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Reduced Vancomycin Susceptibility, MRSA and Treatment Failure in Pediatric *Staphylococcus aureus* Bloodstream Infections

Ethan Canty, MD, MPH[1], **Benjamin Carnahan, MD**[1], **Tara Curley**[2], **Emily Anususinha, MA**[2], **Rana F. Hamdy, MD, MPH, MSCE**[2,3], **Jessica E. Ericson, MD, MPH**[4]

[1]Penn State College of Medicine, Hershey, PA, USA

[2]Division of Infectious Diseases, Children's National Hospital, Washington, DC, USA

[3]Department of Pediatrics, George Washington University School of Medicine and Health Sciences, Washington, DC, USA

[4]Department of Pediatrics, Penn State College of Medicine, Hershey, PA, USA

Abstract

Background: Clinical implications of reduced vancomycin susceptibility (RVS) among pediatric *Staphylococcus aureus* bloodstream infections are unknown.

Methods: We identified all children at 2 children's hospitals with ≥1 blood culture positive for *S. aureus*. We compared patient and clinical factors for RVS and non-RVS infections using Wilcoxon rank sum and chi-squared tests. Treatment failure and the duration of bacteremia for RVS vs. non-RVS and for MRSA vs. MSSA infections were compared using multivariable logistic and Poisson regressions, respectively. For MRSA infections, the association of empiric vancomycin monotherapy with treatment failure was assessed using multivariable logistic regression.

Results: RVS was present in 72% (309/426) of cases. No patient or infection characteristics, including methicillin resistance, were associated with RVS. RVS was associated with an increased duration of bacteremia compared to non-RVS infections, aIRR=1.15 (95% confidence interval: 1.02, 1.30). The odds of treatment failure was similar for RVS and non-RVS infections, aOR=1.04 (0.62, 1.74). In contrast, MRSA infections were more likely to have treatment failure than MSSA infections, aOR=3.03 (95% confidence interval: 1.84, 5.00). For MRSA infections, empiric vancomycin monotherapy was associated with an increased odds of treatment failure compared to non-vancomycin or combination anti-MRSA antibiotics, aOR=3.23 (1.12, 9.26).

Conclusion: RVS was common and was associated with a longer duration of bacteremia but not with treatment failure. Treatment failure was more common for MRSA than for MSSA bloodstream infections. Empiric vancomycin monotherapy increased the odds of treatment failure for MRSA infections.

Corresponding author: Jessica E. Ericson, MD, MPH, 90 Hope Drive, A480, P.O. Box 855, Hershey, PA 17033, Phone: 717-531-0003 x282277, Fax: 717-531-0245, jericson@pennstatehealth.psu.edu.

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Keywords

bacteremia; sepsis; vancomycin; MSSA; minimum inhibitory concentration

Vancomycin is usually used empirically when invasive staphylococcal infections are suspected.[1] The pharmacodynamic parameter best associated with efficacy in clinical studies is a ratio of the area under the concentration curve at 24 hours (AUC_{24}) to vancomycin minimum inhibitory concentration (vMIC) >400.[2, 3] Because the therapeutic target incorporates the MIC of the organism, infections caused by isolates with high vMICs require higher doses of vancomycin. Difficulty achieving sufficient blood concentrations of vancomycin in infants and children is common due to efficient drug metabolism and excretion.[4, 5] Standard vancomycin dosing strategies successfully reach an AUC_{24}/vMIC >400 for 40–60% of young infants and <20% of infants and children ≥2 months of age.[6, 7] In cases where the vMIC is >1 μg/mL, the probability of pharmacodynamic target attainment will be even lower.

Reduced vancomycin susceptibility (RVS) is common among invasive staphylococcal infections in adults with 5–66% having a vMIC ≥1.5 μg/mL.[8, 9] The clinical importance of the RVS phenotype is controversial and reliable determination of the vMIC is difficult due to the lack of precision of most vMIC methods.[10, 11] A large meta-analysis of adult studies found that RVS increased the odds of mortality and treatment failure.[9] Additional studies have failed to find an association of vancomycin MIC with outcomes.[12, 13] Clinical practice guidelines have recommended that an alternative antibiotic be considered for treatment of MRSA infections if the vMIC is ≥2 μg/mL because of the difficulty in achieving the therapeutic target without related toxicity.[3, 11, 14] Alternate agents may be more effective than vancomycin for high MIC infections.[15, 16]

We sought to describe the epidemiology of RVS among *S. aureus* bloodstream infections in infants and children, to identify patient and clinical characteristics associated with the RVS phenotype, and to compare outcomes for children with RVS vs. non-RVS bloodstream infections.

Methods

Study Population

We identified all children <18 years old admitted to 2 tertiary care children's hospitals from 2008–2016 with a positive blood culture for *Staphylococcus aureus* using laboratory records. The electronic medical records of each patient were reviewed using a structured data collection form to confirm the diagnosis. Patients were excluded if they had a polymicrobial infection, received >1 dose of antibiotics prior to admission, or had another culture-proven infection during their *S. aureus* treatment course. A positive culture occurring >30 days from the most recent positive culture was considered to be a new infection. Positive blood cultures occurring <30 days but >3 days from the most recent prior positive culture were considered to represent a recurrence of the initial bloodstream infection.

The Human Subjects Protection Offices of the Penn State College of Medicine and Children's National Hospital approved this study with a waiver of informed consent.

Definitions

RVS was defined as a vMIC=2 μg/mL as recorded in the electronic medical record after determination by the clinical microbiology laboratory. Both institutions used Microscan (Beckman Coulter), an automated broth microdilution (BMD) system, for vMIC determination. Empiric antibiotic treatment was defined as the antibiotics used prior to culture results being available. Empiric anti-MRSA antibiotic therapy was considered to be given if the child received vancomycin, trimethoprim-sulfamethoxazole, linezolid, doxycycline, daptomycin, rifampin, or clindamycin prior to culture results being known. Empiric vancomycin monotherapy was defined as the use of vancomycin as the only anti-MRSA antibiotic prior to culture results being known; additional antibiotics lacking MRSA activity could have been given. The infection was considered to be complicated if any of the following were present: endocarditis, meningitis, osteoarticular infection, septic emboli, deep abscess, acute kidney injury, or pneumonia. These conditions were chosen because treatment duration and the likelihood of treatment success may be altered by these conditions. Treatment failure was defined as having: duration of bacteremia of >3 days, recurrence within 30 days or death from any cause within 30 days.[17, 18] Bacteremia was considered to be prolonged when the duration of bacteremia was >3 days.[17]

Statistical Analysis:

We used Wilcoxon rank-sum, chi-squared, and Fisher's exact tests to compare continuous and categorical variables, respectively. We used a multivariable logistic regression model to evaluate the association of RVS with sex, race, age, infection source, presence of comorbidities, presence of a central venous line (CVL), hospitalization in the prior year, surgery in the prior 30 days, MSSA vs. MRSA, admitting hospital, and the year in which the infection occurred. Each variable was adjusted for all of the other variables in the model.

We compared the proportion of patients with and without RVS who required ICU-level care, had a duration of bacteremia >3 days, had treatment failure, or died using Fisher's exact tests. We compared hospital length of stay, ICU length of stay, and the duration of bacteremia for patients with and without RVS using Wilcoxon rank-sum tests. We used a Poisson regression to compare the duration of bacteremia for infections with and without RVS, adjusting for the year the infection occurred, admitting hospital, use of vancomycin empirically, presence of a CVL at diagnosis, and presence of complicated disease. We compared the odds of treatment failure for patients with and without RVS using a logistic regression model adjusted for the same characteristics. As a sensitivity analyses, additional regression models were calculated that included a term for the interaction of RVS with vancomycin empiric therapy and, for patients with a central line in place, a continuous variable for the number of days from the first positive culture to CVL removal.

Finally, as a *post hoc* analysis of MRSA infections, we compared the odds of treatment failure following empiric vancomycin monotherapy to alternative anti-MRSA antibiotics with or without vancomycin using a logistic regression adjusted for RVS, year the infection

occurred, admitting hospital, presence of complicated disease, admission to the ICU and any use of inotropic agents as surrogates for severity of illness. We repeated the prior analyses including a term for the interaction of RVS and empirical vancomycin as a sensitivity analysis. Covariates used for adjustment for all analyses were chosen a priori based on a directed acyclic graph indicating their likely role as confounders.

Results

Demographics:

We identified 426 *S. aureus* bloodstream infections meeting our inclusion and exclusion criteria (see Table, Supplemental Digital Content 1). RVS was present in 72% (309/426). Most patients (64%, 274/426) had ≥1 underlying medical comorbidity. The primary source of infection was similar between RVS and non-RVS infections, P=0.66; catheter-associated and musculoskeletal infections were the most common sources for both RVS and non-RVS infections.

Risk factors:

Unadjusted analysis found that year and admitting hospital were associated with RVS. However, when adjusted for patient and infection characteristics, the association of admitting hospital with RVS was no longer present but the increased odds of RVS in more recent years persisted (Table 1).

Outcomes:

Unadjusted outcomes were similar between the 2 groups including duration of bacteremia, 1 day (1, 4) vs. 2 days (1, 4), respectively, P=0.28 (Table 2). When adjusted for infection characteristics, RVS was associated with increased duration of bacteremia compared to non-RVS infections, aIRR=1.15 (1.02, 1.30) (Table 3). However, when a term for the interaction of RVS with empiric vancomycin therapy was included, the association of RVS with the duration of bacteremia was no longer significant.

The proportion of patients with treatment failure was similar between RVS and non-RVS infections, 31% (96/309) vs. 32% (37/117), respectively, P=0.91. Following adjustment for patient and infection characteristics, the odds of treatment failure remained similar for both RVS and non-RVS infections, aOR=1.04 (95% confidence interval: 0.62, 1.74). In contrast, MRSA infections were more likely to have treatment failure than MSSA infections, aOR=3.03 (95% confidence interval: 1.84, 5.00). The addition of a term for the interaction of RVS and empiric vancomycin therapy did not significantly change the point estimate for either of these associations.

For the 153/426 (36%) patients with a CVL in place at the time of the first positive blood culture, 71/153 (46%) had their CVL removed. The median time to CVL removal was 3 days (25^{th} percentile, 75^{th} percentile: 1, 6) and was similar for RVS and non-RVS infections, P=0.44. A sensitivity analysis limited to those with a CVL in place on the day of the first positive culture found that, when adjusted for the year the infection occurred, admitting hospital, use of vancomycin empirically, the presence of complicated disease, and

the number of days between the first positive blood culture and removal of the central line, RVS was not associated with increased odds of treatment failure, but was associated with a longer duration of bacteremia, aIRR=1.55 (1.22, 1.96) (Table 3).

For MRSA infections, treatment failure was more common following empiric vancomycin monotherapy than when a non-vancomycin MRSA-active antibiotic or vancomycin combination therapy was used empirically, aOR=3.23 (1.12, 9.26) (Table 4). We were unable to perform an adjusted analysis of the association of empirical vancomycin therapy and 30-day mortality because all of the deaths were in the vancomycin monotherapy group (5/54, 9%, vs 0/41; P=0.07). Vancomycin was used as definitive therapy in 22/32 (69%) non-RVS MRSA cases and 46/72 (64%) RVS MRSA cases, P=0.63.

Discussion

RVS was common among pediatric *S. aureus* bloodstream infections and was associated with an increased duration of bacteremia but not treatment failure. MRSA was associated with increased odds of treatment failure independent of RVS. Empiric vancomycin monotherapy increased the odds of treatment failure.

Outcomes for RVS and non-RVS S. aureus infections

Few studies have evaluated the impact of RVS on clinical outcomes for children with *S. aureus* bloodstream infections. For 341 children with *S. aureus* bacteremia, an E-test vMIC ≥1.5 μg/mL was associated with 1 day longer duration of bacteremia for children with MRSA but had no association with duration of bacteremia for those with MSSA.[19] Among 71 children with *S. aureus* bacteremia, treatment failure was more likely with an E-test vMIC >1 but only if the source of infection was considered to be high risk, ie: graft, device, intraabdominal or respiratory tract.[18] RVS was not associated with increased 30-day mortality or prolonged bacteremia in this study.[18] For 232 children with MRSA bloodstream infections, a vMIC=2 μg/mL was not associated with an increased odds of treatment failure on univariate analysis; there were too few children with a vMIC=2 μg/mL to adjust for potential confounders.[17] Similar to these prior studies, we failed to find a difference in treatment failure for infections with and without RVS. However, we found that a Microscan vMIC=2 μg/mL increased the duration of bacteremia compared to infections with a vMIC <2 μg/mL.

To the best of our knowledge, this is the first attempt to evaluate risk factors and outcomes for children with *S. aureus* bloodstream infections with an RVS phenotype determined by Microscan. We chose to use Microscan-determined vMICs because these are the results that are available to clinicians at the included sites at the time treatment decisions are made. Most pediatric studies addressing this question have used E-test vMICs which are not routinely performed in most clinical laboratories.[18, 19] One study that did use clinically-available vMIC results determined by either the Vitek 2 (bioMerieux) or the BD Phoenix Automated System (BD Diagnostics) for 232 cases of MRSA bacteremia found that a vMIC=2 μg/mL was present in only 7% of cases and that RVS was not associated with treatment failure in an unadjusted analysis.[17] However, the low prevalence of RVS in this cohort did not allow for adjustment for important confounders and resulted in insufficient

statistical power to adequately compare outcomes for RVS vs. non-RVS infections. In adults, Microscan vMIC=2 μg/mL was not associated with differences in mortality, readmission, recurrence or a composite of the three outcomes for 418 adults with *S. aureus* bacteremia[20] but was associated with complicated disease in 252 adults with MSSA bacteremia.[21]

BMD is often considered to be the "gold standard" for MIC determination. E-test is often preferred in the research setting because there is increased resolution compared to BMD methods (i.e. more values are possible including values like 1.5 μg/mL which is between two possible values using serial dilution methods) and it has been shown to have reasonable concordance with standard BMD results.[28] Some have suggested that all isolates determined to have RVS should have their MICs confirmed using an E-test.[22, 29] However, the frequency with which MICs generated by E-test vs. other methods are discordant make it difficult to know how to interpret and respond clinically when the confirmatory E-test results is discordant from the clinically-determined vMIC.[24] Additionally, E-test is more expensive and labor intensive to perform than automated BMD methods so E-test MICs are not always available in the clinical setting and, if available, take an additional 1–2 days to result. To produce results that would have greater clinical applicability, we opted to use the MicroScan automated BMD vMIC results available in patient clinical records for our study. MicroScan has been reported to classify lower standard BMD vMICs as 2 μg/mL in as many as 8% of cases.[10] We would expect this to bias our results toward the null. Since we were able to detect a difference in the duration of bacteremia for RVS isolates vs. non-RVS isolates, it seems likely that MicroScan either accurately assigned a vMIC=2 μg/mL in most cases or that a definition of RVS that includes lower MICs (ie: >1 μg/mL) has clinical relevance for children with *S. aureus* bacteremia.[18]

An obvious hypothesis is that RVS infections are associated with worse outcomes because higher vancomycin concentrations are necessary to reach the therapeutic target.[11] However, some studies have suggested that it is not antibiotic failure that accounts for the differences in outcomes for RVS vs. non-RVS infections. For example, MSSA bloodstream infections with RVS have sometimes been shown to have worse outcomes than MSSA without RVS even though neither are treated with vancomycin due to their susceptibility to beta-lactam antibiotics. A study that included 266 patients with MSSA treated with flucloxacillin found that mortality was increased for RVS infections compared to non-RVS infections.[30] This is possibly due to an increased thickness in the cell wall of RVS isolates compared to non-RVS isolates and an altered ability to survive within the macrophages after phagocytosis.[31] Another study of 252 adults with MSSA BSI failed to find any difference in mortality for patients with RVS vs. non-RVS infections.[21] However, RVS was associated with increased odds of complicated disease.[21] Similarly, RVS was associated with an increased likelihood of severe disease among children with MSSA osteoarticular infections.[32] Additional studies have failed to find an association of RVS with outcomes in MSSA endocarditis,[12] *S. aureus* meningitis,[33] and *S. aureus* bacteremia.[34, 35] At this point, it remains unclear how much of an impact RVS has on clinical outcomes in invasive *S. aureus* infections.

Outcomes for MSSA vs. MRSA bloodstream infections

Although we did not find vMIC to be a good predictor of treatment failure for pediatric *S. aureus* bacteremia, we did find that children with MRSA bacteremia were more likely to experience treatment failure than those with MSSA. Prior studies have shown inconsistent associations of MRSA with worse disease. A single-center study of 394 children with *S. aureus* bloodstream infections found that MRSA was associated with increased odds of developing a complication compared to MSSA, aOR=3.31 (95% confidence interval: 1.60, 6.85).[36] A study of 427 infections found that crude mortality was greater for children with MRSA compared to MSSA bloodstream infections, 33% vs. 15%, respectively, but 1-year mortality adjusted for patient and infection characteristics was not different between the two infection types, hazard ratio = 1.4 (95% confidence interval: 0.6, 3.1). Conversely, a retrospective study that included nearly 4000 infants found no difference in mortality at 7 days, 30 days or at hospital discharge for infants with MRSA vs. MSSA bacteremia.[37]

Association of empiric antibiotic therapy with treatment failure

We found that empirical vancomycin monotherapy was associated with treatment failure compared to non-vancomycin anti-MRSA antibiotic therapy. A prior study of infants with MRSA bacteremia found that inadequate empirical antibiotic therapy was associated with increased 30-day mortality; however, vancomycin was considered to be adequate empiric therapy.[38] No comparison was made of empiric vancomycin monotherapy with non-vancomycin or combination anti-MRSA empirical therapy. Vancomycin monotherapy has previously been shown to be associated with increased mortality for children with influenza-associated MRSA pneumonia compared to combination therapy.[39] In our study, death was not statistically different between the groups but an effective comparison was limited by a low number of deaths overall; all of the deaths in our cohort occurred in patients receiving vancomycin monotherapy. In light of increasing evidence that vancomycin monotherapy is insufficient treatment for severe *S. aureus* infection, consideration should be given to providing adjunctive therapy with another agent with MRSA activity such as clindamycin or linezolid for children with suspected MRSA infections.[39] A similar proportion of RVS and non-RVS MRSA cases received vancomycin as definitive therapy suggesting that treating clinicians did not respond therapeutically to a finding of RVS by using an alternative antibiotic in most cases. We were not able to assess whether or not higher vancomycin concentrations were targeted in RVS cases.

Geographic differences

The prevalence of RVS was 64% at one center and 76% at a second center, with increasing RVS prevalence over time. Prior single center studies have demonstrated a prevalence of RVS as low as 6%[19] and as high as 75%[18] suggesting significant geographic variability.

Limitations

Because this was a retrospective study and clinical isolates were not stored, we were unable to confirm the MICs reported in the electronic medical record using E-test or another method of MIC determination. Similarly, we were not able to perform strain typing, test for virulence factors, nor evaluate for the presence of heteroresistance. Because we were

not able to control for these features, it is possible that these characteristics could have affected treatment outcomes in such a way that a difference in patient outcomes due to RVS among a subpopulation of infections was masked. In our evaluation of the association between empirical anti-MRSA antibiotic therapy and treatment failure, we only considered anti-MRSA agents. We did not assess the potential impact of beta-lactam antibiotics lacking direct anti-MRSA activity on the efficacy of vancomycin. However, even with adjunctive beta-lactam therapy being given in most cases, primarily for gram negative coverage since culture results were not yet known, use of vancomycin as the only anti-MRSA drug was associated with an increased odds of treatment failure, suggesting that this is a robust association. Collection of laboratory tests including the frequency of blood cultures and treatment decisions were at the discretion of the treating physicians. Since our study was not randomized, it is possible that some important confounders were not included in our analysis.

Conclusion

RVS was common among pediatric *S. aureus* bloodstream infections and was associated with a longer duration of bacteremia but not with treatment failure. Patient and clinical features predisposing to RVS were not identified. Treatment failure was more common for MRSA than for MSSA. Empiric vancomycin monotherapy increased the odds of treatment failure; alternate or additional anti-MRSA antibiotics should be considered when MRSA bacteremia is suspected.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Unadjusted and adjusted odds of reduced vancomycin susceptibility for patient and infection characteristics.

Characteristic	OR (95% confidence interval)	aOR (95% confidence interval)*
Age in years	1.00 (0.97, 1.04)	1.00 (0.96, 1.05)
Male sex	1.00 (0.64, 1.56)	0.96 (0.59, 1.54)
Any comorbidity	0.78 (0.50, 1.23)	0.70 (0.35, 1.41)
Race		
White	1	1
Black	1.39 (0.84, 2.30)	1.24 (0.66, 2.32)
Other/Not reported	1.04 (0.61, 1.76)	0.82 (0.44, 1.52)
Hospitalization in prior year	0.82 (0.54, 1.27)	0.96 (0.54, 1.71)
Surgery in prior 30 days	0.78 (0.45, 1.34)	0.88 (0.46, 1.67)
MRSA vs. MSSA	0.81 (0.49, 1.31)	0.69 (0.40, 1.22)
Central venous catheter present	1.00 (0.64, 1.56)	1.64 (0.77, 3.49)
Site (PSU vs CNMC)	1.76 (1.23, 2.76)	1.36 (0.76, 2.44)
Year	1.32 (1.19, 1.46)	1.30 (1.17, 1.45)
Infection source		
Catheter-associated	1	1
Musculoskeletal	1.47 (0.81, 2.65)	1.37 (0.49, 3.83)
Skin soft tissue infection	1.01 (0.49, 2.06)	1.17 (0.43, 3.17)
Pneumonia	1.54 (0.65, 3.64)	1.91 (0.63, 5.83)
No/other source	1.22 (0.67, 2.22)	1.51 (0.66, 3.47)

*Logistic regression, all characteristics adjusted for all other characteristics.

Table 2.

Outcomes following *Staphylococcus aureus* bacteremia with and without reduced vancomycin susceptibility.

Outcome	Non-RVS N=117 (%)	RVS N=309 (%)	P
Required ICU care	44 (38)	112 (36)	0.80
Required intubation	21 (18)	37 (12)	0.11
Needed surgery	23 (20)	49 (16)	0.37
Hospital length of stay *	13 (7, 41)	11 (7, 22)	0.22
ICU length of stay *	0 (0, 13)	0 (0, 5)	0.44
Bacteremia >3 days	31 (26)	85 (28)	0.83
Duration of bacteremia	1 (1, 4)	2 (1, 4)	0.28
Died	7 (6)	21 (7)	0.76
Treatment failure	37 (32)	96 (31)	0.91

* median (25^{th}, 75^{th} percentiles)

Table 3.

Adjusted outcomes of Staphylococcus bacteremia.

	All Sources		Catheter-associated Infections	
Characteristic	**Treatment Failure aOR (95% confidence interval)***	**Duration of Bacteremia aIRR (95% confidence interval)†**	**Treatment Failure aOR (95% confidence interval)***	**Duration of Bacteremia aIRR (95% confidence interval)†**
Reduced vancomycin susceptibility	1.04 (0.62, 1.74)	1.15 (1.02, 1.30)	1.14 (0.41, 3.19)	1.55 (1.22, 1.96)
MRSA vs. MSSA	3.03 (1.84, 5.00)	1.90 (1.71, 2.12)	24.9 (5.40, 114)	2.68 (2.13, 3.37)
Year	0.94 (0.84, 1.04)	0.95 (0.92, 0.97)	0.90 (0.74, 1.09)	0.90 (0.86, 0.95)
Presence of a complication	3.15 (1.88, 5.29)	2.08 (1.84, 2.34)	6.46 (1.82, 22.9)	2.15 (1.72, 2.69)
Site	1.37 (0.83, 2.26)	1.64 (1.44, 1.86)	0.75 (0.28, 2.01)	1.31 (1.05, 1.64)
Central venous catheter in place at diagnosis	1.84 (1.07, 3.17)	1.53 (1.36, 1.72)	-	-
Empiric vancomycin	3.14 (1.67, 5.89)	1.80 (1.54, 2.09)	2.93 (0.29, 29.3)	1.88 (1.09, 3.24)
Days from positive culture to central venous catheter removal			1.76 (1.18, 2.60)	1.11 (1.04, 1.18)

MSSA, methicillin susceptible Staphylococcus aureus; MRSA, methicillin resistant Staphylococcus aureus;

*Logistic regression, all characteristics adjusted for all other characteristics.

†Poisson regression, all characteristics adjusted for all other characteristics.

Table 4.

Adjusted odds of treatment failure for methicillin-resistant *Staphylococcus aureus* bloodstream infections.

Empirical anti-MRSA Therapy	Treatment Failure n/N (%)	aOR (95% confidence interval)*
Alternate anti-MRSA antibiotic with or without vancomycin	17/41 (41)	1
Vancomycin monotherapy	33/54 (61)	3.23 (1.12, 9.26)

Logistic regression adjusted for reduced vancomycin susceptibility, admission to an intensive care unit, any use of inotropic agents, year of the infection, presence of a complication and hospital site.