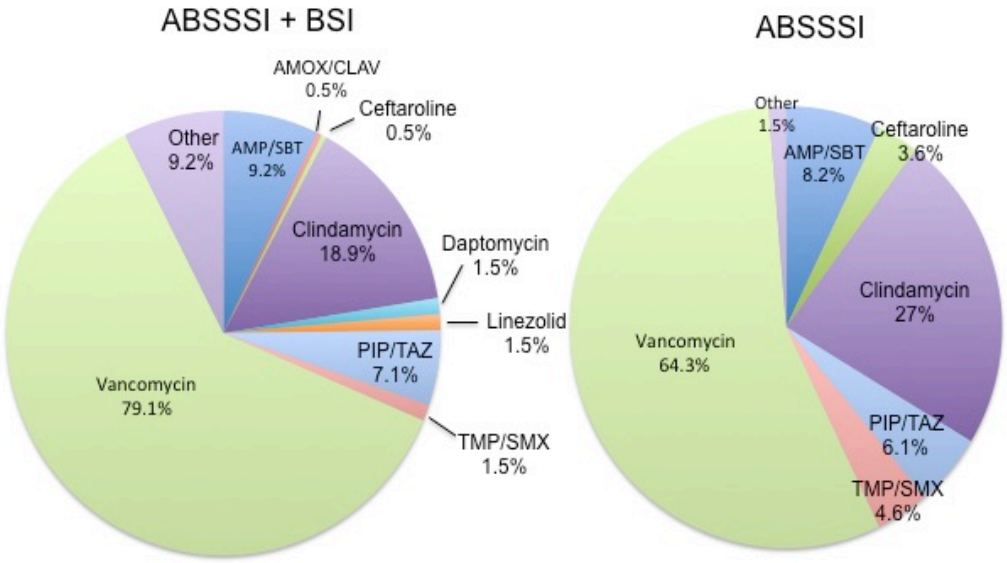

Figure 4. Comparison of antibiotic treatment for ABSSSI + BSI versus ABSSSI patients.

Table 6 displays the results of the logistic regression analysis of all demographic, sociodemographic, and clinical characteristics that met the minimal *p* value of < 0.1 via bivariate analysis. According to the results from the logistic regression analysis, males had higher odds of being ABSSSI + BSI than females; with an *aOR* of 1.85, 95% CI 1.11-3.66 had acute renal failure, *aOR* 2.08, 95% CI 1.18-3.67 ($p = 0.011$), and abused intravenous drugs, *aOR* 4.38, 2.22-8.62 ($P < 0.001$). Additional risk variables that remained in the model and were significant for ABSSSI +BSI included prior hospitalization within 180 days of hospital admission with an *aOR* of 2.41, 95% CI 1.24-4.93 ($p = 0.01$); abnormal temperature, *aOR* 2.86, 95% CI 1.66-4.93 ($p < 0.001$); and, elevated WBC count, *aOR* 4.26, 95% CI 2.43-7.47 ($p < 0.001$) compared to individuals with ABSSSI. Compared to ABSSSI + BSI, individuals who had ABSSSI and abscess or

abscess and cellulitis were protected from bloodstream infection with an *aOR* of 0.220, 95% CI 0.11-0.46 and *aOR* 0.139, 95% CI 0.07-0.28 ($p \leq 0.001$), respectively. The Hosmer-Lemeshow goodness of fit test was not significant ($p = 0.305$) indicating that there was no evidence of a lack of model fit. On the basis of these findings, Research Question 1 hypothesis was rejected, and the alternative hypothesis was accepted indicating that patients with ABSSSI-associated BSIs had significant differences in sociodemographic and clinical factors compared to patients with ABSSSI.

Table 6

Logistic Regression Analysis of Patient Risk Factors for ABSSSI+BSI

Factor	Unadjusted *OR*	95% Confidence Interval	Adjusted *OR*	95% Confidence Interval
Sex (Male)	1.74	1.16-2.61	1.85	1.11-3.66
High School >30% < HS by Zip Code	2.10	0.92-4.80	2.91	0.98-8.64
Acute Renal Failure	3.08	2.0-4.74	2.08	1.18-3.66
IV Drug Use	1.98	1.16-3.39	4.38	2.22-8.62
Charlson Comorbidity Index	1.29	1.18-1.42	1.13	0.99-1.28
Prior Hospitalization within 180 days	3.24	1.93-5.43	2.41	1.24-4.70
Abnormal Temperature	3.25	2.07	2.86	1.66-4.93
Elevated WBC	2.75	1.81-4.16	4.26	2.43-7.47
Abscess	0.659	0.432-1.01	0.220	0.11-0.46
Abscess + Cellulitis	0.420	0.28-0.64	0.139	0.07-0.28

Hosmer-Lemeshow $p = 0.305$

Note. High school > 30% <HS by zip code= indicates a zip code where >30% of population of has not completed high school, Charlson comorbidity index predicts the 1-year mortality for a patient with a range of comorbid conditions, abnormal temperature = temperature > or < 98.6^0 F, elevated WBC = WBC count > 11 x 10^9 cells/liter. Referent group for the following covariates are listed here: male versus female, high school < 30% by zip code versus all other zip codes, acute renal failure versus no renal failure, IV drug use versus no drug use, Charlson comorbidity index; individuals grouped by scores (0-4 and > 4) referent group ≤ 4, prior hospitalization within 180 days versus no hospitalization, abnormal normal temperature and elevated WBC versus normal temperature and WBC, abscess or abscess + cellulitis versus all other types of infection.

Research Question 2 and Hypothesis

2. Is race/ethnicity associated with disease severity (based upon surgical interventions [e.g., incision and drainage, wound debridement, amputation, shock or admission to the ICU]) among ABSSSI-associated BSI?

$H_0$2: Race/ethnicity is not associated disease severity (based upon surgical interventions [e.g., incision and drainage, wound debridement, amputation, shock, or admission to the ICU]) among patients with ABSSSI-associated BSI.

H_a2: Race/ethnicity is associated with disease severity (based upon surgical interventions [e.g., incision and drainage, wound debridement, amputation, shock, or admission to the ICU]) among patients with ABSSSI-associated BSI.

The second research question in this study was designed to evaluate whether race and ethnicity had an impact on the severity of diseases. Analysis of this question by bivariate analysis using chi-square or Fisher's exact test for categorical variables and Mann-Whitney U test for continuous variables is displayed in Table 7. I found that, compared to all other race/ethnicities, African Americans had a higher percentage (66.9 versus 48.3%, $p<0.001$) of severe disease versus nonsevere disease, whereas individuals who were European American had a low rate of severe disease (47 versus 99%, $p = 0.002$) compared to other race/ethnicities.

Table 7

Demographic, Sociodemographic, and Clinical Characteristics by Severity

Variables	Nonsevere n = 226	Severe n = 166	*p* Value
Age (yr.), mean+/-(SD)	48.5 (18.1)	49.3 (16.2)	0.645
Gender, n, (%)			0.213
Male	140 (61.9)	92 (55.4)	
Female	86 (38.1)	74 (44.6	
Race, n, (%)			
African-American	109 (48.3)	111 (66.9)	<0.001
Asian	2(0.9)	0 (0.0)	0.510
Caucasian	99 (43.2)	47 (28.3)	0.002
Other	16 (7.1)	8 (4.8)	0.401
Sociodemographics by zip code, n, (%)			
Education >30% No High School	18 (8.0)	9 (5.4)	0.420
Median Income < poverty	85 (37.6)	55 (33.1)	0.394
Medical Insurance, n, (%)	42 (18.6)	33 (18.9)	0.795
BMI>30 kg/m^2, n, (%)	93 (41.7)	77 (47.2)	0.300
Abnormal Temperature, n, (%)	62 (27.4)	62 (37.3)	0.024
Elevated WBC, n, (%)	113 (50.0)	116 (69.9)	<0.001
Acute Renal Failure, n (%)	73(32.3)	73 (44.0)	0.012
Type of ABSSSI, n (%)			
Abscess	75 (33.26)	55 (33.1)	0.540
Cellulitis	66 (29.2)	10 (6.0)	<0.001
Abscess + Cellulitis	73 (32.3)	83 (50)	<0.001
Infected Wound	12.0 (5.3)	16 (9.6)	0.114
Ulcer	0.0 (0.0)	2 (1.2)	0.179
Infection Site, n, (%)			0.400
Upper Extremity	69 (30.5)	42 (25.3)	
Lower Extremity	93 (41.2)	74 (44.6)	
Head/Neck	32 (14.2)	19 (11.4)	
Torso/Trunk	32 (14.2)	31 (18.7)	
Methicillin-Resistant *S. aureus*, n, (%)	156 (69.0)	122 (73.5)	0.369
Polymicrobial, n, (%)	19 (8.4)	24 (14.5)	0.071
Comorbidities			
Chronic Renal Failure, n, (%)	16 (7.1)	17 (10.2)	0.265
Hepatic Disease, n, (%)	15 (6.6)	8 (4.8)	0.519
Diabetes, n, (%)	67 (29.6)	58 (34.9)	0.266
Paraplegia, n, (%)	1 (0.4)	3 (1.8)	0.315
Hypertension, n, (%)	79 (35.0)	62 (31.6)	0.116
Congestive Heart Failure, n, (%)	12 (5.5)	14 (8.4)	0.226
IV Drug Use, n, (%)	37 (16.4)	32 (19.3)	0.455
Charlson Comorbidity Index[a], median, (IQR)	2 (0-4)	2 (1-5)	0.369
Corticosteroids, n, (%)	1 (0.4)	2 (1.2)	0.576
Prior hospitalization 180 days, n, (%)	63 (32.1)	45 (27.1)	0.058
Prior antibiotic use past 30 days, n (%)	14 (6.2)	20 (12.0)	0.042
Prior MSSA infection 60 days, n, (%)	6 (2.7)	12 (7.2)	0.408
Prior MRSA infection 60 days, n, (%)	11 (5.6)	7 (3.6)	0.033
History of ABSSSI past 60 days, n,(%)	16 (7.1)	20 (12.0)	0.092

Note. The Charlson comorbidity index predicts the one-year mortality for a patient with a range of comorbid conditions.

Table 8 displays the results of the logistic regression analysis of ABSSSI + BSI and ABSSSI patient risk factors by severity. After controlling for confounding variables, African American race and elevated WBC count remained in the model and were significantly (p=0.001) associated with severe infection, *aOR* 2.18, 95% CI; 1.38-3.4 and *aOR* 2.24, 95% CI; 1.41-3.55, respectfully. In addition, prior hospitalization within 180 days of admission was also significantly (p=0.010) associated with severe disease, *aOR*, 2.07, 95% CI; 1.19-3. Although renal failure and polymicrobial ABSSSI had an increased association with severe infection (i.e., with *aOR* of 2.26, 95% CI; 0.932-5.5 and *aOR* of 1.87, 95% CI; 0.930-3.74), these were not statistically significant (p=0.071, 0.079). On the basis of these findings, Research Question 2 and Hypothesis 2 was rejected, and the alternative hypothesis was accepted indicating that race/ethnicity was associated with disease severity (based upon surgical interventions [e.g., incision and drainage, wound debridement, amputation, shock, or admission to the ICU]) among patients with ABSSSI-associated bloodstream infections.

Table 8

Logistic Regression Analysis of Patient Risk Factors by Severity

Factor	Unadjusted *OR*	95% Confidence Interval	Adjusted *OR*	95% Confidence Interval
African American	2.17	1.43-3.28	2.18	1.38-3.44
Elevated WBC	2.32	1.52-4.5	2.24	1.41-3.55
Acute Renal Failure	1.50	0.73-3.06	2.26	0.932-5.49
Cellulitis	0.155	0.087-0.31	0.202	0.92-0.44
Abscess + Cellulitis	3.0	1.39-3.17	1.65	1.03-2.65
Polymicrobial	1.84	0.97-3.49	1.86	0.930-3.74
Prior Hospitalization 180 days	1.58	0.98-2.56	2.07	1.193-3.59

Hosmer-Lemeshow p = 0.843

Note. Referent groups for the following covariates are listed here: African Americans versus all other races, elevated WBC > 11 x 10^9 cells/ L versus < 11 x 10^9 cells/L, acute renal failure versus no renal failure, cellulitis and abscess + cellulitis versus all other skin infection types, polymicrobial infection versus all other types of infection, prior hospitalization 180 days versus no infection.

Summary

In Chapter 4, I provided an overview of the data results analyzed for this research investigation. With regards to the first research question on whether sociodemographic and clinical factors differed between patients with ABSSSI + BSI and ABSSSI, I found that there were several factors that were associated with ABSSSI + BSI including the presence of acute renal failure, a history of intravenous drug use or prior hospitalization, and abnormal temperature and elevated WBC count. ABSSSI that was classified as abscess or abscess plus cellulitis appeared to be protective. With regards to the second research question on whether race and ethnicity was associated with severity of disease, African Americans were more likely to have a more severe disease. An elevated WBC count on admission, a history of prior hospitalization, and the diagnosis of abscess +

cellulitis were also associated with severe disease. In Chapter 5, I will provide an in-depth discussion of the results and their implications as well as concluding statements, intervention recommendations, and the impact of these findings on social change.

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction

The purpose of this investigation was to determine the risk factors that were associated with patients who had *Staphylococcus aureus* ABSSSI with BSI versus individuals who had ABSSSI without BSI from the city of Detroit. The study design was a case control retrospective evaluation. Data collection consisted of evaluating electronic medical charts from two medical centers from January 2010 until December 2015. The DMC and HFH are major medical centers located in downtown Detroit that serve the population of Detroit as well as the surrounding Detroit Metropolitan areas. ABSSSI + BSI (cases) were defined as an individual who had ABSSSI + BSI with BSI diagnosed within 48 hours of hospital admission. Individuals with ABSSSI but without BSI served as the study controls (Lipsky, Kollef, et al., 2010). Overall, 392 patients (196 cases, 196 controls) who were diagnosed with ABSSSI + BSI and ABSSSI made up the study population. Descriptive statistics and logistic regression models were used to analyze Research Question 1 and 2 that dealt with the risk factors for ABSSSI + BSI as well as determining the impact of race and ethnicity on the severity of disease. BSIs are associated with serious complications including mortality. Evaluating risk factors that maybe unique to the population of Detroit was important to identify potential cases early and to direct optimized medical intervention to avoid these complications. In addition, determining whether race and ethnicity had an impact on the severity of disease was important because the city of Detroit has a predominant African American population,

and this underserved population has been previously reported to have higher rates of medical complications.

Interpretation of Findings

Research Question 1

The first research question was designed to determine if there were risk factors for patients who had ABSSSI and acquired BSI who resided in intercity Detroit. This was accomplished by determining if there were any significant differences in clinical or socioeconomic factors between patients with ABSSSI and ABSSSI with BSI. Although limited data exist, several researchers have examined the relationship between patient characteristics and BSI in individuals with ABSSSI, which included the acquisition of MRSA from the community (Tattevin et al., 2012), old age, male sex, coronary heart disease, the presence of infected prosthetic devices, health care-associated infections, abnormal WBC counts, and vital signs such as temperature (Lipsky, Kollef, et al., 2010). However, these investigations included patients who acquired their infection in the hospital, making it difficult to extrapolate these findings to community-acquired ABSSSI with BSI. In addition, the contribution of socioeconomic factors was not examined. I also found that older age, male gender, abnormal temperature, and elevated WBC count on hospital admission was significantly associated with ABSSSI with BSI by descriptive statistical analysis (Table 2). Other factors that were statistically significant for ABSSSI with BSI was the presence of MRSA, prior hospitalization within the last 180 days, and prior MSSA infection within the last 60 days. In addition, < 30% high school education by zip code was significantly associated with ABSSSI with BSI. Although income and

other sociodemographic characteristics had been previously evaluated for MRSA infections, the relationship between education level and ABSSSI with BSI had not been reported previously. In the present study, there were a number of comorbid conditions (Table 3) that were found to be associated with ABSSSI with BSI such as acute and chronic renal failure, hepatic disease, diabetes, hypertension, congestive heart failure, and IV drug use. Several of these factors had been previously reported. However, these scholars focused only on hospitalized patients and, therefore, the data may not be generalizable to patients who derived BSI in the community (Lipsky, Kollef et al., 2010). The number of comorbid conditions present on admission was significant for ABSSSI with BSI and, though this relationship has not been previously reported, it may be useful for predicting whether a patient may be at increased risk for ABSSSI with BSI. As expected, a significantly higher percentage of patients with ABSSSI with BSI required an infectious disease consult, were admitted to the ICU, deemed a failure at time of discharge, and had a higher rate of mortality and reinfection within 30 days of discharge. After adjusting for confounding variables in a logistic regression model (Table 4), male sex, high school < 30% by zip code, acute renal failure, Charlson comorbidity index, IV drug use, prior hospitalization within the last 180 days, abnormal temperature, and elevated WBC were independent predictors of ABSSSI with BSI. Further, abscess or abscess plus cellulitis appeared to have a protective effect (*aOR* 0.220, 0.139, respectively). The most probable explanation for this protective effect may be related to routine medical intervention that commonly includes surgical incision and drainage of the abscess. In many cases, this removes the focus of the infection and, therefore, likely

protects the patients from BSI as a complication of ABSSSI (Moran et al., 2013; Pollack, et al., 2015; Stevens et al., 2014).

Research Question 2

In the second research question, I evaluated whether race/ethnicity was associated with disease severity. A composite definition was used to define severity, which consisted of incision and drainage in the operating room, wound debridement, amputation, and admission to the ICU or shock with patients with ABSSSI or ABSSSI-associated BSI. African Americans have significantly higher rates of SSTIs compared to European Americans (Ray et al., 2013a). In general, African Americans of low socioeconomic status have a higher rate of persistent infection, higher readmission rates, and increased infection complications (Acosta et al., 2013; Morris et al., 2014; Zajacova, Dowd, & Aiello, 2009). However, the impact of ethnicity on severity of disease in patients with ABSSSI and ABSSSI with BSI has not been evaluated.

In the current study, when the cohort was evaluated by bivariate analysis on the basis of severity, African Americans had a significantly higher amount of cases classified as severe (66.9 versus nonsevere 48.3%) while European Americans had a significantly lower amount of cases classified as severe (28.3 versus 43.8%, respectively). Besides having abnormal temperature and elevated WBC on admission, individuals with more severe disease had a higher percentage of acute renal failure as well as a higher percentage of cellulitis and abscess and prior antibiotic use in the past 30 days. When evaluated by logistic regression controlling for potential confounding, African American race, elevated WBC, the presence of abscess plus cellulitis, and prior hospitalization

within the past 180 days remained in the model and had a significantly higher odds of having more severe disease than other groups. Individuals diagnosed with cellulitis without abscess had a significantly lower odds ratio (*aOR* 0.202) for severe disease, which may indicate that cellulitis without abscess may have a protective effect. Individuals with abscess are more likely to have surgical drainage as a part of their treatment intervention. Surgical drainage removes the foci of infection and improves the likelihood of antibiotic success (Moran et al., 2013; Pollack, 2015; Stevens, 2014). This procedure likely prevents patients' localized infection (abscess) from spreading into the surrounding tissue causing cellulitis and potentially BSI. Individuals with abscess and cellulitis already have an extensive infection that has spread into the surrounding tissues and, thus are, more likely to acquire BSI.

Theoretical Framework

The theoretical framework that was chosen for this study was the web of causation. Causation is the event or condition that leads to the outcome of interest. It provides a mechanism that helps to explain the process that leads to the development of disease. Preceding events or conditions lead to the outcome of interest (Kreiger, 1994). Disease development can be related to a variety of factors including underlying genetic abnormalities, microorganisms, environmental factors, and social and behavioral characteristics (Norton, 2015). In the present study, the web of causation applied because the mechanisms in which a patient with ABSSSI acquires BSI had not been defined. Although BSI is known to be a severe complication of ABSSSI, the underlying patient characteristics and conditions that lead to BSI are not known. Further, it is not known if

sociodemographic conditions or race/ethnicity may contribute to the acquisition of BSI or the severity of the disease. African-American race, diabetes, renal failure, hypertension, congestive heart failure, intravenous drug use, prior MRSA infections, prior hospitalization and antibiotic use are some of key risk factor findings in this study that were linked to ABSSSI + BSI and severity of disease. Understanding the factors that contribute to ABSSSI and ABSSSI with BSI—especially as it relates to a relatively underserved population in the city of Detroit—is important for prevention and treatment interventions that could avoid these complications.

Limitations of the Study

This study was a retrospective study design and, therefore, was subject to all of the potential biases associated with this type of investigation. For example, it was possible that there may be missing or incomplete data recorded in the medical charts. While it appeared that incomplete or missing data was minimal during the data collection, it is possible that some data was not recorded or was recorded incorrectly. Another potential limitation was the assumption that in patients with the diagnosis of cellulitis and BSI, the *S. aureus* identified in the bloodstream originated from the patient's cellulitis. Cellulitis is a deep-seated infection of the subcutaneous tissues of the skin and, thereby, difficult to culture the pathogen causing disease. While *S. aureus* is a pathogen associated with cellulitis, other bacterial pathogens such as streptococci are also a frequent cause of cellulitis (Dryden, 2010; Stevens et al., 2014). Therefore, although unlikely, cases of BSI where cellulitis without abscess was identified as the infection type may have been misclassified. Additionally, I evaluated the impact of race and ethnicity

on severity of disease. The composite definition for severity included amputation. However, there were no amputations recorded in the population cohort. It was possible that the exclusion of diabetic foot infections from this study may be the most likely reason for the lack of amputations because surgical intervention including amputation is common among this population. Further, one of the objectives of this investigation was to determine whether sociodemographic characteristics were associated with ABSSSI with BSI. However, this information was derived by zip code that was provided through federal census data. Individual information on education and level of income was not available on an individual basis; therefore, the information was limited. Lastly, the study was conducted on a population of individuals who reside in Detroit or its immediate surrounding areas. It is possible that the results of this investigation cannot be extrapolated to other metropolitan populations.

Recommendations for Future Research

Although a number of potential risk factors that may be associated with ABSSSI with BSI were identified in this investigation including race, additional research should be explored elsewhere to confirm that race or access to medical care is the most likely explanation for this finding. African Americans have been previously identified as at risk for a number of infection related diseases and complications (Klevens, et al., 2007; Ray et al., 2012). However, it is unclear whether this finding is related to race/ethnicity issues or lower socioeconomic status in this population and, therefore, poor access to medical care. Although < 30% high school education by zip code was significantly associated with ABSSSI and BSI, level of income was not. It was possible that the measurement of

these factors by zip code may not be sensitive enough to delineate a relationship between sociodemographic characteristics and ABSSSI with BSI. Future research investigating the relationship between ABSSSI with BSI and sociodemographic factors should evaluate this information on an individual basis. Understanding the relationship between sociodemographic characteristics and complications of infection could lead to interventions including risk assessment for disease development.

Recommendations for Future Action

In this study, I examined a population in urban Detroit Michigan at risk for ABSSSI and ABSSSI with BSI. Although risk factors have been evaluated in patients hospitalized for ABSSSI, there are limited studies on the risk for BSI in patients with ABSSSI from the community (Lipsky, Kollef, et al., 2010). In addition, there are no investigations on the risk for BSI in patients with ABSSSI from an urban environment such as Detroit. It is important to evaluate intercity populations for disease risk for infection because these populations often are of lower socioeconomic status and, therefore, are at risk due to limited access to appropriate medical care (Khabbaz et al., 2014; Lantz & Prichard, 2010). Individuals of lower socioeconomic status are more likely to delay seeking medical attention and are at risk for increased complications including hospitalization, surgery, relapse, and readmission (Acosta et al., 2013; Ray et al., 2013a). A delay in seeking medical attention for ABSSSI can lead to the acquisition of BSI with severe complications including mortality (Acosta et al., 2013; van Hal, 2012).

Implications for Social Change

Patients with *Staphylococcus* aureus BSIs experience a high degree of complications including metastatic spread leading to severe life threatening infections (Corey, 2009; del Rio et al., 2009). If not appropriately and promptly treated, mortality rates can range from 20-40% (Gould, 2007; Kobayashi, Yokota, Takahashi, Arioka & Fukui, 2014). One of the most severe complications from ABSSSI is BSI. The burden of infection is higher in non-Hispanic Blacks and Mexican Americans (Zajacova et al., 2009). In addition, higher readmission rates, risk of infection, and sepsis have been reported among African Americans (Acosta et al., 2013; Morris et al., 2014). Understanding the characteristics and risks associated in patients with ABSSSI with BSI is important to identify the most appropriate intervention to prevent and reduce these complications. There is a need to direct medical resources and social support to individuals in intercity Detroit who are at risk for ABSSSI and BSI. Partnerships between community organizations, public health authorities, and intercity hospitals are needed to educate, screen, and identify individuals at risk to prevent these infections in this patient population.

Conclusion

The acquisition of BSI secondary to ABSSSI can be severe and include a variety of complications such as spread of infection to other vital organs and tissues, sepsis, and shock leading to death. Understanding the risk factors associated with BSI can lead to preventive interventions to reduce complications including mortality. This is particularly important in patient populations of low socioeconomic status because they have been

demonstrated to have worse clinical outcomes. While this relationship has been previously reported, there is little to no information in patients with low socioeconomic status diagnosed with ABSSSI and BSI. Therefore, a knowledge gap existed regarding this patient population and BSI secondary to ABSSSI. In this study, I identified a number of patient characteristics, including sociodemographic factors such as level of education, that may contribute to BSI in patients with ABSSSI. In addition, several factors including African American race was associated with a higher degree of infection severity. According to these findings, there is a need to include sociodemographic characteristics when evaluating patient health outcomes. Further research is warranted to more fully characterize these risks to prevent these complications in this vulnerable patient population.

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