

Clinical and Laboratory Characteristics of Invasive Infections Due to Methicillin-Resistant *Staphylococcus aureus* Isolates Demonstrating a Vancomycin MIC of 2 Micrograms per Milliliter: Lack of Effect of Heteroresistant Vancomycin-Intermediate *S. aureus* Phenotype[∇]

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We describe clinical and laboratory characteristics of invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections with vancomycin MICs of 2 µg/ml and compare heteroresistant-intermediate *S. aureus* (hVISA) to non-hVISA. Health care-associated community-onset infections were the most common and resulted in frequent complications and relapses. hVISA-infected patients were more likely to have been hospitalized in the year prior to MRSA culture.

The emergence of clinical infections due to methicillin-resistant *Staphylococcus aureus* (MRSA) with reduced susceptibility to vancomycin, the most reliable therapeutic agent against MRSA for the past 3 decades, is alarming, but the clinical implications remain controversial (17, 24). Many health care facilities have reported an increasing prevalence of MRSA strains with vancomycin MICs of 2 µg/ml, which is at the upper limit of the Clinical and Laboratory Standards Institute (CLSI) susceptibility range (8, 21, 25), and some have detected an association of such isolates with prolonged bacteremia, greater rates of complications, and vancomycin therapeutic failures (12, 18).

In addition, MRSA with vancomycin MICs of 2 µg/ml are more likely than MRSA with vancomycin MICs of ≤1 µg/ml to represent a heterogeneous population that may include subpopulations with intermediate resistance to vancomycin (16). Designated heteroresistant-intermediate *S. aureus* (hVISA), these isolates have vancomycin MICs in the susceptible range (MIC ≤ 2 µg/ml) but contain subpopulations that express vancomycin-intermediate resistance, with MICs of 4 µg/ml or greater (11), and, like MRSA with defined intermediate resistance to vancomycin (VISA) (vancomycin MICs ≥ 4 µg/ml), hVISA strains have been associated with treatment failure and persistent or prolonged bacteremia (13). The clinical significance of MRSA with a vancomycin MIC of 2 µg/ml, in the presence or absence of hVISA, is still not fully understood, and the relationship between vancomycin MICs and clinical outcomes continues to be debated (1, 15). The variability in MIC results due to different laboratory testing methods further

complicates our understanding of this relationship (7). This report describes the clinical and laboratory characteristics of invasive infections due to MRSA isolates with vancomycin MICs of 2 µg/ml determined by reference broth microdilution (3, 4) and compares those with and without the hVISA phenotype with respect to these characteristics.

Cases of invasive MRSA infections (i.e., patients with MRSA isolated from a normally sterile site) were identified between 1 January 2005 and 31 December 2007 at 5 U.S. metropolitan areas in California, Georgia, Minnesota, New York, and Tennessee that were participating in the Centers for Disease Control and Prevention (CDC) Active Bacterial Core Surveillance (ABCs) system for invasive MRSA disease (9, 10). The ABCs methodology for surveillance of invasive MRSA disease has been described elsewhere (9, 10). Briefly, according to the ABCs methodology, a case of invasive MRSA infection is defined as identification of an MRSA strain isolated from a normally sterile body site in a resident of a surveillance catchment area. An MRSA culture from a normally sterile site obtained within 30 days of an initial MRSA culture is considered part of the same episode, whereas an invasive MRSA culture obtained more than 30 days after an initial culture is considered to represent a recurrent episode. For a convenience sample of cases of invasive MRSA, the initial invasive isolate is obtained and sent to the CDC for microbiologic and molecular characterization. Among 2,537 invasive MRSA isolates collected during the study period, a subset of 138 (5%) isolates exhibited a vancomycin MIC of 2 µg/ml by the reference broth microdilution method and are the focus of this report. All MIC testing was initially performed at the CDC upon isolate arrival, and reference broth microdilution was repeated at the onset of this study, with 100% result agreement. In addition, vancomycin MICs were determined by standard Etest methods and MICs ranged from 1.5 to 3 µg/ml (mode = 2 µg/ml). Vanco-

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TABLE 1. Demographic characteristics of patients with invasive infection due to MRSA with vancomycin MICs of 2 $\mu\text{g/ml}$ from 5 U.S. states^a

Demographic characteristic	n (%)	Median	Range
Age (yr)		61	0–97
Male	85 (62)		
Race			
White	62 (45)		
Black	55 (40)		
Other	10 (7)		
Unknown	11 (8)		
U.S. state			
GA	30 (22)		
TN	21 (15)		
MN	13 (9)		
CA	39 (28)		
NY	35 (25)		
Underlying condition			
HIV	4 (3)		
Diabetes	69 (50)		
Chronic renal failure	51 (37)		
Dialysis (past yr)	28 (20)		
Chronic liver disease	9 (7)		
Immunosuppressive therapy	10 (7)		
Solid-organ malignancy	17 (12)		
Hematologic malignancy	2 (2)		
Resident in a long-term care facility in yr prior to initial culture	42 (30)		
Past MRSA infection or colonization	45 (33)		
Surgery in yr prior initial culture	65 (47)		
Hospitalized in yr prior to initial culture	90 (65)		

^a Data from the Active Bacterial Core Surveillance for Invasive MRSA Project ($n = 138$).

mycin MICs were 1.5 $\mu\text{g/ml}$ for 48 isolates, 2 $\mu\text{g/ml}$ for 83 isolates, and 3 $\mu\text{g/ml}$ for 7 isolates. Since a standard Etest MIC of 1.5 $\mu\text{g/ml}$ can be rounded to the nearest doubling dilution for reporting purposes (i.e., MIC = 2 $\mu\text{g/ml}$), 131/138 (95%) were in agreement with the reference broth microdilution MIC of 2 $\mu\text{g/ml}$.

A standardized medical record abstraction form was used to record demographic data, clinical data, treatment, and outcome characteristics, including comorbidities, length of hospitalization, severity of illness, complications of MRSA infection, surgical treatment, and antimicrobial therapy duration. Patient characteristics, including demographics, underlying conditions, and specific health care risk factors for invasive MRSA infections, are shown in Table 1. Among 138 patients with MRSA infections with vancomycin MICs of 2 $\mu\text{g/ml}$ as identified, the median age was 61 years and 85 (62%) were male. Ninety (65%) were hospitalized in the year prior to the MRSA infection, 42 (30%) resided in a long-term care facility, 45 (33%) had a history of previous MRSA infection or colonization, and 50% had diabetes.

Cases were classified as hospital-onset (HO) when MRSA was isolated from a culture obtained more than 3 calendar days after admission (first day of admission = day 1); were classified as health care-associated community-onset (HACO) when a culture was obtained in the outpatient setting or within the first 3 calendar days after hospital admission and they had docu-

TABLE 2. Infection characteristics of patients with invasive infection due to MRSA with vancomycin MIC of 2 $\mu\text{g/ml}$ from 5 U.S. states^a

Infection characteristic	n (%)
PFGE genotype	
USA100	104 (76)
USA300	13 (10)
USA500	12 (9)
Other	7 (5)
Not typed	2 (1)
PAP-AUC determination	
hVISA (≥ 0.90 ratio to strain Mu3)	21 (15)
non-hVISA (≤ 0.89 ratio to strain Mu3)	117 (85)
Epidemiologic category	
Hospital onset (HO)	42 (30)
Healthcare-associated community onset (HACO)	86 (62)
Community associated (CA)	10 (7)
Syndrome ^b	
Bloodstream infection	115 (83)
Bloodstream infection only	62 (54)
Skin and/or soft tissue infection	24 (17)
Pneumonia	19 (14)
Osteomyelitis	13 (9)
Endocarditis	8 (6)
Surgical site infection	8 (6)
Urinary tract infection	5 (4)
Arthritis	5 (4)
Follow-up blood cultures collected ^c	58 (42)
Persistent bacteremia ^d	32 (55)
Persistent fever ^e	6 (4)
Intensive-care-unit admission after initial culture	26 (18)

^a Data from the Active Bacterial Core Surveillance for Invasive MRSA Project ($n = 138$).

^b Some cases had more than one syndrome.

^c At >24 h after initial culture.

^d Up to 7 days.

^e At least 4 days after first positive culture.

mentation of recent health care exposures; and, finally, were classified as community-associated (CA) when a culture was obtained in the outpatient setting or within the first 3 calendar days after hospital admission but no recent health care exposure was documented. Recent health care exposure was defined as the presence of a central vascular catheter (CVC) at the time of admission or documentation of any the following in the 12 months preceding the MRSA culture: a history of MRSA infection or colonization, surgery, hospitalization, dialysis, or residence in a long-term care facility as defined by Klevens et al. (9). Of the cases, 30% were HO, 62% were HACO, and only 7% were CA infections (Table 2).

Additional clinical and laboratory characteristics, including pulsed-field gel electrophoresis (PFGE) genotypes, clinical syndrome, and hospital course, are also shown in Table 2. PFGE was performed on DNA preparations from clinical isolates after digestion with the *Sma*I restriction enzyme and analyzed using Bionumerics version 5.0 (Applied Maths, Austin, TX). Samples were grouped into pulsed-field types by the use of Dice coefficients and 80% relatedness, as previously described (14). The majority of MRSA isolates (104/138 [76%]) were PFGE type USA100, a type commonly associated

TABLE 3. Outcome characteristics of patients with invasive infection due to MRSA with vancomycin MICs of 2 µg/ml from 5 U.S. states^a

Outcome	n (%)	Median	Range
MRSA-related complications ^b	48 (35)		
Type of complication ^c			
Sepsis	32 (67)		
Acute renal failure	11 (23)		
Endocarditis	5 (10)		
Internal abscess	5 (10)		
Thrombotic event	4 (8)		
Osteomyelitis	4 (8)		
In-hospital mortality	23 (17)		
Recurrent MRSA disease	16 (12)		
Length of hospital stay (days) ^d (n = 105)		14	1–193

^a Data from the Active Bacterial Core Surveillance for Invasive MRSA Project (n = 138).

^b Occurring between 3 and 30 days after initial culture.

^c Not mutually exclusive.

^d Among those who survived hospitalization and were hospitalized.

with health care infections; only 10% were USA300, a type more often associated with CA disease. Of the 138 invasive MRSA infections, 115 (83%) involved a positive blood culture and were classified as a bloodstream infection (BSI). These BSIs were not associated with other syndromes in 54% of the cases. Besides BSI, other common infection syndromes included skin and soft tissue infections (17%), pneumonia (14%), and osteomyelitis (9%) (Table 2). Follow-up blood cultures were drawn more than 24 h after the initial positive MRSA blood culture for 58 of 138 (42%) cases, and 32 of the 58 (55%) had persistent MRSA bacteremia (Table 2). Twenty-six patients (18%) were admitted to an intensive-care unit after the initial MRSA culture, and 17 (12%) required mechanical ventilation.

The primary outcome of interest was in-hospital mortality (Table 3). Secondary outcomes included MRSA-related complications in the 3-month period after the initial culture, including MRSA infections of other intravascular sites (endocarditis) and extravascular sites, organ failure (disseminated intravascular coagulation, sepsis, acute renal failure, etc.), operative procedure related to MRSA infection, recurrent MRSA disease within 3 months after hospital discharge, and length of hospital stay. Twenty-three patients died during hospitalization, with a median time to death of 13 days from the initial MRSA culture. The most common complications included septic shock (67%) followed by acute renal failure (23%), endocarditis (10%), and internal abscess (10%) (Table 3). Among the 105 patients who were hospitalized and survived, the length of hospital stay ranged from 1 to 193 days, with a median of 14 days. Overall, 12% of the patients had recurrent MRSA disease within 3 months after discharge (Table 3).

Information on antibiotic treatment during the hospitalization was available for all 128 patients who were hospitalized and is shown in Table 4. Of 128 patients, 105 (82%) received in-hospital vancomycin therapy, and the median duration of in-hospital vancomycin therapy (for both patients who survived and those who did not) was 8 days. Other antibiotics used

TABLE 4. Treatment characteristics of patients with invasive infection due to MRSA with vancomycin MICs of 2 µg/ml from 5 U.S. states^a

Antibiotic and treatment history	n (%)	Median	Range
Vancomycin	105 (82)		
Length of in-hospital therapy (days)		8	1–56
Linezolid	12 (9)		
Length of in-hospital therapy (days)		8.5	2–49
Rifampin	18 (14)		
Length of in-hospital therapy (days)		6	1–51
No. of patients discharged on therapy with antibiotic active against MRSA (n = 105) ^b	67 (64)		

^a Data from the Active Bacterial Core Surveillance for Invasive MRSA Project (treatment information available for those hospitalized; n = 128).

^b A total of 23 patients died while in the hospital.

either alone or in combination with other antistaphylococcal agents included linezolid in 9% and rifampin in 14% of cases.

Heteroresistance to vancomycin (hVISA) was evaluated for all 138 isolates by population analysis profile-area under the curve (PAP-AUC) as described by Satola et al. (19). Twenty of 138 isolates (15%) were identified as hVISA by PAP-AUC, defined as an area under the curve ratio of ≥ 0.90 compared to that of hVISA reference strain Mu3 (Table 5). Comparison of baseline characteristics between MRSA infections defined as hVISA and non-hVISA by PAP-AUC was performed using SAS 9.2 (The SAS Institute, Cary, NC); the results are shown in Table 5. Differences between categorical variables were evaluated using chi-square analysis or, where appropriate, Fisher's exact test. Differences between continuous variables were evaluated by the Wilcoxon signed-rank test. A *P* of < 0.05 for two-tailed tests was considered statistically significant. hVISA infections were more likely than non-hVISA infections to be associated with hospitalization in the year prior to growth of an invasive MRSA culture (Table 5). Most of hVISA and non-hVISA infections (75% and 71%, respectively) represented strain USA100 infections. A total of 32 patients (4 with hVISA infections and 28 with non-hVISA infections) had persistent bacteremia for up to 7 days; all of the hVISA infections exhibited a duration of bacteremia of ≥ 4 days compared to half of the non-hVISA infections (*P* = 0.06) (Table 5). Finally, a greater proportion of hVISA infections (15%) were found with an initial MRSA culture from bone or joint compared to non-hVISA infections (5%) (*P* = 0.09) (Table 5).

The clinical significance of hVISA infections remains ambiguous. The same group who reported hVISA infection to be significantly associated with treatment failure (defined as persistent bacteremia during the course of vancomycin therapy) (2, 6) also reported in a more recent study that hVISA was not associated with a higher rates of bacteremia (5), and, in all studies, hVISA infection was determined by PAP-AUC. In our study, 4 of 20 (20%) hVISA patients had persistent bacteremia and in all of them the duration was ≥ 4 days. Additional studies have shown hVISA to be associated with osteomyelitis and endocarditis (13), and the impact of this heteroresistant phenotype for deep-seated infections, where vancomycin penetration is limited, is clinically important. Interestingly, we found

TABLE 5. Comparison of patients with invasive infections due to hVISA and non-hVISA MRSA strains

Variable	hVISA (<i>n</i> = 20)	Non-hVISA (<i>n</i> = 118)	Odds ratio (95% confidence interval)	<i>P</i> value
Age (median in yr)	59	62		0.8
Black race [<i>n</i> (%)]	9 (45)	46 (39)	1.2 (0.4–3.3)	0.6
Male [<i>n</i> (%)]	11 (55)	74 (62)	1.3 (0.5–3.6)	0.5
HACO infection [<i>n</i> (%)]	14 (70)	71 (61)	1.5 (0.5–4.3)	0.4
PFGE USA100 [<i>n</i> (%)]	15 (75)	84 (71)	1.2 (0.4–3.6)	0.7
Hospitalized in prior yr [<i>n</i> (%)]	17 (85)	73 (62)	3.5 (1.01–12.6)	0.04
Resident in a long-term care facility in prior yr [<i>n</i> (%)]	9 (45)	33 (28)	2.1 (0.8–5.5)	0.2
ICU admission after initial culture [<i>n</i> (%)]	3 (15)	23 (19)	0.7 (0.2–2.7)	0.6
Duration of therapy (median [days]) ^a	8	11		0.4
Duration of vancomycin (median [days]) ^a	6	8		0.4
Discharged on antibiotic [<i>n</i> (%)]	11 (55)	56 (47)	1.4 (0.5–4.0)	0.6
MRSA-related complications [<i>n</i> (%)]	6 (30)	42 (36)	0.7 (0.3–2.2)	0.6
Surgery in yr prior to infection [<i>n</i> (%)]	7 (35)	58 (49)	0.6 (0.2–1.5)	0.2
Previous MRSA infection/colonization [<i>n</i> (%)]	10 (50)	36 (31)	2.3 (0.9–5.9)	0.08
Initial MRSA culture isolated from bone or joint [<i>n</i> (%)]	3 (15)	6 (5)	3.3 (0.8–14.4)	0.09
In-hospital mortality [<i>n</i> (%)]	3 (15)	20 (17)	0.8 (0.2–3.2)	0.8
No. of patients with persistent MRSA bacteremia for ≥4 days/total no. of patients (<i>n</i> = 32) ^b	4/4 (100)	14/28 (50)		0.06 ^c
MRSA recurrent disease [<i>n</i> (%)]	3 (12)	13 (16)	0.7 (0.2–2.8)	0.6
Length of hospital stay (mean [days])	12	14		0.3

^a Includes only patients with treatment information available.

^b A total of 32 patients had persistent bacteremia, as defined by one or more positive MRSA blood cultures >24 h after the index culture.

^c Undefined odds ratio, as 100% of hVISA cases had ≥4 days of persistent bacteremia.

hVISA infections to be more likely than non-hVISA infections to be associated with MRSA isolated from bone or joint.

Whether our data confirm or contradict other studies, the variability in vancomycin MIC testing methods should be considered, and the accuracy of susceptibility testing methods for detecting MRSA with reduced susceptibility to vancomycin is debatable (20). It can be difficult for both commercial and referenced susceptibility testing methods to differentiate between isolates which have changed biologically such that vancomycin therapy will be less effective but for which the vancomycin MIC changes may represent only a doubling in dilution (e.g., a change from 1 µg/ml to 2 µg/ml or from 2 µg/ml to 4 µg/ml) (22). Recognition of isolates with reduced susceptibility to vancomycin can be medium dependent and require conditions often not routinely used in a clinical laboratory (23).

In conclusion, in this collection of MRSA isolates from patients with invasive infections in 5 different geographic locations in the United States, only 5% of the isolates had vancomycin MICs of 2 µg/ml; of those, only 15% were hVISA by PAP-AUC. The majority of invasive infections due to MRSA with vancomycin MICs of 2 µg/ml were found to be health care-associated community-onset infections and to involve infection by PFGE type USA100. Infections due to strains with a vancomycin MIC of 2 µg/ml were mostly BSIs, and complications, persistent bacteremia, relapse, and in-hospital mortality were common. A significant percentage of hospitalized patients (64%) were discharged with antibiotics active against MRSA. However, it is still unclear how these clinical and outcome characteristics differ from those MRSA infections with a vancomycin MIC < 2 µg/ml. Hospitalization in the year prior to growth of an invasive MRSA culture was the only factor found to be significantly associated with hVISA infections. However, a higher proportion of patients with hVISA infections compared to those with non-hVISA infections had a history of prior MRSA infection or colonization, had initial

cultures from bone or joint, had bacteremia greater than 4 days, and had been hospitalized in the prior year. No differences in clinical outcomes between patients with hVISA and non-hVISA infections were observed in this study, indicating that there is insufficient evidence to recommend routine hVISA testing for patient management. However, continued surveillance to follow the changing patterns of vancomycin MICs among clinical MRSA isolates would be prudent to evaluate whether any effect of reduced susceptibility on clinical characteristics and outcomes of serious MRSA infections becomes apparent.

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