Clinical features of bloodstream infections caused by the two dominant clones of endemic methicillin-resistant *Staphylococcus aureus*

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Abstract

Background: We evaluated the molecular epidemiology of methicillin-resistant *S. aureus* (MRSA) bloodstream infections (BSIs) through an in-depth analysis of BSIs caused by the two dominant clones circulating in New York City at a large urban tertiary- and quaternary-care teaching hospital.

Methods: Comprehensive clinical data extraction from the electronic health records of 227 hospitalized patients ≥18 years old with MRSA bacteremia between August 2014 through April 2017 was collected. The descriptive epidemiology and mortality associated with the two dominant clonal complexes (CCs) was compared using logistic regression.

Results: Analysis revealed that 91% of all single-patient MRSA BSIs were due to two equally represented genotypes, the CC5 (N=117) and the CC8 (N=110). The CC8 caused disease more frequently in younger age groups (60 ± 17 vs 70 ± 17 years old; $p<0.001$) and in non-White race (OR=3.21 95% CI [1.42-7.22]; $p=0.005$). The CC8 caused BSI more frequently in the setting of peripheral intravenous catheters infections (OR=6.46; 95% CI [1.68-24.87]; $p=0.007$). MRSA BSIs were associated with 90-day mortality of 27%.

Conclusions: The clinical features distinguishing the two dominant MRSA clones continue to converge. The association of CC8 with peripheral intravenous catheters infections underscores the importance of classical community clones causing hospital-onset infections. Ongoing monitoring and analysis of the dynamic epidemiology of this endemic pathogen is crucial to inform management to prevent invasive disease.

Introduction

Healthcare-associated infections (HAIs) pose a potentially fatal threat to patients worldwide[1] and *Staphylococcus aureus* is one of the most common causes of HAIs in the United States.[2,3] Methicillin-resistant *S. aureus* (MRSA) bloodstream infections (BSIs) are linked with mortality up to 30% and are associated with longer hospital stays and increased healthcare costs.[4,5] MRSA has long been present in healthcare settings but is now well established in the community.[6] The two dominant MRSA clones in the United States are the clonal complex (CC) 5 and CC8.[3] Historically, the CC5 has been associated with older individuals with hospital or long-term care facility contact.[6] In contrast, the CC8, predominantly the USA300 pulsotype, was first reported in the US in healthy children in 1990s and raised concern for its capacity to cause severe disease in healthy individuals.[7] Over the following two decades, the CC8, driven by the USA300, would become established as the predominant community-associated clone, presenting as skin and soft tissue infections (SSTIs) in athletes, children in day-care centers, injection drug users, and in persons with human immunodeficiency virus (HIV) infection.[8,9] Between 2004 and 2008, the reported prevalence of the CC8 doubled in healthcare settings and was associated with as many inpatient infections as the CC5.[6,9]

We sought to update and expand on the descriptive molecular epidemiology of MRSA BSIs in a major academic medical center in New York City. We examined the differences between the two dominant clonal complexes, CC5 and CC8, and their associated clinical and epidemiological features. We additionally studied clonal associations in the context of current surveillance definitions as defined by the National Healthcare Safety Network (NHSN), which are reportable.[10] We explored clones in the

context of associations with inpatient and outpatient community healthcare networks. Finally, we examined subgroups within the two clones with an interest in the clinical features of the USA500, a relatively understudied clone.[11,12] With extensive clinical detail we describe a more complex picture than current definitions are able to describe.

Methods

Patient Selection

The Mount Sinai Hospital (MSH) is a 1,018-bed tertiary- and quaternary-care facility. Under the approval of the MSH institutional review board, data were captured on a total of 250 adult (≥ 18 years old) patients with MRSA BSI by the MSH Clinical Microbiology Laboratory as part of standard clinical care between August 2014 and April 2017. Identification and susceptibility of MRSA was performed using VITEK®2 (bioMerieux). From a larger hospital-wide genomic surveillance program, we derived the CC and multilocus sequence typing (MLST) *in silico* using the RESTful interface to the *S. aureus* PubMLST[13] database. Staphylococcal protein A (*spa)* and Panton-Valentine Leukocidin (PVL) were generated using a custom script (https://github.com/mjsull/spa_typing) and BLAST+[14] respectively. Core-genome MLST types were determined using the schema available at (https://www.cgmlst.org/ncs/schema/141106/), and a tree for the visualization of clusters was created using GrapeTree[15].

Demographic and clinical data was obtained retrospectively from the electronic medical record system, including geographic admission data, presumed source of the BSI based on Infectious Diseases (ID) consultant, comorbidities, and prior outpatient healthcare exposures. For a description of key variables see Supplementary Table 1. All

patients diagnosed with MRSA BSI received a consultation from an ID specialist at the time of diagnosis as per standard practice at our institution. The online database REDCap[16] was used for data capture and to calculate the Charlson Comorbidity Index (CCI).[17] Patients with non-CC5 or CC8 MRSA were excluded, resulting in a total of 227 patients for analyses. Zip codes were used to create a map of clones using the geographic information system (GIS) software ESRI Spatial Analysis.[18] Surveillance definitions included hospital-onset MRSA (HO-MRSA), defined as positive cultures on or after the fourth day after hospital admission, and community-onset MRSA (CO-MRSA) defined as BSI presenting within the 72-hour hospital admission interval.[10]

Statistical Analysis

We selected established clinical correlates related to prior epidemiological studies, including demographics, baseline comorbidities, admission sources, and infection sources. We also evaluated in-hospital outcomes and death, especially those related to the MRSA BSI. We collapsed variables to make the final set of covariates informative and reflective of current published literature. Analyses were performed in SAS (ver.9.4),[19] and survival curves were produced using R (ver.3.4.2).[20] Non-normally distributed continuous variables were categorized into discrete categorical groups. Variables were first analyzed in a univariate logistic regression model, with variables $p \leq 0.2$ then placed into a multivariate logistic regression model. Mortality analyses were analyzed using a Cox regression model. All variables with $p \leq 0.05$ were considered statistically significant.

Results

Molecular composition of clones involved in MRSA BSI

Molecular analysis of single-patient, first episode MRSA BSI revealed the majority of MRSA BSIs were caused by two dominant clones, the CC5 and CC8 (Supplementary Figure 1, Supplementary Table 2, Supplementary Excel Table 1). The CC8 was the cause of BSI in 110 (44%), and the CC5 in 117 (47%) of the total of 250 cases, representing 91% of the entire population. Only 23 (9%) were non- CC5/CC8. Within the CC5, the majority were either sequence type (ST) 5 (N=49; 42%) or ST105 (N=61; 52%). Six percent (N=7) belonged to other STs within the CC5. The majority of isolates within the CC8 were ST8 (N=108; 98%) with 2 (2%) additional non-ST8 clones. The majority (N=64; 58%) of ST8 were *spa* type t008, along with 20 (18%) non-t008 *spa* types which also clustered with USA300. Additionally, the CC8 included 24 (22%) *spa* type t064, including three (3%) non-t064 *spa* types, all clustering in the USA500 lineage.[11,21]

Baseline Clinical Characteristics of patients with MRSA BSIs

Sixty-seven percent of patients were male, and the median age at diagnosis was 66 years old (Table 1). The racial and ethnic composition included non-Hispanic White (N=98; 43%), non-Hispanic Black (N=63; 28%), Hispanic/Latino (N=46; 20%), Asian (N=8; 4%), and not reported (N=12; 5%). MRSA BSIs were linked to a wide range of causes, with vascular access (N=78; 34%), pneumonia (N=24; 11%), and SSTIs (N=26; 11%) representing the most common causes.

We performed a comprehensive analysis of admission sources. More than half of patients were admitted from home (N=128; 56%) with the remaining patients transferred in from nursing homes/rehabilitation/long-term care facilities (NH/Rehab/LTACH) (N=60; 26%), outside hospitals (N=35; 15%), or homeless shelters (N=4; 2%). Of subjects

144 residing at home or group home settings, 32% (N=56) had frequent contact with
145 healthcare centers either via outpatient dialysis (N=22; 12%) or infusion centers (N=34;
146 19%). Only 27 (12%) study patients had no significant inpatient or outpatient healthcare
147 exposure.

148 The mean CCI of subjects on hospital admission was 5.7. The most common
149 comorbid medical conditions in our dataset were congestive heart failure (N=54; 24%)
150 and chronic renal disease (N=55; 24%). Ten percent (N=22) of patients were co-
151 infected with HIV. Additionally, 32 (14%) had a history of a transplant (solid organ or
152 bone marrow). Injection drug use was reported by 10% (N=23) of our population, and
153 41% (N=94) had a prior history of MRSA colonization.

154 Clinical features and geographic distribution of the two dominant MRSA clones

155 As the CC5 and CC8 were responsible for the majority of BSIs, we anchored our
156 analyses on comparing these two clones. The majority of variables examined were not
157 significantly increased in one clone over the other, with several notable exceptions.
158 Race was found to confound the effects of HIV and injection drug use, so these two
159 variables were retained in the final model. Logistic regression revealed that non-
160 Hispanic Black race (OR=3.09; 95% CI [1.38-6.91]; p=0.006), Hispanic/Latino race
161 (OR=2.87 95% CI [1.22-6.76]; p=0.02), and HIV (OR=3.60 95% CI [1.02-12.75]; p=0.05)
162 had a higher likelihood of being infected with the CC8. Alternately, patients were less
163 likely to have BSI with the CC8 if they were greater than 70 years (OR=0.30 95% CI
164 [0.14-0.67]; p=0.003) or if admitted from an outside hospital (OR=0.35 95% CI [0.12-
165 1.00]; p=0.05) vs. home. Interestingly, the CC8 was increased in patients with peripheral

intravenous catheters (PIVs) as the presumed source of MRSA BSI compared to the CC5 (OR=6.46 95% CI [1.68-24.87]; *p*=0.007) (Table 2).

On multivariate analysis, there were equal proportions of the CC8 vs CC5 across patient admission sources. We mapped the clones according to patient zip code and found no significant clustering aside from the area surrounding the hospital (Figure 1).

Clinical characteristics of patients with MRSA BSI from clonal subgroups

Although we performed our top level analysis at the CC level, we additionally wanted to evaluate for potential clinical differences between the larger subgroups within the CC clones. We found 27 CC8 isolates clustering with the USA500, which is considered healthcare-associated MRSA.[11,12,21] We thus compared the USA500 to the USA300 and found higher rates of USA500 in those with HIV (OR=4.91 95% CI [1.00-24.36]; *p*=0.05) (Supplementary Table 3). We also compared subgroups ST105 and ST5 within the CC5, which revealed few notable distinctions (Supplementary Table 4). Stepwise removal of any of these subgroups did not impact results of our top level CC8 vs. CC5 analyses, thus they were retained in all analyses.

Addressing surveillance definitions in endemic settings

We sought to add clinical detail to the BSIs in relation to NHSN definitions of CO-MRSA and HO-MRSA BSI.[10] The majority of BSIs were classified as CO-MRSA (N=132; 58%) vs. HO-MRSA (N=95; 42%). Logistic regression (Table 3) revealed that patients characterized as CO-MRSA were more likely to have the CC8 (OR=2.30 95% CI [1.22-3.58]; *p*=0.03), and more likely to be receiving hemodialysis (OR=5.58 95% CI [1.71-18.21]; *p*=0.004). Conversely, CO-MRSA was less likely to be associated with

prior invasive procedures (OR=0.20 95% CI [0.09-0.43]; *p*=<0.001), MRSA BSI from a PIV (OR=0.12 95% CI [0.03-0.44]; *p*=0.002), MRSA BSI from vascular access (OR=0.38 95% CI [0.15-0.98]; *p*=0.05), and intensive care unit (ICU) admission prior to BSI (OR=0.12 95% CI [0.04-0.37]; *p*=<0.001). Only 27 (12%) patients had no clear healthcare exposure, thus 88% of our total patient population had healthcare risk factors prior to their MRSA BSI.

We next examined CC8 vs CC5 stratified by NHSN definitions. The CC8 was responsible for 38% of HO-MRSA BSIs and was associated with younger age and non-Hispanic Black race (Supplementary Table 5 & 6). Among patients grouped into the HO-MRSA stratum, those whose MRSA BSI resulting from a PIV (OR=9.84 95% CI [1.46-66.50]; *p*=0.02) were more likely to be from the CC8. We also explored the comorbidities that constitute the CCI, and we found that those with lymphoma and/or multiple myeloma had an increase in HO-MRSA (OR=0.29 95% CI [0.11-0.78]; *p*=0.01), and were more likely to have the CC5 in the HO-MRSA (OR=0.06 95% CI [0.01-0.54]; *p*=0.01) (Supplementary Table 7C & D).

Differences in morbidity and mortality related to MRSA BSIs

We investigated morbidity outcomes associated with MRSA BSI, such as ICU admission, need for mechanical ventilation, and development of metastatic complications. Overall, we found no differences in morbidity between the two clones (Supplementary Table 8). Interestingly, strictly CO-MRSA had overall worse hospital outcomes, with increased ICU admissions (OR=10.73 95% CI [3.94-29.26]; *p*=<0.001), mechanical ventilation (OR=3.45 95% CI [1.30-9.15]; *p*=0.01), and metastatic complications (OR=2.08 95% CI [1.03-4.21]; *p*=0.04) associated with MRSA BSI

(Supplementary Table 8B). Overall, 20% (N=46) had persistent bacteremia (defined as BSI lasting >7 days) with no clonal predominance in these cases.

With regard to mortality, we examined 90-day all-cause and 90-day mortality associated with MRSA BSI. All-cause 90-day mortality was 27% (N=61) and of those that died at 90-days, death was associated with the MRSA BSI in 54% (N=33) of cases. All-cause 90-day mortality had a lower likelihood of death due to CC8 vs. CC5 (OR=0.55 95% CI [0.360-1.00]; *p*=0.05), which was also observed in the CO-MRSA stratum (OR=0.43 95% CI [0.19-0.99]; *p*=0.05).

As a correlate for pathogenesis, we examined whether one clone had higher 90-day mortality in the setting of MRSA BSI. We first looked solely at the survival curves of each clone (Figure 2), which revealed no difference. Second, we examined the clone variable in a multivariate Cox regression with possible confounders (Figure 3). Interestingly, there was no difference in MRSA-related 90-day mortality related to MRSA with respect to clones (OR=0.91 95% CI [0.45-1.85]; *p*=0.79). Ninety-day mortality related to MRSA was more likely to occur in individuals older than 70 years (OR=4.48 95% CI [1.71-11.73]; *p*=0.002) and those with metastatic solid tumors (OR=3.79 95% CI [1.25-11.51]; *p*=0.02). Finally, we examined 90-day mortality associated with MRSA BSI due to primary sources of bacteremia (Supplementary Figure 2), which revealed higher mortality with MRSA BSI from pneumonia (OR=2.93 95% CI [0.98-8.74]; *p*=0.05) or septic arthritis (OR=5.80 95% CI [1.05-32.13]; *p*=0.04).

Discussion

As clones causing invasive MRSA infections are tied to specific populations, syndromes and settings, and are thought to behave differently, we sought to unravel

how these associations manifest clinically in BSIs in a high level care institution in an endemic region. This study represents a large cohort of patients who were selected based strictly on presence of invasive disease (bacteremia) and demonstrate highly complex cases linked to significant morbidity and mortality. Consistent with previous reports from our region[22] and across the United States,[3] the majority of isolates were either CC5 or CC8. Our analyses demonstrate that the CC8, representing half of all MRSA BSIs, was more frequently seen in younger age and non-White race. These data support the described convergence of clinical features classically associated with the two dominant clones.[6,23] Although stratification by surveillance definitions was consistent with clones to an extent, overall it questions the applicability of definitions in endemic regions. These findings provide support for the concept that classic community genotypes involve individuals with frequent healthcare interactions.[24]

Although CC8/USA300 is considered “hypervirulent”, causing disease in younger, healthier individuals,[23,25,26] work performed in animal models does not always actualize in complex human infections.[27,28] Our study did not find significant differences in mortality and other outcomes based on MRSA clone, even after adjusting for comorbidities. Patients in our study had a high CCI of 5.7, with most other studies in the 1.5-3 range.[17,23] We found increased mortality in the setting of MRSA BSI among those older than 70 years and those with metastatic solid tumors. Although these underlying conditions are independently associated with an increased risk for death, these data suggest that these populations have worse outcomes over other types of comorbid conditions when they develop MRSA BSI, and could be a focus in future interventions.

Finally, there was a higher proportion of males in our study, consistent with prior studies.[29,30]

Of interest was the increase in BSIs due to the USA500 in persons with HIV (PWH), a finding only described in several recent conference proceedings.[31,32] This suggests that the types of MRSA infecting PWH may be shifting away from the historial USA300.[6] As the USA500 is considered a healthcare clone,[6,11,12] this may reflect the changing epidemiology and management of HIV as it becomes a more chronic condition.[33]

We also describe an increase in CC8 in PIV-related BSIs, which was additionally evident in the HO-MRSA stratum. Source determination was based on the documentation of thrombophlebitis in all cases, as described in detail by ID consultants. We did not include PIV infection unless it was clearly stated by ID clinicians to be the actual source, and ensured these infections were not incorrectly categorized as other types of skin infections. PIV placement is an aseptic but not a sterile procedure, and more emphasis and attention is placed on maintenance of central venous catheters than on PIVs. Although the incidence of PIV-related BSIs is low, the high frequency of PIV use results in a significant portion of PIVs resulting in BSIs.[34] BSIs derive from colonizing flora,[35] and the CC8 (USA300 in particular) is associated with skin colonization. One possible explanation for our finding is that patients are colonized with the CC8 and subsequently become infected with their colonizing isolate after PIV-related complications.[36] This work further builds upon community origins of HO-MRSA BSIs by adding the association of CC8 with PIVs among patients with HO-MRSA.[37] A larger sample size and access to colonizing isolates would assist in expansion of this

concept, highlight under-recognized HAIs,[29,38] and assist in evaluating the role of patient hygiene.

This study also examined the challenges of current surveillance definitions to describe these infections. A striking 88% of all patients had previous healthcare exposures, and 80% of the strictly CO-MRSA had healthcare exposures. An alternative definition of community-onset healthcare-associated (CO-HCA) for BSIs that present within three days of hospital admission in patients with frequent healthcare exposure[4,25] may be more appropriate to report. We also describe that those presenting with BSIs from the community are also a medically complex group with poor outcomes, findings consistent with studies associating CO-MRSA with complicated bacteremia.[39] Furthermore, those infected with the CO-MRSA with CC5 were well advanced in their disease course, either through delay of presentation to the hospital or through transfers from other facilities for advanced care (as noted that 52 (39%) of admissions in the CO-MRSA group were admitted from other facilities). It appears that future descriptions of these classifications should include the changing epidemiology of the patients and their complex medical experiences.

This study has several limitations. As a retrospective study, it is subject to errors in chart abstraction. Being a single institution study, findings from the medically complex population studied may not be generalizable to smaller community hospitals. Our primary endpoint of mortality may be subject to reporting bias since death occurring outside the hospital may not have been captured in medical records. Although we recognize that methicillin-susceptible *S. aureus* (MSSA) also causes significant disease,

we focused on MRSA-BSI due to the focus of our molecular surveillance program.[40] Similar analyses extending beyond BSIs and including MSSA are critical.

In a highly complex patient population, there remain few distinct differences in the characteristics between the two endemic clones. The CC8 has become even more common in the hospital, and it behaves similarly to the CC5 by infecting infirm individuals. Our study also highlights shifts in molecular epidemiology, at-risk populations, and potential preventative focus areas such as PIVs in order to forestall this fatal disease process. Integration of these clinical correlates with other multiscale analyses will lead to a more complete understanding *S. aureus* pathogenesis.

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Table 1. Demographics and Clinical Characteristics of Patients

Factor, n (%)	MRSA BSI (*n* = 227)
Clonal Complex	
CC8	110 (48)
CC5	117 (52)
Sex	
Male	151 (67)
Female	76 (33)
Race/Ethnicity	
Non-Hispanic White	98 (43)
Non-Hispanic Black	63 (28)
Hispanic/Latino	46 (20)
Asian	8 (4)
Unknown	12 (5)
Age at Time of Infection	
18-54 Years	80 (35)
55-69 Years	68 (30)
≥ 70 Years	79 (35)
History of Injection Drug Use	23 (10)
HIV	22 (10)
Admission Source	
Home	132 (58)
NH/Rehab/LTACH	60 (26)
Outside Hospital	35 (15)
Prior Hospital Admission (90 Days)	162 (71)
Length of Hospital Stay Prior to BSI	
≤3 Days	132 (58)
>3 Days	95 (42)
Frequent Healthcare Interaction	
Hemodialysis	40 (18)
Infusion Center	34 (15)
None	153 (67)
Presence of Invasive Device	179 (79)
Invasive Procedures	109 (48)
Wound Present	94 (41)
Comorbidities	
Myocardial Infarction	23 (10)
Congestive Heart Failure	54 (24)
Peripheral Vascular Disease	37 (16)
Cerebrovascular Disease	20 (9)
Dementia	29 (13)
Chronic Pulmonary Disease	30 (13)
Connective Tissue Disease	5 (2)
Peptic Ulcer Disease	8 (4)
Mild Liver Disease	2 (1)
Diabetes (no complications)	37 (16)
Diabetes with Organ Damage	51 (22)
Para or Hemiplegia	17 (7)
Moderate/Severe Renal Disease	55 (24)
Solid Tumor	23 (10)
Leukemia	13 (6)
Lymphoma/Multiple Myeloma	26 (11)
Moderate/Severe Liver Disease	17 (7)
Metastatic Solid Tumor	14 (6)
Charlson Comorbidity Index (CCI)	
0-3	71 (31)
4-5	48 (21)
6-8	65 (29)
>8	43 (19)
History of Transplant	32 (14)
History of MRSA Colonization	94 (41)
Presumed Source of MRSA BSI	
Peripheral Intravenous Catheter	16 (7)
Skin & Soft Tissue Infection	26 (11)
Pneumonia	24 (11)
Diabetic Foot Infection	17 (7)
Vascular Access	78 (34)
Septic Arthritis	3 (1)
Urinary Source	4 (2)
Sacral Wound	11 (5)
Other/Unknown	28 (12)
ICU Admission Prior to BSI	42 (19)

Table 2. Demographics and Clinical Characteristics of MRSA BSIs in Patients Stratified by Clonal Complex with the Odds of Being CC8 vs CC5

Factor	CC8 N = 110 (%)	CC5 N = 117 (%)	Univariate Analysis OR (95% CI)	Univariate Analysis p value	Multivariate Analysis OR (95% CI)	Multivariate Analysis p value
Male	73 (66)	78 (67)	0.99 (0.57-1.71)	0.96		
Race/Ethnicity						
Non-Hispanic White	31 (28)	67 (57)	Reference		Reference	
Non-Hispanic Black	41 (37)	22 (19)	**3.99 (1.96-8.34)**	**<0.001**	**3.21 (1.42-7.22)**	**0.005**
Hispanic/Latino	27 (25)	19 (16)	**3.05 (1.40-6.77)**	**0.004**	**2.99 (1.25-7.12)**	**0.01**
Asian	4 (4)	4 (3)	2.14 (0.37-12.32)	0.49	3.01 (0.59-15.26)	0.18
Unknown	7 (6)	5 (4)	2.99 (0.75-12.97)	0.14	2.16 (0.52-9.05)	0.29
Age at Time of Infection						
18-54 Years	50 (45)	30 (26)	Reference		Reference	
55-69 Years	37 (34)	31 (27)	0.72 (0.37-1.38)	0.32	0.65 (0.28-1.50)	0.31
≥ 70 Years	23 (21)	56 (48)	**0.25 (0.13-0.48)**	**<0.001**	**0.31 (0.12-0.81)**	**0.02**
History of Injection Drug Use	16 (15)	7 (6)	**2.66 (0.99-8.00)**	**0.05**	0.84 (0.27-2.61)	0.77
HIV	18 (16)	4 (3)	**5.49 (1.73-23.08)**	**0.002**	**3.71 (1.06-13.05)**	**0.04**
Admission Source						
Home	78 (71)	54 (46)	Reference		Reference	
NH/Rehab/LTACH	23 (21)	37 (32)	**0.43 (0.23-0.80)**	**0.008**	0.57 (0.25-1.30)	0.18
Other Hospital	9 (8)	26 (22)	**0.24 (0.10-0.55)**	**<0.001**	0.36 (0.12-1.09)	0.07
Prior Hospital Admission (90 Days)	70 (64)	92 (79)	**0.48 (0.26-0.86)**	**0.01**	0.88 (0.38-2.02)	0.76
Length of Hospital Stay Prior to BSI						
≤3 Days	74 (67)	58 (50)	**2.09 (1.22-3.58)**	**0.007**	2.00 (0.90-4.44)	0.09
>3 Days	36 (33)	59 (50)	Reference		Reference	
Frequent Healthcare Interaction						
Hemodialysis	22 (20)	18 (15)	1.45 (0.72-2.92)	0.30		
Infusion Center	18 (16)	16 (14)	1.33 (0.63-2.81)	0.45		
None	70 (64)	83 (71)	Reference			
[a] Presence of Invasive Device	77 (70)	102 (87)	**0.34 (0.17-0.68)**	**0.002**	0.65 (0.28-1.53)	0.33
[b] Invasive Procedures	44 (40)	65 (56)	**0.53 (0.32-0.90)**	**0.02**	0.71 (0.33-1.56)	0.39
Wound Present	46 (42)	48 (41)	1.03 (0.61-1.75)	0.90		
Charlson Comorbidity Index (CCI)						
0-3	39 (35)	32 (27)	Reference		Reference	
4-5	26 (24)	22 (19)	0.97 (0.47-2.02)	0.93	1.38 (0.52-3.64)	0.52
6-8	30 (27)	35 (30)	0.70 (0.36-1.38)	0.31	1.19 (0.46-3.05)	0.72
>8	15 (14)	28 (24)	**0.44 (0.20-0.96)**	**0.04**	0.76 (0.23-2.50)	0.65
History of Transplant	14 (13)	18 (15)	0.80 (0.38-1.70)	0.57		
History of MRSA Colonization	47 (43)	47 (40)	1.11 (0.66-1.89)	0.70		
Presumed Source of MRSA BSI						
Peripheral Intravenous Catheter	11 (10)	5 (4)	2.48 (0.76-9.43)	0.15	**5.87 (1.50-22.89)**	**0.01**
Skin & Soft Tissue Infection	18 (16)	8 (7)	**2.67 (1.11-6.41)**	**0.03**	2.28 (0.73-7.09)	0.16
Pneumonia	12 (11)	12 (10)	1.07 (0.46-2.50)	0.87		
Diabetic Foot Infection	8 (7)	9 (8)	0.94 (0.35-2.53)	0.90		
Vascular Access	35 (32)	43 (37)	0.80 (0.46-1.39)	0.43		
Septic Arthritis	1 (1)	2 (2)	0.53 (0.01-10.30)	1.00		
Urinary Source	1 (1)	3 (3)	0.35 (0.01-4.44)	0.67		
Sacral Wound	6 (5)	5 (4)	1.29 (0.32-5.52)	0.91		
Other/Unknown	12 (11)	16 (14)	0.77 (0.32-1.85)	0.67		
ICU Admission Prior to BSI	16 (15)	26 (22)	0.60 (0.30-1.18)	0.14	1.37 (0.50-3.73)	0.54

Bold = significant at ≤ 0.05

Abbreviations: MRSA, Methicillin-resistant *Staphylococcus* aureus; BSI, bloodstream infection; NH, nursing home; rehab, rehabilitation facility; LTACH, long-term acute care hospital; BSI, bloodstream infection; HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome; ICU, intensive care unit.

[a] Includes devices such as pacemaker, any vascular access, orthopedic hardware, foley catheter, arteriovenous graft placement, percutaneous endoscopic gastronomy (PEG), ostomy, or any type of urinary collection at the time of first positive bloodstream infection.

[b] Includes invasive procedures or surgery within the month prior to first positive bloodstream infection, excluding electroencephalogram (EEG), electrocardiogram (EKG), or transthoracic echocardiogram (TTE).

Table 3. Demographics and Clinical Characteristics of MRSA BSIs Stratified by CO-MRSA and HO-MRSA with the Odds of being CO-MRSA

Factor	CO-MRSA N = 132 (%)	HO-MRSA N = 95 (%)	Univariate Analysis OR (95% CI)	p value	Multivariate Analysis OR (95% CI)	p value
CC8	74 (56)	36 (38)	**2.09 (1.22-3.58)**	**0.007**	**2.52 (1.16-5.50)**	**0.02**
Male	90 (68)	61 (64)	1.19 (0.68-2.08)	0.53		
Race/Ethnicity						
Non-Hispanic White	50 (38)	48 (51)	Reference			
Non-Hispanic Black	40 (30)	23 (24)	1.66 (0.83-3.37)	0.16		
Hispanic/Latino	30 (23)	16 (17)	1.79 (0.83-4.00)	0.15		
Asian	6 (5)	2 (2)	2.85 (0.48-30.26)	0.35		
Unknown	6 (5)	6 (6)	0.96 (0.24-3.87)	1.00		
Age at Time of Infection						
18-54 Years	44 (33)	36 (38)	Reference			
55-69 Years	44 (33)	24 (25)	1.50 (0.77-2.92)	0.23		
≥ 70 Years	44 (33)	35 (37)	1.03 (0.55-1.92)	0.93		
History of Injection Drug Use	17 (13)	6 (6)	2.19 (0.78-7.06)	0.16	0.48 (0.13-1.82)	0.28
HIV	13 (10)	9 (9)	1.04 (0.39-2.90)	1.00		
Admission Source						
Home	80 (61)	52 (55)	Reference		Reference	
NH/Rehab/LTACH	40 (30)	20 (21)	1.30 (0.69-2.47)	0.42	0.88 (0.35-2.26)	0.80
Other Hospital	12 (9)	23 (24)	**0.34 (0.16-0.74)**	**0.007**	0.80 (0.27-2.40)	0.69
Prior Hospital Admission (90 Days)	91 (69)	71 (75)	0.75 (0.42-1.36)	0.34		
Frequent Healthcare Interaction						
Hemodialysis	33 (25)	7 (7)	**3.46 (1.39-9.87)**	**0.005**	**4.62 (1.33-16.05)**	**0.02**
Infusion Center	11 (8)	23 (24)	**0.36 (0.15-0.82)**	**0.01**	0.35 (0.12-1.04)	0.06
None	88 (67)	65 (68)	Reference		Reference	
[a] Presence of Invasive Device	94 (71)	85 (90)	**0.29 (0.14-0.62)**	**0.001**	0.52 (0.18-1.49)	0.22
[b] Invasive Procedures	37 (28)	72 (76)	**0.12 (0.07-0.23)**	**<0.001**	**0.19 (0.09-0.41)**	**<0.001**
Wound Present	58 (44)	36 (38)	1.29 (0.75-2.20)	0.36		
Charlson Comorbidity Index (CCI)						
0-3	38 (29)	33 (35)	Reference		Reference	
4-5	24 (18)	24 (25)	0.87 (0.42-1.81)	0.71	1.45 (0.51-4.09)	0.48
6-8	39 (30)	26 (27)	1.30 (0.66-2.57)	0.45	1.05 (0.39-2.85)	0.92
>8	31 (23)	12 (13)	**2.24 (1.00-5.06)**	**0.05**	2.11 (0.64-7.00)	0.22
History of Transplant	13 (10)	19 (20)	**0.44 (0.20-0.94)**	**0.03**	1.06 (0.37-3.04)	0.91
History of MRSA Colonization	58 (44)	36 (38)	1.29 (0.75-2.20)	0.36		
Presumed Source of MRSA Infection						
Peripheral Intravenous Catheter	6 (6)	10 (11)	0.41 (0.12-1.29)	0.14	**0.11 (0.03-0.43)**	**0.002**
Skin & Soft Tissue Infection	18 (14)	8 (8)	1.71 (0.67-4.78)	0.31		
Pneumonia	14 (11)	10 (11)	1.01 (0.43-2.38)	0.98		
Diabetic Foot Infection	15 (11)	2 (2)	**5.93 (1.33-54.70)**	**0.01**	2.15 (0.36-12.92)	0.40
Vascular Access	36 (27)	42 (44)	**0.47 (0.27-0.83)**	**0.009**	**0.37 (0.14-0.96)**	**0.04**
Septic Arthritis	1 (1)	2 (2)	0.36 (0.01-6.94)	0.76		
Urinary Source	3 (2)	1 (1)	2.18 (0.17-115.96)	0.89		
Sacral Wound	9 (7)	2 (2)	3.39 (0.68-32.95)	0.18	0.68 (0.11-4.32)	0.68
Other/Unknown	16 (12)	12 (13)	0.95 (0.43-2.12)	0.91		
ICU Admission Prior to BSI	5 (4)	37 (39)	**0.06 (0.02-0.17)**	**<0.001**	**0.12 (0.04-0.39)**	**<0.001**

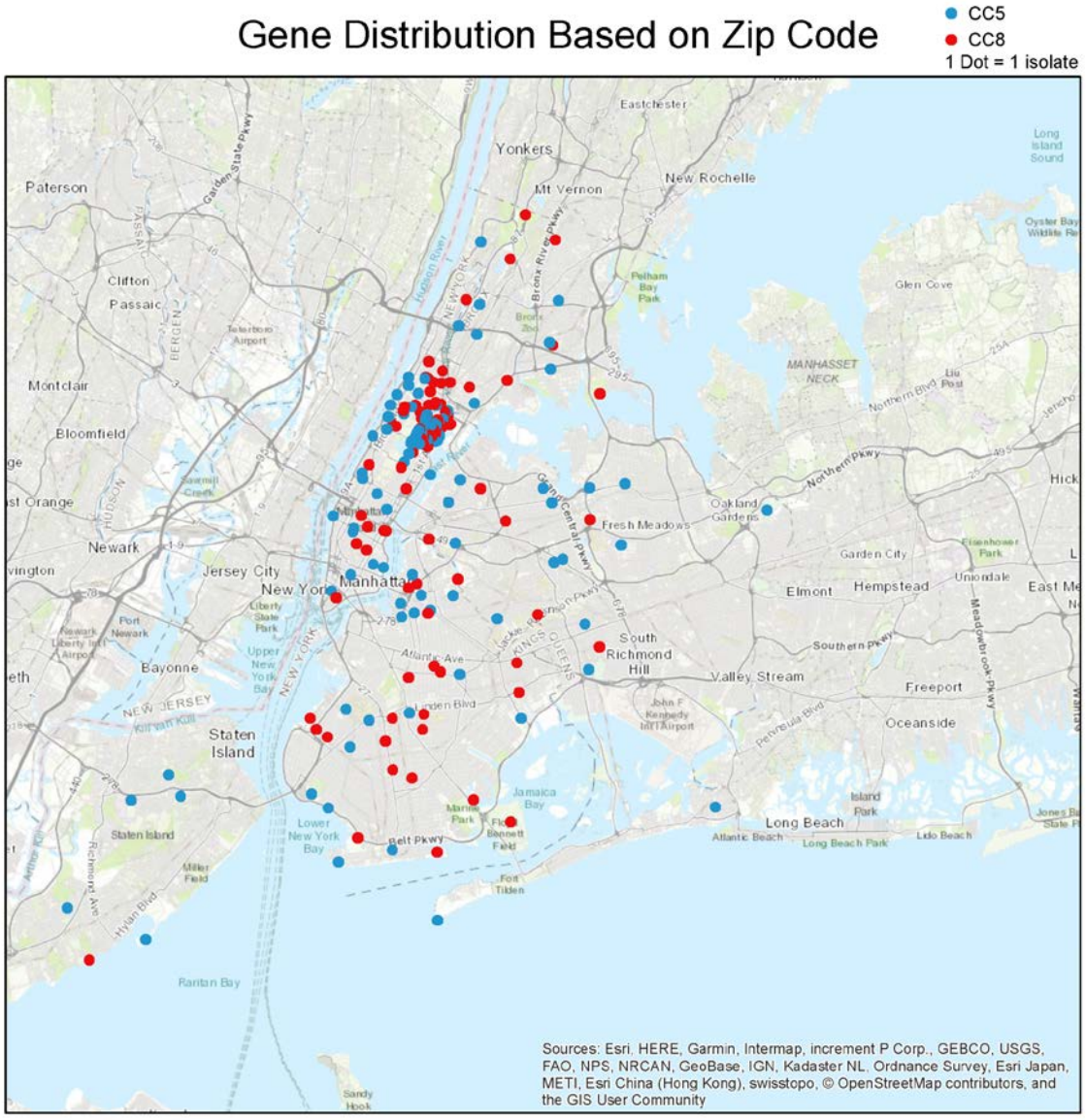
Bold = significant at ≤ 0.05

Abbreviations: MRSA, Methicillin-resistant *Staphylococcus* aureus; BSI, bloodstream infection; CO, community-onset; HO, hospital-onset; NH, nursing home; rehab, rehabilitation facility; LTACH, long-term acute care hospital; BSI, bloodstream infection; HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome; ICU, intensive care unit.

[a] Includes devices such as pacemaker, any vascular access, orthopedic hardware, foley catheter, arteriovenous graft placement, percutaneous endoscopic gastronomy (PEG), ostomy, or any type of urinary collection at the time of first positive bloodstream infection.

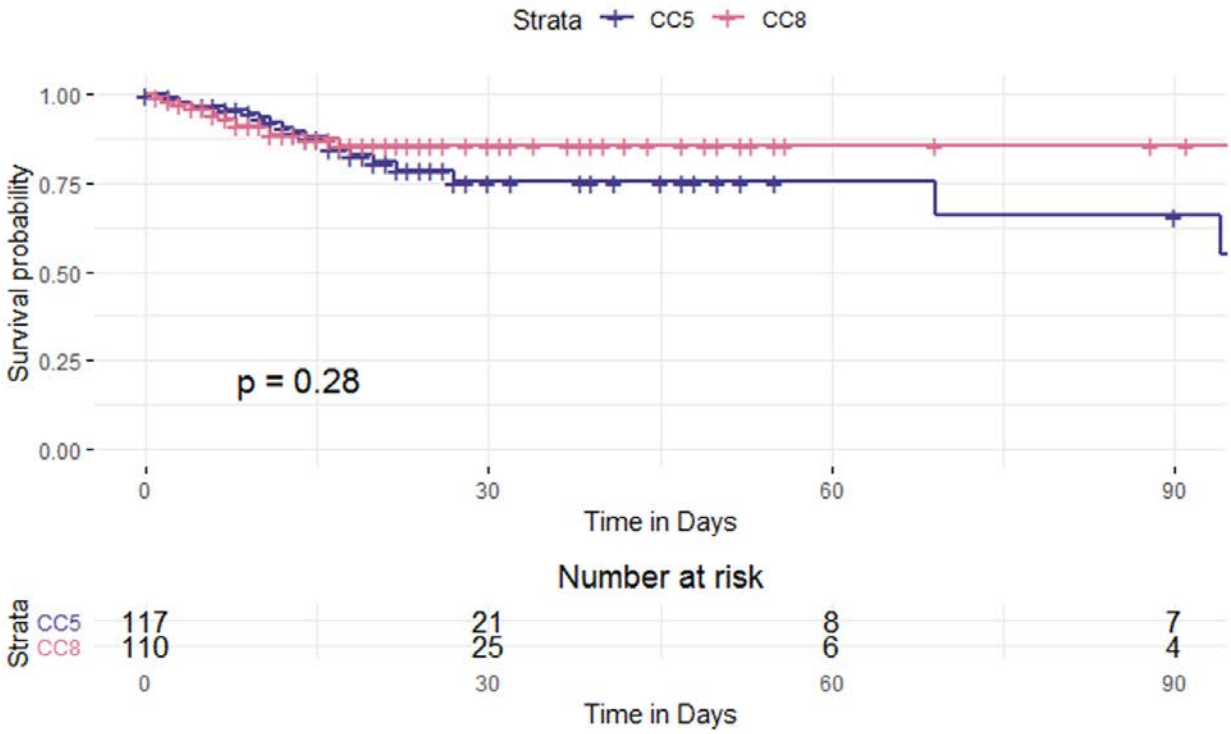
[b] Includes invasive procedures or surgery within the month prior to first positive bloodstream infection, excluding electroencephalogram (EEG), electrocardiogram (EKG), or transthoracic echocardiogram (TTE).

Figure 1. Gene distribution based on zip code.



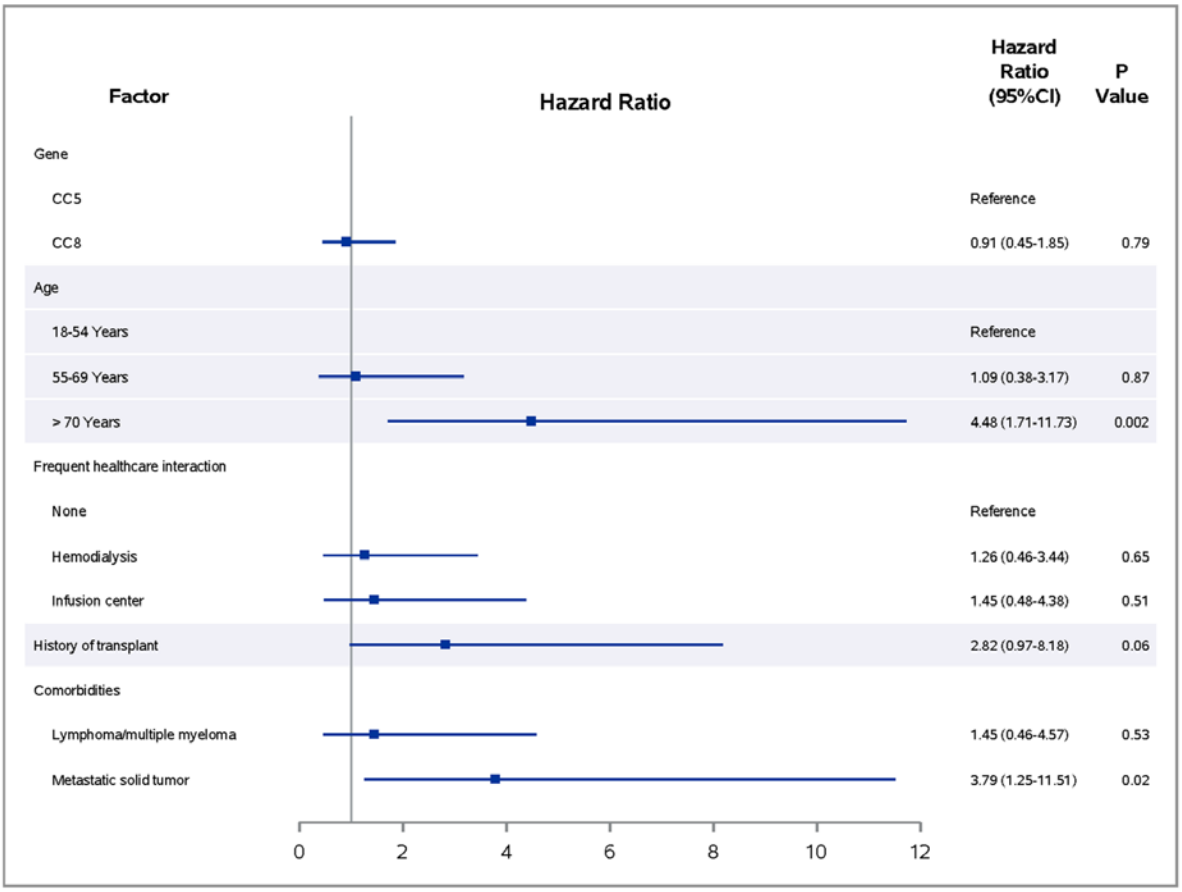
Geographic information system (GIS) map of New York City illustrating the distribution of each patient isolate stratified by clonal complex (CC). The map excludes 40 isolates that were located outside of the New York City borough boundary. Of the 185 isolates mapped, 96 belong to CC5 and 89 belong to CC8.

Figure 2. Death Related to MRSA BSI within 90 Days Stratified by Clone.



Survival analyses of the CC8 and the CC5 clones 90-days from the first positive MRSA culture. Tick marks represent a censored patient due to discharge from the hospital. Risk tables reflect the number of patients still at risk of death at 30, 60, and 90 days.

Figure 3. Multivariate Analysis of Death Related to MRSA BSI within 90 Days.



Forest plot of the multivariate Cox regression for all variables that had $p \leqq 0.2$ in the univariate analysis. The square represents the hazard ratio (HR), and the lines reflect the 95% confidence interval.