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MAJOR ARTICLE

Staphylococcus aureus Bacteremia at 5 US Academic Medical Centers, 2008–2011: Significant Geographic Variation in Community-Onset Infections

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Background. The incidence of community-onset (CO) methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia rose from the late 1990s through the 2000s. However, hospital-onset (HO) MRSA rates have recently declined in the United States and Europe.

Methods. Data were abstracted from infection prevention databases between 1 January 2008 and 31 December 2011 at 5 US academic medical centers to determine the number of single-patient blood cultures positive for MRSA and methicillin-susceptible *S. aureus* (MSSA) per calendar year, stratified into CO and HO infections.

Results. Across the 5 centers, 4171 episodes of bacteremia were identified. Center A (Los Angeles, California) experienced a significant decline in CO-MRSA bacteremia rates (from a peak in 2009 of 0.42 to 0.18 per 1000 patient-days in 2011 [$P = .005$]), whereas CO-MSSA rates remained stable. Centers B (San Francisco, California), D (Chicago, Illinois), and E (Raleigh-Durham, North Carolina) experienced a stable incidence of CO-MRSA and CO-MSSA bacteremia. In contrast, at center C (New York, New York), the incidence of CO-MRSA increased >3-fold (from 0.11 to 0.34 cases per 1000 patient-days [$P < .001$]). At most of the sites, HO-MRSA decreased and HO-MSSA rates were stable. USA300 accounted for 52% (104/202) of genotyped MRSA isolates overall, but this varied by center, ranging from 35% to 80%.

Conclusions. CO-MRSA rates and the contribution of USA300 MRSA varied dramatically across diverse geographical areas in the United States. Enhanced infection control efforts are unlikely to account for such variation in CO infection rates. Bioecological and clinical explanations for geographical differences in CO-MRSA bacteremia rates merit further study.

Keywords. bacteremia; epidemiology; genotyping; MRSA; *Staphylococcus aureus*.

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Methicillin-resistant *Staphylococcus aureus* (MRSA) first appeared clinically in the early 1960s [1]. MRSA isolates became endemic in most US hospitals by the late 1980s [2–4]. In the 1990s, a new wave of MRSA infections occurred in community settings [3–8]. In many centers, MRSA isolates predominate as a cause of *S. aureus* community-onset (CO) infections,

including bacteremia [3–5, 9]. Rather than being "escaped" hospital-based MRSA clones, the community MRSA strains were derived from methicillin-susceptible *S. aureus* (MSSA) strains that acquired a novel resistance element, SCC*mec* type IV [2, 4, 10–12]. These strain types, especially the USA300 genetic background, were highly virulent, often susceptible to multiple non–β-lactam antibiotics, and carried signature toxin genes (most commonly Panton-Valentine leukocidin [PVL]) rarely found in the older, hospital-acquired strain types [13]. USA300 also had a constitutive upregulation of several key virulence genes [14].

Driven by emergence of USA300, the incidence of MRSA infections rose dramatically in the early 2000s. In 2000, the Centers for Disease Control and Prevention (CDC) estimated that there were >30 000 hospitalizations for MRSA bacteremia [15]; however, more recent published reports have described declines in invasive MRSA infection rates, particularly in healthcare settings [16–20]. In the United States and the United Kingdom, the decline in MRSA bacteremia rates appears to have preceded enhanced infection prevention efforts in hospitals [21]. In a study of US military personnel and their dependents, rates of MRSA bacteremia declined between 2008 and 2011 [22]. However, to date, few reports have documented the incidence of MSSA bacteremia in this time period, or assessed potential geographic variations in CO infection rates, as opposed to hospital-onset (HO) rates.

The current study was conducted to define trends in the annual incidence of MRSA and MSSA bacteremia at 5 large, geographically dispersed US academic medical centers to assess the incidence of HO and CO MSSA and MRSA bacteremia during a 4-year period.

METHODS

Aim and Data Abstraction

We conducted a retrospective clinical review and microbial sample study using existing databases and stored bacterial samples. The hypothesis tested was that rates of CO-MRSA bacteremia had declined between 2008 and 2011, whereas MSSA rates were stable or rising. Community-onset bacteremia was defined as a case in which a blood culture yielded *S. aureus* in a specimen collected ≤48 hours after hospital admission. Resistance to methicillin was determined in the clinical microbiology laboratory at each institution. The 5 participating tertiary care academic medical centers included center A, a 470-bed public hospital in Los Angeles County, California; center B, a 460-bed public hospital in San Francisco, California; center C, a private 1491-bed hospital in New York, New York; center D, a 558-bed private university hospital in Chicago, Illinois; and center E, a private 813-bed university hospital in Raleigh-Durham, North Carolina.

Data were abstracted from existing comprehensive infection prevention databases at each institution to determine how many MRSA and MSSA blood cultures from distinct patients were recorded per calendar year; whether the positive culture was drawn at ≤48 hours or >48 hours from hospital admission; and whether the case was in a child (defined as <18 years of age) or an adult (≥18 years of age) patient. In addition, to calculate standardized annual incidences of infection, the number of patient-days for all admitted patients (all services) was abstracted from electronic records. The incidence of infections was reported as the number of patients divided by 1000 patient-days per calendar year. The study was approved by the institutional review board at each institution.

Strain Selection

A sample of isolates, stratified proportionally by the total number of MRSA or MSSA bacteremia episodes at each center and by 2 time periods (2008–2009 and 2010–2011), was retrieved from frozen repositories maintained by the infection prevention services at the 5 institutions. The sample size calculation for the total number of MRSA bloodstream isolates to be typed was determined by the hypothesis that there was an increase in the percentage of MRSA isolates that were USA300, from 20% in 2008–2009 to 35% in 2010–2011. To achieve 80% power with a 2-tailed test for a P value <.05 to assess this hypothesis, we required 122 isolates from each time period. Given anecdotal evidence that PVL-bearing (PVL^+) MSSA isolates were becoming more common among bloodstream infection isolates in the United States, a secondary hypothesis was that the percentage of MSSA isolates that were PVL^+ would increase from 5% in 2008–2009 to 18% in 2010–2011. To achieve 80% power with a 2-tailed test for a P value <.05 to assess this hypothesis, we needed 114 MSSA isolates from each of the 2-year periods. Isolates were randomly selected from those available at each center; in the event that a center did not have the requested number of isolates available, all available isolates for a given time period and MSSA/MRSA group were included.

In total, 472 bloodstream isolates (244 MRSA and 228 MSSA isolates) were requested from the 5 centers, and 363 (76.9%) were available for genotyping. Thus, 109 requested isolates were not available for genotyping. Center C had no stored isolates from 2008–2009 (n = 53 MSSA and n = 29 MRSA were requested for this period), accounting for the majority of the 109 unavailable isolates (82/109 [75%]).

Strain Typing

For each isolate, multilocus sequence typing (MLST) was performed as described [23]. Detection of the PVL genes was performed [24], as was polymerase chain reaction (PCR) for *arcA* [25]. The SCC*mec* type in *mecA*-bearing isolates was determined by a panel of PCR assays defining the *mec* and *ccr* complex [26, 27]. Isolates that were sequence type (ST) 8, PVL^+, and carried SCC*mec* type IV were considered to be USA300, with a

Table 1. Number of Patients With Bacteremia by Center, Methicillin Resistance, Year, and Community or Hospital Onset

		CO *S. aureus* (≤48 h After Admission)						HO *S. aureus* (>48 h After Admission)					
Center	Year	A	B	C	D	E	Total	A	B	C	D	E	Total
All patients													
MRSA	2008	37	39	45	45	104	270	19	14	23	21	29	106
	2009	41	39	90	60	117	347	8	13	39	26	29	115
	2010	28	35	142	39	135	379	6	10	42	24	32	114
	2011	17	40	157	36	121	371	16	4	44	13	12	89
	Total	123	153	434	180	477	1367	49	41	148	84	102	424
MSSA	2008	36	35	215	62	123	471	14	10	103	30	35	192
	2009	33	47	184	55	109	428	9	12	80	30	28	159
	2010	52	52	188	58	117	467	17	6	54	23	18	118
	2011	39	44	178	42	114	417	11	12	63	15	27	128
	Total	160	178	765	217	463	1783	51	40	300	98	108	597
Adult patients													
MRSA	2008	34	39	44	40	100	257	19	14	22	17	27	99
	2009	37	39	89	51	114	330	8	13	38	23	26	108
	2010	26	35	140	33	129	363	5	9	38	19	29	100
	2011	16	40	157	33	113	359	16	4	40	10	11	81
	Total	113	153	430	157	456	1309	48	40	138	69	93	388
MSSA	2008	33	35	213	56	110	447	12	10	95	16	27	160
	2009	32	47	182	53	94	408	7	12	74	13	20	126
	2010	51	52	183	50	100	436	16	6	47	12	14	95
	2011	36	44	174	36	97	387	10	11	58	9	20	108
	Total	152	178	752	195	401	1678	45	39	274	50	81	489
Pediatric patients													
MRSA	2008	3	0	1	5	4	13	0	0	1	4	2	7
	2009	4	0	1	9	3	17	0	0	1	3	3	7
	2010	2	0	2	6	6	16	1	1	4	5	3	14
	2011	1	0	0	3	8	12	0	0	4	3	1	8
	Total	10	0	4	23	21	58	1	1	10	15	9	36
MSSA	2008	3	0	2	6	13	24	2	0	8	14	8	32
	2009	1	0	2	2	15	20	2	0	6	17	8	33
	2010	1	0	5	8	17	31	1	0	7	11	4	23
	2011	3	0	4	6	17	30	1	1	5	6	7	20
	Total	8	0	13	22	62	105	6	1	26	48	27	108

Abbreviations: CO, community onset; HO, hospital onset; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.

99% positive predictive value [28]. Isolates that were ST5, lacked the PVL genes (PVL$^-$), and carried SCC*mec* type II were considered to be USA100.

Endpoints and Statistical Analysis

The primary endpoint was the rate per 1000 patient-days of CO-MRSA and CO-MSSA infections from 2008 to 2011, combining pediatric and adult cases, but separately analyzing the 5 centers. Secondary analyses included the incidence of blood cultures positive >48 hours after admission (ie, HO-MSSA and HO-MRSA), as well as analyses of the cumulative data across all 5 centers. Changes in incidence over time were assessed by Poisson regression, and changes in ratios over time were compared by the χ^2 test (SPSS). Changes over time in molecular types were assessed by the χ^2 test comparing 2008–2009 with 2010–2011. For all analyses, a P value $\leq$.05 was considered significant (Stata, version 12, StataCorp, College Station, Texas).

RESULTS

At the 5 centers combined in 2008–2011, there were 4171 patients with *S. aureus* bacteremia, of which 42.9% (1791/4171) were MRSA infections and 57.1% (2380/4171) were MSSA. Among MRSA patients, 76.3% (1367/1791) were CO- and

23.6% (424/1791) were HO-MRSA. Among MSSA patients, 74.9% (1783/2380) were CO- and 25.1% (597/2380) were HO-MSSA. Among all *S. aureus* bacteremia patients, 92.6% (3864/4171) were adults and 7.4% (307/4171) were children. Among adults, 43.9% (1697/3864) had MRSA infections, whereas among children, a much smaller percentage (30.6% [94/307]) had MRSA. In adults, 77.1% (1309/1697) of MRSA patients had CO-MRSA, and among children, 62% (58/94) had CO-MRSA. Among adult patients, more than three-fourths, 77.4% (1678/2167), of MSSA patients had CO-MSSA; among children, only approximately half (49.3% [105/213]) had CO-MSSA (Table 1).

Incidence of Bacteremia at All Sites

At the 5 centers combined, there was not a significant change in the incidence of all *S. aureus* bacteremia ($P = .4$) from 2008 to 2011. However, MSSA bacteremia rates significantly declined from 0.73 to 0.59 per 1000 patient-days ($P < .001$), whereas MRSA bacteremia rates rose from 0.41 to 0.50 per 1000 patient-days ($P < .001$) (Figure 1). Both changes were driven by CO bacteremia. Specifically, there was a 33% increase in the incidence of CO-MRSA bacteremia, from 0.30 per 1000 patient-days in 2008 to 0.40 in 2011 ($P < .001$; Figure 1). At the same time, CO-MSSA bacteremia incidence decreased significantly, from 0.52 to 0.45 per 1000 patient-days ($P < .001$) in 2008 to 2011.

The incidence of HO-MRSA bacteremia was consistently considerably lower than the CO-MRSA rate (Figure 1). At the 5 centers combined, there was a small but significant decrease in the incidence of HO-MRSA bacteremia from 2008 to 2011, from 0.12 to 0.10 per 1000 patient-days ($P < .001$). There was also a more dramatic decrease in incidence of HO-MSSA bacteremia, from 0.21 to 0.14 per 1000 patient days ($P < .001$).

Geographical Variation

Significant variation was seen in bacteremia rates across the centers studied, particularly in the incidence of CO-MRSA. At center A (Los Angeles), the incidence of CO-MRSA bacteremia declined by 57%, from a peak of 0.42 per 1000 patient-days in 2009 to 0.18 per 1000 patient days in 2011 ($P = .005$; Figure 2). In contrast, at center C (New York), CO-MRSA bacteremia incidence more than tripled, from 0.11 to 0.34 cases per 1000 patient days ($P < .001$; Figure 2). At centers B (San Francisco), D (Chicago), and E (Raleigh-Durham), the CO-MRSA rate was stable (Figure 2). CO-MSSA bacteremia rates were stable at each of the medical centers except for center C, where the rates declined significantly from 0.53 to 0.39 per 1000 patient-days ($P < .001$).

At center B (San Francisco), the HO-MRSA rate declined by 69% ($P = .03$), and a similar drop was observed at center E (Raleigh-Durham) ($P = .009$), whereas at center D (Chicago) ($P = .6$) and center A (Los Angeles) ($P = .6$), the HO-MRSA bacteremia rate did not change significantly. In contrast, at center C (New York), the HO-MRSA rate increased significantly from 0.057 to 0.097 per 1000 patient-days from 2008 to 2011 ($P = .046$).

HO-MSSA rates did not change significantly at centers A (Los Angeles), B (San Francisco), D (Chicago), or E (Raleigh-Durham).

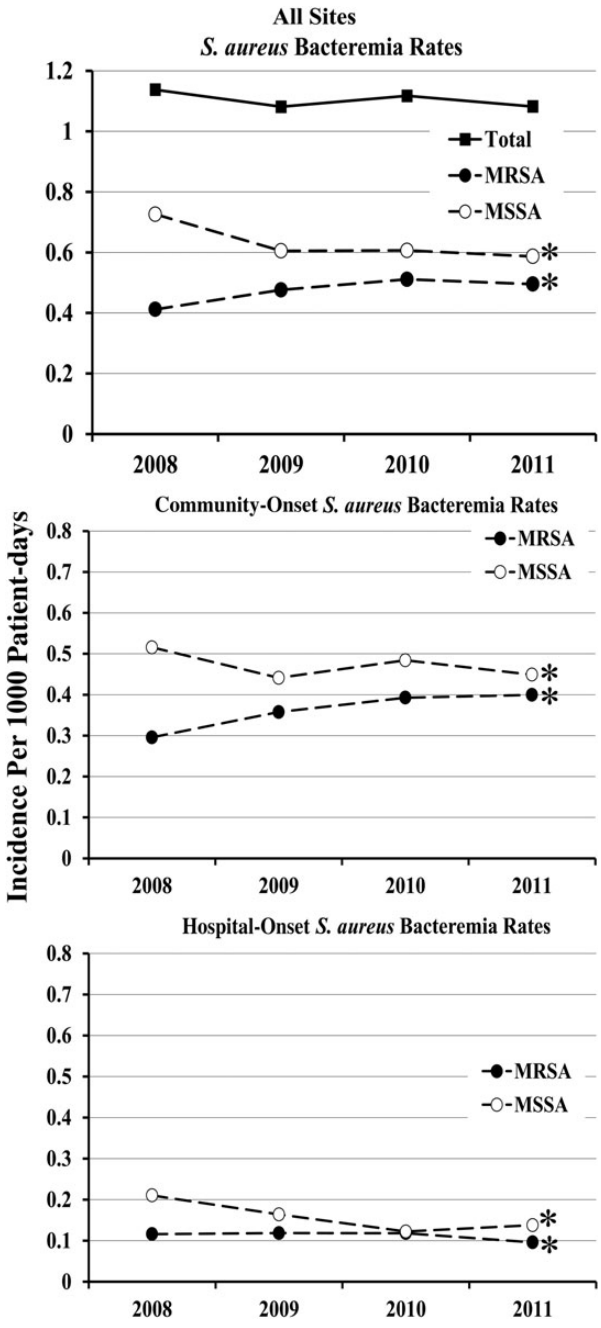

Figure 1. Incidence of overall, community-onset and hospital-onset *Staphylococcus aureus* bacteremia across all sites. *$P < .05$ for trend over time. Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.

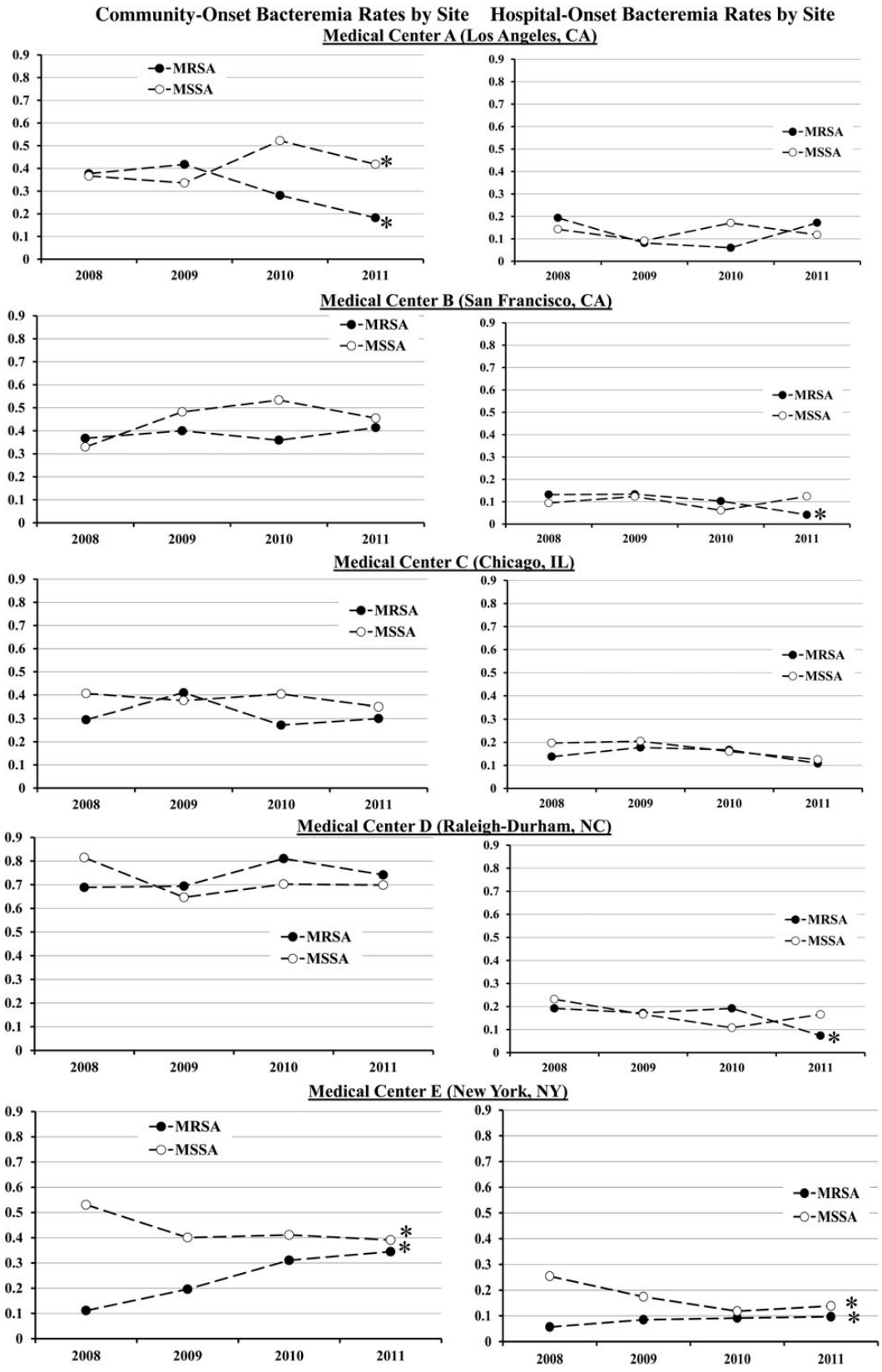

Figure 2. Geographical variation in community-onset and hospital-onset methicillin-resistant *Staphylococcus aureus* and methicillin-susceptible *S. aureus* bacteremia rates. *$P < .05$ for trend over time. Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.

Table 2. Methicillin-Susceptible *Staphylococcus aureus* Genotypes by Center and Time Period

Strain Type[a]	No. (%)	Center A		Center B		Center C		Center D		Center E	
		2008–2009	2010–2011	2008–2009	2010–2011	2008–2009	2010–2011	2008–2009	2010–2011	2008–2009	2010–2011
1/–	13 (8)	2	4		1	NA		1		2	3
5/–	25 (16)	1	1	1		NA	7		1	7	7
8/+	7 (4)					NA	3	1	1	2	
8/–	13 (8)		2	1	2	NA	3		1		4
15/–	12 (8)	1			1	NA	4	1	1	1	3
20/–	4 (3)			1		NA	1	1		1	
25/–	3 (2)					NA					3
30/–	13 (8)			1		NA	4		2	4	2
45/–	7 (4)		1		2	NA	1			2	1
72/–	8 (5)			1		NA	3	1		1	2
87/–	2 (1)		1			NA				1	
88/–	2 (1)					NA			2		
97/–	5 (3)		1		1	NA		1		1	1
188/–	5 (3)	1	2			NA	1	1			
291/–	2 (1)	1				NA					1
508/–	2 (1)					NA	2				
NT/–	5 (3)	1		1	1	NA	1			1	
NT/+	3 (2)					NA		2	1		
Other[b]	30 (19)	1	2	4	3	NA	6	5	5	3	1
Total	161 (100)	8	14	10	11	0	36	14	14	26	28

Abbreviations: NA, not applicable; NT, new type; slv, single locus variant.

[a] Shown as multilocus sequence type/presence (+) or absence (–) of Panton-Valentine leukocidin.

[b] Includes the following single isolates from center A in 2008–2009: 332/–; center A in 2010–2011: 12/–, 45slv/–; center B in 2008–2009: 9/–, 121/–, 121/+, 582/–; center B in 2010–2011: 97slv/–, 333/–, 731/–; center C in 2010–2011: 7/–, 8/+ (carries *arcA*), 47/–, 72slv/–, 182slv/–, 231/–; center D in 2008–2009: 74/–, 868/+, 322/–, 109slv/–, 45slv/+; center D in 2010–2011: 5slv/+ (carries *arcA*), 508slv/–, 580/–, 714/–, 2229/+ (carries *arcA*); center E in 2008–2009: 54/–, 59/–, 536/+; center E in 2010–2011: 398/–.

However, at center C (New York), the HO-MSSA decrease was significant, from 0.25 to 0.14 per 1000 patient-days ($P < .001$).

Genotyping Results

Isolate genotyping results are shown in Table 2 for 161 MSSA and in Table 3 for 202 MRSA isolates. Tested MSSA isolates were polyclonal, with 45 STs represented. The 3 most common STs were ST5 (n = 25 [15.5%]), ST8 (n = 21 [12.4%]), and ST30 (n = 13 [8.1%]). Among the 161 MSSA isolates tested, 18 (11.1%) were PVL$^+$, and the most common background among these was ST8 (8/18 [44%]). Because center C did not contribute isolates for genotyping in 2008–2009, the 2010–2011 center C isolates were eliminated from consideration; without center C isolates included in the analysis, there was a significant decrease in PVL$^+$ MSSA isolates at the remaining 4 centers, from 17% (10/58) to 6.0% (4/67) ($P = .046$).

Tested MRSA isolates were less polyclonal; as shown in Table 3, for the period 2008–2011, there were only 17 STs among the 202 isolates typed. ST8 (n = 110 [55%]) and ST5 (n = 57 [28%]) accounted for 83% of the MRSA isolates. Of the 202 typed isolates, 126 (62%) were PVL$^+$. The *arcA* gene, which is often carried by USA300 isolates and a proxy marker for the ACME element, was identified by PCR in 52% (104/202) of the MRSA isolates of several different genetic backgrounds, including ST5, ST8, ST30, ST632, and a number of STs not previously defined in the MLST database. The USA300 phenotype (ie, ST8, PVL$^+$, SCC*mec* type IV) accounted for 52% (104/202) of isolates, whereas USA100-like isolates (ie, ST5, PVL$^-$, SCC*mec* type II) accounted for 16.8% (34/202). Excluding the 2010–2011 isolates from center C, the percentage of USA300 isolates increased in 2010–2011 (40/71 [56%]) compared with 2008–2009 (42/94 [45%]), but the difference was not statistically significant ($P = .1$). Among typed CO-MRSA, 55% (84/154) were USA300 while among HO-MRSA, 42% (20/48) were USA300.

The percentage of MRSA isolates that were USA300 obtained from each center differed in 2008–2011: They accounted for 35% (28/80) at center E, 68% (25/37) at center C, 70% (14/20) at center A, 80% (20/25) at center B, and 43% (17/40) at center D.

Table 3. Methicillin-Resistant *Staphylococcus aureus* Genotypes by Center and Time Period

Strain Type[a]	No. (%)	Center A		Center B		Center C		Center D		Center E	
		2008–2009	2010–2011	2008–2009	2010–2011	2008–2009	2010–2011	2008–2009	2010–2011	2008–2009	2010–2011
5/II/– (USA100)	34 (17)	1				NA	2	6	8	13	4
5/II/+	2 (1)					NA		1			1
5/II/+[b]	4 (2)					NA					4
5/IV/–	15 (7)					NA	4			7	4
5/IV/+[b]	2 (1)					NA					2
8/IV/–	4 (2)					NA	1		2	1	
8/IV/+	14 (7)		1	2		NA	4	2	2	1	2
8/IV/+[b] (USA300)	90 (45)	9	4	11	7	NA	21	9	4	11	14
8slv/IV/+[b]	2 (1)	1			1	NA					
72/IV/+	2 (1)					NA	1				1
105/II/–	4 (2)					NA	1			2	1
239/III/–	2 (1)	2				NA					
450/IV/+[b]	2 (1)				1	NA	1				
632/II/–	2 (1)					NA				2	
632/IV/–	2 (1)					NA				2	
Other[c]	20 (10)	1	1	1	2	NA	1	6	0	3	5
Total	202 (100)	14	6	14	11	0	37	24	16	42	38

Abbreviation: NA, not applicable.

[a] Shown as multilocus sequence type/SCC*mec* type/presence (+) or absence (–) of Panton-Valentine leukocidin genes. The 8/IV/+ isolates carrying arcA were considered to be USA300; the 5/II/– isolates were considered to be USA100, as indicated.

[b] Carries ACME *arcA*.

[c] Includes the following single isolates from center A 2008–2009: 840/IV/–; center A in 2010–2011: 1/III/–; center B in 2008–2009: 59/IV/–; center B in 2010–2011: 267/IV/–, 576slv/IV/+ (carries *arcA*); center C in 2010–2011: 105/C2,5/–; center D in 2008–2009: 8/C2,4/+, 30/II/–, 72/C2,4/+, 231/II/+, 1771/C2, 4/–, 2512/II/–; center E in 2008–2009: 1/IV/–, 59/II/–, NT/IV/+ (carries *arcA*); center E in 2010–2011: 5slv/IV/–, 30/II/+ (carries *arcA*), 231/II/–, 632/II/+, 632/II/+ (carries *arcA*).

DISCUSSION

At 5 large, geographically distant US medical centers between 2008 and 2011, we examined >4100 patients with *S. aureus* bacteremia. The rates of and trends in HO-MRSA, CO-MRSA, HO-MSSA, and CO-MSSA bloodstream infections varied greatly from center to center. This suggests that there is not a uniform "national epidemic" of MRSA infections, but that the epidemiologic and ecologic dynamics of MRSA vary geographically. At each center, CO bacteremia rates were higher than HO bacteremia rates, underscoring the importance of CO infections as contributors to the infectious burden in subsequently hospitalized patients. This suggests that efforts to prevent MRSA infections should be focused on outpatient settings as well as inpatient settings, as noted by previous studies [20].

The rise in CO-MRSA bacteremia rates, and the inverse decline in CO-MSSA bacteremia rates, suggest ongoing, fundamental changes in bacterial ecology. In contrast, the HO rates of both MRSA and MSSA bacteremia declined, possibly indicative of successful horizontal infection control practices [29]. However, evidence suggesting that this was not universally true is indicated by the fact that at some centers, change in HO-MSSA and HO-MRSA infection incidence was not concordant.

There was substantial geographical variation in both MRSA and MSSA bloodstream infection rates and in the molecular epidemiology of *S. aureus* bacteremia at the 5 studied centers. At 3 centers, CO-MRSA bacteremia rates did not change significantly during the study period, in contrast to recent US reports on the decreasing trend in HO-MRSA infections [20, 22]. However, at one center (Los Angeles), CO-MRSA bacteremia rates markedly declined, whereas at another center (New York) rates significantly rose 3-fold over the same time period. Of note, Los Angeles and Chicago were 2 of the earliest geographical areas in the United States to be affected by the emergence of CO-MRSA infections in the mid-1990s [4, 5, 8]. In contrast, the New England/New York areas were spared initially and only more recently substantially affected by this "epidemic" [4]. Thus, it is possible that the relatively stable incidence of CO-MRSA in Chicago and the decline seen in Los Angeles will begin to be seen in cities on the East Coast in the near future. Geographic differences in the incidence of invasive CA-MRSA infections were noted in CDC surveillance as well [30].

We found that most hospitals experienced declines in the rate of HO-MRSA bacteremia, consistent with the trends identified in CDC surveillance reports [20]. Our results, however, contrast with a recent publication that described a decline in rates of both CO- and HO-MRSA bacteremia in US military personnel and their dependents [22]. It may be that different bacterial ecology or infection control practices predominate in military populations, or that geographic variation is masked in country-wide studies that provide summary statistics of average trends from across the nation.

Surprisingly, in contrast to our expectations, there was a significant decrease in the percentage of PVL^+ MSSA isolates causing bloodstream infections in 2008–2011. PVL positivity in MSSA and MRSA strain types has been associated with isolates causing skin and pulmonary infections, although there has been controversy about the importance of PVL as a virulence factor. USA300 MSSA carrying PVL have been identified in a number of studies [31, 32]; we did not find them to be common causes of bacteremia in our study.

We found that there was a nonsignificant increase in the percentage of USA300 as a cause of MRSA bacteremia. Genotyping revealed important center-specific differences in the prevalence of USA300 among MRSA bacteremia isolates, with a higher prevalence at the 2 California centers (70% and 80%) than the others. This may reflect a difference in the patient populations of the various centers, and perhaps whether hospitals are public or private, sociodemographic variation in patient populations, or a difference in the proportion of patients who have chronic comorbid conditions and therefore more healthcare exposure. Alternatively, this difference in the genotypic spectrum, also noted in CDC surveillance [30], may reflect geographic differences in the spread of USA300 or that each individual center may represent different "time-points on the curve" of the epidemic of USA300 in the United States. These data suggest that a shift in *S. aureus* strain types is involved in changing CO-MRSA bacteremia rates, although the relationship is not simple.

Sequence types of MRSA isolates from invasive infections common in other parts of the world such as ST59 [33, 34], ST30, and ST239 [35, 36] were rarely identified, whereas others, such as ST93, common in Australia [37, 38], and ST228, ST241, ST22 or ST80, common in Europe [35, 36, 39–41], were entirely absent from our typed isolate sample. Why there are marked differences in genotypes of MRSA in different continents is not understood.

A strength of our study was inclusion of data from patients in diverse settings across the United States in a large collective catchment area including millions of residents. Furthermore, use of infection prevention databases designed to capture all patients with a diagnosis of bacteremia enabled comprehensive and unbiased detection of infections.

A limitation of our study was the inclusion of only large, urban academic medical centers. Because a principal finding was the diversity of changing MRSA and MSSA bacteremia rates stratified by geographic areas, it would be anticipated that the diversity would further increase when evaluating smaller, community-based, or rural medical centers. The criteria used for CO and HO infection did not differentiate community- from healthcare-associated infection; we did not abstract medical records to distinguish CO from healthcare-associated CO–*S. aureus* infections. Nevertheless, clear differences in trends over time in CO as compared with HO bacteremia rates were seen, indicating that our classification of "CO" was not merely a surrogate for healthcare-associated, CO infections. We did not have a complete sample of isolates for genotyping from all 5 centers, decreasing our power to compare stratified samples over time. However, our sample size was large, and most missing isolates were from a single center, allowing us to analyze data from just the other 4 centers when assessing change over time in genotypic characteristics of *S. aureus* isolates causing bacteremia.

In conclusion, our study demonstrates that both CO– and HO–*S. aureus* bacteremia remain common at large US academic medical centers in different regions of the country and that the molecular epidemiology of MRSA and MSSA causing bloodstream infections is not homogeneous. MRSA bacteremia was not uniformly decreasing at such centers between 2008 and 2011. Future surveillance studies should be particularly sensitive to the substantial geographical variation in CO-MRSA incidence and ecology.

Notes

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