Predictors of high vancomycin MIC values among patients with methicillin-resistant *Staphylococcus aureus* bacteraemia

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**Background:** Recent evidence suggests that vancomycin demonstrates reduced activity against methicillin-resistant *Staphylococcus aureus* (MRSA) infections when vancomycin MIC values are at the high end of the susceptibility range (≥1.5 mg/L). However, scant research exists on factors predictive of high vancomycin MICs (≥1.5 mg/L) among MRSA bacteraemic patients. Empirical therapy decisions would greatly benefit from such information.

**Objectives:** To identify the parameters predictive of high vancomycin MICs (≥1.5 mg/L) among MRSA bacteraemic patients and to develop an evidence-based clinical prediction tool.

**Methods:** This observational cohort study included adult patients with MRSA bloodstream infections between January 2005 and May 2007. Demographics, co-morbid conditions, and microbiology and antibiotic exposure data were collected. Vancomycin MICs were determined by Etest. Stepwise logistic regression was used to identify independent predictors of high vancomycin MICs.

**Results:** Of the 105 patients who met the inclusion criteria, 77 patients (73.3%) exhibited a high vancomycin MIC (≥1.5 mg/L). In the bivariate analysis, prior vancomycin exposure within 30 days of index culture collection [15 patients (19.5%) versus 1 patient (3.6%), \(P = 0.05\)] and residence in an intensive care unit (ICU) at the onset of infection [27 patients (35.1%) versus 3 patients (10.7%), \(P = 0.02\)] were both significantly associated with a high vancomycin MIC value and both were independent predictors of high MICs in the logistic regression.

**Conclusions:** Patients with MRSA bloodstream infections in the ICU or with a history of vancomycin exposure should be considered at high risk of infection with strains for which vancomycin MICs are elevated. Appropriate and aggressive empirical therapy is required for these patients.

Keywords: susceptibility, epidemiology, outcomes, MRSA

**Introduction**

Data strongly suggest that patients with methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infections with vancomycin MIC values ≥1.5 mg/L respond poorly to vancomycin.\(^1\)–\(^4\) High MRSA prevalence combined with widespread use of vancomycin for empirical Gram-positive coverage has made this a critical concern for patient outcomes.\(^5\)–\(^7\) Additionally, many hospital microbiology laboratories only test for vancomycin susceptibility and do not routinely provide vancomycin MIC values, making it difficult to identify those patients at risk for a relatively poor vancomycin response despite meeting CLSI standard criteria for susceptibility.\(^7\) Until early detection of vancomycin MICs becomes widely available, other predictors of elevated vancomycin MICs should be considered by clinicians in order to promptly institute the most effective therapy. To date, we are unaware of any study that has attempted to identify factors that are predictive...
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of high vancomycin MIC values (≥1.5 mg/L) among MRSA bacteraemic patients.

The objectives of the current study were 2-fold: (i) to identify parameters predictive of high vancomycin MIC values (≥1.5 mg/L) among MRSA bacteraemic patients; and (ii) to develop a clinical prediction tool to estimate the likelihood of high vancomycin MIC values among patients with MRSA bloodstream infections. We studied the risk factors for vancomycin MIC values ≥1.5 mg/L based on data from our hospital and from other institutions that used the Etest method to determine the vancomycin MIC value and found higher rates of failure among these patients.

Methods

Study population

An observational cohort study was conducted at the Albany Medical Center Hospital (AMCH), a 631 bed tertiary care, academic hospital located in Upstate New York. All patients with a positive MRSA bloodstream infection between January 2005 and May 2007 were eligible. Patients were included in the study if they: (i) were at least 18 years old; (ii) were non-neutropenic (absolute neutrophil count ≥1000 cells/mm³); and (iii) had an MRSA culture meeting CDC criteria for bloodstream infection. If a patient had more than one episode of positive MRSA bloodstream culture during the study period, only the first episode was considered. For patients with multiple MRSA blood cultures, the vancomycin MIC value of the index bloodstream isolate was considered in the analysis. This study was approved by the AMCH IRB committee (expedited review).

Patient data

Data were extracted from patients’ medical records by a trained reviewer using a structured data instrument. Data elements included: age, sex, weight, height, medical history and co-morbidities, health-care institution exposure for >72 h within 180 days of hospital admission, recent antibiotic exposures (receipt of antibiotics in the 30 days prior to index blood culture collection), length of hospitalization prior to collection of index blood culture, hospital unit residence at the time of index blood culture collection, creatinine clearance (CLCR) estimated by the Cockcroft–Gault formula at index blood culture collection, illness severity and microbiological data. Disease severity was calculated with two measures: the Acute Physiological and Chronic Health Evaluation (APACHE II) and the Chronic Disease Score-Infectious Diseases (CDS-ID).

The APACHE II score was calculated from the worst physiological score in the 48 h prior to the collection of the index MRSA blood culture. The CDS-ID was calculated upon admission.

Microbiological data

All clinical MRSA isolates from blood cultures were collected at AMCH during the study period and the Etest method was used to determine the vancomycin MIC value for the index bloodstream isolate as previously described.

Data analysis

Bivariate associations between high vancomycin MIC values (≥1.5 mg/L) and potential risk factors were assessed using the Pearson χ² test or the Fisher exact test. Logistic regression was employed to estimate the predicted probability of high vancomycin MICs. All variables associated with high vancomycin MICs in the bivariate analysis (P < 0.2) were considered for inclusion in the explanatory regression model. A stepwise approach was used to derive a parsimonious model, and variables retained in the final model if their significance was P ≤ 0.05 and adjusted odds ratios (OR) were calculated for significant variables. All calculations were performed with SYSTAT for windows (version 11.0) and SPSS version 11.5 (SPSS, Chicago, IL, USA).

Results

During the study period, 105 patients with a positive MRSA bloodstream culture met the eligibility criteria and were included. The majority (n = 77, 73.3%) of patients exhibited a high vancomycin MIC (≥1.5 mg/L), and 28 patients (26.7%) had a low vancomycin MIC (<1.5 mg/L). No vancomycin-resistant S. aureus isolates were found in the study cohort.

The bivariate comparison of clinical characteristics between high and low vancomycin MICs is represented in Table 1. Prior vancomycin exposure within 30 days of index culture collection and residence in an intensive care unit (ICU) at the onset of infection were both significantly associated with a high vancomycin MIC value. In contrast, the recent use of a non-vancomycin antibiotic was significantly associated with a low vancomycin MIC value. The logistic regression analysis indicated that recent vancomycin exposure [OR 9.4 (95% CI 1.1–80.7); P = 0.04] and residence in the ICU at culture collection [OR 5.3 (95% CI 1.4–20.4); P = 0.02] were independently associated with having a high vancomycin MIC. Recent total antibiotic exposure had a protective effect against having a high vancomycin MIC [OR 0.3 (95% CI 0.1–0.8); P = 0.01] in the logistic regression analysis.

The predicted and actual likelihoods of high vancomycin MIC values stratified by residence in the ICU and non-ICU are presented in Table 2. After stratification, the predicted probability was based on the prior antibiotic exposure history (prior vancomycin, non-vancomycin antibiotic or none). Overall, the model accurately estimated the likelihood of a high vancomycin MIC in this study population, and the predicted likelihood was within 5% for all but one of the resulting groups. For patients in an ICU with no prior antibiotic exposure, the difference between the predicted and the actual value was 7.1%. We found that residence in an ICU at the start of infection had a high predicted value for high vancomycin MIC (>80%) regardless of antibiotic exposure, although patients with prior vancomycin exposure retained the highest risk (97.8%). For patients in a non-ICU setting at the start of infection, only those with prior vancomycin exposure had a predicted value above 80%.

Discussion

In the current analysis, residence in the ICU at the time of culture collection and prior exposure to vancomycin within 30 days of index culture collection were most predictive of high vancomycin MIC values. These findings are consistent with the study by Moise et al. which noted that patients with prior exposure to vancomycin had a higher percentage of elevated vancomycin MIC values compared with patients without prior exposure to vancomycin. It also appears that prior exposure to non-vancomycin antibiotics had a protective effect. Although this
remains unexplained, it is probably caused by antibiotic selective pressures in a hospitalized setting.

This clinical prediction model is straightforward: patients are first stratified by residence in the ICU at the time of initial culture collection, and the probability in each resultant stratum is based on prior antibiotic exposure history. Among patients in the ICU strata, the probability of having a high vancomycin MIC value was >80%, irrespective of prior antibiotic exposure history. For patients developing infection in a non-ICU location, prior exposure to vancomycin was the strongest driver of high vancomycin MIC values. Based on this prediction model, we assume that the following two groups of patients will have a high vancomycin MIC value until proven otherwise: (i) patients with MRSA in our ICU; and (ii) patients with a prior vancomycin exposure regardless of inpatient setting.

Limitations to the current study exist and should be noted. First, this study explored only data from a single site. Institutional differences in resistance patterns, patient populations and antibiotic prescribing patterns may affect the applicability of these results to other institutions. Additionally, only MRSA bacteraemia was examined in the current analysis and MRSA cultures from other sites were not explored. It is unknown whether the risk factors for high vancomycin MICs found in the current analysis are applicable to infections at other sites. Lastly, we cannot exclude the possibility of patient-to-patient transmission of high vancomycin MIC strains, and additional molecular studies are needed to determine whether one clone or several clones are driving the observed results. However, an MRSA bloodstream infection with a high vancomycin MIC value was usually identified in patients residing in the ICU and with prior vancomycin exposure within 30 days of culture collection. If patient-to-patient transmission did occur, this may have weakened the association between high vancomycin strains and receipt of prior vancomycin.

In summary, we found a high prevalence of elevated vancomycin MIC values among patients with MRSA bloodstream infections. Patients residing in the ICU at culture collection and with prior exposure to vancomycin were at highest risk for elevated vancomycin MIC values. The clinical prediction tool proposed here incorporates these factors and accurately predicts the risk for elevated vancomycin MIC values among patients with MRSA bacteraemia. Until institutions report MRSA MIC values routinely, these clinical characteristics and prediction tool may help to identify those patients at heightened risk for poor vancomycin response.
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Transparency declarations

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