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Letters to the Editor

Vancomycin Bactericidal Activity as a Predictor of 30-Day Mortality in Patients with Methicillin-Resistant *Staphylococcus aureus* Bacteremia▽

Vancomycin has been the drug of choice for the treatment of serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections for over 5 decades. It demonstrates slower bactericidal activity in comparison to the results seen with antistaphylococcal beta-lactams against *S. aureus* (1). Moise et al. showed that 30-day mortality was related to the *in vitro* bactericidal activity of vancomycin (3). This study sought to determine whether the *in vitro* bactericidal activity of vancomycin, as well as other MRSA strain-specific characteristics, such as a polymorphism at accessory gene regulator (*agr*) locus (4, 5) and vancomycin MIC (2, 7), impacts the mortality associated with MRSA bacteremia.

A total of 129 consecutive MRSA blood isolates recovered from patients with MRSA bacteremia admitted to the First Department of Internal Medicine (52 beds) and Emergency Medical Care Center (32 beds), Fukuoka University Hospital, from 1991 through 2004 were identified. This study focused on 66 isolates recovered from the 66 patients initially treated with glycopeptides (vancomycin [n = 42 patients] or teicoplanin [n = 24 patients]) after the onset of bacteremia. Bactericidal assays were performed over 72 h as reported by Sakoulas et al., using a concentration of 16 μg/ml against MRSA at an initial inoculum of approximately 10^8 CFU/ml (6). The clinical data were extracted from patients' medical records, and mortality that occurred within 30 days after the onset of bacteremia was examined.

The *in vitro* bactericidal activity of vancomycin showed high heterogeneity among the isolates, with reduction in viable bacteria at 72 h ranging from 2.5 $\log_{10}$ to 7.2 $\log_{10}$ CFU/ml. The median (interquartile range) bactericidal activity was 4.4 (3.8 to 5.4) $\log_{10}$ CFU/ml. Overall, 26 (39.4%) of the 66 patients died during the first 30 days after the onset of MRSA bacteremia. There was no difference in the 30-day mortality between the patients treated with vancomycin and those treated with teicoplanin (42.9% versus 33.3%, P = 0.45). Univariate analysis indicated a statistically significant relationship between mortality and the *in vitro* bactericidal activity of vancomycin (P = 0.017), renal failure indicated by the necessity for dialysis (P = 0.025), the Acute Physiological and Chronic Health Evaluation II (APACHE II) score (P = 0.007), and the presence of shock (P = 0.005), while *agr* group (P = 0.36), *agr* function (P = 0.07), and vancomycin MIC (P = 0.13) were not significant. Multivariate logistic regression analysis with forward stepping on mortality using independent variables, with a P value of <0.2 in the univariate analysis, showed that decreased *in vitro* bactericidal activity of vancomycin (odds ratio [OR], 2.04; P = 0.021), APACHE II score (OR, 1.16; P = 0.018), and the presence of shock (OR, 6.56; P = 0.025) were predictors of mortality. In addition, a Hill-type mathematical model (Fig. 1) identified a very close relationship between vancomycin bactericidal activity and mortality in patients with MRSA bacteremia (R^2 = 0.983), with a 3.8-log reduction in bacteria necessary to achieve a 50% probability of survival.

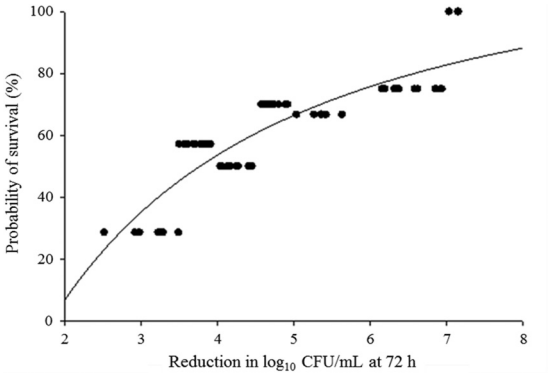

FIG. 1. Vancomycin pharmacodynamics showing the relationship between the probability of survival and bactericidal activity, which was fit to a Hill-type mathematical model (R^2 = 0.983). The probability of survival based on the 30-day mortality data for patients was determined using the categorical breakpoints for reduction in $\log_{10}$ CFU/ml: <3.5 (2/7, 29%), 3.5 to <4.0 (8/14, 57%), 4.0 to <4.5 (7/14, 50%), 4.5 to <5.0 (7/10, 70%), 5.0 to <6.0 (4/6, 67%), 6.0 to <7.0 (9/12, 75%), and >7.0 (3/3, 100%).

Although previous studies have examined the relationship of vancomycin killing activity and treatment failure (3, 6), this current study is the first to demonstrate a relationship with attenuated vancomycin bacterial killing and an increased probability of mortality in the multivariate analysis. In addition, the attenuated vancomycin bactericidal activity was more frequently observed in isolates from endovascular sources than in other sources (P = 0.043). This result demonstrates that reduced vancomycin killing *in vitro* could therefore be a surrogate marker of high-risk sources of bacteremia.

Although performing vancomycin bactericidal assays over 72 h may be too labor-intensive to successfully implement in clinical microbiological analyses, this study highlights the potential problems associated with suboptimal vancomycin killing. These findings suggest that the evaluation of this characteristic may therefore be useful through other phenotypic markers of tolerance, such as those measured by minimal bactericidal concentration (MBC)/MIC and serum bactericidal assays, when considering antimicrobial therapies that can be used as alternatives to either vancomycin or teicoplanin for the treatment of MRSA bacteremia.

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