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Predictors of Relapse of Methicillin-Resistant *Staphylococcus aureus* Bacteremia after Treatment with Vancomycin▽

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The risk factors for relapse of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia after vancomycin treatment are unknown. Diversilab typing was used to classify recurrent bacteremia as relapse or reinfection. Bacteremia for >7 days and staphylococcal cassette chromosome *mec* element (SCC*mec*) type II were independently associated with relapse of MRSA bacteremia after vancomycin treatment.

Vancomycin is recommended as the initial treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia. However, a number of studies report high rates of vancomycin failure defined as persistent bacteremia (13, 14, 19, 22, 23, 31, 33). While certain investigations have used recurrence as a component of their definition of vancomycin treatment failure (13), few have specifically explored this outcome. Prior studies of recurrent *S. aureus* bacteremia included both methicillin-susceptible and -resistant infections, used a variety of drug regimens, and did not always differentiate between relapse and reinfection (3, 4, 6, 9, 15–17, 21, 26, 27, 30).

The purpose of this study was to determine the microbial virulence determinants and patient characteristics that predict relapse of MRSA bacteremia after treatment with vancomycin. We performed a retrospective review of patients with MRSA bacteremia from August 2005 to May 2007 hospitalized at Memorial Hermann Hospital, a 700-bed tertiary care hospital. Patients who were ≥18 years old and who received >5 days of vancomycin as initial therapy for MRSA bacteremia were selected. Clinical characteristics, including age, gender, onset and source of infection, comorbidities (prior antibiotics, previous hospital and nursing home contact, immunosuppression, diabetes, liver disease, dialysis, mechanical ventilation, cardiovascular disease, and chronic obstructive pulmonary disease [COPD]), and vancomycin treatment initiation and duration, were extracted from patient medical records. Recurrence of MRSA bacteremia was defined as the return of MRSA bacteremia 2 weeks after documented negative blood cultures. The recurrence was considered a relapse if the Diversilab (DL) (bioMérieux, Durham, NC) typing results of sequential isolates were identical, defined as 95% similarity and no band differences (29). Persistent bacteremia was defined as bacteremia for >7 days. This study was approved by the Institutional Review Board for the University of Texas Health Science Center at Houston (HSC-MS-09-0076).

MICs were performed in duplicate using vancomycin, daptomycin, or linezolid Etest strips (bioMérieux) according to the manufacturer's instructions. Screening for the heterogeneously vancomycin-intermediate *S. aureus* (hVISA) phenotype was performed using the Etest macromethod (32, 33), with confirmation by population analysis profile-area under the curve (28). Testing for the *agr* type, the staphylococcal cassette chromosome *mec* element (SCC*mec*), and the Panton-Valentine leukocidin (PVL) gene was performed as previously described (11, 12, 33, 34). Data management and analysis were performed using SAS version 9.1.3 (SAS, Cary, NC). Bivariate analysis was conducted by the χ^2 test or Fisher's exact test for categorical variables. Variables with an individual effect (P value < 0.15) were tested in a multivariate logistic regression model, with assessment for multicollinearity as previously described (1).

A total of 113 adult patients with MRSA bacteremia treated with vancomycin for >5 days were identified. Twelve of these patients had recurrent MRSA bacteremia. DL typing determined that recurrent isolates were identical to the primary bloodstream isolates in 11/12 (91.7%) of the patients; these patients were thus considered to have had a relapse of MRSA bacteremia. Detailed clinical characteristics of the patients who had a relapse of MRSA bacteremia are shown in Table 1. Patient clinical characteristics, comorbidities, times until vancomycin treatment administration, and durations of vancomycin therapy did not differ between patients with and without relapse (data not shown).

The microbiologic characteristics of isolates from relapsed MRSA bacteremia compared to those from patients with a single episode are shown in Table 2. Factors significantly associated with relapse included *agr* type II ($P = 0.0006$) and SCC*mec* type II ($P = 0.0002$). The vancomycin MIC of the isolate was not associated with relapse of MRSA bacteremia. SCCmec II was present in 10/13 isolates with vancomycin MICs of >1.5 μg/ml, compared to 22/100 isolates with MICs of ≤1.5 μg/ml ($P = 0.0002$). PVL was present in 63 isolates (55.6%) and was not associated with relapse of bacteremia.

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TABLE 1. Clinical characteristics of the patients who experienced relapse of MRSA bacteremia after vancomycin treatment

Case	Bacteremia no.	Patient age (yr)	Source[a]	TEE performed[a,b]	Treatment length (days)[a]	Days to relapse	Days of bacteremia/outcome	MIC (μg/ml)[d]		
								Vanc	Dapto	Linezolid
1	1	62	Unknown	Yes	14		8	1.5	0.5	1.5
	2					14	1/death	1.5	0.5	0.75
2	1	64	Skin	Yes[c]	17		16	0.75	0.75	1
	2					16	6/death	0.5	0.5	0.5
3	1	51	Unknown	Yes	13		1	1.5	0.38	0.38
	2					102	15	2	0.5	0.38
4	1	58	Catheter	Yes	28		14	2	0.75	0.5
	2					20	22/death	3	1	0.75
5	1	62	Skin	No	17		5	1.5	0.19	1
	2					120	6	3	1	0.75
6	1	67	Unknown	Yes	30		19	1.5	0.38	0.75
	2					14	10	1.5	0.25	0.75
7	1	20	Unknown	Yes	14		1	1.5	0.38	0.75
	2					36	3	1.5	0.25	0.5
8	1	27	Respiratory	Yes	14		10	1.5	0.38	1
	2					23	20	1.5	0.38	0.75
9	1	32	Unknown	Yes	18		4	1.5	0.38	0.75
	2					41	5	1.5	0.25	0.5
10	1	18	Unknown	No	19		2	1.5	0.25	0.75
	2					45	5	1.5	0.38	0.75
	3					35	4	2	0.38	0.75
11	1	66	Multiple sites	Yes	22		14	1.5	0.38	0.75
	2					79	16/death	1.5	0.5	2

[a] Refers to the initial bacteremic episode.
[b] TEE, transesophageal echocardiogram.
[c] Endocarditis was diagnosed on the second episode of bacteremia for case 2. No other cases of endocarditis were detected.
[d] Vanc, vancomycin; Dapto, daptomycin.

The hVISA phenotype was significantly associated with relapse of MRSA bacteremia ($P = 0.009$) on bivariate analysis. Persistent bacteremia in the first bacteremic episode of patients who later had a relapse of bacteremia was significantly more likely ($P = 0.004$) than such bacteremia in patients with a single episode.

Multivariate analysis was performed to determine independent predictors of relapse of MRSA bacteremia after treatment with vancomycin. Persistent bacteremia was significantly associated with relapse (odds ratio [OR] = 10.1; 95% confidence interval [CI] = 2.0 to 49.6). SCC*mec* II was also associated with relapse of bacteremia (OR = 19.1; 95% CI = 3.3 to 110.0). DL typing of the first isolate from patients with relapsed MRSA bacteremia is shown in Fig. 1. There were at least seven different clones among the 11 patients with a relapse of bacteremia. Thus, a common clone expressing the virulence determinants identified in this study is not responsible for causing relapse of MRSA bacteremia.

Recurrence of MRSA bacteremia occurred in roughly 10% of patients in this study, consistent with other reports in the literature (4). The majority of recurrent episodes of MRSA bacteremia after vancomycin treatment in our institution were due to relapse (91.7%), as described by other investigations (4,

TABLE 2. Microbiologic characteristics of isolates from patients with multiple episodes of MRSA bacteremia compared to those from patients with a single episode[a]

Variable	No. (%) of patients with:		*P* value
	Relapse ($n = 11$)	Single episode ($n = 102$)	
agr type II	10 (90.9)	37 (36.3)	0.0006*
SCC*mec* type II	9 (81.8)	23 (22.6)	0.0002*
PVL	6 (54.6)	57 (55.9)	1.00
Vancomycin MIC of >1.5	3 (27.3)	10 (9.8)	0.11
hVISA	2 (18.2)	0 (0.0)	0.009*
Persistent bacteremia	6 (54.5)	14 (13.7)	0.004*

[a] *, statistically significant.

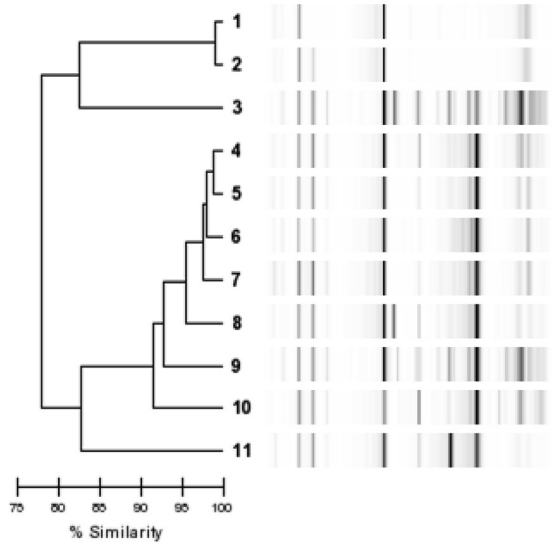

FIG. 1. Dendrogram of the first isolate from each patient with relapsed MRSA bacteremia.

7, 10). However, the possibility of reinfection with the same clone cannot be excluded. Multivariate analysis identified persistent bacteremia as an independent risk factor for later relapse of MRSA bacteremia following vancomycin treatment. It is possible that persistence of bacteremia enables the establishment of occult foci of infection. Indeed, persistence of MRSA bacteremia during treatment with vancomycin is associated with metastatic infections (23). It should be noted that all patients in this study were afebrile and clinically well prior to hospital discharge, with no evidence of metastatic infection. Persistent MRSA bacteremia despite adequate vancomycin treatment is associated with isolates with higher vancomycin MIC values, even those considered "susceptible" (13, 14, 23, 31), as well as *agr* type II (18).

This investigation additionally identified SCC*mec* type II as a predictor for relapse of MRSA bacteremia after treatment with vancomycin. Other studies have linked SCC*mec* II with mortality from *S. aureus* bacteremia (5, 8). It has been reported that isolates with SCC*mec* II may have reduced vancomycin susceptibility compared to organisms harboring other SCC*mec* types (20). Indeed, SCC*mec* II was associated with elevated vancomycin MICs in this investigation. The precise mechanism by which isolates with SCC*mec* II predispose to relapse following vancomycin treatment is unknown. In addition to having reduced vancomycin susceptibility, such isolates may have variable expression of proteins that enable persistence following antimicrobial therapy (25).

This investigation has important limitations, including its retrospective design and the focus of a single clinical site. The number of patients that experienced relapse of bacteremia was small. Thus, it is possible that some predictors of relapse were not identified; however, the identified factors associated with relapse are likely powerful predictors. DL typing used to classify recurrence as relapse or reinfection may have less discriminatory power than pulsed-field gel electrophoresis (2). Furthermore, we did not assess the impact of vancomycin dosing and serum concentrations, which are difficult to evaluate due to their high variability throughout the treatment course (24). Nonetheless, nearly 10% of patients treated with vancomycin for MRSA bacteremia experienced a relapse of bacteremia. Patients with persistent bacteremia or isolates with certain microbiologic characteristics such as SCC*mec* II should be monitored for relapse if vancomycin is used as the primary agent.

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