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Anthony M. Casapao

N. Leonard

Susan L. Daivs

Thomas P. Lodise

Nimish Patel

*See next page for additional authors*

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### Authors

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# Clinical Outcomes in Patients with Heterogeneous Vancomycin-Intermediate *Staphylococcus aureus* Bloodstream Infection

**Anthony M. Casapao,[a] Steven N. Leonard,[c] Susan L. Davis,[a,d] Thomas P. Lodise,[e] Nimish Patel,[e] Debra A. Goff,[f,g] Kerry L. LaPlante,[h,i] Brian A. Potoski,[j,k] Michael J. Rybak[a,b]**

Anti-Infective Research Laboratory, Pharmacy Practice Department, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, Michigan, USA[a]; School of Medicine, Wayne State University, Detroit, Michigan, USA[b]; Bouvé College of Health Sciences, School of Pharmacy, Northeastern University, Boston, Massachusetts, USA[c]; Department of Pharmacy Services, Henry Ford Hospital, Detroit, Michigan, USA[d]; Department of Pharmacy Practice, Albany College of Pharmacy and Health Sciences, Albany, New York, USA[e]; Department of Pharmacy, The Ohio State University Medical Center, Columbus, Ohio, USA[f]; Pharmacy Practice and Administration, The Ohio State University College of Pharmacy, Columbus, Ohio, USA[g]; Department of Pharmacy Practice, The University of Rhode Island College of Pharmacy, Kingston, Rhode Island, USA[h]; Infectious Diseases Research Program, Veterans Affairs Medical Center, Providence, Rhode Island, USA[i]; Department of Pharmacy and Therapeutics, University of Pittsburgh School of Pharmacy, Pittsburgh, Pennsylvania, USA[j]; Antibiotic Management Program, University of Pittsburgh Medical Center, Presbyterian University Hospital, Pittsburgh, Pennsylvania, USA[k]

**The prevalence of heterogeneous vancomycin-intermediate *Staphylococcus aureus* (hVISA) infections varies in the literature, a problem complicated by the lack of routine screening procedures; however, limited data suggest that hVISA has been associated with persistent bloodstream infections (BSI) and vancomycin failure, yet these studies have been confounded by design issues. We conducted this study to compare the characteristics of patients with BSI caused by hVISA with those with vancomycin-susceptible *Staphylococcus aureus* (VSSA) treated with vancomycin. This retrospective, multicenter matched (1:1) cohort study compared the clinical characteristics and outcomes of hVISA and VSSA. Patients with hVISA methicillin-resistant *Staphylococcus aureus* (MRSA) BSI from 2004 to 2012 were matched to VSSA-MRSA BSI patients. The primary outcome was failure of vancomycin treatment, defined as a composite of persistent bacteremia (≥7 days), persistent signs and symptoms, change of MRSA antibiotic, recurrent BSI, or MRSA-related mortality. We identified 122 matched cases. The overall vancomycin failure rate was 57% (82% hVISA versus 33% VSSA; $P < 0.001$). The individual components of failure in hVISA versus VSSA were persistent bacteremia, 59% versus 21% ($P < 0.001$); change in MRSA therapy, 54% versus 25% ($P = 0.001$); MRSA-related mortality, 21% versus 10% ($P = 0.081$); and recurrence of BSI, 26% versus 2% ($P < 0.001$). Using logistic regression analysis and adjusting for covariates, hVISA (adjusted odds ratio [aOR], 11.1; 95% confidence interval [CI], 4.3 to 28.7) and intensive care unit (ICU) admission (aOR, 4.5; 95% CI, 1.8 to 11.6) were still independently associated with vancomycin failure. Relative to VSSA BSI, patients with hVISA were more likely to experience failure of vancomycin treatment, including persistent bacteremia and recurrence. Our results indicate that hVISA was responsible for considerable morbidity.**

Methicillin-resistant *Staphylococcus aureus* (MRSA) infections continue to pose a dilemma in the hospital environment as well as in the community setting (1, 2). Vancomycin has been the primary treatment for infections caused by MRSA; however, reduced susceptibility to vancomycin has emerged in vancomycin-intermediate *S. aureus* (VISA) and vancomycin-resistant *S. aureus* (VRSA) as well as heterogeneous vancomycin-intermediate *S. aureus* (hVISA), compromising the utility of this antibiotic (3–5). In previous studies, the prevalence of the hVISA phenotype has ranged from 0 to 29.2% of MRSA isolates. Several factors may influence the wide variance in prevalence, including geographical area, site of infection, and screening/detection methods (macro-Etest versus population analysis profile) (6–11). In contrast to VISA or VRSA strains, hVISA strains are often undetected since these organisms are considered vancomycin susceptible on the basis of traditional MIC testing performed by clinical microbiology laboratories (12–14). The gold standard for detecting hVISA is the modified population analysis profile (mPAP), referencing the area under the curve (AUC) of the test strain to hVISA control strain Mu3 (15). Due to the labor-intensive nature of the PAP method and the lack of standardization by the Clinical and Laboratory Standards Institute (CLSI), it is not routinely performed as a screening/detection method for hVISA. The inability to detect subpopulations with reduced vancomycin susceptibility in routine practice makes accurate estimation of the prevalence and clinical impact of hVISA difficult to establish.

Understanding and managing patients with hVISA is a major therapeutic challenge, because it has been shown that patients with hVISA infections are likely to fail therapy with vancomycin (14, 16, 17). A recent systematic review and meta-analysis evaluated the significance of hVISA and reported a 2.37-fold-increased risk of glycopeptide failure (95% confidence interval [CI], 1.53 to 3.67) compared to vancomycin-susceptible *S. aureus* (VSSA) (8). This is even more concerning considering that hVISA has been linked to high bacterial load infections, prolonged fever and bacteremia, and increased hospital length of stay (10, 18, 19). Other clinical characteristics that have been correlated with hVISA are elevated vancomycin MICs (e.g., >1 mg/liter) and prior vancomycin use (6, 17, 19, 20).

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Address correspondence to Michael J. Rybak, m.rybak@wayne.edu.

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Prior studies have associated hVISA with poorer outcomes; however, these studies differed in detection methods and outcome analysis, making it difficult to determine the true significance of hVISA. Further, the severity of illness and frequency of high-risk infection sources among hVISA patients complicated the ability to directly compare their outcomes to those of patients with VSSA infections. Therefore, we investigated the morbidity and mortality of a multicenter cohort of patients with bloodstream infection (BSI) caused by hVISA and compared the results to those of patients with VSSA treated with vancomycin by matching patients according to infection source. A secondary aim was to correlate success or failure on the basis of organism characteristics such as vancomycin susceptibility including heteroresistance, MIC, genetic polymorphism (*agr* and staphylococcal cassette *mec* [SCC*mec*] type), delta-hemolysin activity, and vancomycin trough concentrations in serum.

(An abstract containing results from this study was presented in platform format at the 52nd Interscience Conference on Antimicrobial Agents and Chemotherapy [ICAAC] in San Francisco, CA, on 10 September 2012.)

## MATERIALS AND METHODS

**Study design and population.** This was a retrospective, multicenter (the Detroit Medical Center, the Ohio State University Medical Center, the Albany Medical Center, the University of Pittsburgh Medical Center, and the Veterans Affairs Medical Center in Providence, RI), matched (1:1) cohort study comparing the outcomes of hVISA infections versus VSSA infections in patients with MRSA BSI treated with vancomycin from January 2004 to August 2012. The institutional review board at each of the participating medical centers approved the study. MRSA BSI patients were defined as patients with MRSA in blood cultures that met the Centers for Disease Control and Prevention (CDC) criteria for primary bloodstream infection (21). Adult patients aged $\geq$18 years identified from clinical blood cultures positive for MRSA with susceptible vancomycin MIC ($\leq$2 mg/liter) and who received vancomycin for $\geq$72 h were eligible for inclusion in this study. Patients with hVISA were matched 1:1 to VSSA patients based on age group ($<$50 years, 50 to 70 years, and $>$70 years), site of infection (including concomitant site of MRSA infection), and year of infection ± 2 years.

**Microbiological and molecular data.** For patients with multiple MRSA blood cultures, the first MRSA isolate for each patient was obtained for extensive microbiology evaluation at the Anti-Infective Research Laboratory (Detroit, MI). Vancomycin MIC was determined by broth microdilution performed in agreement with CLSI guidelines using the current susceptible breakpoint of $\leq$2 mg/liter and the Etest method according to the manufacturer's instructions (bioMérieux, Durham, NC) (22).

A random selection of 1,249 MRSA bloodstream isolates from all involved institutions were initially screened using the Macro Etest method described by Wootton and colleagues (15, 23) and confirmed by vancomycin mPAP. Vancomycin mPAP was determined on all strains at an inoculum of approximately $1 \times 10^8$ CFU/ml. Fifty microliters of this suspension was plated on vancomycin containing BHI at increasing concentrations (0, 0.5, 1, 1.5, 2, 3, 4, and 8 mg/liter) using an automated spiral dispenser (Whitley Automated Spiral Plater, Bon Whitley Scientific, West Yorkshire, United Kingdom). After incubation at 35°C for 48 h, colony counts ($\log_{10}$ CFU/ml) were determined using a laser colony counter (ProtoCOL; Synbiosis, Cambridge, United Kingdom). The AUC was determined for each test isolate and compared to the AUC of the reference strain, Mu3 (ATCC 700698). The test isolate was considered an hVISA or VSSA if the population analysis profile area under the curve (PAP-AUC) ratio of the test isolate to Mu3 was $\geq$0.9 or $<$0.9, respectively, as previously described by Wootton and colleagues (6, 15).

The staphylococcal cassette *mec* (SCC*mec*) type and the *agr* group for the isolates were characterized using multiplex PCR, as described elsewhere (24, 25). The expression of the *agr* gene cluster was determined by quantitating delta-hemolysin production utilizing a previously described method by cross-streaking test strains perpendicular to RN4220 as previously described (26).

**Data collection.** Patient data collection included baseline demographics such as age, sex, comorbidities, hospitalization history within 180 days before admission, receipt of prior antibiotic therapy ($>$48 h in the previous 30 days), use of concomitant antibiotics, concurrent sites of MRSA infection, acute physiology and chronic health evaluation II (APACHE II) score, and Charlson comorbidity index at the first positive blood culture. Additional data collected were duration of bacteremia, pharmacokinetic variables (dosing and vancomycin concentrations in serum), length of hospital stay, and infection outcomes including duration of signs and symptoms and 30-day mortality. Calculation of vancomycin AUC/MIC was estimated from the daily dose given during the first 24 h of therapy divided by clearance derived from previous literature (27). The concomitant site with MRSA infection was determined by assessment of other MRSA-positive cultures at the time of onset of MRSA and/or clinical description by the treating physician in the medical record.

**Outcome assessment.** For the purposes of data analysis, patients were stratified into 2 groups according to the presence of hVISA (hVISA versus non-hVISA [VSSA]). Thirty-day MRSA-related mortality, time to clearance of MRSA from the bloodstream, resolution of signs and symptoms of infection, and length of hospital stay after the first positive blood culture were assessed. The length of hospital stay was defined as the number of days after the onset of infection. Failure of vancomycin treatment was defined by the following criteria: (i) nonresolving bacteremia for at least 7 days while on vancomycin (17, 20, 28); (ii) new onset or worsening of signs or symptoms of infection while on vancomycin therapy (7, 28); (iii) either change of MRSA intravenous antibiotic or addition to vancomycin of a second antimicrobial agent targeted against MRSA, necessitated by lack of resolution (2, 29, 30); and (iv) recurrent BSI defined as a positive blood culture for MRSA within 60 days of completion of antimicrobial therapy (30). Death was considered to be attributed to MRSA infection as described previously (28, 31) if one of the following criteria was present: (i) blood cultures were positive for MRSA at the time of death, (ii) death occurred before resolution of signs and symptoms of MRSA infection, (iii) death occurred 14 days after the onset of MRSA without another explanation, (iv) autopsy findings indicated MRSA as a cause of death, and (v) MRSA was indicated as a cause of death on the death certificate. Length of hospital stay after the onset of infection was defined as the time from the first MRSA-positive culture until discharge or death (31).

**Statistical analysis.** Categorical variables were compared by McNemar's test, continuous variables were compared by paired Student's *t* test, and ordinal variables were compared by the Wilcoxon signed rank test. Appropriateness of age matching was examined by paired Student's *t* test. Multivariable analyses were performed to determine the independent association of vancomycin treatment failure while adjusting for confounding variables. All variables significantly associated with the outcome on univariate analysis ($P \leq 0.2$) were included in the explanatory multivariable model using a backward stepwise approach. All tests were two-tailed, and $P$ values of $<$0.05 were considered to be statistically significant. SPSS Statistics, IBM SPSS software, version 20.0 (SPSS Inc., Chicago, IL), was used for all calculations.

## RESULTS

We identified and included 61 matched pairs during the study period that met the criteria, for a total of 122 BSI. All 122 patients received vancomycin for initial treatment for MRSA BSI for at least 72 h, and the median duration of vancomycin treatment was 9 days (interquartile range [IQR], 5 to 14). The primary sources of infection for these cases were as follows: infective endocarditis, 48 patients (39.3%); pneumonia, 10 patients (8.2%); intravenous (IV) catheter-related infection, 30 patients (24.6%); bone and

**TABLE 1** Baseline demographic and clinical features of MRSA associated with hVISA compared to VSSA[a]

| Feature | hVISA ($n = 61$) | VSSA ($n = 61$) | $P$ value |
|---|---|---|---|
| Baseline demographics | | | |
| Age (mean yr ± SD) | 57.5 ± 14.3 | 56.5 ± 16.7 | 0.745 |
| Weight (kg) | 72.6 (63–87.3) | 75 (67.9–85) | 0.278 |
| Creatinine clearance (ml/min) | 41.1 (18–82.1) | 55 (29.6–95.3) | 0.134 |
| APACHE II score | 12 (8–18) | 10 (7–15) | 0.251 |
| Charlson index | 3 (1–4) | 2 (1–4) | 0.404 |
| Female sex | 30 (49.2) | 21 (34.4) | 0.099 |
| ICU admission | 29 (47.5) | 23 (37.7) | 0.272 |
| Previous hospitalization | 32 (52.5) | 34 (55.7) | 0.716 |
| Previous surgery | 4 (6.6) | 10 (16.4) | 0.088 |
| Previous antibiotics | 30 (49.2) | 24 (39.3) | 0.274 |
| Previous VAN | 13 (21.3) | 11 (18) | 0.649 |
| Prior MRSA infection | 9 (14.8) | 8 (13.1) | 0.794 |
| Renal disease | 28 (45.9) | 26 (42.6) | 0.715 |
| Chronic kidney disease | 6 (9.8) | 8 (13.1) | 0.570 |
| Hemodialysis | 17 (27.9) | 10 (16.4) | 0.127 |
| Diabetes | 20 (32.8) | 16 (26.2) | 0.427 |
| Decubitus ulcer | 11 (18) | 3 (4.9) | 0.044 |
| Injection drug user | 17 (27.9) | 19 (31.1) | 0.691 |
| Prosthetic device/hardware | 4 (6.6) | 4 (6.6) | 1.00 |
| Clinical characteristics | | | |
| VAN BMD MIC, 2 mg/liter | 18 (29.5) | 7 (11.7) | 0.015 |
| VAN Etest MIC, >1 mg/liter | 43 (71.7) | 32 (53.3) | 0.038 |
| VAN duration (days) | 8 (5–15) | 9 (5–15) | 0.640 |
| VAN initial trough ($n = 109$) | 12.1 (6.8–18.3) ($n = 56$) | 11.7 (8.4–16) ($n = 53$) | 0.790 |
| Initial VAN trough, ≥15 mg/liter | 20 (35.7) | 14 (26.4) | 0.295 |
| AUC/MIC | 445.4 (282.3–855) | 467 (344–728.4) | 0.605 |
| AUC/MIC, ≥400 | 34 (55.7) | 39 (63.9) | 0.356 |
| SCC*mec* type II | 28 (46.7) | 20 (33.3) | 0.136 |
| *agr* group II | 29 (48.3) | 28 (46.7) | 0.855 |
| *agr* dysfunctional activity | 11 (19.3) | 11 (19.3) | 1.000 |
| Clinical outcomes | | | |
| Duration of bacteremia (days) | 7 (3–11) | 4 (2–7) | 0.003 |
| Duration of signs/symptoms (days) | 3 (1–10) | 2 (1–3) | 0.031 |
| Length of stay (days) | 24 (14–44.5) | 16 (9.5–30.5) | 0.022 |
| Length of stay after first positive blood culture (days) | 22 (12–39) | 13 (9–28) | 0.021 |

[a] Values are followed by percentage in parentheses for categorical data, unless otherwise specified; median values are followed by the interquartile range in parentheses. BMD, broth microdilution; VAN, vancomycin; AUC, area under the concentration-time curve over 24 h.

joint infections, 18 patients (14.8%); skin and soft tissue infection, 12 patients (9.8%); and unknown source, 4 patients (3.3%). Overall, 40 (32.8%) patients received source control, and there was no difference between hVISA and VSSA groups in source control: 32.8% versus 32.8%, respectively ($P > 0.99$). Within the specific primary source of infection, no statistical difference was found between hVISA and VSSA. There were no differences in baseline demographics and clinical characteristics of patients with hVISA and VSSA except for two characteristics (Table 1). Presence of hVISA was significantly associated with decubitus ulcers ($P = 0.044$) and a vancomycin MIC of >1 mg/liter by the Etest method ($P = 0.038$) compared to VSSA. However, there was no statistical difference between patients with hVISA and VSSA with respect to age, severity of illness (APACHE II), Charlson comorbidity index, or history of vancomycin use, hospitalization, and MRSA infection. Vancomycin concentrations in serum did not differ between the two groups, with median initial vancomycin trough concentrations in serum of 12.1 mg/liter (IQR, 6.8 to 18.3 mg/liter) and 11.7 mg/liter (IQR, 8.4 to 16 mg/liter) for the hVISA and VSSA groups, respectively ($P = 0.790$). The vancomycin MIC distribution determined by broth microdilution and Etest susceptibility methods and the hVISA frequency are presented in Fig. 1 and 2, respectively.

Overall vancomycin treatment failure was 57.3% (70/122), and patients with hVISA were associated with a significantly higher vancomycin treatment failure (82%) than patients with VSSA (32.8%; $P < 0.001$) (Fig. 3). Of interest, each criterion for vancomycin treatment failure was more common with hVISA: persistent bacteremia (59% versus 21.3%, $P < 0.001$), change or addition of anti-MRSA antibiotic (54.1% versus 24.6%, $P = 0.001$), and recurrence of MRSA BSI after 60 days from end of treatment (25.5% versus 1.9%, $P < 0.001$). Signs and symptoms were more prolonged, by an average of 1 day, in the hVISA group than in the VSSA group with a median of 3 days (IQR, 1 to 10) versus 2 days (IQR, 1 to 3), respectively ($P = 0.031$). Median duration of bacteremia was 3 days longer in the hVISA group than in the VSSA group: 7 days (IQR, 3 to 11.5) versus 4 days (IQR, 2 to 7), respectively ($P = 0.003$). Thirty-day MRSA infection-related mortality

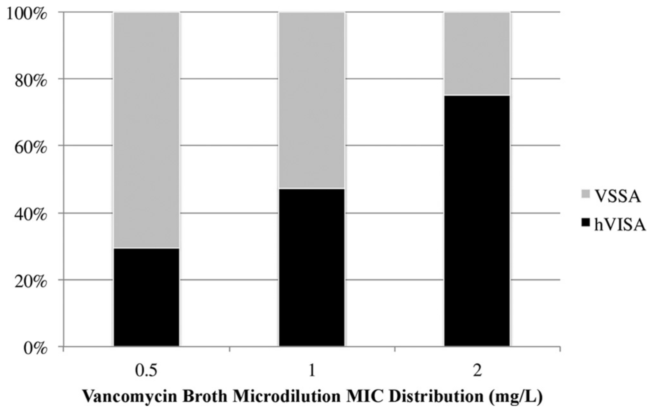

**FIG 1** Vancomycin MIC distribution by the broth microdilution method and hVISA frequency for all MRSA isolates.

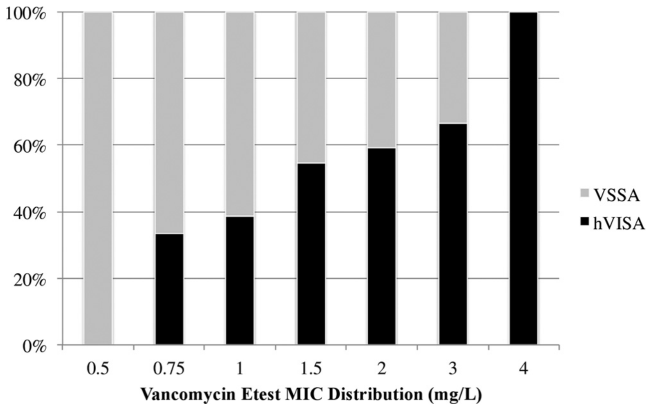

**FIG 2** Vancomycin MIC distribution by the Etest method and hVISA frequency for all MRSA isolates.

was doubled in the group with hVISA infection, yet its incidence was not statistically significant compared to VSSA-related mortality (21.3% versus 9.8%, respectively; $P = 0.081$). Likewise, no difference in all-cause 30-day mortality was detected between hVISA and VSSA patients (24.6% versus 11.5%, respectively; $P = 0.076$). Compared to VSSA, hVISA was associated with longer total hospital length of stay (median difference of 8 days, $P = 0.022$) as well as longer length of stay after the onset of infection (average difference of 9 days, $P = 0.021$). Overall, a total of 47 cases (38.5%) were treated with an alternative agent to vancomycin or with combination therapy. Of these, 33 cases (70.2%) switched to daptomycin as an alternative agent; 23 (48.9%) of these were in the hVISA group versus 10 (21.3%) in the VSSA group. The remaining alternative agents used were intravenous trimethoprim-sulfamethoxazole (4 cases, 8.5%), intravenous linezolid (5 cases, 10.6%), and gentamicin in combination with vancomycin (5 cases, 10.6%).

Characteristics associated with vancomycin treatment failure in univariate and multivariable analyses are shown in Tables 2 and 3. No relationship with vancomycin treatment failure was identified, with initial vancomycin trough concentrations in serum of $<$15 mg/liter compared to $\geq$15 mg/liter, 60% versus 55.9%, respectively ($P = 0.686$). Additionally, there was no relationship of vancomycin treatment failure, with an AUC$_{24}$/MIC (ratio of area under the concentration curve over 24 h divided by the MIC) of $<$400 compared to $\geq$400, 59.2% versus 56.2%, respectively, ($P = 0.741$). There was a higher frequency of hVISA and ICU admission among the patients with vancomycin treatment failure than of successful treatment in the univariate analyses. These covariates along with APACHE II score, SCC*mec* type II, renal disease, and high-risk infection source (31) (infective endocarditis, pneumonia, or bone and joint infection) were evaluated in the logistic regression model, and three covariates remained in the model. Heterogeneous vancomycin-intermediate *Staphylococcus aureus* (adjusted odds ratio [aOR], 11.1; 95% CI, 4.3 to 28.7) and intensive care unit admission (aOR, 4.5; 95% CI, 1.8 to 11.6) were independently associated with vancomycin treatment failure.

## DISCUSSION

Our study implies that the odds of vancomycin treatment failure were 11 times greater for a patient with hVISA BSI than for a patient with VSSA BSI. Similar to what was reported in previous literature, vancomycin treatment failure was common in MRSA bacteremia and was more pronounced in patients infected with hVISA. Prior studies reported comparable failure proportions with a range from 68.4% to 100% of hVISA infections (10, 17, 32–34), using similar definitions of vancomycin treatment failure. The most frequently observed component of failure was persistent bacteremia, which was a commonly used criterion in other studies (16–18, 20, 33). Change of vancomycin to an alternative therapy (e.g., daptomycin) or addition of another anti-MRSA antibiotic (e.g., gentamicin) was also a common contributor to the vancomycin failure rate. This criterion of the composite for vancomycin treatment failure has been included in a previous study (29) but has not always been considered in the MRSA bacteremia literature. All of our 33 patients with hVISA and 13/15 patients with VSSA that changed in MRSA therapy were also deemed to have experienced failure of vancomycin treatment by persistent bacteremia. The remaining 2 VSSA cases that had a change in MRSA therapy occurred before 2008, indicating that the change may be due to an overall poor clinical response to vancomycin and not necessarily to an elevated high vancomycin MIC as noted in the recommendations of the 2011 MRSA clinical practice guidelines by the Infectious Diseases Society of America (2). Another important outcome in patients with hVISA for vancomycin treatment failure was recurrence of MRSA BSI 60 days from the end of therapy. The percentage of 60-day recurrence that we observed was similar to that reported by Lodise and colleagues (13%) in a single-center cohort of MRSA bacteremia (30). However, this is the first study that evaluated recurrence and found an association with hVISA infection.

Despite the association with prolonged bacteremia, prolonged symptoms, and recurrence, this study did not observe a difference in 30-day MRSA-related mortality associated with hVISA. The overall 30-day MRSA infection-related mortality in this group of MRSA BSI was 15.6%, which is lower than rates reported by other studies, which range from 17.3% to 28.4% (7, 17, 20). While patients with hVISA infection had a higher mortality rate than patients with VSSA, this did not reach statistical significance. Since hVISA is associated with factors known to influence mortality such as high vancomycin MIC, persistent bacteremia, and recurrence of BSI, one might expect an increased mortality compared to that of VSSA BSI. One explanation for the lack of a mortality difference in our study is that the sample size was chosen to detect

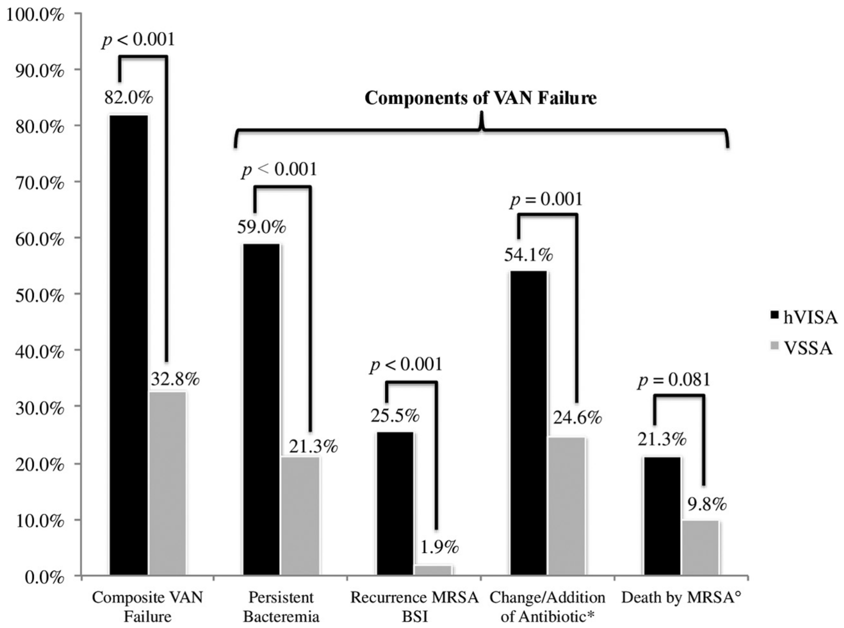

**FIG 3** Comparison of hVISA and VSSA for composite vancomycin treatment failure. VAN, vancomycin; MRSA, methicillin-resistant *Staphylococcus aureus*; BSI, bloodstream infection; *, change of MRSA intravenous antibiotic or addition to vancomycin of a second antimicrobial agent targeted against MRSA; °, 30-day mortality MRSA infection related.

a difference in vancomycin failure and not specifically infection-related mortality. However, the observed phenomenon may also be related to hVISA strain characteristics that contribute to persistence, rather than virulence. It has been suggested that hVISA and VISA strains have reduced virulence factors, leading to a decreased host immune response, resulting in reduced mortality but an increase in persistent infections (35, 36). van Hal and colleagues recently reported that the presence of hVISA is an independent predictor of survival, specifically in ST239 MRSA strains (19). In contrast, our current findings did not find hVISA to be correlated with survival. No molecular typing (e.g., *spa* typing or pulsed-field gel electrophoresis) was completed for this study, as the clonal relatedness of isolates is unlikely to have a direct influence on response to therapy; however, identification of specific MRSA clones would be advantageous for epidemiological purposes.

High vancomycin MIC has also been associated with hVISA in the literature (6, 19, 20) and is consistent with our findings indicating that the frequency of hVISA increases with vancomycin MIC by both broth microdilution and Etest methods. Our Etest method displayed statistical significance with patients with hVISA when MICs were greater than 1 mg/liter, analogous to the results of Musta and colleagues (20). Prior literature in MRSA bacteremia suggests that high vancomycin MIC is associated with treatment failure (37). However, our data indicated that a vancomycin Etest MIC of >1 mg/liter had higher treatment failure but the difference was not statistically significant (66.7% versus 56.9%; $P = 0.273$) compared to treatment success; therefore, these data may imply that hVISA BSI irrespective of vancomycin MIC may fail on vancomycin treatment. Patients with hVISA had similar proportions of having adequate vancomycin trough concentrations and an $AUC_{24}$/MIC of >400. However, these patients still had a higher proportion of treatment failure. Rose and colleagues have previously demonstrated using *in vitro* pharmacokinetics and pharmacodynamics models that even high-dose vancomycin exposure (5 g IV every 12 h; $AUC_{24}$/MIC for the free, unbounded fraction of vancomycin [$fAUC_{24}$/MIC], 799) did not result in a significant impact on hVISA strains (38).

We controlled for potential confounding variables by matching in this retrospective multicenter cohort study; however, this study does have some limitations. First, all of these MRSA isolates were obtained from the first positive culture for screening and identification of hVISA by mPAP, which could overlook hVISA arising in subsequent cultures. Second, although the macro Etest method for screening for hVISA has been found to have a high specificity (39), it is possible that some hVISA strains may be misclassified as negative; however, all strains were confirmed by mPAP for matching purposes if the macro Etest initially identified the strain as VSSA or hVISA. It was not possible to complete the removal of the source of infection in all patients, and this confounding factor may affect our primary outcome since it was not controlled by our matching design. The small sample size precludes extensive analysis of confounding factors; nonetheless, this multicenter study is the first matched-cohort comparative study of hVISA confirmed by the gold standard of mPAP, representing a significant advancement in the available evidence (15). Finally, selection bias is a potential concern with clinical outcomes in retrospective studies when vancomycin susceptibility has been identified; however, clinicians were unaware of hVISA presence, thus not altering therapy or management during hospitalization.

In conclusion, the results propose that patients with MRSA BSI caused by hVISA are at increased risk of vancomycin treatment failure. Irrespective of high vancomycin MIC, hVISA is independently associated with vancomycin treatment failure. One of the major issues for identifying patients infected with this organism is the lack of a reliable and minimized-labor commercial product for routine screening. Current methods are expensive, lack sufficient sensitivity, are labor-intensive,

**TABLE 2** Univariate analysis of clinical features of MRSA associated with vancomycin treatment failure[a]

| Feature | Success ($n = 52$) | Failure ($n = 70$) | $P$ value |
|---|---|---|---|
| Patient characteristics | | | |
| Age (mean yr ± SD) | 56.7 ± 17.9 | 57.2 ± 13.5 | 0.868 |
| Weight (kg) | 75.3 (67.2–86.4) | 72.6 (63–86.8) | 0.303 |
| Creatinine clearance (ml/min) | 52.8 (28.1–93.9) | 49 (19.8–89) | 0.669 |
| APACHE II score | 10 (6–14.8) | 11.5 (8–18) | 0.174 |
| Charlson index | 2 (0.5–3) | 3 (1–5) | 0.090 |
| Female sex | 22 (42.3) | 29 (41.4) | 0.922 |
| ICU admission | 13 (25) | 39 (55.7) | 0.001 |
| Previous hospitalization | 27 (51.9) | 39 (55.7) | 0.678 |
| Previous surgery | 8 (15.4) | 6 (8.6) | 0.243 |
| Previous antibiotics | 22 (42.3) | 32 (45.7) | 0.708 |
| Previous VAN | 9 (17.3) | 15 (21.4) | 0.571 |
| Prior MRSA infection | 8 (15.4) | 9 (12.9) | 0.690 |
| Renal disease | 19 (36.5) | 35 (50) | 0.120 |
| Chronic kidney disease | 8 (15.4) | 6 (8.6) | 0.243 |
| Hemodialysis | 10 (19.2) | 17 (24.3) | 0.506 |
| Diabetes | 14 (26.9) | 22 (31.4) | 0.589 |
| Decubitus ulcer | 4 (7.7) | 10 (14.3) | 0.390 |
| Injection drug user | 15 (28.8) | 21 (30) | 0.890 |
| Prosthetic device/hardware | 2 (3.8) | 6 (8.6) | 0.464 |
| Infective endocarditis | 18 (34.6) | 30 (42.9) | 0.357 |
| Pneumonia | 3 (5.8) | 7 (10) | 0.400 |
| Bone or joint infection | 7 (13.5) | 11 (15.7) | 0.729 |
| High-risk infection group[b] | 28 (53.8) | 48 (68.6) | 0.097 |
| MRSA isolate characteristics | | | |
| hVISA | 11 (21.2) | 50 (71.4) | <0.001 |
| VAN BMD MIC, 2 mg/liter | 9 (17.6) | 16 (22.9) | 0.485 |
| VAN Etest MIC, >1 mg/liter | 29 (56.9) | 46 (66.7) | 0.273 |
| SCC*mec* type II | 16 (31.4) | 32 (46.4) | 0.097 |
| *agr* group II | 24 (47.1) | 33 (47.8) | 0.934 |
| *agr* dysfunctional activity | 7 (14.9) | 15 (22.7) | 0.300 |
| Clinical characteristics | | | |
| VAN duration (days) | 9.5 (6–14) | 8 (4–15) | 0.226 |
| VAN initial trough ($n = 109$) | 11.7 (8.3–18) ($n = 45$) | 11.7 (7.8–16.6) ($n = 64$) | 0.638 |
| Initial VAN trough, ≥ 15 mg/liter | 15 (34.1) | 19 (29.7) | 0.628 |
| AUC/MIC | 446.9 (334.9–717.6) | 466.1 (289.3–853.5) | 0.979 |
| AUC/MIC, ≥400 | 32 (61.5) | 41 (58.6) | 0.741 |
| Length of stay (days) | 15.5 (9–29.8) | 24 (13–45) | 0.003 |
| Length of stay after first positive blood culture (days) | 11 (8–26.3) | 22 (13–42) | <0.001 |

[a] Values are followed by percentage in parentheses for categorical data, unless otherwise specified; median values are followed by the interquartile range in parentheses. BMD, broth microdilution; VAN, vancomycin; AUC, area under the concentration-time curve over 24 h.

[b] Infection caused by infective endocarditis, pneumonia, or bone and joint infection.

and are not standardized. It is still considered difficult to have a prospective study without proper and rapid identification of hVISA. This may be only the tip of the iceberg, as larger surveillance studies are needed to evaluate the true prevalence of hVISA. Our data would support that hVISA identification is important based on the overall impact on patient outcomes including the association of prolonged days of bacteremia, longer days of persistent signs and symptoms, extended length of hospitalization, higher frequencies of MRSA BSI recurrence, and an 11-times-greater risk of vancomycin treatment failure.

**TABLE 3** Logistic regression analysis of risk factors associated with vancomycin treatment failure

| Factor | Adjusted OR (95% CI) | $P$ value |
|---|---|---|
| hVISA | 11.138 (4.316–28.742) | <0.001 |
| Admission to ICU | 4.507 (1.751–11.597) | 0.002 |
| High-risk infection[a] | 2.528 (1.000–6.391) | 0.050 |

[a] Infection caused by infective endocarditis, pneumonia, or bone and joint infection.

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