MAJOR ARTICLE

Emergence of Community-Associated Methicillin-Resistant *Staphylococcus aureus* USA300 Genotype as a Major Cause of Health Care–Associated Blood Stream Infections

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Background. Whether community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) genotypes (e.g., USA300) are a major cause of bloodstream infections (BSIs) and health care–associated infections has been poorly defined.

Methods. Consecutive MRSA isolates recovered from patients with BSIs were prospectively collected at an urban public hospital. Molecular typing studies were performed. Prevalence and risk factors for the MRSA USA300 genotype were assessed.

Results. One hundred thirty-two cases of MRSA BSI were documented over 7.5 months in 2004 (incidence, 6.79 per 1000 admissions); 116 isolates were available for genotyping. Characteristics of the 116 evaluable cases included: a mean age 47 years; 62% were male, 82% were African American, and 22% were HIV seropositive. The crude in-hospital mortality rate was 22%. In 107 cases (92%), there was contact with a health care facility within the year prior to infection, and a nosocomial infection (defined as positive blood culture results obtained >48 h after admission) occurred in 49 cases (42%). PFGE demonstrated that 39 (34%) of the 116 isolates were the MRSA USA300 genotype; 34 (29%) were USA100; 42 (36%) were USA500; and 1 (1%) was USA800. MRSA USA300 accounted for 28% of health care–associated BSIs and 20% of nosocomial MRSA BSIs. In multivariate analysis, isolation of the USA300 genotype was associated with injectiondrug use (OR, 3.67; 95% CI, 1.10–12.28) and skin and soft tissue infection (OR, 4.26; 95% CI, 1.08–16.84). Patients who resided in long-term care facilities (OR, 0.09; 95% CI, 0.01–0.82) and those who were treated with antimicrobials in the prior year were less likely to have MRSA USA300 genotype recovered (OR, 0.10; 95% CI, 0.02–0.49).

Conclusions. MRSA USA300 genotype, the predominant cause of community-associated MRSA infections in our area (Atlanta, GA), has now emerged as a significant cause of health care–associated and nosocomial BSI. MRSA USA300 as a nosocomial pathogen presents new challenges to infection control programs.

The incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) infection in the United States and worldwide has dramatically increased over the past 3 decades [1]. MRSA is endemic in most US hospitals and long-term care facilities. MRSA accounts for about 60% of *S. aureus* isolates recovered from patients admitted to the intensive care unit in the United States [2]. In recent reports, MRSA caused 4.6%–19% of health care–associated bloodstream infections (BSIs) [3, 4], and a meta-analysis suggested a significantly higher mortality for MRSA bacteremia, compared with methicillin-susceptible *S. aureus* bacteremia [5].

MRSA has traditionally been a nosocomial pathogen. However, over the past few years, MRSA has emerged as an important cause of community-associated infections in both pediatric and adult populations [6–24]. Community-associated MRSA (CA-MRSA) infections have occurred in the absence of health care–associated risk factors traditionally associated with MRSA infection [6, 8, 25] and have predominantly involved skin

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and soft tissue [1, 16]. CA-MRSA isolates have been reported to possess a novel staphylococcal chromosomal cassette *mec* element (SCC*mec*IV), which is smaller than the SCC*mec* found in the isolates usually responsible for health care–associated MRSA (HA-MRSA) infections [26]; and unlike HA-MRSA isolates, CA-MRSA isolates frequently contain genes encoding for Panton-Valentine leukocidine (PVL), a leukocyte-killing exotoxin linked to development of furuncles, cutaneous abscesses, and severe necrotic infections [27].

Among MRSA isolates recovered from patients in the United States, 8 distinct clusters were originally identified by PFGE and designated USA100–USA800 [28]. Of these, PFGE types USA300 and USA400 were from CA-MRSA infections, while the others were from HA-MRSA infections. A recent study at our institution demonstrated that 72% of all *S. aureus* skin and soft tissue infections in patients with community onset of infection were caused by MRSA, and that 87% of these MRSA isolates represented CA-MRSA strains (99% of which were PFGE type USA300) [19]. Despite the reported increase in prevalence of CA-MRSA infections, it has not been known to what extent the CA-MRSA strains USA300 and USA400 cause nosocomial infections, especially BSIs. The purpose of our study was to assess whether USA300 strains were a cause of MRSA bacteremia, to assess whether they were a common cause of nosocomial and health care–associated infections, and to determine risk factors associated with BSI due to the USA300 genotype.

PATIENTS, MATERIALS, AND METHODS

Case Definitions and Case Ascertainment

The study took place at Grady Memorial Hospital, a 1000-bed, urban, public hospital in Atlanta, Georgia. The institutional review board at Emory University and the Grady Memorial Hospital Research Oversight Committee approved the study. Prospective laboratory surveillance for blood cultures positive for MRSA was performed during 7.5 months in 2004. *S. aureus* identification and antimicrobial resistance testing for all isolates were performed in the Grady Memorial Hospital microbiology laboratory according to Clinical and Laboratory Standards Institute standards [29]. A case of MRSA BSI was defined by the first MRSA-positive blood culture (index culture). A second positive blood culture for the same patient defined a new case only if the blood sample for that second index culture was recovered during a subsequent hospitalization >28 days after the first index culture. Medical, laboratory, and pharmacy records were abstracted to collect patient demographic information; past medical history was recorded, including information on substance abuse, prior MRSA infections, HIV serologic status, past or present health care–associated risk factors, time between admission and collection of the sample for the index culture, hospital location where the sample for the index culture was obtained, other bacteriological studies performed during hospitalization, length of stay, and death due to any cause during the hospital stay. "Health care–associated" was defined using previously published definitions [6, 8, 25], which include nosocomial infection (defined below, in this paragraph) or the presence of any of the following health care–associated risk factors within the year prior to the index culture: (1) receipt of systemic antimicrobial treatment, (2) residence in a long-term care facility, (3) prior admission to an acute care facility, regardless of the duration of hospitalization (excluding clinic visits), (4) use of central intravenous catheters or long-term venous access devices, (5) use of urinary catheters, (6) use of other long-term percutaneous devices (i.e., thoracostomy tubes, nephrostomy tubes, biliary drains, percutaneous endoscopic gastrostomy tubes, traction pins, and external fixtures), (7) prior surgical procedures, and/or (8) need for any form of dialysis. Nosocomial (i.e., hospital-onset) infection was defined by an MRSA-positive culture of a blood sample obtained >48 h after admission. Community-onset infection was defined by an MRSA-positive culture of a blood sample obtained from an outpatient or from an inpatient within 48 h of admission. Health care–associated infections included both community-onset and nosocomial infections. CA-MRSA infection was defined by a community-onset infection in the absence of the health care–associated risk factors described above.

Antimicrobial Susceptibility Testing

In vitro antimicrobial susceptibility testing was done using the Vitek legacy system (bioMérieux) according to manufacturer's instructions and with the Kirby-Bauer disk diffusion method, if needed, in accordance with Clinical and Laboratory Standards Institute standards [29]. Tests to determine inducible clindamycin resistance (the D-zone test) were not performed. Reports of intermediate antimicrobial susceptibility (defined as an MIC of gentamicin of >2 μg/mL but <16 μg/mL, an MIC of erythromycin of >0.5 μg/mL but <8 μg/mL, and an MIC of levofloxacin of >1 μg/mL but <8 μg/mL) and resistant *S. aureus* were grouped as "non-susceptible."

Molecular Typing Studies

Restriction-enzyme digestion, PFGE, and cluster analysis. After restriction-enzyme digestion was performed with *Sma*I (Roche Molecular Biochemicals), PFGE of MRSA isolates was performed. Gel photographs were digitized and saved as TIFF files for analysis with BioNumerics Software (Applied Maths). Cluster analysis was performed using unweighted pair-group methodology based on Dice coefficients. PFGE type clusters were defined using a coefficient of similarity of 80%. MRSA isolates were assigned to PFGE type clusters as described elsewhere [28].

Table 1. Univariate analysis of patient characteristics from past medical history that are risk factors for the recovery of methicillin-resistant *Staphylococcus aureus* (MRSA) USA300 genotype.

Patient characteristic	Patient group			OR	95% CI	*P*
	All cases (N = 116)	Infection due to the USA300 genotype (n = 39)	Infection due to other genotypes[a] (n = 77)			
Demographic data						
Age in years, mean (range)	47 (0–92)	42 (0–65)	50 (0–92)	0.98[b]	0.95–1.00	.03
Male sex	72 (62)	27 (69)	45 (58)	1.60	0.71–3.62	.26
Race and/or ethnicity						
African American	95 (82)	30 (77)	65 (84)	0.62	0.23–1.62	.32
White	16 (14)					
Other	5 (5)					
Admission from private residence	84 (72)	33 (85)	51 (66)	2.80	1.04–7.54	.04
Incarcerated	9 (8)	3 (8)	6 (8)	0.99	0.23–4.17	1.00[c]
Substance abuse history						
Cocaine use	31 (27)	14 (36)	17 (22)	1.98	0.85–4.61	.11
Injection drug use	19 (16)	11 (28)	8 (10)	3.39	1.23–9.31	.01
Health care–associated risk factors[d]						
Antimicrobial use	98 (84)	26 (67)	72 (94)	0.14	0.05–0.43	<.001
Residence in long-term care facility	17 (15)	1 (3)	16 (21)	0.10	0.01–0.79	.01[c]
Hospitalization	65 (56)	14 (36)	51 (66)	0.29	0.13–0.64	.002
Use of an indwelling device						
CVC or long-term venous access device	66 (57)	10 (26)	56 (73)	0.13	0.05–0.31	<.001
Urinary catheter	39 (34)	6 (15)	33 (43)	0.24	0.09–0.65	.003
Other long-term percutaneous device	34 (29)	4 (10)	30 (39)	0.18	0.06–0.56	.001[c]
Surgery	69 (59)	12 (31)	35 (45)	0.53	0.24–1.20	.13
Dialysis	21 (18)	4 (10)	17 (22)	0.40	0.13–1.29	.13[c]
Community-associated infection[e]	9 (8)	9 (23)	0 (0)	…	…	<.001[c]
History of prior MRSA infections						
BSI	17 (15)	3 (8)	14 (18)	0.38	0.10–1.39	.17[c]
Any	36 (31)	12 (31)	24 (231)	0.98	0.43–2.26	.97

NOTE. Unless otherwise noted, data are no. (%) of cases. CVC, central intravenous catheter.

[a] Other MRSA genotypes included PFGE types USA100, USA500, and USA800, which have been traditionally associated with health care–associated infection [28].

[b] OR per year.

[c] Fisher's exact test; 2-sided *P* value.

[d] In the 12 months prior to hospital admission.

[e] Defined by an index culture (first blood culture positive for MRSA) within 48 h of admission and the absence of health care–associated risk factors within 1 year prior to the index culture.

SCC*mec *element type assignment and PVL genotyping. SCC*mec* genotyping of MRSA isolates was performed using a multiplex PCR method as described elsewhere [30]. The presence of *lukS-PV* and *lukF-PV* genes coding for PVL in MRSA isolates was determined by PCR as described elsewhere [27].

Statistical analysis. Univariate and multivariate analyses were performed using SAS software, version 8.2 (SAS Institute). A case-control study was carried out to assess risk factors associated with recovery of MRSA USA300 from patients with MRSA BSIs. Patients in the case group had MRSA BSI due to the USA300 genotype; patients in the control group had BSI due to HA-MRSA genotypes (i.e., non-USA300 or non-USA400 genotypes), including PFGE types USA100, USA500, and USA800. In addition, risk factors for crude in-hospital mortality rates were assessed in a separate analysis using a case-control study design. In this analysis, patients in the case group were those with MRSA BSI who died of any cause during the hospital stay; patients in the control group were those with MRSA BSI who survived to the time of hospital discharge. Potential risk factors were first assessed by univariate analysis. Proportions were compared using Pearson χ^2 test and Fisher's exact test, as appropriate. For dichotomous variables, the Mantel-Haenszel ORs and corresponding 95% CIs were calculated. Variables significantly associated with the outcome of interest (PFGE type USA300 and increased risk of death) in univariate analysis, potential effect modifiers and confounders were entered in the respective multivariate models. Multivariate analysis was performed using an unconditional logistic regression model. Possible two-way interactions among main effect variables and confounding were examined. The final model was derived by

Table 2. Univariate analysis of patient characteristics from their current hospitalization that are risk factors for the recovery of methicillin-resistant *Staphylococcus aureus* (MRSA) USA300 genotype.

Patient characteristic	Patient group			OR	95% CI	*P*
	All cases ($N = 116$)	Infection due to the USA300 genotype ($n = 39$)	Infection due to other genotypes[a] ($n = 77$)			
Clinical syndrome at time of index culture						
Endocarditis	7 (6)	3 (8)	4 (5)	1.52	0.32–7.16	.69[b]
Pulmonary infection	20 (17)	8 (21)	12 (16)	1.40	0.52–3.77	.51
Urinary tract infection	15 (13)	4 (10)	11 (14)	0.69	0.20–2.31	.77[b]
SSTI	33 (28)	21 (54)	12 (16)	6.32	2.62–15.25	<.001
Secondary BSI	47 (41)	22 (56)	25 (32)	2.69	1.22–5.95	.01
SSTI as source of BSI	28 (24)	19 (49)	9 (12)	7.18	2.81–18.32	<.001
Other medical conditions at time of index culture						
HIV infection	26 (22)[d]	11 (28)	15 (19)	1.62	0.66–3.98	.29
Diabetes mellitus	30 (26)	7 (18)	23 (30)	0.51	0.20–1.33	.17
Noninfectious skin condition	13 (11)	3 (8)	10 (13)	0.56	0.14–2.16	.54[b]
Course of hospitalization						
Nosocomial MRSA infection[c]	49 (42)	10 (26)	39 (51)	0.34	0.14–0.78	.01
Time between admission and index culture						
Mean	8.7	4.2	11.0	0.96	0.93–1.00	.059[e]
Median (range)	1 (0–118)	0 (0–53)	2 (0–118)			
Blood for index culture drawn in intensive care unit	22 (19)	3 (8)	19 (25)	0.25	0.07–0.92	.04[b]
Length of stay				1.00	0.99–1.00	.59[e]
Mean	30.2	27.5	31.6			
Median (range)	18.8 (1–241)	19 (1–241)	18 (1–163)			
Crude in-hospital mortality	25 (22)	3 (12)	22 (88)	0.21	0.06–0.75	.009[b]

NOTE. Unless otherwise noted, data are no. (%) of cases. BSI, bloodstream infection; SSTI, skin and soft tissue infection.

[a] Other MRSA genotypes included PFGE types USA100, 500, or 800, which have been traditionally associated with health care–associated infection [28].

[b] Fisher's exact test; 2-sided *P* value.

[c] Defined by an index culture (first blood culture positive for MRSA) obtained >48 h after admission (hospital-onset infection).

[d] The mean CD4 cell count was 71 cells/μL, and the median cell count was 28 cells/μL (range, 0–241 cells/μL).

[e] Two-sided, unpaired *t* test *P* value.

incorporating a hierarchical backward elimination approach. Goodness of fit for the final logistic regression model was assessed. A *P* value of $\leq$.05 was defined as statistically significant.

RESULTS

A total of 132 cases of MRSA BSI were observed in 128 patients during the 7.5–month study period, for an incidence of 6.79 cases per 1000 patient admissions. A total of 116 MRSA isolates were available for further study. There was no statistically significant difference in demographic characteristics between the 16 cases without isolates available and the 116 cases with isolates available for genotyping (data not shown).

Patient and infection characteristics. Patient demographic information and other characteristics of the 116 cases of MRSA BSI are shown in table 1 and table 2. The mean age of patients was 47 years, 62% were male, 38% were female, and 82% were African American. Seventy-two percent of patients were admitted from a private residence. There were 7 patients (6%) with endocarditis evidenced by echocardiogram findings; 22% were HIV seropositive, with a median CD4 cell count of 28 cells/μL. There were 107 cases (92%) with at least one health care–associated risk factor as defined in the Methods section, and only 9 (8%) did not have any and were classified as community-associated infection (figure 1). Sixty-seven (58%) MRSA BSIs were community-onset (of which 58 occurred in patients with $\geq$1 health care–associated risk factor and 9 were community-associated) and 49 (42%) MRSA BSIs were nosocomial, defined by index cultures obtained >48 h after admission of the patient (figure 1). The mean length of hospital stay was 30.2 days (median, 18 days; range, 1–241 days). The crude in-hospital mortality rate was 22%.

Genotyping of MRSA isolates. Molecular typing results of MRSA isolates by PFGE and PCR are shown in tables 3 and 4, and PFGE cluster analysis is shown in figure 2. A total of 39 (34%) of 116 MRSA isolates were PFGE type USA300; 34 (29%) were USA100; 42 (36%) were USA500; and 1 (1%) was

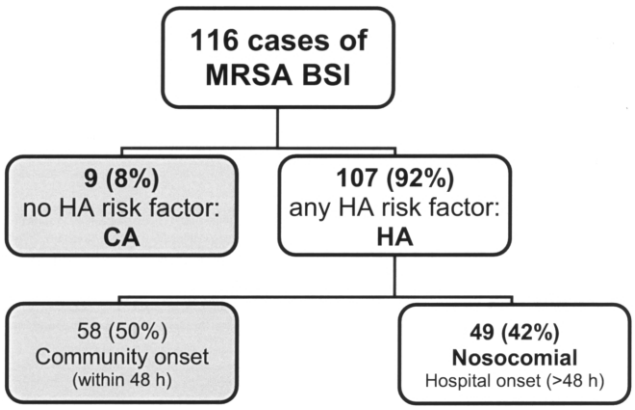

Figure 1. Categorization of methicillin-resistant *Staphylococcus aureus* blood stream infections (BSIs) by epidemiologic characteristics. For definitions, see Methods. There were a total of 67 (58%) cases of community-onset infection (9 were community-associated [CA] and 58 health care–associated [HA]).

USA800. All isolates could be assigned to 1 of these 4 PFGE types, and there were no USA200, USA400, USA600, or USA700 isolates recovered from patients with MRSA bacteremia. Thirty (28%) of 107 isolates from health care–associated cases (i.e., those from patients with ⩾1 health care–associated risk factor) and 10 (20%) of the 49 nosocomial MRSA isolates were the USA300 genotype (table 3).

All isolates of the USA300, USA500, and USA800 genotypes carried the SCC*mec*IV element, and all isolates with PFGE type USA100 carried the SCC*mec*II element (table 4). All USA300 isolates were positive for the PVL genes *lukS-PV* and *lukF-PV*. None of the USA100, USA500, or USA800 isolates contained PVL genes (table 4). HIV infection was significantly more common among the cases with USA300 and USA500 genotypes than the cases with PFGE type USA100 (26 [32%] of 82 vs. 0 [0%] of 34; $P < .001$). The mean and median time from admission to index culture for cases with isolates that had the SCC*mec*IV element (for USA300, a mean of 4.1 days and a median of 0 days, and for USA500, a mean of 5.6 days and a median of 0 days) were significantly shorter than the time for cases infected with USA100 isolates carrying SCC*mec*II (mean, 18.0 days; median 8.0 days) (OR, 1.06 per day; 95% CI, 1.01–1.11; $P = .01$). The crude in-hospital mortality rate was lowest among patients infected with MRSA USA300, compared with patients infected with the USA100 or USA500 genotypes (3 [8%] of 39 vs. 22 [29%] of 76; OR, 0.21 for USA300 vs. the other PFGE types; 95% CI, 0.06–0.75) (table 4).

Antimicrobial susceptibility. All MRSA isolates were vancomycin-susceptible. MRSA blood isolates with the health care–associated genotypes USA100, USA500, or USA800 were significantly more likely to be nonsusceptible to antibacterials other than β-lactams and erythromycin (i.e., clindamycin, levofloxacin, rifampin, gentamicin, and trimethoprim-sulfamethoxazole) compared with USA300 isolates (74 [96%] of 77 vs. 12 [31%] of 39; OR, 55.50; 95% CI, 14.54–211.89; $P < .001$).

Univariate analysis. Demographic and clinical characteristics associated in univariate analysis with the recovery of the USA300 genotype, compared with those associated with the recovery of the traditional health care–associated genotypes USA100, USA500, and USA800 are shown in tables 1 and 2. These include younger age, admission to the hospital from a private residence, injection drug use, the absence of any health care–associated risk factors, BSI secondary to a skin and soft tissue infection, and lower mortality. Conversely, residence in a long-term care facility, previous hospitalization, systemic antimicrobial use, nosocomial BSI, and current hospitalization in an intensive care unit were factors less likely to be associated with the recovery of the USA300 genotype (tables 1 and 2).

Multivariate analysis. In a multivariate analysis, independent risk factors for recovery of MRSA USA300 from blood culture included concurrent skin and soft tissue infection (OR, 3.67; 95% CI, 1.10–12.28) and injection drug use (OR, 4.26; 95% CI, 1.08–16.84). Patients who had lived in a long-term care facility (OR, 0.09 for USA300; 95% CI, 0.01–0.82) and persons who had a history of antimicrobial use (OR, 0.10 for USA300; 95% CI, 0.02–0.49), both within the prior year, were significantly less likely to have had PFGE type USA300 recovered (table 5). Multivariate analysis for independent risk factors associated with in-hospital mortality is shown in table 6.

DISCUSSION

Over the past few years, MRSA has emerged as a cause of community-associated infections among patients without the traditional risk factors associated with health care contact [6–24]. CA-MRSA genotypes appear to have evolved in the community as opposed to having spread from the health care en-

Table 3. Distribution of pulsed-field gel electrophoresis (PFGE) types among methicillin-resistant *Staphylococcus aureus* (MRSA) isolates recovered from bloodstream infection cases.

PFGE type	No. (%) of cases ($N = 116$)	No. (%) of cases with HA risk factors[a] ($n = 107$)	No. (%) of nosocomial cases[b] ($n = 49$)
USA300	39 (34)	30 (28)	10 (20)
USA100	34 (29)	34 (32)	21 (43)
USA500	42 (36)	42 (39)	18 (37)
USA800	1 (1)	1 (1)	0 (0)

NOTE. HA, health care–associated.

[a] Cases with HA risk factors were defined by an index culture (first blood culture positive for MRSA) >48 h after hospital admission or by the presence of any HA risk factors within 1 year prior to the index culture; HA cases include both community-onset cases of infection and HA risk factors as well as nosocomial cases of infection.

[b] Nosocomial cases of infection were defined by an index culture obtained >48 h after admission (hospital-onset).

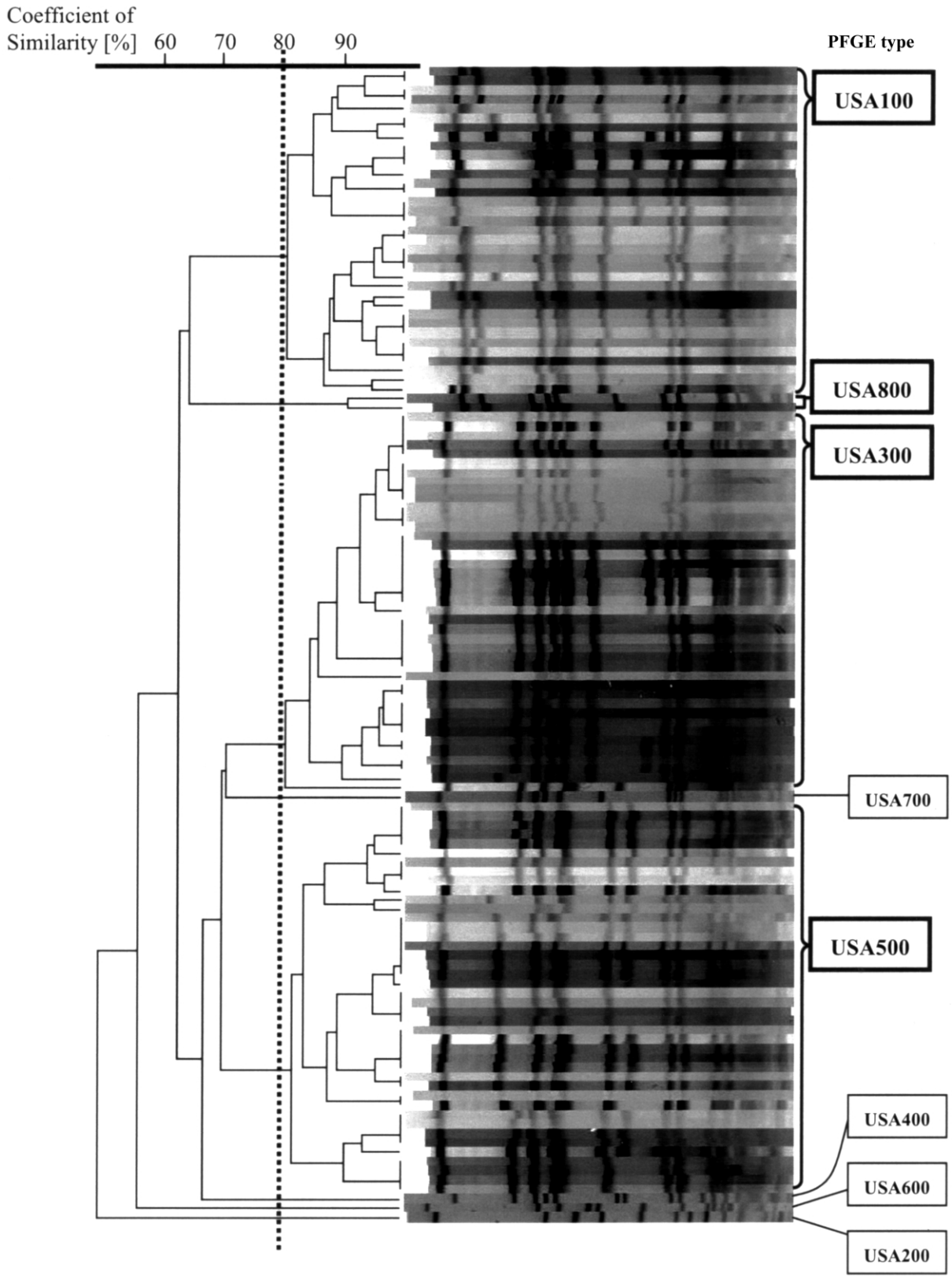

Figure 2. Dendrogram of PFGE types for methicillin-resistant *Staphylococcus aureus* (MRSA) recovered from patients with bloodstream infections (BSIs) at Grady Memorial Hospital, Atlanta, Georgia. PFGE types determined by molecular typing of 116 MRSA-BSI isolates are grouped with their respective Centers for Disease Control and Prevention standards [28]; unweighted pair-group methodology based on Dice coefficients was used. PFGE type clusters are shown from top to bottom: USA100, 34 isolates; USA800, 1 isolate; USA300, 39 isolates; USA500, 42 isolates. All isolates recovered from MRSA BSIs could be assigned to 1 of these 4 PFGE types. No USA700, USA400, USA600, pr USA200 isolates were detected.

Table 4. Selected characteristics of 116 methicillin-resistant *Staphylococcus aureus* (MRSA) isolates recovered from cases of blood stream infection, by pulsed-field gel electrophoresis (PFGE) type.

PFGE type	No. of isolates	SCC*mec* element type[a]	PVL genes present[a]	Time to index culture, in days[b]		No. (%) of HIV-seropositive patients	Crude in-hospital mortality, no. (%) of patients who died
				Mean	Median		
USA300	39	IV	Positive	4.1	0	11 (28)	3 (8)[c]
USA100	34	II	Negative	18.0	8[c]	0 (0)[c]	12 (35)
USA500	42	IV	Negative	5.6	0	15 (36)	10 (24)
USA800	1	IV	Negative	0	0	0	0

[a] There was no variation of SCC*mec* element type or presence of PVL genes *(lukS-PV* and *lukF-PV)* within the PFGE type clusters.

[b] Days from hospital admission to index culture.

[c] Statistically significant difference when compared to the 2 other major genotypes in univariate analysis, $P < .05$ (the single case with a USA800 genotype was excluded for these analyses).

vironment. Evidence to support this comes in part from the fact that CA-MRSA PFGE types USA300 and USA400 contain the novel SCC*mec*IV element, which is considerably smaller than SCC*mec* elements I, II, and III, which are found in traditional HA-MRSA strains [26]. The smaller SCC*mec*IV element may enable more-efficient horizontal transfer and a potentially faster growth rate. These factors may be related to the emergence and explosive spread infection due to CA-MRSA strains in the United States and other countries [10, 31, 32].

CA-MRSA has been described primarily in patients with skin and soft tissue infections [1, 16]. At our institution, we have noted that 72% of community-onset *S. aureus* skin and soft tissue infections were caused by MRSA, 87% of which were caused by CA-MRSA strains [19]—almost exclusively the USA300 genotype. The frequency of other types of infections due to CA-MRSA genotypes has been unclear. The very first reports of CA-MRSA infection described patients with severe pneumonia and BSI, with some fatal outcomes [6, 7]. More recently, cases of necrotizing pneumonia and necrotizing fasciitis have been linked to PVL-producing MRSA strains [21, 24]. To date, there have been limited data on the potential of CA-MRSA genotypes to cause nosocomial infections. Saiman et al. [33] described a total of 8 postpartum women who developed skin and soft tissue infections due to MRSA USA400 between 4 and 73 days after delivery; all but 1 developed the infection after being discharged from the hospital. Kourbatova et al. [34] recently reported a cluster of MRSA USA300–associated prosthetic joint infections at our institution.

Our current investigation demonstrates that infection due to CA-MRSA USA300 has emerged as a major cause of health care–associated and nosocomial MRSA BSI. We have shown with molecular typing studies that the MRSA USA300 genotype

Table 5. Multivariate analysis of risk factors associated with methicillin-resistant *Staphylococcus aureus* bloodstream infections due to the USA300 genotype.

Risk factor	OR (95% CI)	*P*
Concurrent skin and soft-tissue infection	3.67 (1.10–12.28)	.04
Injection drug use	4.26 (1.08–16.84)	.04
Antimicrobial use within past 12 months	0.10 (0.02–0.49)	.004
Residence in long-term care facility within past 12 months	0.09 (0.01–0.82)	.03
Blood for index culture drawn in the intensive care unit	0.50 (0.11–2.30)	.37
Indwelling device[a]	0.55 (0.17–1.77)	.31
Nonsurgical procedure[b]	0.21 (0.04–1.22)	.08

NOTE. The model controls for collecting blood in the intensive care unit, indwelling device, and nonsurgical procedures within 12 months. No significant interaction was detected during multivariate analysis. The main risk factor was concurrent skin and soft-tissue infection; important confounders were collection of blood in the intensive care unit, having an indwelling device, undergoing a nonsurgical procedure, and antimicrobial use, all within 12 months prior to having an index culture performed.

[a] Indwelling devices include central intravenous catheters, long-term venous access devices, urinary catheters, and other long-term percutaneous devices.

[b] Nonsurgical procedures include cardiac catheterization, arterial angiogram, upper endoscopy, colonoscopy, bronchoscopy, tracheostomy, bone marrow biopsy, and renal biopsy.

Table 6. Multivariate analysis of risk factors associated with overall mortality.

Risk factor	OR (95% CI)	*P*
Blood for index culture drawn in the intensive care unit	16.61 (4.44–62.18)	<.001
Age >55 years	8.09 (2.02–32.50)	.003
Female sex	3.88 (1.23–12.20)	.02
HIV seropositive	3.90 (0.76–20.15)	.10

NOTE. The model controls for HIV seropositivity.

accounted for more than one-third of MRSA BSIs, including 28% of 107 HA–MRSA BSIs, and 20% of 49 nosocomial MRSA BSIs. Even though 58% of the cases were community-onset disease, as evidenced by the results of index culture samples obtained within 48 h after admission, only 9 cases of 116 did not have any health care–associated risk factors. Thus, the PVL-positive USA300 genotype is no longer solely a cause of community-associated infections, but it has also been introduced into our health care facility and causes a significant proportion of health care–associated and nosocomial MRSA infections at our institution.

In multivariate analysis, independent risk factors for recovery of the USA300 genotype from patients with MRSA BSI included concurrent skin and soft tissue infections (OR, 3.67) and injection drug use (OR, 4.26). Both risk factors have been linked to CA-MRSA infections in previous reports [16, 35–37]. The association of infection due to USA300 with these specific comorbidities may be related to the presence of PVL as a virulence factor in USA300 isolates and suggests that specific types of health care exposure may play a role in the transmission of USA300 strains. In addition, for some patients with health care–associated infection but not nosocomial infection, acquisition of the MRSA USA300 genotype may have occurred in the community. Patients who resided in a long term care facility (OR for USA300, 0.09) and those who had had systemic antimicrobial treatment (OR, 0.10) within the prior year were less likely to have PFGE type USA300 recovered and more likely to have one of the "traditional" health care–associated genotypes (USA100, USA500, or USA800) recovered.

These findings demonstrate that our current infection control practices, aimed at the prevention of MRSA infection spread from patients with symptomatic disease and mainly limited to the hospital setting, may not be sufficient to contain this highly adaptive organism. A recent report by our group demonstrated that >7% of patients admitted to our institution were colonized with MRSA at the time of hospital admission; one-third of them (2.2% of all admissions) were colonized with the USA300 genotype [38]. Such patients may have served as a source of introduction of MRSA USA300 into health care settings with subsequent cross-transmission. Alternatively, some patients may have been colonized with MRSA USA300 before they arrived, and they subsequently developed nosocomial infection after hospitalization. Whether the routine implementation of the "search and destroy" strategy (performing active surveillance cultures for MRSA and isolating those who are infected or colonized), as suggested by the Society for Healthcare Epidemiology of America [39], will be able to control the prevalence of MRSA infection in areas of endemicity is still being debated [40], and routine surveillance is not part of the current guidelines for isolation precautions in hospitals, which were recommended by the Centers for Disease Control and Prevention [41]. An ongoing, randomized, controlled trial on the effect of performing routine surveillance cultures for MRSA and vancomycin-resistant *Enterococcus* species by the Bacteriology and Mycology Study Group of the National Institute of Allergy and Infectious Diseases/National Institutes of Health may provide the data needed to assess whether these measures should be included in future guidelines.

MRSA BSIs were common at our institution, with a rate of 6.79 infections per 1000 hospital admissions, higher than those reported from other institutions, which ranged from 10 cases in 5 years at a university hospital in Germany [42] to 2.10 cases per 1000 intensive care unit admissions at a 1060-bed university hospital in Belgium [43], and, more recently, 0.44 cases per 1000 hospital admissions in an 850-bed community hospital in Italy [44] and 1.48 cases per 1000 hospital admissions in 17 Australian hospitals [32]. This may, in part, be related to the high prevalence of both community- and hospital-onset MRSA infection and predisposing factors, such as low socioeconomic status and injection drug use, in the community served by our institution [19, 22].

The crude in-hospital mortality rate of 22% we found is on the lower side of the range reported by previous studies on *S. aureus* BSI (the median mortality rate for MRSA BSI reported in a recent meta-analysis of 31 cohort studies was 32%, with a range of 0%–83.3% [5]). Reasons for this may be the relatively young average age of patients and the frequent inclusion of vancomycin in the empirical antimicrobial regimen for gram-positive bacteria recovered from blood cultures at our institution. Multivariate analysis for independent risk factors associated with mortality identified treatment in an intensive care unit (OR, 16.61), an age of >55 years (OR, 8.09), as well as female sex (OR, 3.88). Comorbidity, age, and female sex all have been associated with increased risk of death in a previous study of *S. aureus* bacteremia, which also demonstrated a large proportion of community-associated disease [45].

In conclusion, BSIs due to MRSA USA300 isolates containing PVL genes have been introduced into the hospital environment from the community. Infection with this genotype now accounts for 20% of all nosocomial and 28% of all health care–associated MRSA BSIs at our institution. The emergence of MRSA USA300 in the community and its status as a major

cause of health care–associated bacteremias present new and additional challenges to infection control programs.

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