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The Relationship Between Obesity and Recurrent Methicillin-resistant *Staphylococcus aureus* (MRSA) Infection Among Individuals with Initial Invasive Community-Associated MRSA Infection: A Pilot Study

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ABSTRACT

The Relationship Between Obesity and Recurrent Methicillin-resistant *Staphylococcus aureus* (MRSA) Infection Among Individuals with Initial Invasive Community-Associated MRSA Infection: A Pilot Study

By Alyssa Parr

Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infections have been increasing in incidence over the past decade, and while some studies have looked at recurrence in skin and soft tissue CA-MRSA infections, there is no current literature on recurrence for invasive CA-MRSA infections. Obesity has been linked to skin and soft tissue infections as well as recurrent skin and soft tissue MRSA infections, and might have an impact on invasive MRSA infections as well. This pilot study aimed to examine the relationship between obesity and recurrent invasive MRSA infections among individuals with an initial CA-MRSA infection in the year prior. Data were obtained from the Active Bacterial Core surveillance (ABCs) system of the Center for Disease Control and Prevention's Emerging Infections Program from 2005-2011. A case-control study was performed for initial CA-MRSA infections between 2006-2010, comparing cases, defined as individuals with an initial invasive CA-MRSA infection that went on to have a second invasive MRSA infection in the year following the initial infection (recurrence), and controls, defined as individuals with invasive CA-MRSA infection who did not go on to have recurrence. There were 253 cases and 2,876 controls identified, for a total sample size of 3,129, indicating an average recurrence incidence of 8% annually. Multivariate modeling revealed a significant relationship between obesity and recurrence (OR 1.84, 95% CI 1.26-2.69, p-value=0.0016), after controlling for age, diabetes, bacteremia, pneumonia, osteomyelitis, urinary tract infection, endocarditis, bursitis, and surgical incision infection. Confounding assessment led to a simpler model that again showed a significant relationship between obesity and recurrence (OR 1.99, 95% CI 1.40-2.86, p=0.0002). Since recurrence is assumed to be rare, this indicates that the risk of recurrent invasive MRSA infections among individuals with an initial invasive CA-MRSA infection is twice the risk of recurrence among non-obese individuals. Given the high prevalence of obesity in the United States and the evidence for increasing incidence of CA-MRSA, this pilot study should help generate hypotheses for future studies examining the relationship between obesity and recurrence in CA-MRSA infections. In particular, these preliminary results emphasize the need for further analysis using several variables introduced in 2010 to the ABCs invasive MRSA surveillance case report form, such as BMI.

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INTRODUCTION

Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infections have been increasing in incidence over the past decade.(1-4) While the majority of CA-MRSA cause skin and soft tissue infections, , CA-MRSA can also present as invasive infections, including bloodstream infections, which can cause severe morbidity and mortality.(5, 6) Recurrent MRSA infections have been well-documented in specific populations,(7-10) but there are no published studies that look at MRSA infection recurrence among people who had invasive CA-MRSA infections.

Like MRSA, the incidence of obesity has also been increasing over the past few decades and only recently have researchers begun to explore the intersection between obesity and infectious diseases.(11-13) Furthermore, obesity has been found to be associated with MRSA infections as well as been identified as a risk factor for recurrent MRSA skin and soft tissue infections.(14-16) There could be an association between obesity and recurrence in invasive CA-MRSA infections, but currently there are no published studies examining this possibility.

In 2005, the Active Bacterial Core surveillance (ABCs) system of the Center for Disease Control and Prevention's Emerging Infections Program added MRSA to their list cof invasive infections under surveillance. This pilot study examines ABCs invasive MRSA data from 2006-2010 to determine incidence and analyze the association between obesity and recurrent invasive MRSA infections in people whose initial infection was invasive CA-MRSA, with the hope of identifying areas for future study.

BACKGROUND

Community-Associated Methicillin-Resistant Staphylococcus aureus

Methicillin-resistant *Staphylococcus aureus* (MRSA) was first seen in healthcare settings in the late 1960's,(17) and soon became one of the more prominent healthcare-associated infections, estimated to be the cause of 50-60% of all hospital-acquired *S. aureus* infections in 2010.(18) In the late 1990's, cases of MRSA were increasingly reported in persons with limited or no prior healthcare exposure.(19-25) Termed community-associated MRSA (CA-MRSA), it soon became the leading cause of skin and soft tissue infections seen in US emergency rooms.(26) CA-MRSA infections tend to be attributed to microbiologically and genetically distinct MRSA strains from healthcare-associated MRSA (HA-MRSA). CA-MRSA is typically caused by strain US300, while HA-MRSA infections are more-commonly caused by US100, although these distinctions are rapidly blurring due to the spread CA strains into healthcare facilities.(27-29)

Active Bacterial Core surveillance (ABCs) in the Emerging Infections Program (EIP) of the Centers for Disease Control and Prevention (CDC) defines CA and HA-MRSA based on the location of disease onset and the presence specific traditional risk factors for MRSA infection (i.e., exposure to healthcare settings).(30) HA-MRSA is further split into two categories, hospital-onset (HO) and healthcare-associated community-onset (HACO). The definitions for HO, HACO, and CA-MRSA are as follows:

1. Hospital-onset (HO): culture positive for MRSA >2 days after hospital admission, where the day of admission counts as day one

2. Healthcare-associated community-onset (HACO): culture positive for MRSA either in outpatient setting or ≤ 2 days after hospital admission, and have at least one of the following healthcare risk factors:
    a. History of hospitalization, surgery, dialysis, or residency in a long-term care facility within a year prior to the positive culture
    b. Presence of invasive device (such as a central venous catheter) at time of positive culture
3. Community-associated (CA): culture positive for MRSA and have none of the HO or HACO healthcare risk factors

CA-MRSA infections are further differentiated by the type of infection they cause: skin and soft tissue infections (SSTI) or invasive infections. In order to better understand the distribution and incidence of invasive MRSA infections in the United States, the CDC's ABCs system added invasive MRSA to their list of surveillance pathogens in 2005. ABCs is an active population and laboratory-based collaboration between CDC and 10 state health departments, although only 9 sites participate in invasive MRSA surveillance.

ABCs defines invasive MRSA disease as the isolation of MRSA from a normally sterile site, such as blood, bone, cerebrospinal fluid, pleural fluid, joint/synovial fluid, internal body sites, etc.(1, 28) In 2011, there were an estimated 16,560 invasive CA-MRSA cases in the United States, at a rate of 5.32 (95% CI: 4.11-7.00) per 100,000 population per year.(30) Invasive disease is generally more severe than SSTI and has higher rates of treatment failure and mortality.(5, 6) The most common clinical conditions presented by invasive CA-MRSA infections are bacteremia (65.1%), cellulitis (22.7%), pneumonia (14.0%), and endocarditis (12.6%).(28)

In recent years, studies have shown a decrease or leveling off of HA-MRSA infections, but during the same time period there appears to be an increase in the number of CA-MRSA infections.(1-4) In addition, it has been estimated that invasive and non-invasive CA-MRSA infections impose a societal financial burden and productivity loss of $1.4-13.8 billion annually.(31) These trends highlight the importance in preventing and controlling CA-MRSA infections, and emphasize how much of a serious and common challenge CA-MRSA has become.

Recurrent MRSA Infections

Another challenge in recent years has been the recurrence of MRSA infections in certain individuals. Researchers have looked into factors that lead to recurrence in HIV positive individuals(7, 8), in hospital settings(9), and for SSTI CA-MRSA.(10) At this time, there are no published studies on the risk of a recurrent invasive MRSA infection among persons whose initial infection was invasive CA-MRSA. Given that invasive disease is more severe than SSTI and that CA-MRSA cases are increasing, it is vital that this knowledge gap be investigated soon.

Obesity as Risk Factor

The proportion of obese people in the United States (defined as having a BMI>30 kg/m^2) has steadily been increasing in the past couple of decades. In 1995, 15.9% of the population was considered obese, whereas in 2007 that proportion grew to 27.5%.(32) While much has been studied on the effects of obesity on chronic conditions, researchers have only recently started to examine the association between obesity and infectious diseases.(11-13) Current hypotheses are that obesity has an effect on immunologic function, which seems to predispose obese patients for increased risk of infection and severe complications from infection.(11-13)

Obese individuals are also more likely to experience chronic skin conditions and breakdown, which put them at higher risk for acquiring SSTI.(12, 33) Additionally, both skin breakdown and obesity have been identified as risk factors for CA-MRSA infections. (4, 14-16) Sreeramoju et. al reported that the odds of obesity among recurrent SSTI MRSA cases was 3.4 times those without recurrence.(9) Given these studies, it is possible that obesity could have an effect on recurrence for invasive CA-MRSA. Therefore, this pilot study aims to explore effects of obesity on invasive CA-MRSA infections and whether obesity increases the chances of recurrent invasive MRSA infection.

METHODS

Null Hypothesis

There is no difference in the odds of being obese among individuals who get recurrent MRSA infection within one year after an initial CA-MRSA infection compared to those with a CA-MRSA infection who do not develop recurrence in that year.

Alternative Hypothesis

There is a difference in the odds of being obese among individuals who get recurrent MRSA infection within one year after an initial CA-MRSA infection compared to those with a CA-MRSA infection who do not develop recurrence in that year.

Data Collection

Data for all invasive MRSA cases from 2005-2011 were obtained from ABCs invasive MRSA surveillance program. As mentioned above, the ABCs system is an active population and laboratory-based surveillance system, and the method of data collection has been described previously. (28) There are nine EIP sites participating in the ABCs system invasive MRSA surveillance, and as of 2011 they covered a population of 19,154,389 [Table 1]. These sites mimic the distribution of US residents by race and gender and therefore are often used to make nationwide estimates for invasive disease incidence. Rather than making nationwide estimates, in this study the sites served as a convenience sample from which to model the association between obesity and recurrence.

Study Design

This is a pilot case-control study, with cases defined as initial CA-MRSA cases that went on to have recurrent infection and controls as initial CA-MRSA cases that did

not have recurrence and who did not die prior to 30 days after their culture date. Recurrent infection was defined as any initial CA-MRSA cases that were reported to having at least one positive invasive MRSA culture between 30 and 365 days after the initial CA-MRSA culture. ABCs considers any recurrent culture prior to day 30 as part of the initial infection, and therefore is not considered a new case.(34) Recurrence was arbitrarily defined as occurring within one year from the initial culture to fit the data years that were available. Due to the current definitions for HO, HACO, and CA-MRSA cases, a recurrent case could be considered as occurring in any one of these classifications, as long as the initial case was CA-MRSA. Since there were no data available for 2004, it was not clear whether the new CA-MRSA cases in 2005 had a previous infection the year before, therefore new CA-MRSA cases were limited to 2006-2010. For the initial CA-MRSA cases in 2010, recurrent infections were identified in 2011, but no new cases were collected in 2011.

The age groups examined were defined as 18-34, 35-49, 50-65, and 65+ years for easy comparison with past ABCs invasive MRSA studies(28), and all those under 18 years were excluded because there were not enough recurrent cases to analyze (1 case out of 309 total invasive CA-MRSA infections in people under 18 years). Other covariates under consideration were race (White, Black or African American, Asian, American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander), sex (male or female), type of MRSA infection (bacteremia, empyema, meningitis, peritonitis, pneumonia, osteomyelitis, urinary tract, abscess[not skin], internal surgical site, bursitis, septic shock, cellulitis, traumatic wound, surgical incision) and specific underlying conditions (obesity, abscess/boil, current smoker, diabetes, peripheral vascular disease). Some patients could be coded with multiple infection types and underlying conditions. All variables were classified into single, dichotomous yes/no variables, except sex which

was dichotomous with male/female. The main exposure variable was obesity and the outcome was whether or not the patient developed recurrence.

Statistical Analysis

Univariate analyses were conducted on the frequencies for the main exposure and covariates between cases and controls using chi-square tests, or Fisher's exact test when expected cell counts were less than 5. A p-value < 0.05 was considered statistically significant. All significant covariates were analyzed as possible interaction terms with the main exposure, obesity, using the Breslow-Day test for interaction. Then, all significant covariates were added to multivariate models with obesity and reduced via backward elimination comparing the effect of removing a variable on the obesity OR in order to identify confounding variables. Several models were examined, including the Gold Standard model, which was defined as one with all univariate-identified covariates, and a final model reduced to those covariates that were found to be significant via a table of odds ratios. All data manipulation and analyses were conducted using SAS 9.3 software (Cary, NC).

RESULTS

Total CA-MRSA Infections

From 2006-2010, there were 3,129 initial CA-MRSA infections in individuals 18 years or older [Table 1]. The majority of these CA-MRSA cases were from Georgia (20.2%) and California (20.2%), which is consistent with the relative size of the population under surveillance at these two sites (19.2% and 17.6% of the population, respectively). Maryland represents 7.4% of the total ABCs invasive MRSA surveillance population, but they had a disproportionately high proportion of CA-MRSA cases (17.9%).

Univariate Analyses

From 2006-2010, there were 253 cases and 2,876 controls identified, for a total sample size of 3,129. The average time between the initial CA-MRSA culture and the date of the first recurrent MRSA infection within 1 year was 118 days (stand dev = 81.9). Of the 253 cases, the first recurrent event was classified as HACO for 195 individuals (77.08%), HO for 31 (12.25%), CA for 26 (10.28%), and unknown for 1 (0.40%). The distribution of cases among the different EIP sites was: 44(17.4% of total cases) from Georgia, 40(15.8%) from Connecticut, 41(16.2%) from California, 20(7.9%) from Colorado, 9(3.6%) from Minnesota, 18(7.1%) from Oregon, 54(21.3%) from Maryland, 7(2.8%) from New York, and 20(7.9%) from Tennessee [Table 1]. There were no significant differences between the distribution of cases and controls for any of the EIP sites; all chi-square p-values were greater than 0.05. On average, about 8% of CA-MRSA cases per year went on to develop recurrence, with no definitive secular trend apparent by year [Figure 1].

Univariate analysis for the covariates of interest yielded several variables showing statistically significant associations with recurrence: age 18-34 years (p=0.0003), bacteremia (p<0.0001), pneumonia (p=0.0393), osteomyelitis (p=0.0328), endocarditis (p<0.0001), bursitis (p=0.0033), obesity (p=0.0002), and diabetes (p=0.0072) [Table 2]. When modeled as independent risk factors for recurrence without controlling for any other variable, surgical incision infection type had the highest degree of association (OR 4.9, 95% CI 1.3,19.1), followed by endocarditis infection (OR 2.1, 95% CI 1.5-3.1), urinary tract infection (OR 2.1, 95% CI 1.4-3.2), and obesity (OR 2.0, 95% CI 1.4-2.9) [Table 3]. Pneumonia (OR 0.6, 95% CI 0.4-0.99), bursitis (OR 0.3, 95% CI 0.1-0.7), and age 18-34 years (OR 0.4, 95% CI 0.3-0.7) were all inversely associated with recurrence.

Multivariate Analyses

All the statistically significant variables identified in univariate analyses (age, bacteremia infection, pneumonia infection, osteomyelitis infection, urinary tract infection, endocarditis infection, bursitis infection, surgical incision infection, and diabetes) were assessed for interaction with obesity prior to multivariate modeling[Table 4]. There were no statistically significant interactions between obesity and any of the covariates, therefore no product terms were included in the initial multivariate model. The Gold Standard model was defined to include all of the statistically significant variables identified in univariate analyses and obesity [Table 5]. In this full model, the odds ratio for obesity was 1.85 (95% CI 1.27-2.71), indicating the odds of an individual being obese was 1.85 times higher in cases than in controls.

To investigate whether a simpler model could be obtained, individual variables were dropped in turn from the full model and then assessed for a confounding effect on obesity [Table 6]. All the reduced models gave an obesity OR within 10% of the Gold Standard model obesity OR (indicating valid estimates). To assess for precision, the

confidence interval ratio for each model's obesity OR was calculated, with the lowest ratio indicating better precision. The reduced model containing only obesity as a variable had the smallest CI ratio and the OR was within 10% of the Gold Standard model OR; therefore this model was chosen as the final model. This final model results in a statistically significant association between obesity and recurrent MRSA infection among people with an initial CA-MRSA infection (OR 1.99, 95% CI 1.39-2.89, p-value=0.0002), which supports the alternative hypothesis described above [Table 7].

DISCUSSION

This pilot study investigated the association between obesity and recurrent MRSA infections in individuals with an initial CA-MRSA infection. Obesity has recently been connected to infectious diseases, with findings that obese individuals are more-likely to get infections and have worse outcomes than non-obese individuals.(11-13) Additionally, SSTI are common among CA-MRSA sufferers, and obesity has been linked to chronic skin conditions and breakdown.(12, 33) Therefore the study of obesity on recurrence in CA-MRSA infections is very timely and should provide important information for future public health program planning.

On average, around 8% of persons with CA-MRSA infections went on to develop a recurrent MRSA infection within one year of the CA-MRSA culture. The majority of the first recurrent infections were considered HACO cases, which is expected given the ABCs HACO-MRSA definition of having a hospitalization within the prior year. Of the 26 recurrent infections classified as CA, only 7 of them were not hospitalized during their first CA-MRSA infection, so it is unclear why the 19 that were hospitalized in the year prior to the recurrence were classified as CA instead of HACO; it is most-likely due to human error that these recurrent events were classified incorrectly. This misclassification should have no impact on this study's results because most of the univariate and multivariate analyses were performed using data related to the initial CA-MRSA case, but researchers looking to study recurrent cases in the future should be aware of this possible misclassification issue.

Previous ABCs invasive MRSA surveillance studies have found that some EIP sites have unusually high incidence of MRSA infections compared to others,(28) which was also apparent in this study, evidenced by Maryland having a disproportionately high number of total CA-MRSA cases. The reasons for this discrepancy have yet to be studied.

In contrast, this pilot study did not find a significant difference in recurrence for each site from 2006-2010. This disparity in findings requires further investigation.

The final model included obesity without controlling for any other variables since there did not seem to be any confounding associations between obesity and the other covariates. The final obesity OR was 1.990 (95% CI 1.386, 2.858), indicating that the odds of being obese and developing recurrence was 2 times the odds of not being obese and developing recurrence. Given that in this study the average prevalence of recurrence was 8%, and in none of the 5 years examined was the incidence of recurrence greater than 9%, one could say that recurrence fulfills the rare disease assumption and therefore the odds ratio will approximate the risk ratio. Thus, under the rare disease assumption, obese individuals have twice the risk of developing a recurrent MRSA infection after having an initial invasive CA-MRSA infection than non-obese individuals. This risk is staggering, given the high prevalence of obesity in the United States and the evidence for increasing incidence of CA-MRSA.

There were several limitations to this study. One is that the ABCs' directions for coding obesity as an underlying condition on the invasive MRSA case report form states to only mark obesity if it is indicated in the patient's medical chart, and to not calculate BMI. Accurate reporting of patient risk factors in medical charts has been scrutinized in the past and shown to be lacking in completeness.(35) In this study, however, it was equally as likely for a case to not be recorded as obese as a control, as the information was recorded before recurrence status was known. Thus, if any bias is present, it should be non-differential and the estimate obtained in this study should not differ drastically if a new study were to be conducted that calculated BMI based on a patient's height and weight.

Another limitation was the inability to assess the effects of chronic skin conditions on the relationship between obesity and recurrent MRSA infection. In 2009, the ABCs invasive MRSA case report form added chronic skin disease as an underlying condition, but since this study looked at data from 2006-2010, any analysis on chronic skin conditions would have been incomplete. Future studies should be conducted including this variable as it could be a confounder for obesity and MRSA infection and might shed more light on the association seen between obesity and recurrence in this study.

This study did not make any adjustments for individuals who presented with more than one type of CA-MRSA infection or underlying condition. Multiple co-morbidities have been shown to increase risk of MRSA treatment failure (36, 37), so the possibility that individuals who get recurrence might be more likely to have several underlying conditions or types of infection could be further examined. Bacteremia in particular was present in 71% of cases, indicating an overlap with other infection types. Additionally, for the sake of completeness, very rare infection types in this study, such as surgical incision infection and bursitis, were included in the multivariate analysis, but the clinical relevance of these infection types might not be important in determining the risk for recurrence. Future modeling may decide to only look at those infection types which affect a larger proportion of cases.

This study also has several strengths. The ABCs system captures information from a large, geographically diverse population in the United States which has very similar demographics to the United States as a whole. The representativeness and size of the sampling population allows for studies that look at rare outcomes (such as this one) to get enough power to detect meaningful associations that might be missed in smaller studies. Additionally, this study in particular made use of a unique dataset that has

never been analyzed in this context before, thereby filling a knowledge gap in the current literature.

The purpose of this study was to provide preliminary analyses of MRSA recurrence for initial invasive CA-MRSA infections and to facilitate generating questions and hypotheses for future directions of study. One possible direction is to further examine the relationship between recurrence and age. Even though there have been many cases of invasive CA-MRSA identified persons younger than 18 years(2, 15, 20, 23, 38), there were so few recurrent cases identified in this study (1 out of 309 invasive CA-MRSA infections) that the age group had to be excluded prior to analysis to avoid collinearity issues. Furthermore, in this study the individual risk of recurrence in those 18-34 years old was 0.43 times the risk in those 35 years and older (OR 0.43, 95% CI 0.27-0.69, $p<0.001$, assuming recurrence is rare), indicating an inverse association between recurrence and younger age. Older age is generally considered a risk factor for disease, but with the evidence of high CA-MRSA incidence in children, the fact that so few recurrent events were found in younger individuals warrants further attention.

The results of this study also warrant further evaluation of the effects of obesity on recurrence using a more standard assessment of obesity, such as BMI, since as mentioned above extracting underlying conditions from medical charts can be unreliable. Additionally, assessing the impact of potential confounders not measured in the study, such as chronic skin breakdown and the presence of implants or invasive devices, could yield a more robust estimate of the effects of obesity on recurrence. The ABCs invasive MRSA surveillance system added chronic skin breakdown to the case report form in 2009, and added BMI and presence of invasive devices in 2010.(34) Future ABCs studies on invasive CA-MRSA recurrence should emphasize the inclusion of

these variables, and further assessment for other possible confounders or interactions with obesity is warranted.

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TABLES AND FIGURES

Table 1.Distribution of CA-MRSA Cases Who Developed Recurrence and CA-MRSA Controls Without Recurrence by EIP Site

Surveillance Site	Total Population (2011)[a]		All CA-MRSA Infections (2006-2010)		Cases[b]		Controls[b]		M-H[c] Chi-Square	
	n	%	n	%	#	%	n	%	Stat	P-value
Georgia (8 county Atlanta area)	3,682,873	19.2	632	20.2	44	17.39	588	20.45	1.345	0.246
Connecticut	3,574,097	18.7	440	14.1	40	15.81	400	13.91	0.696	0.404
California (3 county Bay area)	3,364,531	17.6	631	20.2	41	16.21	590	20.51	2.681	0.102
Colorado (5 county Denver area)	2,433,772	12.7	255	8.2	20	7.91	235	8.17	0.022	0.882
Minnesota (2 metro Twin Cities counties)	1,661,065	8.7	108	3.5	9	3.56	99	3.44	0.009	0.924
Oregon (3 county Portland area)	1,641,036	8.6	233	7.5	18	7.11	215	7.48	0.044	0.834
Maryland (1 county Baltimore area)	1,425,990	7.4	559	17.9	54	21.34	505	17.56	2.269	0.132
New York (1 Rochester county)	744,344	3.9	97	3.1	7	2.77	90	3.13	0.102	0.750
Tennessee (1 Nashville county)	626,681	3.3	174	5.6	20	7.91	154	5.35	2.880	0.090
Total	19,154,389		3129		253		2,876			

a. Total population under surveillance for ABCs invasive MRSA in 2011
b. Case = Developed recurrent MRSA infection within 1 year after initial invasive CA-MRSA culture
Control = Did not develop a recurrent MRSA infection within 1 year after initial CA-MRSA culture
c. Mantel-Haenszel

Table 2. Demographics, Type of MRSA Infection, and Underlying Conditions for Cases and Controls[c] (N=3,129)

Characteristics	**Cases (n=253)**		**Controls (n=2,876)**		**M-H[d] Chi-Square**
	n	%	n	%	p-value
Race					
White	131	0.518	1505	0.523	0.866
Black or African American	82	0.324	861	0.299	0.411
American Indian or Alaska Native[a]	1	0.004	17	0.006	1.000
Asian[a]	7	0.028	46	0.016	0.195
Native Hawaiian or Other Pacific Islander[a]	2	0.008	8	0.003	0.191
Unknown	30	0.119	441	0.153	0.138
Sex					
Male	174	0.688	1892	0.658	0.336
Age (years)	*(mean=54.9)*		*(mean=52.3)*		
18-34	20	0.079	477	0.166	<0.001[b]
35-49	84	0.332	893	0.311	0.479
50-64	80	0.316	825	0.287	0.324
65+	69	0.273	681	0.237	0.199
Type of Infection					
Bacteremia	181	0.715	1696	0.590	<0.001[b]
Empyema	1	0.004	69	0.024	0.039[b]
Meningitis[a]	3	0.012	13	0.005	0.134
Peritonitis[a]	0	0.000	12	0.004	0.615
Pneumonia	25	0.099	420	0.146	0.039[b]
Osetomyelitis	38	0.150	306	0.106	0.033[b]
Urinary Tract	27	0.107	155	0.054	0.001[b]
Endocarditis	39	0.154	225	0.078	<0.001[b]
Abscess (not skin)	27	0.107	294	0.102	0.821
Surgical Site (internal)[a]	3	0.012	21	0.007	0.437
Bursitis	6	0.024	208	0.072	0.003[b]
Septic Shock	6	0.024	86	0.030	0.577
Cellulitis	44	0.174	644	0.224	0.066
Traumatic Wound[a]	6	0.024	41	0.014	0.271
Surgical Incision[a]	3	0.012	7	0.002	0.041[b]
Decubitus/Pressure Ulcer[a]	8	0.032	53	0.018	0.151
Underlying Condition					
Obesity	40	0.158	248	0.086	<0.001[b]
Abscess/Boil	19	0.075	295	0.103	0.163

Current Smoker	87	0.344	1008	0.350	0.833
Diabetes	88	0.348	774	0.269	0.007[b]
Peripheral Vascular Disease	16	0.063	110	0.038	0.053

a. Used Fisher's Exact Test
b. Significant result (alpha ≤ .05)
c. Case = Developed recurrent MRSA infection within 1 year after initial invasive CA-MRSA culture
   Control = Did not develop a recurrent MRSA infection within 1 year after initial CA-MRSA culture
d. Mantel-Haenszel

Table 3: Independent Associations for Significant Characteristics with Invasive MRSA Recurrence in People with Initial CA-MRSA Infection

Characteristics	OR	95% CI		P-value
		Lower	Upper	
Age (years)				
18-34	0.432	0.271	0.689	<0.001
35-49	1.104	0.840	1.451	0.479
50-64	1.150	0.871	1.517	0.324
65+	1.209	0.905	1.615	0.200
Type of Infection				
Bacteremia	1.749	1.318	2.321	<0.001
Pneumonia	0.641	0.419	0.981	0.041
Osetomyelitis	1.484	1.031	2.138	0.034
Urinary Tract	2.097	1.364	3.226	0.001
Endocarditis	2.147	1.487	3.101	<0.001
Bursitis	0.312	0.137	0.709	0.005
Surgical Incision	4.918	1.264	19.137	0.022
Underlying Condition				
Obesity	1.990	1.386	2.858	0.000
Diabetes	1.448	1.104	1.900	0.008

Table 4: Assessment of Interaction for Obesity with Covariates Meeting Selection Criteria

	Breslow-Day	
Characteristic	**Statistic**	**P-value**
Age	6.955	0.073
Bacteremia	2.592	0.107
Pneumonia	0.552	0.458
Osteomyelitis	0.292	0.589
Urinary Tract Infection	3.620	0.057
Endocarditis	0.089	0.765
Bursitis	0.299	0.584
Surgical Incision	Und	--
Diabetes	0.071	0.789

Table 5. Multivariate Analysis of Obesity on Recurrent MRSA Infection Among People with Initial CA-MRSA Infection: Gold Standard Model

Parameter	OR	95% CI		P-value
		Lower	Upper	
Obesity	1.852	1.265	2.711	0.002
Age (years)				
18-34	Ref	--	--	--
35-49	2.065	1.244	3.428	0.005
50-64	2.141	1.274	3.598	0.004
65+	2.214	1.305	3.756	0.003
Bacteremia	1.573	1.166	2.122	0.003
Pneumonia	0.579	0.375	0.895	0.014
Osteomyelitis	1.482	1.009	2.175	0.045
Urinary Tract	1.749	1.120	2.732	0.014
Endocarditis	2.407	1.641	3.530	<0.001
Bursitis	0.487	0.208	1.137	0.096
Surgical Incision	6.551	1.618	26.527	0.008
Diabetes	1.153	0.857	1.551	0.348

Table 6: Assessment of Confounding on Obesity: Table of Odds Ratios

Parameters in Model	Obesity OR	Within 10%	95% CI		CI Ratio
			Lower	Upper	
Gold Standard	1.852	--	1.265	2.711	2.143
Obesity, age group, bacteremia, pneumonia, urinary tract, endocarditis, bursitis, surgical incision, diabetes (drop osteomyelitis)	1.847	Yes	1.262	2.704	2.143
Obesity, age group, bacteremia, pneumonia, urinary tract, endocarditis, surgical incision, diabetes (drop osteomyelitis and bursitis)	1.843	Yes	1.259	2.697	2.142
Obesity, age group, pneumonia, urinary tract, endocarditis, surgical incision, diabetes (drop osteomyelitis, bursitis, and bacteremia)	1.871	Yes	1.28	2.735	2.137
Obesity, age group, pneumonia, endocarditis, surgical incision, diabetes (drop osteomyelitis, bursitis, bacteremia, and urinary tract)	1.849	Yes	1.266	2.700	2.133
Obesity, age group, pneumonia, endocarditis, diabetes (drop osteomyelitis, bursitis, bacteremia, urinary tract, and surgical incision)	1.832	Yes	1.255	2.675	2.131
Obesity, pneumonia, endocarditis, diabetes (drop osteomyelitis, bursitis, bacteremia, urinary tract, surgical incision, and age group)	1.863	Yes	1.277	2.717	2.128
Obesity, pneumonia, diabetes (drop osteomyelitis, bursitis, bacteremia, urinary tract, surgical incision, age group, and endocarditis)	1.838	Yes	1.263	2.675	2.118
Obesity, diabetes (drop osteomyelitis, bursitis, bacteremia, urinary tract, surgical incision, age group, endocarditis, and pneumonia)	1.817	Yes	1.25	2.642	2.114
Obesity (drop osteomyelitis, bursitis, bacteremia, urinary tract, surgical incision, age group, endocarditis, pneumonia and diabetes)	1.990	Yes	1.386	2.858	2.062

Table 7. Multivariate Analysis of Obesity on Recurrent MRSA Infection Among People with Initial CA-MRSA Infection: Final Model

Parameter	OR	95% CI		P-value
		Lower	Upper	
Obesity	1.990	1.386	2.858	0.0002

Figure 1: Annual Distribution of Individuals with Initial CA-MRSA Infection Who Later Develop Recurrent MRSA Infection (Cases) Compared to Those Without Recurrence (Controls) - with Case Percent of Total