

# Characterization of methicillin-resistant *Staphylococcus aureus* isolates from patients with persistent or recurrent bacteremia

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**BACKGROUND:** Methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infections (BSI) are associated with considerable morbidity and mortality, especially with persistent (PB) or recurrent bacteremia (RB).

**OBJECTIVE:** To determine the frequency of PB and RB in patients with MRSA BSI, and to characterize the isolates from these patients.

**METHODS:** Surveillance for MRSA BSI was performed for one year in 13 Canadian hospitals. PB was defined as a positive blood culture that persisted for  $\geq 7$  days; RB was defined as the recurrence of a positive blood culture  $\geq 14$  days following a negative culture. Isolates were typed using pulsed-field gel electrophoresis (PFGE). Vancomycin susceptibility was determined using Etest.

**RESULTS:** A total of 183 patients with MRSA BSI were identified; 14 (7.7%) had PB and five (2.7%) had RB. Ten (5.5%) patients were known to have infective endocarditis, and five of these patients had PB or RB. Initial and subsequent MRSA isolates from patients with PB and RB had the same PFGE type. There were no significant differences in the distribution of PFGE types in patients with PB or RB (37% CMRSA-2/USA100; 37% CMRSA-10/USA300) compared with that in other patients (56% CMRSA-2/USA100; 32% CMRSA-10/USA300). All isolates were susceptible to vancomycin, but patients with PB or RB were more likely to have initial isolates with vancomycin minimum inhibitory concentration = 2.0  $\mu\text{g/mL}$  (26% versus 10%;  $P=0.06$ ).

**CONCLUSIONS:** Persistent or recurrent MRSA bacteremia occurred in 10.4% of patients with MRSA BSIs. Initial isolates from patients with persistent or recurrent MRSA BSIs were more likely to exhibit reduced susceptibility to vancomycin, but were not associated with any genotype.

**Key Words:** Bacteremia; Bloodstream infection; Methicillin-resistant *Staphylococcus aureus*; MRSA

Invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections may be associated with persistent or recurrent bacteremia, and these complications are often associated with increased mortality, prolonged duration of hospitalization and increased costs (1-4). Studies have identified variables associated with persistent staphylococcal bloodstream infection; however, few have described microbial characteristics associated with persistence or recurrence of MRSA bacteremia (1,4-7). In the present study, we characterized bloodstream isolates of MRSA to determine whether specific microbial characteristics were associated with persistence or recurrence.

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## La caractérisation des isolats de *Staphylococcus aureus* résistant à la méthicilline chez les patients atteints de bactériémie persistante ou récurrente

**HISTORIQUE :** Les infections sanguines (IS) par le *Staphylococcus aureus* résistant à la méthicilline (SARM) s'associent à une morbidité et une mortalité considérables, particulièrement en présence d'une bactériémie persistante (BP) ou récurrente (BR).

**OBJECTIF :** Déterminer la fréquence de BP et de BR chez les patients atteints d'une IS par le SARM et en caractériser les isolats.

**MÉTHODOLOGIE :** Les chercheurs ont surveillé les IS par le SARM dans 13 hôpitaux canadiens pendant un an. La BP se définissait par une hémoculture positive qui persistait au moins sept jours, tandis que la BR désignait la récurrence d'une hémoculture positive au moins 14 jours après une hémoculture négative. Les chercheurs ont typé les isolats au moyen de l'électrophorèse sur gel en champ pulsé (ECP). Ils ont déterminé la susceptibilité à la vancomycine par Etest.

**RÉSULTATS :** Les chercheurs ont retracé un total de 183 patients ayant une IS par le SARM. De ce nombre, 14 (7,7 %) avaient une BP et cinq (2,7 %), une BR. Dix patients (5,5 %) étaient atteints d'une endocardite infectieuse diagnostiquée, dont cinq avaient une BP ou une BR. Les isolats initiaux et subséquents de SARM chez les patients ayant une BP ou une BR présentaient le même type d'ECP. Il n'y avait pas de différence significative dans la distribution des types d'ECP chez les patients ayant une BP ou une BR (37 % de souche CSARM-2/USA100; 37% de souche CSARM-10/USA300) par rapport à celle des autres patients (56 % de souche CSARM-2/USA100; 32 % de souche CSARM-10/USA300). Tous les isolats étaient susceptibles à la vancomycine, mais les patients atteints d'une BP ou d'une BR étaient plus susceptibles de présenter des isolats initiaux de vancomycine dont la CMI = 2,0  $\mu\text{g/mL}$  (26 % par rapport à 10 %;  $P=0,06$ ).

**CONCLUSIONS :** Les chercheurs ont observé une BP ou une BR par le SARM chez 10,4 % des patients atteints d'une IS par le SARM. Les isolats initiaux des patients atteints d'une IS persistante ou récurrente par le SARM risquaient davantage d'être moins susceptibles à la vancomycine, mais ne s'associaient à aucun génotype.

## METHODS

### Surveillance methods and definitions

Thirteen hospitals in Ontario conducted prospective laboratory-based surveillance for MRSA bacteremia in adults ( $\geq 18$  years of age) from January 1 to December 31, 2011. Persistent bacteremia was defined as MRSA bacteremia of  $\geq 7$  days duration (2,3). Recurrent MRSA bacteremia was defined as a recurrence of the bacteremia  $\geq 14$  days after documented negative blood cultures (4). Patients with infective endocarditis based on modified Duke's criteria (8) were identified. Blood cultures were obtained at the discretion of the attending physician.

**TABLE 1**  
**Characteristics of blood culture isolates from patients with methicillin-resistant *Staphylococcus aureus* bacteremia**

	All patients (n=183)	Persistent/recurrent bacteremia		P
		Yes (n=19)	No (n=164)	
Isolates tested*	122 (66.7)	19 (100)	103 (62.8)	
PFGE type				
CMRSA-2/USA100	65 (53.3)	7 (36.8)	58 (56.3)	0.14
CMRSA-10/ USA300	40 (32.8)	7 (36.8)	33 (32.0)	0.79
Other	17 (13.9)	5 (26.3)	12 (11.7)	0.14
SCCmec type				
II	66 (54.1)	8 (42.1)	58 (56.3)	0.32
IV	52 (42.6)	10 (52.6)	42 (40.8)	0.45
Other	4 (3.3)	1 (5.3)	3 (2.9)	0.50
PVL gene detected	37 (30.3)	6 (31.6)	31 (30.1)	1.00
Vancomycin MIC, µg/mL†				
≤1.0	60 (49.2)	7 (36.8)	53 (51.5)	0.32
1.5	47 (38.5)	7 (36.8)	40 (38.8)	0.99
≥2.0	15 (12.3)	5 (26.3)	10 (9.7)	0.06
hVISA‡	8 (6.6)	2 (10.5)	6 (5.8)	0.61

Data presented as n (%) unless otherwise indicated. \*Initial blood culture isolates tested from individuals with persistent or recurrent bacteremia. †Vancomycin minimum inhibitory concentration (MIC) determined using Etest; ‡Heterogeneous intermediate vancomycin resistance (hVISA) determined using Etest GRD. PFGE Pulsed-field gel electrophoresis; PVL Panton-Valentine leukocidin; SCCmec *Staphylococcal cassette chromosome mec*

The study was approved without any requirement for patient consent by the Research Ethics Board, Sunnybrook Health Sciences Centre (Toronto, Ontario).

#### Laboratory characterization of isolates

MRSA were typed using pulsed-field gel electrophoresis (PFGE) following DNA extraction and digestion with *Sma*I (9,10). PFGE-generated profiles were digitized and analyzed using BioNumerics software version 5.10 (Applied Maths, USA). Strains designated as CMRSA-10/USA300 resemble the major community-associated clone in North America (multilocus sequence type 8, clonal complex 8); CMRSA-2/USA100 resembles common health care-associated strains (sequence type 5, clonal complex 5). The staphylococcal cassette chromosome *mec* (SCCmec) was characterized (11) and the presence of the Panton-Valentine leukocidin (PVL) gene was assessed using polymerase chain reaction (12). Antimicrobial susceptibilities to vancomycin, daptomycin and linezolid were determined using Etest (bioMérieux Inc, USA). Susceptibility testing was also performed using broth microdilution on isolates with Etest vancomycin minimum inhibitory concentration (MIC) ≥2.0 µg/mL (13). Isolates with vancomycin MIC ≥1.5 µg/mL as determined by Etest were screened for the presence of heterogeneous intermediate resistance to vancomycin (hVISA) using the Etest GRD, as recommended by the manufacturer (bioMérieux Inc) (14,15).

#### Statistical analysis

Statistical analyses were performed using SPSS version 16.0 (IBM Corporation, USA). Patient-level and microbial characteristics from individuals with or without persistent or recurrent bacteremia were compared using Fisher's exact test or the  $\chi^2$  test for categorical variables, and Student's *t* test for continuous variables.

### RESULTS

A total of 183 patients with MRSA bacteremia were identified during one year of surveillance. Sixty-nine (56.6%) were male and the median age was 64 years (range 18 to 96 years). All cases of bacteremia were monomicrobial. Fourteen (7.7%) patients had persistent MRSA

bacteremia and five (2.7%) had recurrent bacteremia. Patients with persistent bacteremia were older (mean age 66.7 years) than those with recurrent bacteremia (mean age 46.2 years) ( $P=0.003$ ). For individuals with persistent bloodstream infection, the median interval between the first and last positive blood cultures was 21 days, compared with 57 days for individuals with recurrent bacteremia. Infective endocarditis was identified in 10 (5.5%) patients: five (26.3%) with persistent or recurrent bacteremia, and five (3.0%) without persistent or recurrent bacteremia ( $P=0.007$ ).

MRSA blood culture isolates from all patients with persistent or recurrent bacteremia and from 103 patients without persistent or recurrent bacteremia were available for laboratory characterization; results are summarized in Tables 1 and 2. Slightly more than one-half (53.3%) of the MRSA isolates recovered from bacteremic patients resembled health care-associated strains (CMRSA-2/USA100) as determined using PFGE. The second most common strain was a community-associated clone (CMRSA-10/USA300), accounting for bacteremia in nearly one-third (32.8%) of patients. In all patients with persistent or recurrent bacteremia, the PFGE type of subsequent blood culture isolates was identical to that of the initial bloodstream isolate, suggesting that all recurrences represented relapses. The distribution of PFGE and SCCmec types did not differ between isolates from patients with or without persistent or recurrent bacteremia. Isolates from 37 (30%) patients had the PVL gene; however, no association with persistent or recurrent bacteremia was observed.

Isolates resistant to vancomycin, daptomycin or linezolid were not detected. Two isolates (from patients with persistent/recurrent bacteremia) had vancomycin Etest MICs of 3.0 µg/mL. However, when tested using microbroth dilution, the MICs for these isolates were 1.0 µg/mL and 1.5 µg/mL. The MICs to vancomycin of initial and subsequent blood culture isolates in patients with persistent or recurrent bacteremia did not vary significantly (Table 2). Initial blood culture isolates with vancomycin MIC ≥2.0 µg/mL as determined using Etest were more often recovered from patients with persistent or recurrent bacteremia (26.3% versus 9.7%;  $P=0.06$ ) (Table 1). There were six possible hVISA isolates identified using Etest GRD; however, this phenotype was not associated with persistent or recurrent bacteremia.

### DISCUSSION

MRSA has been associated with a greater risk for persistent bacteremia than has methicillin-susceptible *S aureus*, and persistence has been associated with worse outcomes (2,3,16). However, few studies have determined the frequency of persistent or recurrent MRSA bacteremia. In the present study, the rate of persistent MRSA bacteremia (7.7%) was similar to that reported previously (6.2% to 12.7%) (1,3). However, the rate of recurrent MRSA bacteremia (2.7%) appeared to be lower than that previously reported (10.6% to 31.8%) (1,4). The reasons for this variability in observed rates is uncertain, but may be related, in part, to differences in criteria used to determine persistence or recurrence, different thresholds for repeating blood cultures and variable patient populations included in the studies.

Several microbial characteristics have been associated with the development of persistent or recurrent MRSA bacteremia. MRSA isolates associated with persistent bacteremia were found to have *agr* locus dysfunction, and a reduced capacity to be killed in vitro by thrombin-induced platelet microbial protein (1). One study determined that MRSA with SCCmec type II were more likely to be associated with relapsing bloodstream infection (4). In the current study, neither SCCmec nor PFGE type was associated with persistence or recurrence; however, there were a relatively small number of patients with these complications.

Reduced susceptibility to vancomycin has frequently been reported to be associated with persistent and recurrent MRSA bloodstream infection (5-7). In the present study, we did not identify any strains that were resistant to vancomycin, and despite the relatively small numbers of patients with persistence or recurrence, we found that strains with a vancomycin MIC ≥2.0 µg/mL as determined using Etest

**TABLE 2**  
**Characterization of methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream isolates in patients with persistent or recurrent bacteremia**

Patient (age, years)	Bloodstream infection	Interval between first and last positive blood culture, days	MRSA type (PFGE/SCCmec/PVL)	Etest minimum inhibitory concentration, µg/mL					
				Vancomycin*		Daptomycin		Linezolid	
				First isolate	Last isolate	First isolate	Last isolate	First isolate	Last isolate
1 (76)	Persistent + IE	21	CMRSA-10/IVa/+	1.5	1.5	0.19	0.125	0.75	1.5
2 (90)	Persistent	18	CMRSA-2/II/-	0.75	1.0	0.38	0.19	0.75	1.0
3 (90)	Persistent	186	CMRSA-2/II/-	2.0	2.0	0.38	0.25	1.0	1.0
4 (68)	Persistent	9	CMRSA-2/II/-	1.5	2.0	0.25	0.19	0.5	0.75
5 (N/A)	Persistent	12	CMRSA-10/IVa/+	1.0	1.0	0.38	0.5	1.0	0.75
6 (66)	Persistent	27	CMRSA-2/II/-	1.5	2.0	0.5	0.2	1.5	1.0
7 (75)	Persistent	17	Other/IVnt/-	0.38	0.38	0.19	0.19	1.0	1.5
8 (59)	Persistent	96	CMRSA-10/IVa/+	1.5	2.0	0.38	1.5	0.5	1.0
9 (74)	Persistent	19	CMRSA-2/IVnt/-	2.0	2.0	0.38	0.5	1.0	1.0
10 (74)	Persistent	7	CMRSA-2/IVnt/-	1.0	2.0	0.38	0.38	1.0	0.5
11 (80)	Persistent	9	Other/III/-	2.0	2.0	0.38	0.38	1.0	1.0
12 (40)	Persistent + IE	7	Other/VI/-	1.0	1.0	0.19	0.25	0.5	0.5
13 (20)	Persistent + IE	9	CMRSA-10/IVa/+	1.0	1.0	0.5	0.38	0.75	0.5
14 (55)	Persistent	9	CMRSA-10/IVa/-	3.0 (1.0)	1.5 (0.5)	1.0	0.5	0.38	1.0
15 (56)	Recurrent	63	CMRSA-2/II/-	1.5	1.5	0.38	0.5	0.5	1.0
16 (46)	Recurrent + IE	57	CMRSA-10/IVa/+	1.5	1.5	0.38	0.38	0.5	0.5
17 (33)	Recurrent + IE	31	CMRSA-10/IVa/+	1.5 (0.5)	3.0 (1.5)	0.75	0.75	1.0	0.75
18 (56)	Recurrent	25	CMRSA-2/II/-	1.0	1.0	0.25	0.25	0.75	0.75
19 (41)	Recurrent	175	CMRSA-2/II/-	3.0 (1.0)	1.5 (0.5)	0.75	0.38	0.75	0.75

\*Minimum inhibitory concentrations determined using broth microdilution in parentheses. IE Infective endocarditis; N/A Information not available; PFGE Pulsed-field gel electrophoresis; PVL Panton-Valentine leukocidin; SCCmec *Staphylococcal cassette chromosome mec*

were more likely to be associated with persistent or recurrent bacteremia (Table 1). hVISA strains have also been associated with persistent or recurrent MRSA bacteremia in some (17-19), but not all, studies (20,21). These different results may be due to variability in the methods used to detect hVISA (19). In the present study, there were too few isolates that may have been hVISA to determine whether this phenotype was associated with persistent or recurrent bacteremia.

Laboratory-based surveillance involving every diagnostic laboratory in Ontario (population approximately 12.8 million) identified 560 patients with MRSA bloodstream infection in 2011 (an increase of 13% from the previous year), and MRSA represented 17% of all *S aureus* isolated from blood cultures (22). Our study included nearly one-third (32.7%) of these patients. In this cohort, persistent or recurrent bacteremia occurred in 10.4% of patients. Important study limitations include the lack of available clinical, treatment or outcome data; in addition, the length of follow-up for these patients was variable. Because cultures were obtained at the discretion of the attending physician, cases with recurrent or persistent bacteremia may have been

missed or misidentified. The small number of patients with persistent or recurrent infection may have precluded the ability to detect microbial characteristics associated with these complications. However, the present study does confirm an association between reduced susceptibility to vancomycin (as determined using Etest) and the development of persistent or recurrent MRSA bacteremia. Additional studies are required to better understand the clinical and microbial factors associated with these important complications.

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