Reduced Mortality of *Staphylococcus aureus* Bacteremia in a Retrospective Cohort Study of 2139 Patients: 2007–2015

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Background. Understanding the changing epidemiology of *Staphylococcus aureus* bacteremia, as well as the variables associated with poor outcomes, can yield insight into potential interventions.

Methods. This study was a retrospective, observational cohort study of adult patients at an academic medical center in New York City who had *S. aureus* bloodstream infections between 1 January 2007 and 31 December 2015. Participants were divided into 3 periods: group 1 (2007–2009), group 2 (2010–2012), and group 3 (2013–2015) for trend analysis. All clinical strains were genotyped (*spa.*). The main outcome was 30-day all-cause mortality.

Results. There were 1264 episodes of methicillin-susceptible *S. aureus* (MSSA) and 875 episodes of methicillin-resistant *S. aureus* (MRSA) bacteremia, with a rising proportion due to MSSA (55% group 1; 59% group 2; 63% group 3; $P = .03$). There were no significant changes in average age, gender, Charlson score, and distribution of strain genotypes. Mortality in MRSA infection was unchanged (25% group 1; 25% group 2; 26% group 3), while mortality in MSSA infection significantly declined (18% group 1; 18% group 2; 13% group 3). The average time to antistaphylococcal therapy (AST) in MSSA infection declined during the study (3.7 days group 1; 3.5 group 2; 2.2 group 3). In multivariate analysis, AST within 7 days of initial positive MSSA culture was associated with survival.

Conclusions. Mortality in MSSA bloodstream infection is declining, associated with a decrease in time to targeted therapy. These results emphasize the potential for rapid diagnostics and early optimization of treatment to impact outcomes in MSSA bacteremia.

Keywords. *Staphylococcus aureus*; MRSA; MSSA; bacteremia.

Staphylococcus aureus bacteremia (SAB) is the source of significant morbidity worldwide, with 30-day mortality ranging from 15% to 40% even with effective antibiotic therapy [1–3]. Understanding large-scale epidemiologic trends in clinical characteristics and outcomes is important for designing prevention measures and treatment protocols. Additionally, inclusion of not only clinical but also genotypic and phenotypic data into epidemiologic studies can provide a clearer picture of the relative contributions of host, pathogen, and environment [4, 5].

Trends in the incidence of SAB over the past decade have varied by region and clinical setting [6–9]. Compared with methicillin-susceptible *S. aureus* (MSSA), invasive infections with methicillin-resistant *S. aureus* (MRSA) have traditionally been associated with higher mortality, complication rates,

and hospital length of stay [1, 10], although some studies have failed to detect mortality differences after adjustment for confounding factors [11]. However, while MRSA bacteremia receives greater attention in research aimed at prevention and treatment, MSSA accounts for a larger portion of SAB cases at many centers and therefore should be a major focus of efforts to improve SAB outcomes [8, 12]. Similarly, while MRSA has often been considered as the dominant cause of hospital-acquired *S. aureus* infections, recent studies have suggested a potential shift in characteristics of MSSA bloodstream infection (BSI) toward a more healthcare-associated clinical profile, as the relative frequency of community-associated MRSA has increased [6, 7, 13].

A major aim of epidemiologic surveys that look at characteristics of SAB is to develop tools for predicting mortality and to identify modifiable factors, such as diagnostic and treatment interventions, that can become targets for intervention. Prior studies have shown an association between increased age, comorbidity burden, and individual comorbid diseases on mortality in SAB [14, 15]. A recent large retrospective study also suggested female gender to be a risk factor for mortality in community-associated SAB, although the underlying

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mechanism for this association remains poorly understood [16, 17].

Fewer studies have examined mortality trends in the context of bacterial genotypes that, along with the antimicrobial susceptibility phenotype, are increasingly being included in analyses of SAB [7, 18]. An examination of temporal trends in SAB clinical outcomes must include the context of host factors, bacterial genotype, and treatment practices, since shifts in any of these areas can impact outcomes.

In this study, we determined whether there were significant changes in mortality in SAB cases over a 9-year period and whether there were corresponding changes in genotypic and clinical factors in these SAB cases. We then looked at the contribution of molecular and clinical variables to mortality.

METHODS

Population and Study Design

This was a retrospective, observational cohort study of all adult patients aged ≥ 18 years at a large tertiary care medical center in New York City who had ≥ 1 blood culture positive for *S. aureus* between 1 January 2007 and 31 December 2015. Only the first episode of BSI per patient in a given year was included. The participants were divided into cohorts based on 3-year time periods: group 1 (2007–2009), group 2 (2010–2012), and group 3 (2013–2015). Patients with *S. aureus* bacteremia were identified through a query of the electronic medical record (EMR) system performed by the Clinical Data Warehouse Navigator. The Columbia University Irving Medical Center (CUIMC) Institutional Review Board approved this study. Demographic and clinical data were extracted from the EMR, and research staff entered these data into a database. Data on age, gender, hospital admission, and discharge; subsequent positive blood cultures; antibiotic treatment; antimicrobial susceptibilities; and infectious diseases (ID) consultation were extracted from the EMR. ID consultation was defined as a formal consultation documented in the chart within 14 days of the index culture or primary medical management by an ID specialist. ID consultation data were not available for 2007–2009 and were analyzed only for the 2010–2015 period. Data on comorbidities were extracted from the EMR through a query of *International Classification of Diseases, Ninth Revision, Clinical Modification*, and *International Classification of Diseases, Tenth Revision, Clinical Modification*, codes corresponding to the comorbidity categories.

Genotyping and Antibiotic Susceptibility

Antibiotic susceptibility and minimum inhibitory concentrations (MICs) were determined using the automated MicroScan method, based on Clinical and Laboratory Standards Institute standards [19]. To perform molecular typing, we sequenced the repeat region of the staphylococcal protein A (*spa*) gene and assigned *spa* type using the SpaType

RIDOM software [20]. Distribution of genotype into clonal lineages was determined using the Based Upon Repeat Pattern clustering algorithm [21].

Definitions

Mortality was determined through extraction of CUIMC EMR mortality data, manual review of charts, and query of the Social Security Administration Master Death File. Duration of bacteremia was determined based on the number of days with positive blood cultures; instances where the patient died on the same day of the index blood culture were excluded from duration analysis. Bloodstream infections were considered to be “community-onset” (CO) if the positive index culture was collected ≤ 48 hours of presentation. Infections with index cultures collected > 48 hours from time of admission were given the designation “hospital-onset” (HO).

Outcomes

The primary outcome was 30-day all-cause mortality.

Statistical Analyses

All statistical analyses were performed using SAS v9.4 (SAS Institute, Inc). The Cochran–Armitage trend test was used to test the mortality significance of trends over the 3 time periods. The χ^2 test or analysis of variance was used to examine univariate associations depending on categorical or continuous variables. Univariate logistic regression was used to examine the association between the mortality outcome and each covariate or factor. The multivariate logistic regression model included age and gender variables a priori and variables with univariate *P* value $< .2$. Odds ratios with 95% confidence intervals are presented.

RESULTS

Overall Study Population

Overall, there were 1264 episodes of MSSA and 875 episodes of MRSA BSI during the 2007–2015 study period. The incidence of MSSA infection was 2.2 cases per 1000 admissions and the incidence of MRSA infection was 1.52 cases per 1000 admissions during the study. Demographic variables, including average age (60 ± 18 vs 63 ± 18 years), were similar between MSSA and MRSA cohorts (Table 1). The majority of patients in both MSSA and MRSA cohorts were male ($n = 775/1264$, 61% vs $n = 518/875$, 59%), and 71% ($n = 898$) of the MSSA and 68% ($n = 592$) of the MRSA infections were CO.

Patients with MSSA and MRSA differed in a number of important clinical variables. The average hospitalization length was longer for MRSA patients (25 days ± 17 vs 22 days ± 24 days). The average Charlson comorbidity score was higher for the MRSA infections (4.1) than for MSSA infections (3.6), as was the proportion of patients with a Charlson score ≥ 3 (69% of MRSA; 61% of MSSA). The average Pitt bacteremia

Table 1. Characteristics of Patients With *Staphylococcus aureus* Bloodstream Infections

Variable	All <i>Staphylococcus aureus</i> Bloodstream Infections	Methicillin-susceptible <i>Staphylococcus aureus</i>	Methicillin-resistant <i>Staphylococcus aureus</i>
	(N = 2139) n (%)	(n = 1264) n (%)	(n = 875) n (%)
Average age (median), y	61 (62)	60 (61)	63 (63)
Age >65 y	903 (42)	506 (40)	397 (45)
Male gender	1293 (60)	775 (61)	518 (59)
Hospital-onset (≥ 48 hours)	649 (30)	366 (29)	283 (32)
Community-onset (≤ 48 hours)	1490 (70)	898 (71)	592 (68)
Infectious disease consultation	874 (61) ^a	525 (61) ^a	349 (63) ^a
PBS	2.1 (1)	1.8 (1)	2.6 (2)
PBS ≥ 4	430 (20)	198 (16)	232 (26)
Comorbidity burden			
Charlson score, average (median)	3.8 (4)	3.6 (3)	4.1 (4)
Charlson score ≥ 3	1373 (64)	770 (61)	603 (69)
Diabetes	226 (11)	133 (11)	93 (11)
Prior myocardial infarct	61 (2.9)	33 (2.6)	28 (3.2)
Peripheral vascular disease	188 (8.9)	91 (7.2)	97 (11)
Chronic heart failure	292 (14)	178 (14)	114 (13)
Chronic kidney disease	537 (25)	294 (23)	243 (28)
End-stage renal disease/dialysis	256 (12)	136 (11)	120 (14)
Liver disease	174 (8.1)	102 (8.1)	72 (8.2)
Chronic pulmonary disease	199 (9.3)	94 (7.4)	105 (12)
Malignancy	229 (11)	154 (12)	75 (8.6)
Connective tissue disease	6 (0.2)	4 (0.3)	2 (0.2)
HIV	137 (6.4)	59 (4.7)	78 (8.9)
HIV/AIDS	121 (5.6)	51 (4.0)	70 (8)
Prior transient ischemic attack/cerebrovascular accident	47 (2.2)	20 (1.6)	27 (3.1)
Dementia	123 (5.7)	68 (5.4)	55 (6.3)
Chemotherapy	180 (8.4)	124 (9.8)	56 (6.4)
Duration of bacteremia			
≥ 3 days	631 (29)	358 (28)	273 (31)
≥ 5 days	283 (13)	137 (11)	146 (17)
≥ 10 days	58 (2.7)	20 (1.6)	38 (4.4)
Admission days, average (median)	23 (15)	22 (15)	25 (16)
Antibiotic susceptibility			
Vancomycin minimum inhibitory concentration ≥ 1.5	918 (43)	540 (43)	378 (43)
Genotype			
<i>spa</i> -type	...	...	...
t002	400 (19)	121 (9.6)	279 (32)
t008	326 (15)	64 (5.1)	262 (30)
<i>spa</i> -CC group	...	...	...
<i>spa</i> -CC002/ST5	548 (26)	198 (16)	350 (40)
<i>spa</i> -CC008/ST8	560 (26)	177 (14)	383 (44)

Abbreviations: CC, clonal complex; HIV, human immunodeficiency virus; PBS, Pitt bacteremia score.

^aData for infectious disease consultation missing for 2007–2009 period.

score (PBS) and the proportion of patients with a PBS ≥ 4 was higher in the MRSA than the MSSA cohort (2.6 vs 1.8; 26% vs 16%). The average duration of bacteremia was longer for the MRSA cohort (2.7 ± 3.1 days vs 2.2 ± 2.4 days), and there were more patients in the MRSA cohort with bacteremia ≥ 3 days ($n = 273/875$, 31% vs $n = 344/1264$, 28%). There were also more patients with persistent bacteremia (≥ 5 days) in the

MRSA ($n = 146$, 17%) than in the MSSA cohort ($n = 137$, 11%). During the 2010–2015 period for which there was available consultation data, ID consultation took place for 61% of SAB patients overall, with 61% of MSSA and 63% of MRSA patients receiving consults. The 30-day mortality for the overall cohort was higher for MRSA (221/875, 25%) than for MSSA infections (203/1264, 16%).

Genotyping of the MSSA cohort showed a highly diverse genetic background, with 370 *spa* types, whereas *spa* types t002 and t008 accounted for nearly two-thirds of isolates in MRSA SAB. *spa* clonal complex CC002 (ST5) and *spa*-CC008 were the most frequent clonal cohorts seen in both MSSA ($n = 198$, 16% *spa*-CC002; $n = 177$, 14% *spa*-CC008) and MRSA ($n = 350$, 40% *spa*-CC002; $n = 383$, 44% *spa*-CC008) infections.

Time-trend Analyses

The incidence of MSSA BSI rose during the study (2.1 per 1000 admissions, $n = 396$ /group 1; 2.0 per 1000 admissions, $n = 402$ /group 2; 2.5 per 1000 admissions, $n = 467$ /group 3), and the incidence of MRSA BSI decreased (1.7 per 1000 admissions, $n = 318$ /group 1; 1.4 per 1000 admissions, $n = 276$ /group 2; 1.5 per 1000 admissions, $n = 281$ /group 3).

There were no significant changes in average age or gender during the study, either in the overall cohort or individually for MRSA and MSSA cohorts (Tables 2, 3). However, the proportion of patients aged ≥ 65 years increased in the overall cohort (40% in group 1 to 46% in group 3, $P = .01$). This was driven by an increase in patients aged ≥ 65 years with MSSA infections (36% in group 1 to 45% in group 3, $P = .01$; Table 2). There was no significant change in the proportion of HO vs CO infections over the 3 periods. SAB with duration ≥ 3 days, ≥ 5 days, and ≥ 10 days increased in frequency across the study period for both MSSA and MRSA (Table 2). Comparing frequency of ID consultation in group 2 vs group 3 (data for G1 was not available), using χ^2 analysis, there was a significant increase in ID consultation in the overall SAB cohort (59% to 64%) and MRSA group (58% to 67%); however, there was no significant change in the MSSA group (59% to 62%).

The average PBS overall and for MRSA SAB did not change significantly during the study; however, the average PBS for MSSA SAB increased (1.5 in group 1, 2.1 in group 2, 1.8 in group 3, $P = .02$), as did the proportion of patients with PBS ≥ 4 (12% in group 1 to 16% in group 3, $P = .02$). The Charlson scores did not change significantly for either the MSSA or MRSA cohorts (Table 2).

The distribution of bacterial genotypes across the CC cohorts remained stable, with CC002 (group 1, 25%; group 3, 26%) and CC008 (group 1, 25%; group 3, 27%) remaining the most frequently represented CCs. The proportion of isolates with vancomycin MIC ≥ 1.5 increased significantly for both MRSA and MSSA cohorts across the 9-year period (group 1, 36%; group 3, 61%), and fluoroquinolone resistance decreased (group 1, 47%; group 3, 39%; Table 3).

The time to first dose of targeted antistaphylococcal therapy (AST) for MSSA (cefazolin or oxacillin, based on hospital practice in MSSA treatment) decreased significantly, with the average number of days before AST declining from 3.7 days during 2007–2009 and 3.5 days during 2010–2012 to 2.2 days during 2013–2015 ($P < .0001$; Table 3). The proportion of

patients receiving a first dose of cefazolin or oxacillin within 3 days of positive culture increased from 42% ($n = 167$) in group 1 and 46% ($n = 186$) in group 2 to 62% ($n = 288$) in group 3 ($P < .0001$). Patients who received vancomycin alone, in combination with another agent, or another antibiotic therapy decreased from 31% ($n = 123$) and 29% ($n = 117$) in groups 1 and 2 to 26% ($n = 119$) in group 3. Likewise, the proportion of patients who failed to receive any effective antibiotic therapy (either not treated with antibiotics or received antibiotics without any staphylococcal coverage) decreased from 6% ($n = 24$) in group 1 to 2.6% ($n = 12$) in group 3.

Temporal Changes in 30-Day Mortality

There was a trend toward decline in all-cause 30-day mortality for *S. aureus* BSIs, from 21% ($n = 153/714$, group 1; $n = 140/678$, group 2) mortality in group 1 (2007–2009) and group 2 (2010–2012) to 18% mortality in the group 3 (2013–2015; $P = .06$; Table 2). This decline was driven by a significant decrease in MSSA mortality from 18% in both group 1 and group 2 to 13% in group 3 ($P = .02$; Table 3). In contrast, there was no significant change in 30-day mortality for MRSA infections, with 25% mortality in group 1 (2007–2009; $n = 81/318$) and group 2 (2010–2012; $n = 68/276$) periods and 26% ($n = 72/281$) in the group 3 (2013–2015) period (Table 2).

Predictors of Mortality

In univariate analysis, predictors of 30-day mortality for the entire SAB cohort, as well as the MSSA and MRSA cohorts, included age ≥ 65 years, female gender, PBS ≥ 4 , Charlson score ≥ 3 , and HO infection (Tables 3 and 4). Methicillin resistance was also a significant predictor of 30-day mortality in the univariate analysis in the SAB cohort. Infection with *spa*-CC008/ST8 or *spa*-CC002/ST5 genotypes vs non-ST8/ST5 genotypes was associated with higher mortality in the overall SAB cohort but not in the individual MSSA and MRSA cohorts. Additionally, in MSSA infection, malignancy was a predictor of mortality, while Human immunodeficiency virus/AIDS appeared protective. In MRSA infection, in addition to the above variables, use of chemotherapy was a predictor of mortality. A higher vancomycin MIC was not a significant predictor of mortality for either the overall or MSSA and MRSA cohorts. For the MSSA bacteremia group, patients who received targeted AST with cefazolin or oxacillin ≤ 7 days of a positive index culture had a significantly lower 30-day mortality.

In the adjusted analyses for the SAB cohort, age ≥ 65 years, female gender, PBS ≥ 4 , Charlson score ≥ 3 , HO infection, and chemotherapy remained significant predictors of all-cause 30-day mortality (Table 4). For both MRSA and MSSA, age ≥ 65 years, PBS ≥ 4 , Charlson score ≥ 3 , and HO infection were predictors of mortality in the multivariate model. In the MRSA cohort, in addition to the above variables, female gender and use of chemotherapy remained significant predictors. In MSSA infection,

Table 2. Time-trend Analysis: All *Staphylococcus aureus* Bloodstream Infections (SABs), Methicillin-susceptible *S. aureus*-SABs, and Methicillin-resistant *S. aureus*-SABs

Variable	All SAB (2007–2009)		All SAB (2010–2012)		All SAB (2013–2015)		PValue	MSSA (2007–2009)		MSSA (2010–2012)		MSSA (2013–2015)		PValue	MRSA (2007–2009)		MRSA (2010–2012)		MRSA (2013–2015)		PValue
	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3		Group 1	Group 2	Group 3	Group 1	Group 2	Group 3		Group 1	Group 2	Group 3				
All SAB (n = 2139)	714	678	747				...	396	402	466				...	318	276	281			...	
Average age (median), y	61 (61)	61 (61)	62 (63)				.29	59 (60)	61 (60)	61 (63)				.12	63 (63)	62 (63)	63 (65)			.90	
Age ≥65 y	285 (40)	271 (40)	347 (46)				.01	144 (36)	150 (37)	212 (45)				.01	141 (44)	121 (44)	135 (48)			.55	
Male gender	444 (62)	389 (57)	460 (62)				.14	249 (63)	239 (59)	287 (62)				.60	195 (61)	150 (54)	173 (62)			.14	
Admit duration, average (median)	24 (15)	23 (15)	22 (15)				.74	22 (15)	21 (14)	20 (14)				.60	26 (16)	26 (15)	25 (17)			.57	
Time from admit to <i>S. aureus</i> bloodstream infection																					
Average (med)	5.6 (1)	5.2 (0)	3.4 (0)				.0004	4.4 (0)	4.1 (0)	3.0 (0)				.005	7.0 (1)	6.8 (0)	4.5 (0)			.04	
Hospital-onset (≥48 hours)	236 (33)	207 (31)	206 (28)				.07	126 (32)	114 (28)	126 (27)				.29	110 (35)	93 (34)	80 (29)			.24	
Community-onset (≤48 hours)	478 (67)	471 (69)	541 (72)				.07	270 (68)	288 (72)	340 (73)				.29	208 (65)	183 (72)	201 (72)			.24	
Infectious diseases consultation	NA ^a	397 (59)	477 (64)				.04	NA ^a	237 (59)	288 (62)				.37	NA ^a	160 (58)	189 (67)			.02	
PBS, average (median)	2.1 (1)	2.3 (1)	2.1 (1)				.20	1.5 (1)	2.1 (1)	1.8 (1)				.02	2.8 (2)	2.5 (2)	2.6 (2)			.60	
PBS ≥ 4	134 (19)	146 (22)	150 (20)				.44	47 (12)	77 (19)	74 (16)				.02	87 (28)	69 (25)	76 (27)			.77	
Comorbidity burden																					
Charlson score (average)	4.0 (4)	3.8 (4)	3.7 (3)				.07	3.7 (3)	3.6 (4)	3.6 (3)				.82	4.4 (4)	4.1 (4)	3.8 (4)			.04	
Charlson score ≥3	472 (66)	435 (64)	466 (62)				.33	242 (61)	245 (61)	283 (61)				.99	230 (72)	190 (69)	183 (65)			.16	
Diabetes	85 (12)	76 (11)	65 (8.7)				.11	42 (11)	50 (12)	41 (8.8)				.22	43 (14)	26 (9.4)	24 (8.5)			.10	
Prior myocardial infarct	28 (3.9)	14 (2.0)	19 (2.5)				.09	14 (3.5)	8 (2.0)	11 (2.4)				.36	14 (4.4)	6 (2.2)	8 (2.8)			.28	
Peripheral vascular disease	57 (8.0)	65 (9.6)	66 (8.8)				.57	26 (6.6)	26 (6.5)	39 (8.4)				.47	31 (9.7)	39 (14)	27 (9.6)			.15	
Chronic heart failure	89 (12)	86 (13)	117 (16)				.14	45 (11)	54 (13)	79 (17)				.06	44 (14)	32 (12)	38 (14)			.69	
Chronic kidney disease	176 (25)	172 (25)	189 (25)				.94	86 (22)	95 (24)	113 (24)				.67	90 (28)	77 (28)	76 (27)			.94	
End-stage renal disease/dialysis	110 (15)	81 (12)	65 (8.7)				.0004	50 (13)	45 (11)	41 (8.8)				.18	60 (19)	36 (13)	24 (8.5)			.001	
Liver disease	61 (8.5)	59 (8.7)	54 (7.2)				.53	34 (8.6)	35 (8.7)	33 (7.1)				.61	27 (8.5)	24 (8.7)	21 (7.5)			.85	
Chronic pulmonary disease	66 (9.2)	57 (8.4)	76 (10)				.52	25 (6.3)	27 (6.7)	42 (9.0)				.26	41 (13)	30 (11)	34 (12)			.75	
Malignancy	79 (11)	76 (11)	74 (9.9)				.68	56 (14)	49 (12)	49 (11)				.27	23 (7.2)	27 (9.8)	25 (8.9)			.53	
Connective tissue disease	3 (0.4)	3 (0.4)	0 (0)				.20	2 (0.5)	2 (0.5)	0 (0)				.31	1 (0.3)	1 (0.3)	0 (0)			.62	
HIV	67 (9.4)	43 (6.3)	27 (3.6)				<.0001	27 (6.8)	18 (4.5)	14 (3.0)				.03	40 (13)	25 (9.1)	13 (4.6)			.003	
HIV/AIDS	60 (8.4)	38 (5.6)	23 (3.1)				<.0001	24 (6.0)	16 (4.0)	11 (2.3)				.02	36 (11)	22 (8.0)	12 (4.3)			.007	
Prior transient ischemic attack/cerebrovascular accident	16 (2.2)	15 (2.2)	16 (2.1)				.60	4 (1)	9 (2.2)	7 (1.5)				.26	12 (3.8)	6 (2.2)	9 (3.2)			.31	
Dementia	38 (5.3)	39 (5.8)	46 (6.2)				.79	11 (2.8)	28 (7.0)	29 (6.2)				.02	27 (8.5)	11 (4.0)	17 (6.0)			.08	
Chemotherapy	73 (10)	58 (8.6)	49 (6.6)				.04	54 (14)	38 (9.5)	32 (6.9)				.004	19 (6.0)	20 (7.2)	17 (6.0)			.79	
Duration of bacteremia																					
≥ 3 days	163 (23)	210 (31)	258 (35)				.0001	75 (19)	120 (30)	163 (35)				<.0001	88 (28)	90 (33)	95 (34)			.22	
≥ 5 days	63 (8.8)	98 (14)	122 (16)				<.0001	23 (5.8)	52 (13)	62 (13)				.0005	40 (13)	46 (17)	60 (21)			.02	
≥ 10 days	9 (1.3)	21 (3.1)	28 (3.8)				.01	3 (0.8)	7 (1.7)	10 (2.1)				.25	6 (2)	14 (5)	18 (6)			.02	
Days to oxacillin/cefazolin (median)	NA	NA	NA				NA	...	...	...				...	...	...	...			...	
Days to targeted antimicrobial therapy	NA	NA	NA				NA	3.7 (3)	3.5 (3)	2.2 (2)				<.0001	NA	NA	NA			...	

Table 2. Continued

Variable	All SAB		All SAB		MSSA			MRSA			P Value	P Value
	Group 1	Group 2	Group 3	(2013–2015)	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3		
No treatment/inappropriate antibiotics	NA	NA	NA	NA	24 (6)	10 (2.5)	12 (2.6)	NA	NA	NA	<.0001	...
Vancomycin/other	NA	NA	NA	NA	123 (31)	117 (29)	119 (26)	NA	NA	NA	...	...
≤3 days to first dose	NA	NA	NA	NA	167 (42)	186 (46)	288 (62)	NA	NA	NA	...	...
≤7 days to first dose	NA	NA	NA	NA	249 (63)	275 (68)	335 (72)	NA	NA	NA	...	...
Vancomycin minimum inhibitory concentration ≥1.5	254 (36)	208 (31)	456 (61)	<.0001	146 (37)	121 (30)	273 (59)	108 (34)	87 (32)	183 (65)	<.0001	<.0001
Genotype												
<i>spa</i> -CC002	176 (25)	181 (27)	191 (26)	.79	54 (14)	70 (17)	74 (16)	122 (38)	111 (40)	117 (42)	.32	.16
<i>spa</i> -CC008	181 (25)	181 (27)	198 (27)	...	48 (12)	61 (15)	68 (15)	133 (42)	120 (43)	130 (46)	...	...
Other	357 (50)	316 (47)	358 (48)	...	294 (74)	271 (67)	324 (69)	63 (20)	45 (16)	34 (12)	...	...
30-day mortality	153 (21)	140 (21)	131 (18)	.06	72 (18)	72 (18)	59 (13)	81 (25)	68 (25)	72 (26)	.02	.97

Abbreviations: CC, clonal complex; HIV, human immunodeficiency virus; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; NA, not applicable; PBS, Pitt bacteremia score; SAB, *Staphylococcus aureus* bloodstream infection.

*Infectious diseases consultation data not available for 2007–2009 period.

treatment with targeted AST within 7 days of the index culture was significantly associated with survival.

DISCUSSION

In this retrospective cohort study of *S. aureus* bloodstream infections at a large academic medical center during a 9-year period, we found a significant decrease in mortality for MSSA bacteremia cases, corresponding with a significant decrease in the time to targeted AST (cefazolin or oxacillin). This mortality trend in MSSA infection occurred in the setting of stable variables such as average age, gender, comorbidity burden, and bacterial genotypes. Furthermore, mortality in MSSA infections decreased, despite an increasing proportion of patients aged ≥65 years with PBS ≥4 and longer bacteremia episodes, variables typically associated with increased mortality. In contrast, 30-day mortality rates for MRSA remained high and did not significantly change during the study.

Underlying the observed decrease in time to AST for MSSA cases, in 2011 our medical center adopted rapid diagnostic testing for methicillin resistance through PBP2a agglutination testing, and in 2014, rapid organism identification through Cepheid GeneXpert/Biofire was implemented. Providers were notified by phone by the Microbiology Lab with identification of MSSA or MRSA in blood cultures. The PBP2a test shortened the time between blood culture collection and pathogen identification and susceptibility compared with prior routine culturing techniques. Along with this change, there was a corresponding effort in antimicrobial stewardship and an emphasis on narrowing antibiotic coverage when indicated.

As the proportion of MSSA-associated BSI is rising in some settings, there has been increasing focus on the impact of rapid susceptibility identification to enable earlier adjustment in therapy [9, 22–24]. Early tailoring of antibiotics from vancomycin to targeted therapy (usually an antistaphylococcal penicillin, such as nafcillin or oxacillin, or cefazolin) has been shown to improve outcomes in MSSA SAB and reduce complications, such as nephrotoxicity and persistent bacteremia [24, 25]. Some studies have shown improvements in mortality comparing beta-lactams to vancomycin alone as definitive therapy and potentially further mortality benefit with use of cefazolin or targeted AST as definitive therapy [25–28]. Currently there is debate over the best choice of targeted antistaphylococcal treatment [29–31]. Our study did not compare outcomes by different AST choices, but this remains an important area of inquiry.

The association between mortality and decreased time to targeted AST was not necessarily causal and may signal other changes in medical care, such as improvement in care processes including earlier ID consultation and echocardiography in endocarditis, that have been shown to significantly improve mortality outcomes in SAB [32, 33]. While there were no significant shifts in demographic categories, such as average age, gender, CO vs HO status, and overall comorbidity burden, there also

Table 3. Predictors of 30-Day Mortality, All *Staphylococcus aureus* Bloodstream Infections

Variable at Bacteremia Onset	Univariate		Multivariate	
	OR (95% CI)	PValue	OR (95% CI)	PValue
Age >65 y	2.9 (2.3–3.6)	<.0001	1.7 (1.2–2.2)	.001
Female gender	1.6 (1.3–1.9)	<.0001	1.6 (1.3–2.0)	.0002
CO vs HO				
CO	0.6 (0.5–0.8)	<.0001	...	...
HO	1.6 (1.3–2.1)	<.0001	1.5 (1.2–2.0)	.0007
Infectious diseases consultation	0.86 (0.63–1.19)	.33	...	...
Pitt bacteremia score ≥4	7.3 (5.7–9.2)	<.0001	6.6 (5.1–8.6)	<.0001
Comorbidity burden				
Charlson score ≥3	2.7 (2.1–3.5)	<.0001	2.1 (1.4–3.0)	.0001
Diabetes	0.7 (0.5–1.0)	.06	0.7 (0.4–1.1)	NS
Prior myocardial infarct	1.6 (0.9–2.8)	.11	1.0 (0.5–1.9)	NS
Peripheral vascular disease	1.0 (0.7–1.5)	.89	...	...
Chronic heart failure	1.2 (0.9–1.7)	.15	1.0 (0.7–1.5)	NS
Chronic kidney disease	0.9 (0.7–1.2)	.50	...	...
End-stage renal disease/dialysis	0.8 (0.6–1.1)	.19	0.9 (0.6–1.3)	NS
Liver disease	1.0 (0.7–1.5)	.92	...	...
Chronic pulmonary disease	1.0 (0.7–1.4)	.79	...	...
Malignancy	1.5 (1.1–2.1)	.01	1.1 (0.7–1.7)	NS
Connective tissue disease	0.8 (0.1–6.9)	.84	...	...
HIV	0.5 (0.3–0.8)	.008	...	...
HIV/AIDS	0.5 (0.3–0.9)	.02	0.6 (0.3–1.3)	NS
Prior transient ischemic attack/cerebrovascular accident	3.7 (1.4–9.5)	.008	1.7 (0.6–5.2)	NS
Dementia	0.9 (0.6–1.5)	.75	...	...
Chemotherapy	1.6 (1.1–2.2)	.01	1.9 (1.2–2.9)	.007
Bacteremia duration				
≥3 days	1.0 (0.8–1.3)	.92	...	...
≥5 days	1.1 (0.8–1.5)	.65	...	...
≥10 days	0.7 (0.4–1.5)	.41	...	...
Antimicrobial resistance				
Methicillin resistance	1.8 (1.4–2.2)	<.0001	1.3 (1.0–1.8)	NS
Vancomycin minimum inhibitory concentration ≥1.5	1.0 (0.80–1.2)	.75	...	...
Genotype				
<i>spa</i> -CC008/ST8 vs. other	1.4 (1.1–1.8)	<.0001	1.1 (0.8–1.5)	NS
<i>spa</i> -CC002/ST5 vs. other	1.8 (1.4–2.3)	<.0001	1.1 (0.8–1.6)	NS
Other (non-CC002/CC008)	Ref	...	...	...

Abbreviations: CC, clonal complex; CI, confidence interval; CO, community-onset; HIV, human immunodeficiency virus; HO, hospital-onset; NS, not significant; OR, odds ratio.

may have been other changes in the patient population or clinical features (such as source of infection).

Surprisingly, the distribution of bacterial genotypes by *spa*-CC did not change significantly over the 9-year study period. This stability of strain background is in contrast to what has been seen at other centers and geographic locations [34]. *spa*-CC008 was a dominant CC in not only the MRSA infections but also MSSA cases in our study. The most notable member of *spa*-CC008 in MRSA is the pandemic clone USA300, which causes most community-associated and, increasingly, hospital-associated MRSA infections in the United States [35, 36]. MSSA infections are typically caused by a diverse group of genotypes [37]; however, *spa*-CC008 represented a significant proportion of MSSA infectious strains overall and throughout the study. Genotypes did not significantly predict mortality, consistent

with findings from other studies [4, 38]. The proportion of isolates with vancomycin MIC ≥1.5 also increased across the SAB cohort study period; however, it was not a predictor of mortality for either MSSA or MRSA infections. Other studies have shown a similar lack of correlation between vancomycin MIC and mortality, although there is controversy over whether elevated MIC for non-vancomycin-intermediate *S. aureus* strains is associated with other poor outcomes, such as endocarditis and metastatic seeding [39, 40]. One limitation of the MIC data is that they were determined using MicroScan rather than the E-test, potentially leading to less-accurate MIC quantification.

Limitations of this study include that it occurred at a single study site and geographic location, perhaps not fully reflecting microbiologic and clinical patterns elsewhere. There was also a lack of information about infective source, such as pneumonia, and of

Table 4. Predictors of 30-Day Mortality, Methicillin-susceptible *Staphylococcus aureus* and Methicillin-resistant *S. aureus*

Variable	MSSA				MRSA			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	PValue	OR (95% CI)	PValue	OR (95% CI)	PValue	OR (95% CI)	PValue
Age >65 y	2.9 (2.1–3.9)	<.0001	1.8 (1.2–2.7)	.006	2.7 (2.0–3.8)	<.0001	1.7 (1.1–2.7)	.02
Female gender	1.6 (1.2–2.1)	.004	1.4 (1.0–1.9)	NS	1.5 (1.1–2.1)	.008	1.7 (1.2–2.4)	.004
CO vs HO								
CO	0.6 (0.4–0.8)	.001	...	...	0.6 (0.5–0.9)	.006	...	...
HO	1.7 (1.2–2.3)	.001	1.6 (1.1–2.3)	.02	1.6 (1.1–2.1)	.006	1.5 (1.0–2.1)	.03
Infectious diseases consultation	0.75 (0.5–1.12)	.19	0.8 (0.5–1.3)	.4	1.0 (0.6–1.6)	.89	...	...
Pitt bacteremia score ≥4	7.9 (5.6–11.1)	<.0001	6.7 (4.6–9.7)	<.0001	6.1 (4.4–8.6)	<.0001	6.3 (4.4–9.0)	<.0001
Comorbidity burden								
Charlson score ≥3	2.8 (1.9–3.9)	<.0001	1.9 (1.2–3.1)	.007	2.5 (1.7–3.6)	<.0001	1.8 (1.1–3.1)	.03
Diabetes	0.7 (0.4–1.3)	.28	...	...	0.6 (0.4–1.1)	.10	0.7 (0.4–1.3)	NS
Prior myocardial infarct	1.2 (0.5–2.9)	.74	...	...	2.0 (0.9–4.3)	.09	1.5 (0.6–3.6)	NS
Peripheral vascular disease	1.0 (0.6–1.8)	.91	...	...	0.9 (0.6–1.5)	.71	...	...
Chronic heart failure	1.1 (0.7–1.7)	.60	...	...	1.4 (0.9–2.2)	.10	1.3 (0.8–2.2)	NS
Chronic kidney disease	1.0 (0.7–1.4)	.83	...	...	0.8 (0.6–1.2)	.27	...	...
End-stage renal disease/dialysis	0.8 (0.5–1.3)	.34	...	...	0.8 (0.5–1.2)	.23	...	...
Liver disease	1.0 (0.6–1.7)	.92	...	...	1.1 (0.6–1.8)	.82	...	...
Chronic pulmonary disease	0.6 (0.3–1.2)	.14	0.6 (0.3–1.2)	NS	1.1 (0.7–1.7)	.72	...	...
Malignancy	1.8 (1.2–2.7)	.004	1.6 (0.9–2.8)	NS	1.3 (0.8–2.3)	.26	...	...
Connective Tissue Disease	0.0 (0.0)	.98	...	...	3.0 (0.2–47)	.44	...	...
HIV	0.2 (0.04–0.7)	.02	...	...	0.6 (0.3–1.1)	.07	...	...
HIV/AIDS	0.2 (0.05–0.9)	.03	0.3 (0.1–1.5)	NS	0.6 (0.3–1.1)	.11	0.9 (0.4–1.9)	NS
Prior transient ischemic attack/ cerebrovascular accident	1.3 (0.4–4.7)	.68	...	...	3.0 (0.96–9.4)	.06	1.6 (0.4–6.1)	NS
Dementia	0.7 (0.3–1.5)	.32	...	...	1.1 (0.6–2.1)	.72	...	...
Chemotherapy	1.4 (0.9–2.2)	.19	1.0 (0.5–1.8)	NS	2.4 (1.4–4.1)	.002	3.4 (1.8–6.2)	.0001
Bacteremia duration								
≥3 days	1.0 (0.7–1.4)	.93	...	...	1.0 (0.7–1.4)	.99	...	...
≥5 days	1.1 (0.7–1.7)	.81	...	...	1.0 (0.6–1.5)	.86	...	...
≥10 Days	0.6 (0.1–2.5)	.46	...	...	0.7 (0.3–1.5)	.33	...	...
Targeted AST ≤7 days	0.3 (0.2–0.4)	<.0001	0.4 (0.3–0.6)	<.0001	NA	NA	...	...
Vancomycin minimum inhibitory concentration ≥1.5	1.0 (0.7–1.3)	.9	...	...	0.9 (0.7–1.3)	.70	...	...
Genotype								
<i>spa</i> -CC008/ST8 vs other	1.2 (0.8–1.8)	.5	1.3 (0.8–2.1)	NS	1.0 (0.6–1.5)	.90	...	...
<i>spa</i> -CC002/ST5 vs other	1.4 (1.0–2.1)	.07	1.1 (0.7–1.7)	NS	1.3 (0.9–2.1)	.21	...	...
Other (non-CC002/CC008)	Ref	Ref	...	...	Ref	Ref	...	...

Abbreviations: CC, clonal complex; CI, confidence interval; CO, community onset; HIV, human immunodeficiency virus; HO, hospital onset; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; OR, odds ratio.

infectious complications, such as endocarditis and secondary metastatic seeding of infection. Complications such as endocarditis and metastatic seeding are known to increase mortality in SAB. Changes in rates of such complications over time (ie, a decrease in rates of endocarditis) could have contributed to the mortality trends. Unmeasured bacterial factors may have also influenced mortality but were not captured by our genotyping approach.

Our study of a large SAB cohort spanning 9 years showed a substantial decrease in mortality in invasive MSSA bacteremia, corresponding to a narrowing of the time to targeted AST. It is likely that other factors, such as rapid organism identification and susceptibility data, have contributed to the improved

outcomes. Our results emphasize the potential for significant mortality reduction in SAB when hospitals implement early diagnostic techniques and antibiotic stewardship efforts.

Notes

Author contributions. A.-C. U. and E. D. A. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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