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Elevated BMI-associated Characteristics of Patients with Invasive MRSA Infection in the Atlanta, Georgia Metro Area, 2005-2008

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ABSTRACT

Lauren R. Lorentzson

Elevated BMI-associated characteristics of patients with invasive MRSA infection in the Atlanta, Georgia metro area, 2005-2008

(Under the direction of IKE S. OKOSUN, MS, MPH, PhD, FRSPH)

INTRODUCTION: The national obesity epidemic is leading to higher rates of Type 2 Diabetes, putting an increasing number of people at risk of exposure to bloodstreams infections with Methicillin Resistant *Staphylococcus aureus* (MRSA) upon onset of end stage renal disease and initiation of hemodialysis. While the risk of invasive bacterial infection in patients undergoing hemodialysis is well documented, a link between greater adiposity and risk of invasive MRSA infection has not been researched.

AIM: The purpose of this study is to describe the epidemiological characteristics of patients with invasive MRSA in the Atlanta, Georgia metro area between 2005-2008; to examine associations between BMI-related health outcomes within the cohort; and to compare the proportions of BMI categories in this cohort to Georgia BRFSS BMI data.

METHODS: Population-based surveillance data collected by the CDC EIP ABCs program on invasive cases of MRSA in metro Georgia was used. BMI was calculated for each case with sufficient height and weight data. Statistical analysis was carried out in SPSS. Univariate and multivariate binary logistic regression analysis was performed on select variables. A p-value of < 0.05 and a 95% confidence interval (CI) were used to determine significance. BRFSS BMI data for Georgia was compared to the study population.

RESULTS: Overweight (BMI=25-29.9) and obese (BMI=30+) cases were more likely to be diagnosed with diabetes compared to individuals of normal BMI in both univariate and multivariate analysis. Invasive MRSA patients suffering from diabetes were at greater odds of having undergone dialysis within the previous year (*univariate analysis* OR=2.3, p=0.000; *multivariate analysis* OR=2.5, p=0.000). The proportion of invasive MRSA patients within this cohort with diabetes is much greater (42.8%) than in the general population of the United States (7.8-10.7%). The percent of obese cases was higher each year in the EIP iMRSA cohort compared to BRFSS data, though whether these differences are statistically significant cannot be determined from these data.

DISCUSSION: The results indicate that there may be a higher risk for iMRSA in overweight and obese individuals, particularly if other adiposity-related health problems are present. Risk

cannot be calculated from these data. A prospective cohort study is suggested to determine the significance of the relationship between greater BMI and invasive MRSA.

INDEX WORDS: body mass index, BMI, Methicillin Resistant *Staphylococcus aureus*, MRSA, diabetes, dialysis, invasive infection, obesity

Elevated BMI-associated characteristics of patients with invasive MRSA infection in the Atlanta, Georgia metro area, 2005-2008

by

Lauren R. Lorentzson

B.A., Agnes Scott College

A Thesis Submitted to the Graduate Faculty
of Georgia State University in Partial Fulfillment
of the
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MASTER OF PUBLIC HEALTH

ATLANTA, GEORGIA

2010

Elevated BMI-associated characteristics of patients with invasive

MRSA infection in the Atlanta, Georgia metro area, 2005-2008

By

LAUREN R. LORENTZSON

Approved:

__Ike Okosun, MS, MPH, PhD, FRSPH_____
Committee Chair

__Sandra Bulens, MPH_____
Committee Member

_Russell Kempker, MPH_____
Committee Member

_12-6-2010_____
Date

DEDICATION

To my mother, for all her love, hard work, and sacrifice. To my father, for all of his dedication to me and my education. To Sandie and Stepy for believing in and encouraging me from the beginning. To Katie for years of guidance and unwavering support.

Thank you.

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Author's Statement Page

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The author of this thesis is:

Lauren Lorentzson
2111 Jefferson Square Court
Decatur, GA 30030

The Chair of the committee for this thesis is:

Ike Okosun
Institute of Public Health
Health and Human Services
Georgia State University
P.O. Box 4018
Atlanta, Georgia 30302-4018

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NAME OF USER	ADDRESS	DATE	TYPE OF USE (EXAMINATION ONLY OR COPYING)

Lauren Lorentzson
2111 Jefferson Square Court
Decatur, GA 30030
404-769-8741
lalorentzson@dhr.state.ga.us

Education

Georgia State University, Atlanta, GA
Master of Public Health, Prevention Sciences – Fall 2010

Agnes Scott College, Decatur, GA
Bachelors of Arts, Anthropology/Sociology 2005 – Fall 2005

Work Experience

Georgia Division of Public Health, Atlanta, GA — October 2005 - Present
Professional Healthcare Worker; Student Employee

Georgia State University, Institute of Public Health, Atlanta, GA — December 2007 - Present
ING Marathon Study; Graduate Research Assistant

Georgia Division of Public Health, Atlanta, GA — August 2009 – November 2009
Coverdell Stroke Registry; Student Practicum

Publications

Shendell, DG, Alexander, MS, Lorentzson, LR, McCarty, FA. Knowledge and awareness of heat-related morbidity among adult recreational endurance athletes. *International Journal of Biometeorology*, *54*(4), 441-448. DOI: 10.1007/s00484-009-0295-3

Daily, P, Aragon, D, Burnite, S, Daniels, A, Fraser, Z, et. al. Trends in perinatal group B streptococcal disease - United States, 2000-2006. *Morb Mortal Wkly Rep* 2009, *58*(5):109-12. (PMID: 19214159)

Skills

SPSS, Chart Abstraction, Microsoft Excel, Microsoft Word, Microsoft PowerPoint, Public Speaking, Spanish Language, Database Development, Surveillance, Case Report Interviews

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LIST OF ABBREVIATIONS

ABCs – Active Bacterial Core surveillance

BMI – Body Mass Index

CA – Community Associated

CA-MRSA – Community Associated Methicillin Resistant *Staphyloccocus aureus*

CAPD – Continuous Ambulatory Peritoneal Dialysis

CCPD – Continuous Cycling Peritoneal Dialysis

CDC – Centers for Disease Control and Prevention

CHF – Congestive Heart Failure

CSF – Cerebrospinal Fluid

CVC – Central Venous Catheter

CVD – Cardiovascular Disease

DRFI – Diabetes Related Foot Infection

EIP – Emerging Infections Program

ESRD – End Stage Renal Disease

FFM – Fat Free Mass

FM – Fat Mass

ICU – Intensive Care Unit

iMRSA – Invasive Methicillin Resistant *Staphyloccocus aureus*

MRSA – Methicillin Resistant *Staphyloccocus aureus*

NHANES – National Health and Nutrition Examination Survey

PFGE – Pulse Field Gel Electrophoresis

PN – Peripheral Neuropathy

SHIELD – Study to Help Improve early evaluation and management of risk factors Leading to Diabetes

SSTI – Skin and Soft Tissue Infection

USRDS – United States Renal Data System

UTI – Urinary Tract Infection

VA – Veterans Administration

CHAPTER I
INTRODUCTION

1.1 Background

Staphylococci are common bacteria, and many humans carry *Staphylococcus aureus* on the skin and nares (the nostrils and nasal passages) as part of typical bacterial flora in healthy individuals (Kluytmans, van Belkum , & Verbrugh, 1997; Davis, Stewart, Crouch, Flores, & Hospinthal, 2004; Hidron, Kourbatova, Halvosa, Terrell, & McDougal, 2005). An emerging public health problem is the rising pervasiveness of antibiotic resistant strains of common bacteria. Methicillin Resistant *Staphylococcus aureus* (MRSA) is a multi-drug resistant gram-positive bacterium (Porter, & Kaplan, 2008) now common in hospitals and other healthcare delivery settings (National Institute of Allergy and Infectious Diseases, 2009). MRSA strains have developed intermediate and complete resistance to a wide spectrum of antibiotics, particularly beta-lactam antibiotics such as cephalosporins and penicillin derivatives traditionally used to treat *Staphylococcus aureus* infections (Centers for Disease Control and Prevention, 2005; Chambers, 2001). MRSA is now a widespread, virulent nosocomial pathogen typically showing intermediate or complete resistance to multiple antibiotics, and infections can be difficult to treat (Cooper, & Medley, 2004). Complicating this problem, as a consequence of these protective mutations, MRSA organisms concurrently developed virulence factors that can lead to more severe and fatal infections, even in previously healthy individuals (Baba, Takeuchi, Kuroda, Yuzawa, & Aoki, 2002; Chambers, 2005).

Invasive infections with MRSA are serious and can be fatal (Klevens, Morrison, Nadle, Petit, & Gershman, 2007). An infection is defined as invasive if laboratory culture grows organisms from a body site that is considered sterile under normal conditions ("Sterile," Mosby's Medical Dictionary, 2009). That is, the site is not normally open to contact with the outside environment and possible bacterial, viral, or fungal contamination. Invasive culture sources include blood, cerebrospinal fluid (CSF), synovial fluid, pericardial fluid, peritoneal fluid, pleural fluid, bone, surgical aspirate, and internal body sites (such as samples of tissues surgically obtained from the heart, brain, liver, lymph nodes, etc.) (CDC, 2010c).

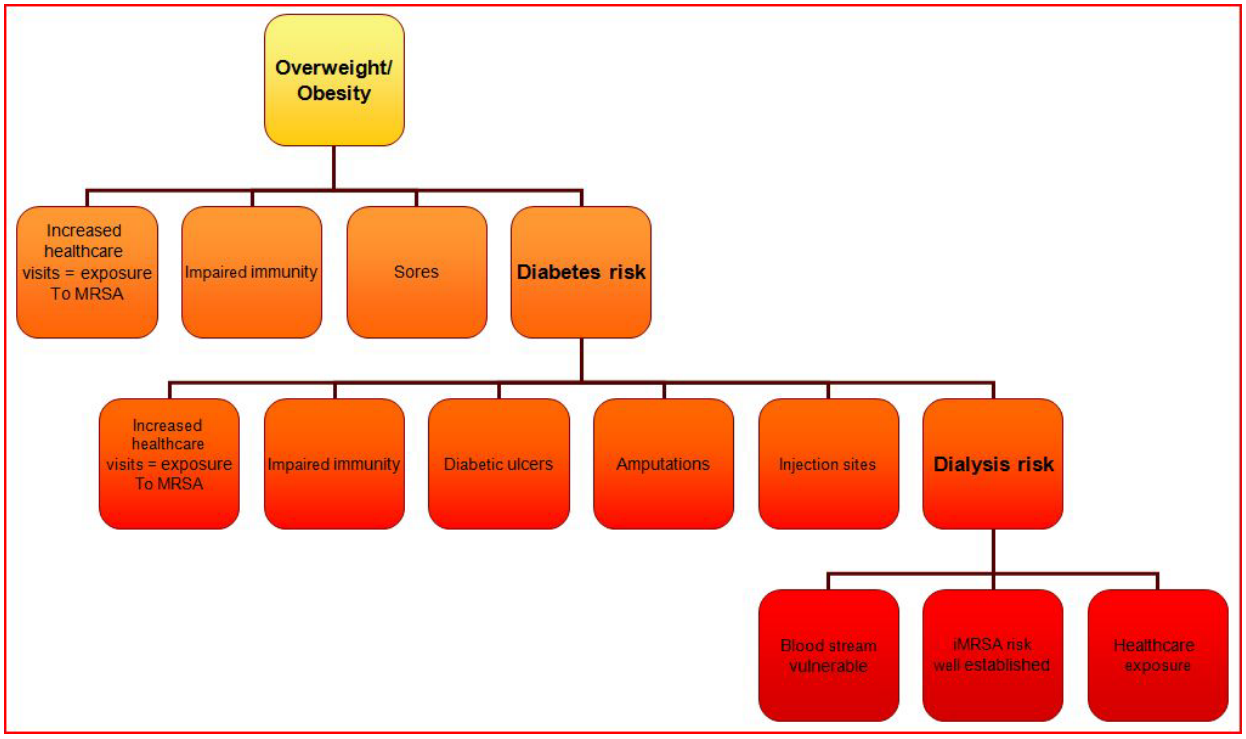
Another emerging public health concern is the climbing national obesity rate. The prevalence of obesity in the United States has been increasing since the 1970s (Flegal, Carroll, Ogden, & Curtin, 2010), and the 2005-2006 the National Health and Nutrition Examination Survey (NHANES) survey revealed that 32.7 percent of adults over twenty are overweight, and 40.2 percent are either obese (BMI ≥ 30) or extremely obese (BMI ≥ 40) (Centers for Disease Control and Prevention, 2010d). Some chronic health consequences of high adiposity include onset of chronic diseases such as cardiovascular disease (CVD) (American Heart Association, 2010), congestive heart failure (CHF) (Kenchaiah, Evans, Levy, Wilson, & Benjamin, 2002), end stage renal disease (ESRD) (Hsu, McCulloch, Iribarren, Darbinian, & Go, 2006), hypertension (Thorpe, Florence, Howard, & Joski, 2004), dyslipidemia (Coenen, & Hasty, 2007), and cancer (American Cancer Society, 2001).

Increasing rates of overweight and obesity in the United States have a positive statistical relationship with rising rates of Type 2 Diabetes (CDC, 2007). The overweight are particularly at risk of developing insulin resistance (World Health Organization, 2003; Fowler, 2010). One consequence of diabetes is ESRD—failure of the kidneys (Keene, 2003), making dialysis treatment necessary (American Diabetes Association, 2010b). According to the Centers for Disease Control and Prevention National Diabetes Fact Sheet 2007, "Diabetes is the leading cause of kidney failure, accounting for 44% of new cases in 2005" in the United States and Puerto Rico (CDC, 2007). According to data from the Medical Expenditure Panel Survey-Household Component (MEPS-HC), 79% of diabetic patients were overweight or obese in 2001 (Stagnitti, 2001), and a study published in the Journal of Renal Nutrition found that 60 of 296 chronic hemodialysis patients (20%) were obese (BMI≥28), with poorer morbidity and mortality outcomes for the obese members of this population (Wallace, Kleinfeld, Schlereth, & Letteri, 1996). Due to the nature of dialysis treatment, during which the blood is cleansed by a machine, a patient's vascular system is vulnerable to invasion by outside organisms. Dialysis centers are common sites for the acquisition of healthcare-associated infection (Morbidity and Mortality Weekly Review, 2001), and dialysis patients are at increased risk of invasive and fatal infection (Allon, Radeva, Bailey , Beddhu, & Butterly, 2005; MMWR, 2007a). Considering all of these factors, the overweight and obese are vulnerable to bacterial infection via multiple potential avenues, including skin infections, impaired immune response, development of Type 2 Diabetes

and its subsequent complications (including foot ulcers that may become infected (Freykberg, 2002), increased exposure to healthcare settings where drug-resistant bacteria are common, and the necessity for chronic hemodialysis if diabetic nephropathy progresses to renal failure.

Invasive bloodstream infections with MRSA are associated with dialysis treatment, and dialysis is necessary for survival upon onset of ESRD. End stage renal failure is commonly a consequence of long-term or poorly managed type 2 Diabetes, and Type 2 Diabetes develops as a result of chronic obesity. Therefore, obesity may raise the risk of iMRSA infection. In fact, exposures and susceptibilities to MRSA arise at each step in the chain of increased risk of iMRSA from obesity to dialysis, illustrated in Figure 1.1.

Figure 1.1 Possible Disease Pathways to Susceptibility to MRSA and iMRSA Infection in the Obese



Multiple obesity-related factors increase the likelihood of exposure to environments notorious for MRSA contamination. An obese individual may develop health conditions that necessitate visits to healthcare facilities, increasing exposure. Also, in some obese individuals, immune function is somewhat weakened, which increases susceptibility to infection. If obesity leads to

development of diabetes, new risks for MRSA infection emerge, such as ulcers that may become infected and hospital admission for amputations. This figure is not meant to imply that progression to chronic disease and dialysis is inevitable, only that some proportion within each group will progress to the next stage of disease. The factors presented in this figure are explained in more detail in the literature review.

1.2 Purpose of the Study

Due to the prevalence of overweight and obesity in developed countries, as well as the severity of invasive Methicillin Resistant *Staphylococcus aureus* (iMRSA) infections, an association between greater adiposity and iMRSA would be of significant concern. If obesity is a risk factor for iMRSA infection, higher rates of death and disability from this infectious disease may be seen due to the rising prevalence of obesity. Body mass index has emerged as a potential risk factor for general MRSA infections in some studies (Kellner, Yeung, Cook, Kornblum, & Wong, 2009). This study will focus on adiposity-related risk factors, such as diabetes and hemodialysis, among a population of patients with an invasive MRSA infection.

The purpose of this study is to:

1.) describe the demographics of a population of iMRSA patients in the metro Atlanta Georgia area from 2005-2008

2.) describe proportions of BMI categories, patients with diabetes, and patients undergoing dialysis within this population

3.) to compare proportions of BMI categories in this population to BRFSS data for Georgia

4.) perform univariate and multivariate logistic regression analysis of the association between selected independent variables with diabetes and dialysis within the iMRSA population

1.3 Hypothesis

It is anticipated that:

1.) the proportion of iMRSA patients with Type 2 Diabetes and/or undergoing dialysis in the EIP iMRSA population will be higher than is found in the general population of Georgia

2.) elevated BMI is associated with greater rates of iMRSA

CHAPTER II

REVIEW OF THE LITERATURE

2.1 Methicillin Resistant *Staphyloccocus aureus* (MRSA)

Staphylococcal bacteria are gram-positive cocci that tend to form in clusters (Carrico, 2005, p. 69-2) and grape-like bunches, associated with boils, skin infections, and septicemias ("Staphylococcus," The American Heritage Dictionary, 2009). *Staphylococcus aureus* is one of many *Staphylococcus* species ("*Staphylococcus aureus*," Mosby's Medical Dictionary, 2009), and causes a variety of localized and invasive infections, as well as three toxin-medicated syndromes ("*Staphylococcus* infections," Pickering, Baker, & Long, 2006; "*Staphylococcus*." The American Heritage Science Dictionary). Due to its many surface proteins, which help the bacteria to "stick" to skin and objects, *Staphyloccocus aureus* often causes foreign body infections, such as those associated with intravascular and peritoneal catheters, prosthetic valves, and other devices (Pickering, Baker, & Long, 2006; Darouiche, Landon, Patti, Nguyen, & Fernau, 1997). Identification of staphylococcal infections is made by Gram stain and culture of infected, purulent material (Isselbacher, Brunwald, Wilson, Martin, & Fauci, 1994).

Historically, *Staphylococcus aureus* infections have been associated with healthcare facilities (Thompson, Cabezudo , & Wenzel, 1982), and are widespread in nosocomial infections. The prevalence of antibiotic-resistant organism infections in healthcare settings and outpatient dialysis centers has been increasing rapidly over the last ten years (Berns, 2003). Notably, "*S. aureus* is one of the most common organisms causing all types (primary and secondary) of healthcare-associated bacteremia (Carrico, 2005, p. 69-7)." *Staphylococcus aureus* and MRSA are spread primarily through skin-to-skin direct contact (Georgia Department of Community Health, 2010), making hand washing an essential tactic for prevention of spread, especially for hospital personnel (Mandell, Bennett, & Dolin, 2000). Estimates of carriers within the general population range from 20% to 50% (Carrico, 2005, p. 69-5; Mandell, Bennett, & Dolin, 2000; Pickering, Baker, Long, & McMillian, 2006; Kluytmans, van Belkum, & Verbrugh,

1997). Healthcare workers have a higher nasal carriage rate, estimated to be between 50% and 90% (Carrico, 2005, p. 69-5; Mandell, Bennett, & Dolin, 2000).

Since the 1970s, *Staphylococcus aureus* has become increasingly resistant to penicillin and semi-synthetic penicillin antimicrobials such as methicillin, oxacillin, and nafcillin. By producing an enzyme called beta-lactamase, *S. aureus* has become resistant to beta-lactam antibiotics through intrinsic resistance, also known as "methicillin resistance" (Mandell, Bennett, & Dolin, 2000). Methicillin-susceptible *Staphylococcus aureus* is abbreviated MSSA, and Methicillin-resistant *Staph aureus* is abbreviated MRSA. MRSA bacteria are not only resistant to methicillin, however. Resistance to cephalosporins, erythromycins, clindamycin, tetracyclines, and aminoglycosides is also common (Carrico, 2005), with resistance to the glycopeptide antibiotic vancomycin rare, but on the rise (Evans, & Brachman, 1998; Fridkin, Hageman, McDougal, Mohammed, & Jarvis, 2003). According to the *Control of Communicable Diseases Manual*, "The majority of clinical isolates of *Staphylococcus aureus*, both hospital and community acquired, are resistant to penicillin G, and multiresistant (including methicillin resistant) strains have become widespread (Chin, 2000)." Likewise, the *APIC Text of Infection Control and Epidemiology* states that, "At present [2005] more than 90% of community- and hospital-acquired *Staphylococcus aureus* isolates are resistant to penicillin (Carrico, 2005)." There are currently many major MRSA strains and clones (Enright, Robinson, Randle, Feil, & Grundmann, 2002) representing a complicated spectrum of resistance and susceptibility.

MRSA infections are defined epidemiologically in various ways, depending on the location of likely exposure. A common definition of 'healthcare-associated, healthcare onset' (HAHO) infection identifies patients that have been admitted to a hospital or healthcare facility for more than forty-eight hours at the time of first positive culture (Evans, & Brachman, 1998). Some non-hospital healthcare facilities that represent possible exposures include dialysis centers and long-term care facilities such as nursing homes, chronic care facilities, and rehabilitation centers. Alternatively, an MRSA infection may be considered 'healthcare-acquired, community onset' (HACO) or 'community associated' (CA). A patient with a HACO invasive MRSA infection is a patient with a laboratory confirmed sterile site isolate of MRSA that was collected from a surveillance area resident within two calendar days after admission to an acute care

hospital and has had one or a combination of the following: history of hospitalization, surgery, dialysis, central venous catheter or residence in a long term care facility in the previous year. HACO infections with MRSA are of increasing concern (Larsen, Stegger, Böcher, Sørum, & Monnet, 2009; Limbago, Fosheim, Schoonover, Crane, & Nadle, 2009). Community acquired (CA) infections are identified if an infection site culture is collected within less than forty-eight hours after admission and no healthcare exposures are known within the last year (CDC, 2006).

2.2 MRSA in Georgia

Passive surveillance of 'severe' community-associated MRSA (CA-MRSA) has been ongoing at the Georgia Department of Community Health, Division of Public Health (all counties) since 2004. The case definition for "severe community-associated" infection is restricted to cases leading to death, intensive care unit (ICU) admission, operative debridement, pneumonia, or invasive infection, and limited to cases that have not been resident in a chronic care or other healthcare facility within the past year, no hospitalizations within the last year, and a positive culture within 48 hours of hospital admission. According to the 2008 Georgia Data Summary on CA-MRSA (Georgia Department of Human Resources, 2008), cases of severe CA-MRSA reported to the surveillance system have averaged 568 per year, with 589 reported in 2008. In 2008, 57% of cases were white, and 39% of cases were black. In 2005, the incidence was 5.1/100,000. Adult males are affected by CA-MRSA more than any other age or sex group. Skin and soft tissue infections (SSTIs) were the most common types of infection, with primary bacteremia and pneumonia next, in that order. Twenty-four patients with severe CA-MRSA died in 2008. Around half of these were aged 60 or older.

A report on severe CA-MRSA in Georgia from the Georgia DHR Division of Public Health (Arnold, Bulens, 2005) reports 564 confirmed reports, 59% male. Thirteen deaths were reported, 8 among previously healthy young people. Also noted is a cluster of necrotizing MRSA pneumonia cases during the 2005 flu season, and an association between SSTIs and methamphetamine use. CA-MRSA rates were higher in the north and northwestern counties of the state. The highest rates were reported in children 2 years old or younger.

An MMWR article entitled Severe Methicillin-Resistant Staphylococcus *aureus* Community-Acquired Pneumonia Associated with Influenza --- Louisiana and Georgia, December 2006--January 2007 (MMWR, 2007b) describes ten cases from Louisiana and

Georgia of CA-MRSA pneumonia secondary to influenza infection in 2006 (reported in January 2007). The article emphasizes the potential for CA-MRSA pneumonia infections to become necrotic and fatal citing the poor outcomes for the 10 cases, including 6 deaths, among previously healthy young people, including an 8 year old from Georgia. Another MMWR report includes descriptions of three MRSA skin infection outbreak investigations within the Georgia corrections system (MMWR, 2003). The investigations described included a total of 192 confirmed and 29 possible cases of MRSA SSTIs among inmates in 3 jails. No deaths were reported.

In 2005, a prospectively enrolled case-control study of increased SSTI MRSA infections among patients at a sliding-scale fee clinic in rural Georgia (Cohen, & Shuler, 2007) uncovered a link between methamphetamine use and the risk of MRSA SSTIs. MRSA accounted for greater than two-thirds of the SSTIs in the community, among the highest reported rates in the United States. The crude OR for methamphetamine use and the MRSA SSTI was 5.64 (1.80–17.69), and the adjusted OR was 5.10 (1.55–16.79) for those who reported drug use within the last three months prior to the survey.

A 2009 report on iMRSA predictors for mortality based on the CDC EIP data (Kempker, 2009) showed 4,791 total cases of iMRSA that met the EIP case definition, with 58% being classified as HACO, 26.8% as HAHO, and 14.4% as CA. Less than 1% were unidentified. The incidence rate was 38/100,000 in 2005, decreasing to 26.9/100,000 in 2008. Rates were highest among males, African Americans, persons 65 years of age or older, and HIV positive cases each year. The USA300 (most common community-associated DNA strain of MRSA) genotype was associated with higher in-hospital mortality than other genotypes (determined by pulse field gel electrophoresis (PFGE)). Using the Cox proportional hazards method, hazards ratios (HR) were determined to be significant for increased in-hospital mortality for MRSA with USA300 genotype (HR 1.73, 95% CI 1.21-2.48), and increasing age per year (HR 1.04, 95% CI 1.03-1.05).

2.3 BMI

BMI is a score based on the ratio of height to weight, squared (Garrow, & Webster, 1985). It is one of many tools used by health professionals to asses an individual's nutritional status. Often,

an elevated BMI is an indicator of greater weight than would be expected of a normal person of the same height (National Institutes of Health, 1998). This extra weight is often attributed to excess body fat. BMI is one of the most commonly used measurement tools for determining nutritional status in regards to a healthy body composition (CDC, 2010a).

It is important to note that BMI is an index, and is therefore best applied to an aggregate, and is not an appropriate measure on its own to determine excess adiposity in an individual. A person's weight, and therefore BMI, may fluctuate based on relative changes in fat-free mass (FFM), such as muscle mass, and fat mass (FM). Since raw weight and height data are used to calculate BMI, this measure is occasionally criticized as a poor measure of true adiposity and health for an individual (Guida, 2005). For example, BMI may be 'artificially' elevated for an individual with greater FFM (Prentice, & Jebb, 2001). An individual may, through exercise and diet, lose fat mass, gain an equal amount of muscle mass, and have the same BMI. Therefore, BMI is limited as a measure of health risk and adiposity, especially for an individual, but is useful to measure trends at the population level (Keyes, Fidanza, Karvonen, Kimura, & Taylor, 1972), and is useful when only raw height and weight data are available to the researcher.

2.4 Obesity in America

Obesity rates and prevalence have risen sharply since the 1980s in the United States (CDC, 2009) and in many countries around the world (WHO, 2003). This increase is a threat to public health due to the association of obesity with chronic disease (Mokdad, Serdula, Dietz, Bowman, & Marks, 1999). It is estimated that each year 300,000 adults die as a result of adiposity-related disease (Allison, Fontaine, Manson, Stevens, & VanItallie, 1999). Fortunately, some data indicate that the increase in the prevalence of overweight may be slowing. NHCS data detected no statistically significant change in obesity prevalence from 2003-2004 and 2004-2005 (Ogden, Carroll, McDowell, Flegal, 2007). However, thirty-three states had an obesity prevalence of at least 25%, and nine states had an obesity rate of 30% or above in 2009, according to the CDC (CDC, 2010f). Obesity increases the likelihood of Type 2 Diabetes and infections, discussed below. The prevalence of obesity (BMI≥30) was 20.9% in 2001 (Mokdad, Mokdad, Bowman, Dietz, & Vinicor, 2003).

2.5 Diabetes

When endogenously produced insulin fails to control blood glucose levels due to impaired insulin secretion or action—or a combination of the two—the resulting condition is called diabetes (Childs, Cypress, & Spollett, 2005, p. 2). The three most common types of diabetes are Type 1, Type 2, and gestational, though there are other, less common causes (National Institute of Diabetes and Digestive and Kidney Diseases, 2008). Diabetes is diagnosed by one of three tests: a causal blood glucose test given without regard to time of last meal, along with symptoms of diabetes, with a resulting plasma glucose level of >200 mg/dl; a fasting (no food within the previous eight hours, at least) blood glucose level of >126 mg/dl; an oral glucose tolerance test with a plasma glucose level of >200 mg/gl (American Diabetes Association, 2005). It is estimated that of those diagnosed with diabetes, around 5-10% have Type 1 Diabetes (ADA, 2009). Type 2 Diabetes is also called adult onset diabetes mellitus (AODM), and is often caused by preventable behaviors such as a combination of poor diet and low exercise (New England Journal of Medicine, Diabetes Prevention Program Group, 2002). Physician-guided diet and exercise are the ideal interventions and treatments for diabetes mellitus, particularly those in the earliest stages of insulin resistance (Bennett, & Plum, 1996).

Type 2 Diabetes progresses through a stage identified as 'pre-diabetes.' If mediated in this stage by a healthcare professional, pre-diabetes can be managed, treated, and reversed, and chronic Type 2 Diabetes can be avoided. Pre-diabetes is defined by Dorland's Medical Dictionary as "a state of latent impairment of carbohydrate metabolism in which the criteria for diabetes mellitus are not all satisfied (Dorland, 1981)." Chronic diabetes mellitus (insulin resistance) is not inevitable, though it is eminent if lifestyle changes do not take place. In the year 2000, diabetes was the sixth leading cause of death in the United States (CDC, 2002).

Patients with Type 2 Diabetes must control their glucose levels with insulin injections, pumps, or pills to remain healthy (CDC, 2010e). Complications of diabetes include potential loss of eyesight, decreased circulation in the extremities, ulcers in the feet and extremities, damage to the kidneys, and chronic/permanent renal failure requiring the patient to submit to dialysis treatments. Without proper management and cooperation between patient and doctor, diabetes can lead to severe complications and premature death.

2.6 Obesity and Type 2 Diabetes

According to the American Diabetes Association, there are 17.9 million diagnosed cases of Type 2 Diabetes in America, with approximately 5.7 million cases undiagnosed. In addition, there are about 57 million pre-diabetic citizens who may go on to develop the disease. The incidence is increasing annually, with "1.6 million new cases of diabetes…diagnosed in people aged 20 and older in 2007 (ADA, 2010c)." The majority of adults with diabetes are overweight or obese (MMWR, 2004). Higher BMI is associated with an increased prevalence of diabetes mellitus in both SHIELD and NHANES national surveys (Bays, Chapman, & Grandy, 2007).

2.7 Diabetes and Infections

Diabetic patients are at higher risk for certain infections due to complications of the disease. Although skin infections in patients with well-maintained diabetes occur at a comparable rate to the general population, around 20-50% of Type 2 diabetes patients experience some form of skin infection, and these infections are often more severe and difficult to treat (Childs, Cypress, & Spollett, 2005, p.152). Diabetes is a risk factor for peripheral artery disease (Murabito, D'Agostino, & Silbershatz, 1997), which can lead to gangrene and foot or limb amputations (Childs, Cypress, & Spollett, 2005, p.369). Diabetic cystopathy predisposes diabetics to urinary tract infections (UTIs) (Childs, Cypress, & Spollett, 2005, p.369). Diabetic neuropathy, or peripheral neuropathy (PN) due to chronic hyperglycemia, is the most common long-term complication in diabetic patients (Childs, Cypress, & Spollett, 2005, p.155). This is in part due to reduced circulation and sensation in the extremities that occurs over time as diabetes advances. PN can cause loss of sensation, and in the absence of pain calluses may form in areas of pressure, eventually leading to tissue breakdown and ulcers (Childs, Cypress, & Spollett, 2005, p.157). These ulcers are susceptible to invasive infection.

2.8 Obesity and Infection Risk

There are several factors that may increase the likelihood of infection in obese and morbidly obese individuals. This population is at greater risk for intertrigo, a condition of inflammation of the skin due to friction between opposing cutaneous surfaces, such as those within natural skin

folds (Janniger, Schwartz, Szepietowski, & Reich, 2005). Obesity can increase the number and surface area of skin folds, and therefore the likelihood of developing intertrigo (Hahler, 2006). The inflamed skin can become infected if not treated properly. Good hygiene practices are essential in the prevention of these types of infections. Although the reasons are still poorly understood, studies have shown that obese individuals have a lowered immune response compared to normal weight individuals (Falagas, & Kompoti, 2006; Marti, Marcos, & Martinez, 2001; Tanaka, Inoue, Isoda, Waseda, & Ishihara, 1993), heightening risk for infection.

Obese patients are more likely to suffer from post-surgical and nosocomial infections, such as pneumonia and surgical site infections (Dossett, Dageforde, Swenson, Metzger, & Bonatti, 2009; Jørgensen, Ravlo, & Richelsen, 2006). Although the reasons are still poorly understood, studies have shown that obese individuals have a lowered immune response compared to normal weight individuals (Falagas, & Kompoti, 2006; Marcos, & Martínez, 2001; Tanaka, Inoue, Isoda, Waseda, & Ishihara, 1993), which heightens their risk for infectious disease (Marti, Marcos, & Martinez, 2001; Tanaka, Inoue, Isoda, Waseda, & Ishihara, 1993). Although obesity is most often associated with chronic disease (WHO, 2010; Haslam, & James, 2005), the risk of infectious disease among the overweight population is worthy of attention due to possible impaired immune response.

2.9 Diabetes and MRSA

Underlying conditions of interest for *Staphylococcus aureus* infection include diabetes and chronic renal failure (Evans, & Brachman, 1998). The *Red Book* 2006 Report of the Committee on Infectious Diseases states that, "Risk factors for severe S *aureus* infections include chronic disease, such as diabetes mellitus (Pickering, Baker, & Long, 2006)." It is important to note that diabetics receiving insulin injections (as well as intravenous drug users), and hemodialysis or peritoneal dialysis patients have a higher nasal carriage rate *Staphylococcus aureus* than the general population (Carrico, 2005; Mandell, Bennett, & Dolin, 2000; Evans, & Brachman, 1998, p.661). In addition to greater rates of colonization and the necessity for skin barrier-breaching injections of insulin, diabetic foot ulcers are also susceptible to MRSA infection. In a study of diabetes-related foot infections (DRFIs), 43% of isolates were staphylococci, and 23% were

MRSA (Yates, May, Hale, Allard, & Rowlings, 2009). DRFIs caused by MRSA are related to MRSA nasal carriage (Stanaway, Johnson, Moulik, & Gill, 2007).

2.10 Type 2 Diabetes and Dialysis

End-stage renal failure requiring **dialysis** is one of the most serious complications of **diabetes** mellitus. According to the *Cecil Textbook of Medicine*, "End-stage renal disease (ESRD)…in the Type 2 diabetic population…constitutes the majority of diabetic patients seeking therapy for ESRD. Overall, diabetes is the leading cause and accounts for one third of the ESRD cases in the United States (Bennett, & Plum, 1996 p.1273)."

Diabetes is the most common cause of chronic kidney disease and kidney failure (National Institute of Diabetes and Digestive and Kidney Diseases, 2009). Though 70-80% of diabetics never develop kidney failure (Childs, Cypress, & Spollett, 2005, p. 122), diabetes accounted for approximately 44% of new reported cases of kidney failure as of 2009, according to the U.S. Renal Data System (USRDS, 2009). The prevalence of diabetes-related dialysis is increasing. According to the results of one population-based cohort study in Ontario, Canada (with over 8 million participants), "the average annual incidence rate of **dialysis** was 12 times greater in persons with **diabetes** (130 per 100,000) vs. without **diabetes** (11 per 100,000)…The average annual prevalence rate was 10 times greater in the diabetic cohort (Lok, Oliver, Rothwell, & Hux, 2004)."

2.11 Dialysis

There are two dialysis types: hemodialysis and peritoneal dialysis. Both are described in the *APIC Text of Infection Control and Epidemiology* (Carrico, 2005). Hemodialysis is the most common. With hemodialysis, most often an arteriovascular fistula is created in the forearm of the patient using their own blood vessels, to which an artificial kidney machine can be hooked for each dialysis session. During hemodialysis, blood travels through a tube into a specially designed machine, where a semi-permeable membrane allows waste molecules and excess water to filter out of the blood. The cleansed blood then circulates back into the patient through a second tube. Hemodialysis is usually done 2 to 3 times per week and lasts 3 to 5 hours. In

hemodialysis, exposure to infectious agents is most likely during initiation and termination of treatment (Carrico, 2005, p.49-13).

Peritoneal dialysis uses the patient's own abdominal tissues as a semi-permeable membrane/filter. A catheter is implanted into the patient's abdomen. Then, a bag containing a fluid called dialysate is emptied into the catheter by the patient themselves, rather than by a machine or doctor. The dialysate and waste products are then drained back out through the abdominal catheter. This process needs to be repeated every 4 to 6 hours, and lasts 40 to 50 minutes in "continuous ambulatory peritoneal dialysis" (CAPD), or is done overnight by a machine, as in "continuous cycling peritoneal dialysis" (CCPD). With peritoneal dialysis, placement and removal of the catheter is the riskiest time for pathogen exposure (Carrico, 2005, p.49-11).

2.12 Dialysis and MRSA

The risk of developing an iMRSA infection among dialysis patients has been documented and is increasingly well known and understood. According to the CDC's Guidelines for the Prevention of Intravascular Catheter-related Infections, "The use of catheters for hemodialysis is the most common factor contributing to bacteremia in dialysis patients (O'Grady, Alexander, Dellinger, Gerberding, Heard, 2005)." Diabetes is considered an underlying risk factor for infection for patients undergoing dialysis in the *APIC Text of Infection Control and Epidemiology* (Carrico, 2005, p.49-3).

Dialysis increases the risk of invasive infection because of the nature of intravenous treatment, allowing direct access into the bloodstream for any contaminants or microbes. Dialysis-associated infections tend to be either access site infections or bacteremia. Because *Staphylococcus aureus* (and therefore MRSA) colonization is common on the skin and in the nares of dialysis patients, infections with *Staphylococcus aureus* and MRSA are also common in dialysis patients (Carrico, 2005, p.49-11). Those on hemodialysis are considered high-risk patients in regard to MRSA infection (Carrico, 2005, p.69-9). For example, *Bacterial Infections in Humans* states that, "Colonized dialysis patients are at high risk for staphylococcal infection, particularly bacteremia, arteriovenous fistula infections, and peritonitis. The strain isolated from the site of infection is typically the same as that carried in the nose (Evans, & Brachman, 1998)."

CHAPTER III
METHODS

3.1 Data Source

Secondary data on invasive MRSA cases was obtained from the Georgia Emerging Infections Program ABCs Invasive MRSA Surveillance system. The Georgia EIP is a collaboration of the Georgia Division of Public Health and academic partners at Emory University and the VA Medical Center. iMRSA surveillance is conducted by Emory/VAMC partners in the eight county Atlanta MSA (Georgia Emerging Infections Program, 2006). ABCs conducts laboratory population-based iMRSA (MRSA cultures from a normally sterile body site) surveillance with medical record abstraction (Arnold, 2005; Tuttle, Arnold, Tobin-D'Angelo, 2007). The VA agreed to allow use of a de-identified use of the dataset for this thesis. Case patients are residents of the eight county Atlanta metro statistical area (Fulton, Dekalb, Gwinnett, Clayton, Newton, Douglas, Cobb and Rockdale counties). Cultures were collected from 2005 through 2008. Cases were assigned an individual ID number, and identifying information was removed, ensuring patient confidentiality. The database primarily consists of data collected through chart abstraction.

BMI was not included as a variable in the original database, it is not a requested data item covered on the case report forms (CRFs). A BMI column was created using data on height and weight reported in the medical records reviewed by surveillance officers. For each case with both height and weight data available, a BMI score was calculated. An online calculation tool provided by the Department of Health and Human Services National Institutes of Health's National Heart Lung and Blood Institute for the purposes of BMI calculation was used (NIH NHLBI, 2009). BMI was not calculated for cases with incomplete or missing height or weight data.

Height and weight data for each case was available in many possible combinations of metric and American standard measurements. Height was reported either in feet and inches, total

inches, or in centimeters. Weight was reported as pounds, pounds and ounces, or as kilograms. For cases with weight reported in kilograms and height reported in inches, kilograms were converted to pounds for the BMI calculation. For cases with weight in pounds and height in centimeters, weight was converted to kilograms for the calculation. For cases with inches, centimeters, kilograms, and pounds and/or ounces filled in (i.e. all fields contained an entry), centimeter and kilogram measurements were used for the BMI calculation.

3.2 Inclusion/Exclusion Criteria

Original EIP Dataset Inclusion Criteria -- The dataset used for these analyses represents the cohort of iMRSA in the 8 Atlanta metro counties in Georgia from 2005 through 2008. The original EIP dataset included each incident case of iMRSA infection per patient, with "incident" cases of disease defined as iMRSA isolates collected thirty or more days apart for a single case patient. The total N for the database was 4,832 prior to applying inclusion/exclusion parameters.

Incomplete Height and Weight Data -- Cases were excluded if data were inadequate for BMI calculation. The majority of excluded cases were dropped due to inadequate and missing height and weight data. The majority (2078 cases; 43%) of excluded cases were rejected due to this criteria.

Age -- Cases were excluded if under the age of 18, eliminating neonatal and childhood cases. This study aims to focus on adults with risk factors for iMRSA, and individuals under the age of 18 are at low risk of developing adult onset Type 2 Diabetes (ADA, 2010a; National Diabetes Information Clearinghouse, 2007). Cases aged over 85 were also excluded to reduce the probability of personal identification, incorrect age due to data entry error, and to reduce skew in measures of central tendency from outliers. Persons over age 85 were also excluded due to privacy issues; to satisfy IRB requirements, no cases over age 85 were allowed to be included.

Extreme BMI -- Cases were excluded if apparently extreme or absurd data had been entered into the EIP iMRSA database. These unexpected data may be due to inaccurate entries in the height and/or weight columns during chart abstraction, errors during data entry into the ABCs database, misreading of medical charts by abstractors, or some other computer or human error. Extreme cases were eliminated by excluding cases with a BMI below 14 (a BMI of 13 or below is rarely

survivable (Henry, 2001; WHO, 2004)), or a BMI of above 57 (indicating a weight to height ratio so extreme as to indicate possible data entry error (NHLBI, 2010)). For example, a 45 year old male with height and weight data that result in a BMI of 8 is not survivable, and would be excluded, and this BMI score attributed to data entry error.

Height -- Cases with a height below 120 cm (129.9 cm = 4 feet) were excluded. This eliminated 5 cases only.

Ounces -- Ounces were excluded from the BMI calculation altogether, as only 9 cases had ounces data, and ounces would have negligible effect on a case's BMI, since only one pound of difference could occur. Ounces reported ranged from 3 to 11 among these 9 cases. Therefore 9 cases may have been up to 11 ounces heavier than the weight used to calculate their BMI at the time of BMI calculation.

3.3 BMI Calculation

BMI was calculated for each case with sufficient height and weight data. Statistical analysis was carried out in SPSS. The association between variables was determined using binary logistic regression analysis. A secondary data source was used. A p-value of ≤ 0.05 and a 95% confidence interval (CI) was used to determine statistical significance. Data from the EIP iMRSA database was compared to CDC BRFSS data for the state of Georgia. All data are from the year 2005 through 2008.

BMI calculation formula =

weight[kg]/(height[m]*height[m]) = 703*weight[lb]/(height[in]*height[in])

3.4 Definitions

3.4.1 BMI Categories

According to the National Institutes of Health's National Heart Lung and Blood Institute, BMI categories are as follows: underweight = 18.4 or lower; normal weight = 18.5-24.9; overweight = 25-29.9; obesity = 30+.

These categories are widely accepted in the literature (NHANES, 2007; NHLBI, 1998), and were used to define adiposity categories cases in this study. Underweight and normal cases were combined into the 'normal' category.

3.4.2 EIP Definitions

The following definitions were used by surveillance officers working for the Georgia EIP program abstracting charts for iMRSA and come directly from the data dictionary provided surveillance for instruction and reference. Definitions are in alphabetical order.

Central vascular catheter (CVC)—Single double, or triple lumen, Shiley (dialysis), Broviac, Hickman, PICC, Swan Ganz catheter, Pulmonary artery catheter, Port-a-cath, passport, Vas cath, perm cath. Does not include peripheral IV.

Ethnicity—Ethnicity of patient as noted in chart or reported by physician or ICP. To be checked even if race already indicated. For example, a patient may be White and also Hispanic or Latino. If not noted or unsure, indicate as 'unknown.' Assumptions not to be made based on name. Some institutions combine race/ethnicity coding. For example, a person's race may be indicated as 'Hispanic' or 'Latino.' In this case race would be coded as unknown on the CRF, and ethnicity would be Hispanic or Latino.

Diabetes mellitus—Includes either Type 1 or Type 2 (both 'insulin-dependent' and 'adult-onset." Also includes glucose intolerance and new-onset diabetes. Do not include patients noted as "pre-diabetic." It is not necessary to look at the results of glucose tolerance test in laboratory results section of the chart for an indication of diabetes. Common abbreviations: DM, AODM, IDDM, NIDDM.

Dialysis—if dialysis occurred within one year prior to invasive specimen collection date.

Height—Optional pilot variable (2005). Indicate height in feet (ft) and inches (in) OR in centimeters (cm).

Hospitalized—if hospitalization occurred within one year of invasive specimen collection date.

Obesity—The condition of being significantly overweight. It is usually appliecd to a condition of 30 percent or more over ideal body weight OR to individuals with a body mass index (BMI) of 30 or more (*added 2005*).

Previous MRSA infection—if a previous MRSA infection is noted in the chart, OR patient is already in the database, OR if a non-sterile culture was positive >24 hours prior to initial invasive culture.

Race—Race of patient as noted in chart or reported by physician or ICP. Multiple boxes can be checked. If race is unknown, indicate as unknown.

Sterile Site—Indicate ALL sterile sites from which MRSA was isolated on the date of initial culture. [These include blood, cerebral spinal fluid, pleural fluid, peritoneal fluid, pericardial fluid, joint/synovial fluid, and bone.] If isolated from an internal body site or other normally sterile site, please specify the site. Internal body site should be specified as one of the following: lymph node, brain, heart, liver, spleen, vitreous fluid, kidney, pancreas, or ovary. Specimens from skin infections such as skin abscesses, boils, or furuncles or specimens from middle ear, amniotic fluid, placenta, sinus, wound, lung, gallbladder, appendix, cornea, cord blood or throat are not considered sterile sites for any ABCs organism. Non-sterile culture sites that should not be investigated include urine, eye, ear, sputum, wound, swab, and drainage.

Pleural fluid: includes ‘chest fluid,’ thoracentesis fluid

Peritoneal fluid: includes abdominal fluid, ascites

Joint: includes synovial fluid; fluid, needle aspirate, or culture of any specific joint (knee, ankle, elbow hip wrist)

Bone: includes bone marrow

Muscle: includes muscle tissue or biopsy that is sterilely obtained such as tissue obtained surgically or through a needle aspirate. A surgically obtained specimen would be included UNLESS from a wound. If a wound such as a decubitus ulcer has exposed the fascia or the muscle then those sites would no longer be considered sterile. If the culture is obtained surgically or through needle aspirate, for example, and the skin was intact

over the muscle and fascia when the tissue was obtained this would be considered a sterile site…superficial skin cultures obtained surgically (e.g., during debridement) are not considered sterile sites.

Internal body site: specimen obtained from surgery or aspirate from one of the following: lymph node, brain, heart, liver, spleen, vitreous fluid, kidney, pancreas, or ovary.

Surgery—if patient had surgery during the period of one year before the collection date to 48 hours before the collection date. Surgery is defined as at least taking place during a single trip to the operating room where a surgeon makes at least one incision through skin or mucous membrane, including laparoscopic approach. Excluded if surgery occurred within 48 hours of culture collection.

Weight—indicate weight in pounds (lbs) and ounces (oz) OR in kilograms (kg).

3.5 Analysis

Statistical analysis was performed in SPSS. Univariate and multivariate binary logistic regression analysis was performed on select variables. A p-value of < 0.05 and a 95% confidence interval (CI) was used to determine significance.

CHAPTER IV

RESULTS

4.1 Demographics

Table 4.1 Frequencies and Descriptive Statistics for BMI Among iMRSA Cases, Georgia Metro Atlanta Area

BMI		
n		2478
Minimum		14
Maximum		56.70
Mean		27.39
Median		25.90
Mode		23.10
Std. Deviation		7.58
Variance		57.52
Skewness		1.03
Std. Error of Skewness		0.05
Kurtosis		1.07
Std. Error of Kurtosis		0.098
Percentiles	25	21.8
	50	25.9
	75	31.2

The n for iMRSA patients in the Georgia 8 county metro Atlanta area with iMRSA after inclusion and exclusion criteria was 2,478. Mean BMI was 27.39 (overweight).

Table 4.2 Frequency and Percent of iMRSA Cases by Demographic Category, Georgia Metro Atlanta Area, 2005-2008

		Frequency	Percent
Race			
	White	1,017	41.0
	Black	1,357	54.8
	Asian	20	0.8
	Unknown	84	3.4
	Total	2,478	100
Ethnicity			
	Hispanic	38	1.5
	Non-Hispanic	2,395	96.7
	Total	2,433	98.2
	Unknown	45	1.8
	Total	2,478	100
Sex			
	Male	1,406	56.7
	Female	1,072	43.3
Calculated BMI Categories*			
	Underweight	181	7.3
	Normal	905	36.5
	Overweight	642	25.9
	Obese	750	30.3

* BMI Categories: underweight = 18.4 or lower; normal weight = 18.5-24.9; overweight = 25-29.9; obesity = 30+

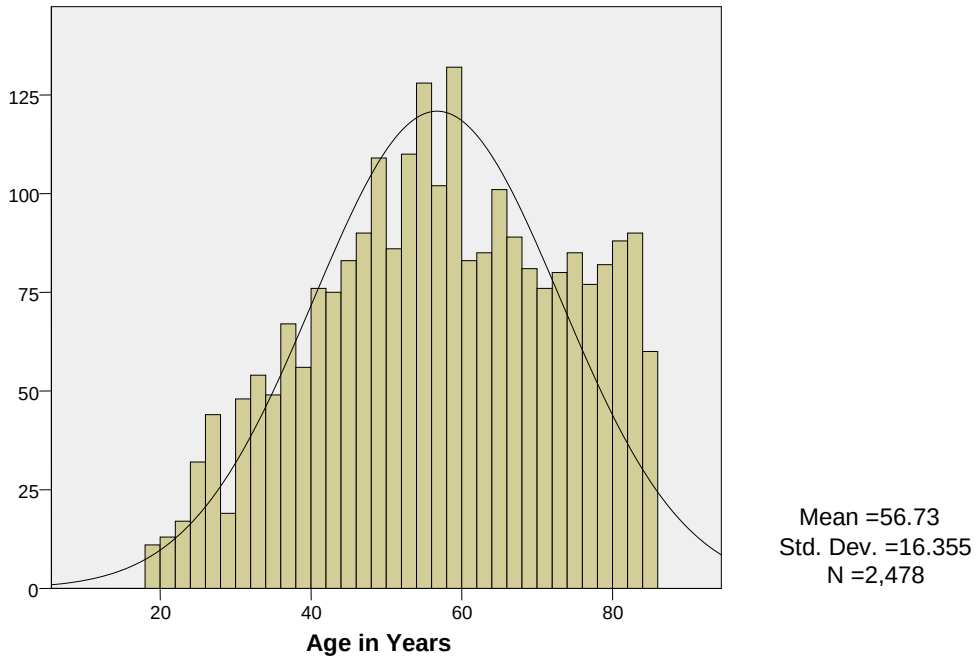
Table 4.2 presents basic demographic information for the invasive MRSA cases. The majority of cases were black, non-Hispanic, and male. Few Asians were represented in this cohort. 3.4% of cases are unknown race. 55% of patients were either overweight or obese.

Table 4.3 Frequency and Percent of Selected Health Risks Among iMRSA Cases in the Georgia Metro Atlanta Area, 2005-2008

		Frequency	Percent
Diabetes			
	No	1,418	57.2
	Yes	1,060	42.8
Chart-Abstracted Obesity			
	No	2,195	88.6
	Yes	283	11.4
MRSA-Previous Year			
	No	1,938	78.2
	Yes	540	21.8
Hospitalization-Previous Year			
	No	1,043	42.1
	Yes	1,435	57.9
Surgery-Previous Year			
	No	1,725	69.6
	Yes	753	30.4
Dialysis-Previous Year			
	No	1,783	72.0
	Yes	695	28.0
Percutaneous Device			
	No	1,771	71.5
	Yes	707	28.5
Central Venous Catheter			
	No	1,966	79.3
	Yes	512	20.7

The frequency and percent of iMRSA cases with potentially significant dichotomous health risk factors for the development of disease. Almost half of iMRSA patients were diagnosed with diabetes (42.8%). This is a much higher proportion than is found in the general population. According to the American Diabetes Association, 7.8% of the population had diabetes in 2007 (ADA, 2007). According to the National Institute of Diabetes and Digestive and Kidney Diseases, the prevalence of diabetes in the United States in 2007 among adults twenty years old and older was 10.7 % (American Census Bureau, 2008).

Figure 4.1 Histogram Curve of Age of iMRSA Cases in the Georgia Metro Atlanta Area, 2005-2008 with Normal Curve and Descriptive Statistics



Mean age for the cohort was 56 years, skewed to the left. Individuals in the 65+ age range are represented here at a greater rate than in the general U.S. population, which skews to the right (U.S. Census Data, 2008).

Figure 4.2 Histogram of Raw BMI Scores Among iMRSA Cases in the Georgia Metro Atlanta Area, 2005-2008 with Normal Curve and Descriptive Statistics

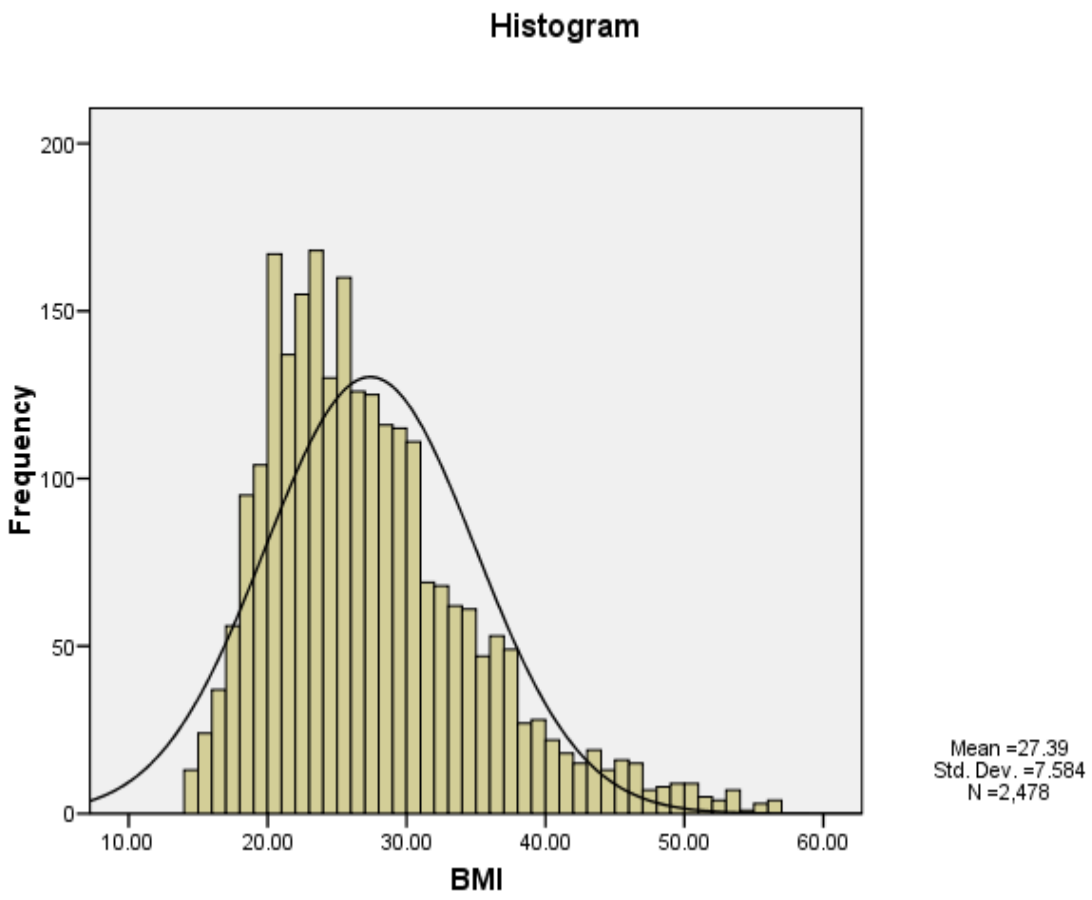
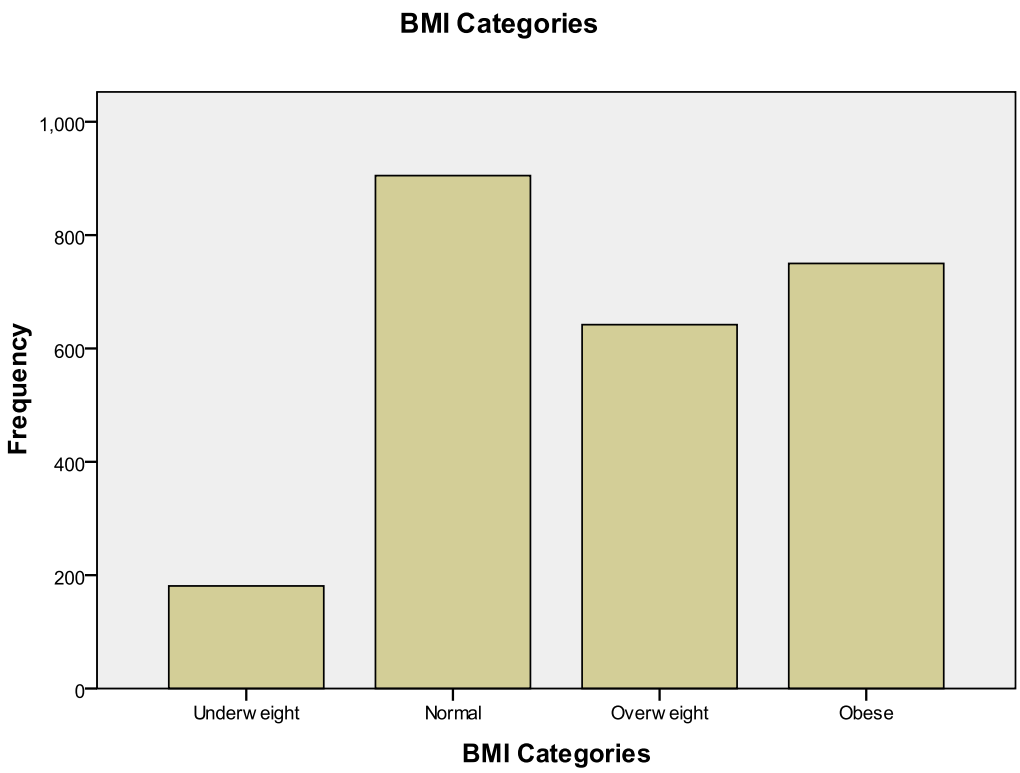


Figure 4.5 depicts the histogram of raw BMI scores for the Georgia EIP database. Although a BMI of 27 (the mean for this population) is 'normal,' the curve skews to the right. The cohort has a higher proportion of BMI over 40 compared to BMI bell curves in the U.S., for example Mississippi 2003 (Mean 27.73, S.D. 6.119) (Penman, A, Williams, J, 2006).

Figure 4.3 Bar Graph of BMI Categories (Underweight, Normal, Overweight, Obese) Among iMRSA Cases in the Georgia Metro Atlanta Area, 2005-2008 with Normal Curve and Descriptive Statistics



The bar graph above in Figure 4.3 shows the number of cases in each of the four BMI categories: underweight, normal, overweight, and obese. Normal weight patients were the most numerous, followed by obese, overweight, and underweight, respectively.

Table 4.4 Proportions of iMRSA Cases in the Georgia Metro Atlanta Area, 2005-2008 with Diabetes and/or Dialysis Diagnosis

	Proportion Diagnosed with Diabetes Only	Proportion Undergone Dialysis* Only	Proportion Both Diabetic and Undergoing Dialysis*
Adiposity			
Normal	28.6%	54.3%	33.1%
Overweight	27.4%	24.9%	30.1%
Obese	44.1%	20.8%	36.6%
Sex			
Female	42.2%	34.8%	51.5%
Male	57.8%	65.2%	48.5%
Race			
White	47.7%	15.4%	20.6%
Black	48.8%	82.3%	75.9%
Asian	0.9%	0.7%	1.5%
Unknown	2.6%	1.7%	2.0%
Ethnicity			
Hispanic	0.9%	0.7%	1.0%
Non-Hispanic	97.7%	98.6%	97.8%
Unknown	1.4%	1.0%	1.2%
Prior MRSA*	16.3%	40.3%	34.3%
Hospitalization*	58.7%	65.5%	64.7%
Surgery*	31.2%	36.2%	33.6%
CVC in place	8.2%	52.9%	50.5%
Total Cases	658	293	402

*Within one year of present illness.

The table above shows the proportion of patients with either diabetes diagnosis, dialysis within the last year, and both health concerns simultaneously. The majority of cases with diabetes only were obese (44.1%). The highest proportion of cases that had undergone dialysis without diabetes as a comorbidity were of normal weight (54.3%). Although the highest proportion of patients with concurrent diabetes and dialysis treatment were obese (36.6%), each category of adiposity represented approximately equal proportions of the total (about one-third normal, overweight, and obese). Males represent a large proportion of patients undergoing dialysis without underlying diabetes comorbidity (65.2%) as were patients of black race (82.3%). Black patients were also more likely to both have diabetes and undergo dialysis (75.9%)

Table 4.5 Comparison of Diabetes and Obesity Proportions in MSA Counties and EIP iMRSA Data, 2005-2008

		MSA Counties	iMRSA Database
	Year	Proportion	Proportion
Diabetes	2005	8%[1]	35.1%
	2006	~	29.1%
	2007	10.1%[2]	35.8%
	2008	9.9%[3]	44.6%
Obesity	2005	27%[4]	27.9%
	2006	27%[5]	29.3%
	2007	29%[6]	31.6%
	2008	28%[7]	32.4%

[1]BRFSS Healthy People, Progress Towards Healthy People 2010 Objectives, 2001-2005
[2]2008 Georgia Program and Data Summary, Diabetes
[3]Diabetes in Georgia 2009.
http://health.state.ga.us/pdfs/epi/cdiee/Diabetes%202009%20Report%2011-18.pdf
[4]Fact Sheet, Georgia Adult Obesity by County.
http://health.state.ga.us/pdfs/epi/cdiee/Obese%20Adults%20in%20Georgia%20by%20County_final3.pdf
[5]Obesity Program and Data Summary 2006. http://health.state.ga.us/
[6]Obesity Program and Data Summary 2007. http://health.state.ga.us/
[7]Obesity Program and Data Summary 2009. http://health.state.ga.us/

The proportion of diabetes in the iMRSA database was consistently much higher in the iMRSA data than in the general population of the Atlanta MSA for all years. Obesity proportions were similar in both populations, with iMRSA obesity rising steadily each year.

Table 4.6 Dialysis Rates in the both iMRSA Cohort and General Population, Georgia Atlanta Metro Statistical Area, 2005-2008

Year	MSA Population*	MSA Dialysis Total**	Rate per 100,000	iMRSA Population Total	iMRSA Dialysis total	Rate per 100,000 of both iMRSA and Dialysis	Rate of iMRSA patients on Dialysis	Rate of iMRSA patients on Dialysis per 100,000
2005	2,398,162	1105	46	634	156	6.5	0.25	24605.7
2006	2,489,452	1231	49.2	583	156	6.2	0.27	26758.1
2007	2,551,551	1228	48.2	651	198	7.8	0.3	30414.7
2008	2,592,151	1281	49.3	610	185	7.1	0.3	30327.9
Total	10,031,316	4845	48.5	2478	695	7	0.28	28046.8

*Georgia OASIS query data. http://oasis.state.ga.us/

**U.S. Renal Data System, Renal Data Extraction and Reference. http://www.usrds.org/odr/xrender_home.asp

Table 4.6 presents unadjusted incident disease rate of dialysis in the MSA general population and the rates of dialysis among iMRSA patients. When rates of dialysis among iMRSA patients are calculated per 100,000 by the MSA population, rates of dialysis are much higher than is seen in the general population.

4.2 Correlations

Table 4.7 Univariate and Multivariate Analysis of the Association Between Selected Independent Variables with Diabetes in Subjects with Invasive MRSA Infections within the 8 County Metro Area of Georgia, 2005-2008 (α=0.05; 95% C.I.)

	Univariate				Multivariate			
		95% C. I.				95% C. I.		
	OR	Lower	Upper	p-value	OR	Lower	Upper	p-value
Adiposity								
Normal	*Reference*				*Reference*			
Overweight	2.104	1.718	2.576	0.000	2.231	1.805	2.756	0.000
Obese	3.346	2.753	4.066	0.000	3.776	3.067	4.649	0.000
Age	1.027	1.021	1.032	0.000	1.036	1.030	1.042	0.000
Sex								
Male	*Reference*				*Reference*			
Female	1.194	1.017	1.402	0.030	0.973	0.817	1.159	0.761
Race								
White	*Reference*				*Reference*			
Black	1.337	1.134	1.577	0.001	1.968	1.631	2.373	0.000
Asian	2.343	0.949	5.782	0.065	3.268	1.241	8.601	0.016
Unknown	0.662	0.408	1.074	0.095	1.082	0.364	3.170	0.888
Ethnicity								
Hispanic	*Reference*				*Reference*			
Non-Hispanic	2.135	1.032	4.414	0.041	1.157	0.362	3.692	0.888
Unknown	1.265	0.485	3.299	0.631	0.849	0.295	2.439	0.760

Table 4.8 Univariate and Multivariate Analysis of the Association Between Selected Independent Variables with Dialysis within the Year Prior to Invasive MRSA Infection within the 8 County Metro Area of Georgia, 2005-2008 (α=0.05; 95% C.I.)

	Univariate				Multivariate			
		95% C. I.				95% C. I.		
	OR	Lower	Upper	p-value	OR	Lower	Upper	p-value
Adiposity								
Normal	*Reference*				*Reference*			
Overweight	1.178	0.949	1.460	0.137	0.993	0.785	1.255	0.953
Obese	1.050	0.853	1.294	0.643	0.827	0.654	1.046	0.113
Diabetes	2.346	1.962	2.805	0.000	2.462	2.011	3.015	0.000
Age	0.991	0.986	0.996	0.001	0.994	0.988	1.001	0.083
Sex								
Male	*Reference*				*Reference*			
Female	1.070	0.897	1.277	0.452	1.042	0.859	1.264	0.679
Race								
White	*Reference*				*Reference*			
Black	4.676	3.772	5.796	0.000	4.359	3.481	5.458	0.000
Asian	4.630	1.857	11.544	0.001	3.920	1.538	9.992	0.004
Unknown	1.272	0.684	2.363	0.447	1.216	0.314	4.703	0.777
Ethnicity								
Hispanic	*Reference*				*Reference*			
Non-Hispanic	2.628	1.022	6.759	0.045	1.207	0.291	5.014	0.796
Unknown	1.427	0.425	4.795	0.565	1.606	0.455	5.673	0.462

Table 4.4 presents the results of logistic regression analysis to determine if, compared to individuals of normal BMI, overweight and obese cases are more likely to be diagnosed with diabetes. Greater adiposity is associated with increased risk of Type 2 Diabetes in both univariate and multivariate analysis.

Table 4.5 shows invasive MRSA patients are at 2.3 times greater odds of having undergone dialysis within the year prior to their infection if they suffer from diabetes by univariate analysis, and 2.5 times greater odds by multivariate analysis.

4.3 Comparison of BRFSS Georgia BMI data for Georgia to EIP Metro Atlanta Area iMRSA BMI Data.

A comparison between BMI category proportions within the general population of Georgia to the iMRSA cohort population is of interest if it is to be determined whether higher BMI results in greater risk for an invasive infection of MRSA.

Table 4.9 BRFSS and EIP iMRSA Populations' BMI Proportion by Category (Normal, Overweight, and Obese) for Georgia 2005-2008

		BRFSS % *(reference)*	EIP %	Difference
2005	Normal	37.0	39.0	-2%
	Overweight	36.4	24.9	11.5%
	Obese	26.5	27.9	-1.4%
2006	Normal	38.2	37.4	0.8%
	Overweight	34.6	24.9	9.7%
	Obese	27.1	29.3	-2.2%
2007	Normal	35.0	34.4	0.6%
	Overweight	36.3	28.4	7.9%
	Obese	28.7	31.6	-2.9%
2008	Normal	35.3	35.4	-0.1%
	Overweight	36.9	25.2	11.7%
	Obese	27.8	32.4	-4.6%

Figure 4.4 Bar Graph Comparison of BMI Category Proportions by Population for BRFSS and EIP metro Atlanta area Invasive MRSA for Georgia 2005-2008

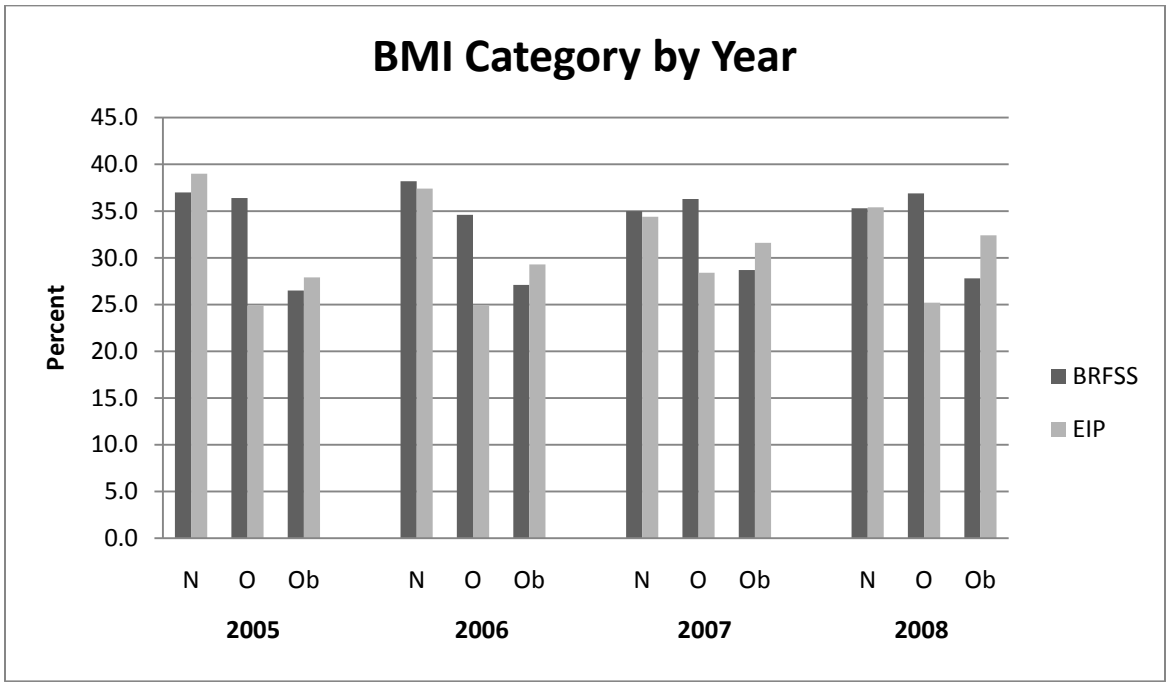


Figure 4.4 presents a comparison by year of the BRFSS BMI category data for the state of Georgia to BMI data from the EIP iMRSA data for the 8 county Georgia metro Atlanta area from 2005 to 2008. The proportion of 'normal' weight individuals is similar for both populations; the difference does not exceed 2 percentage points in any year. The percent of 'overweight' individuals is higher every year for the BRFSS state-wide sample. The percent of individuals in the 'obese' category is somewhat higher for the EIP iMRSA cohort each year. Normal weight individuals in both populations apparently bear equal risk of infection with iMRSA; normal weight seems neither to confer protection nor increase risk of iMRSA. Whether there is a statistically significant difference between the means cannot be determined from these data.

CHAPTER V
DISCUSSION

5.1 Discussion of Results

Among the 2,478 patients in the iMRSA cohort, it was found that 56.2% of patients were either overweight or obese by BMI category. Almost half of iMRSA patients had been diagnosed with diabetes (42.8%). This is a much higher proportion than is found in the general population (approximately between 7.8% and 10.7%) (NIDDK, 2007; ADA, 2007). Twenty-eight percent of this cohort had undergone dialysis within the year prior to culture. Among the general popultion of the Georgia MSA, this proportion is less than 1% (USRDS, 2010). Greater adiposity was associated with increased risk of Type 2 Diabetes in both univariate and multivariate analysis. Invasive MRSA patients suffering from diabetes were at greater odds of having undergone dialysis within the previous year (univariate analysis OR=2.3, p=0.000; multivariate analysis OR=2.5, p=0.000). The population was primarily African America, non-Hispanic, and male. Mean age was fifty-six years old. Mean BMI was 27.39, or overweight.

Comparison to Georgia BRFSS data show that the proportion of patients in the overweight BMI category are higher each year for the general population than in the iMRSA cohort, suggesting a protective effect of a somewhat greater than ideal BMI. This is an interesting and unexpected result that seems to contradict the hypothesis, at least for overweight individuals as opposed to the obese. One explanation may be that in the iMRSA data, high rates of mordities like diabetes and kidney failure—indicated by a high proportion of cases on dialysis—may indicate medical interventions such as nutrition and excersize counsiling. The dialysis treatment may indicate severe disease, and patients may have lost weight as a result of advanced illnesses. The iMRSA cohort is also has a relatively high proportion of elderly cases, and advanced age may contribute to a need for long-term care, difficulties in mobility, and other health issues that can lead to wasting and atrophy. Contraction of invasive disease in otherwise healthy individuals is somewhat rare, and may indicate an immunocompromised state, such as

cancer treatment or HIV, which both lead to decreased appetites and wasting disease. Further research is necessary to understand the potential protective effects of being overweight.

5.2 Limitations

Although some results provide support for the hypothesis that greater BMI may increase risk for invasive MRSA, there are several limitations to this study. First, cohort data presents challenges, and there are limitations to comparing proportions within a cohort to proportions in other populations. Comparison of the means of the BRFSS sample and the EIP iMRSA cohort by independent sample methods, such as by t-test, to determine if there is any statistically significant difference between the means is, though desirable, not appropriate here because t-test analysis assumes both samples being compared are sampled at random from the same population. In this case, the two means come from a non-random, complete cohort of cases from a population limited to eight counties, and a stratified random sample of residents from all over the state of Georgia. Therefore the null hypothesis H_0: $\mu_1=\mu_2$, with alternative hypothesis H_A: $\mu_1<\mu_2$, cannot be tested for rejection or acceptance in this case.

Poor recording of height and weight data by the EIP, due perhaps to difficulty in finding height data in hosptial charts, human error, and the relative low importance of these data in the EIP's surveillance goals, resulted in many missing values and extreme BMI scores. Since some extreme BMI values were certainly a result of data entry or collection error, it is unknown how many of the cases that were retained after extreme cases were excluded had an accurate BMI. Some of these apparently 'normal' BMI scores may have reflected errors that did not cause them to fall into the excluded groups.

Also, this study only looked at data from Georgia, and may not be generalizeable to other states or the U.S. population. In Georgia there is a great variablility of urban/rural and socioeconomic classes, even within single counties. Studying the iMRSA cohort, with a population taken only from the MSA poses generalization limitations.

5.3 Recommendations

To assess whether higher BMI leads to greater risk of an invasive MRSA infection, a twenty-year prospective cohort study with a sample size of 5,000 would be optimal. Participants

selected would be between the ages of thirty and sixty. (Individuals younger than thirty are less likely to manifest the detrimental effects of chronic disease within the twenty year timeframe. Patients over sixty are more likely to already have established chronic diseases and other health problems.) Enrolled participants' BMI and MRSA nasal carriage would be assessed at the beginning of the study. Data would be collected on each participants' health, such as symptoms of prediabetes, diagnosis of diabetes mellitus, BMI, kidney function, healthcare exposures such as hospital admission and surgeries, and any positive cultures for MRSA. Follow-up would occur every two years by interview, plus chart reviews if patient was hospitalized for MRSA. It could then be established if:

1.) increased body mass predisposes a person to iMRSA infection

2.) rates of iMRSA infection are higher among patients with higher BMI

3.) the incidence of MRSA infections increases with greater body mass

4.) rates of iMRSA among patients with Type 2 Diabetes and/or undergoing dialysis are higher for patients with higher body mass

The population can be observed over time to determine which patients already have risk factors of interest, whether these risk factors become more prevalent among the obese, and which patients develop an iMRSA infection. Care should be taken to compensate for nonresponses and losses to follow-up to account for possible bias. Though this study design is ideal, it may be impractical, and expensive. Matched case-control studies may be necessary when taking these considerations into account. Cases would be matched on age, sex, and race, and confounders like diabetes and dialysis could be controlled for.

5.4 Public Health Significance

The obesity epidemic in the United States and other developed countries is expected to continue for years, perhaps for many decades, and the incidence of obesity is rising in many other nations around the world. Although chronic diseases are the most cited consequences of long-term obesity, obesity may also increase vulnerability to infectious disease. Public health education campaigns warn the public of chronic diseases diabetes mellitus, heart disease, hypertension,

congestive heart failure, and even cancer in relation to elevated body fat, poor nutrition, and lack of adequate exercise, but rarely if ever mention the risks of infection. When clinicians and public health work discusses the health consequences of diabetes, often there is no mention of risk of infection, even when discussing amputations as a result of peripheral arterial disease, even though major surgeries always carry risk of infection.

It is important to understand and highlight the complex connections and relationships between chronic and infectious disease. Unfortunately, these health issues are often considered separately in research and intervention designs. This may obscure connections between chronic and infectious disease rates. Rising incidence of a given chronic disease may result in concurrent increases in rates of certain infections that are connected to the health consequences of that chronic disease. For example, if obesity increases risk for MRSA infection, successful interventions resulting in lower rates of obesity would also lead to fewer MRSA infections. As another example, osteoarthritis may become severe enough to limit mobility to the point that sores develop from inactivity, leading to skin and soft tissue infections. The connection between the two occurrences may be obscured to public health workers looking at these data separately. Further complicating the problem is the complexity of the chain of causation, making establishing connections difficult. Obesity may increase risk for invasive disease due to dialysis, but the relationship is obscured by the intermediary condition of Type 2 Diabetes. Investigating the interplay between chronic and infectious disease is important, even when causation can be difficult to establish.

An intervention targeting the earliest link in the chain of morbidity is ideal. Thankfully, health behavior interventions aimed at lowering the obesity rate are already being designed and implemented. Nutrition education and access is essential to lowering obesity rates and improving the immune system. Exercise also helps to both prevent chronic disease and decrease likelihood of infection through boosting the immune system. Environmental interventions to help make it easier for the public to exercise and obtain healthy food have proven more difficult, but successful when designed and implemented well. Education on the problems associated with obesity helps the public to make healthy choices. Each of these interventions offers an

opportunity to help the public to understand that their nutrition and activity not only cause chronic disease, but may help prevent infections as well.

. Healthcare providers and patients should be informed of possible risks of infection associated with elevated BMI. Studies on the increased risk of iMRSA infection relative to increased BMI are uncommon. Literature on diabetes seldom mentioned the risk of invasive infections as the disease progressed. Further research on this subject is important due to the large proportion of overweight and obese individuals, and the possibility of continued or worsening antibiotic resistance in bacteria such as MRSA. Should future case-control studies uncover an association between greater adiposity and invasive MRSA infection, then counseling patients with elevated BMI, pre-diabetes, or Type 2 Diabetes on MRSA infection risk would not only be an important part of patient education, but also serve as an added incentive to the patient to make lifestyle changes to avoid serious infections. In addition to advice on weight loss and management, physicians may discuss the risks and consequences of infection with patients with higher than normal BMI to encourage lifestyle changes that deter eventual development of Type 2 Diabetes and its complications.

5.5 Conclusion

Proportions of cases with Type 2 Diabetes and on dialysis are higher in the Atlanta, Georgia MSA iMRSA cohort than is seen in the general population. Overweight and obese cases were at greater risk of Type 2 Diabetes compared to normal weight cases, and diabetes diagnosis increased the risk for also having been on dialysis within the year prior to invasive MRSA infection. The percent of obese cases was slightly higher each year in the iMRSA cohort compared to BRFSS data for Georgia, though whether these differences are statistically significant cannot be determined from these data. Further research is needed to determine risk and if there is a significant association between greater BMI and invasive infection rates of MRSA.

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