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Absence of Correlation Between Vancomycin Consumption and Minimum Inhibitory Concentration of Methicillin-Resistant *Staphylococcus aureus* Isolates

Methicillin-resistant *Staphyloccocus aureus* (MRSA) is an important human pathogen; it is among the most common causes of healthcare-associated infection.[1] Despite the use of appropriate antimicrobial therapy, MRSA invasive infections carry a high mortality rate.[2,3] Vancomycin is a mainstay of therapy in MRSA infections, and although it has been used since 1950, resistance is uncommon.[1] Vancomycin minimal inhibitory concentration (MIC) "creep" is a phenomenon in which the vancomycin MIC in *S. aureus* isolates progressively reaches higher values (MIC ≥1.5 mg/L) within the susceptibility range.[4]

Monitoring antimicrobial usage remains a cornerstone of antimicrobial stewardship programs. There is limited evidence of a correlation between MRSA active antimicrobial agent consumption and the emergence of resistance.[5] In this study, we aimed to assess the existence of vancomycin MIC creep among MRSA isolates obtained from blood cultures and to determine whether a correlation exists between vancomycin consumption and variations in the MIC over time.

This study was performed at the Hospital Nossa Senhora da Conceição, a tertiary-care public hospital located in Porto Alegre, Brazil. The study period extended from June 2012 to February 2016, and data for the period were obtained from computerized databases. Isolates from the same episode of bacteremia were counted only once. The isolates were identified using a Vitek-2 system (bioMérieux, Marcy-I'Etoile, France). The vancomycin MIC was determined either by broth microdilution (BMD), according to Clinical & Laboratory Standards Institute (CLSI) recommendations, or by Etest strips (bioMérieux). Vancomycin utilization was expressed in defined daily doses (DDD) per 100 patient days, processed according to the Anatomical Therapeutic Chemical classification system, in which the DDD of vancomycin is 2 g.

The χ^2 test was used to compare proportions. Correlation between variables was tested using the Pearson correlation coefficient, and variation of MIC over time was calculated using analysis of variance (ANOVA). Two-tailed *t* tests were utilized, and a value of $P \leq .05$ was considered significant. Statistical analyses were performed using the JMP 9 program (SAS Institute, Cary, NC).

A total of 186 isolates were included in the analysis. During the study period, the laboratory applied 2 different methodologies: for data from June 2012 to November 2013, BMD was used, and for data from December 2013 to February 2016, an Etest was performed. The MIC ranged from 0.25 to 2.0 mg/L in the first period (for which BMD was used), and the MIC varied from 0.5 to 2.0 mg/L in the second period (for which an Etest was used).

Vancomycin MIC geometrical mean increased significantly in the study period from 0.766 to 1.966 mg/L ($P < .0001$) when the 2 different methodologies were combined. Analyzing the 2 periods separately, no significant variation was observed for the BMD period. However, for the second period (ie, the Etest period), a significant increase in MIC geometrical mean from 0.791 to 1.966 mg/L was observed ($P = .0003$) (Figure 1). There was an increase in the modal MIC from 0.5 to 2.0 mg/L over the whole period ($P < .0001$). Analyzing modal MIC only in the Etest period, there was an increase from 1.0 to 2.0 mg/L ($P = .003$). The proportion of isolates with MIC > 1.0 mg/L ranged from 6.5% to 100% ($P = .001$) during the Etest period.

Both vancomycin utilization and its relation to the total number of hospitalized patients remained stable, varying between 4,488 and 6,449 DDD per 100 patient days ($P = .223$). No correlation was observed between vancomycin utilization and the MIC geometric mean, nor with modal MIC, even when the 2 different methodology periods were analyzed separately. A separate correlation coefficient between MIC geometrical mean and vancomycin utilization for the Etest period alone was poor ($r = 0.524$; $P = .148$).

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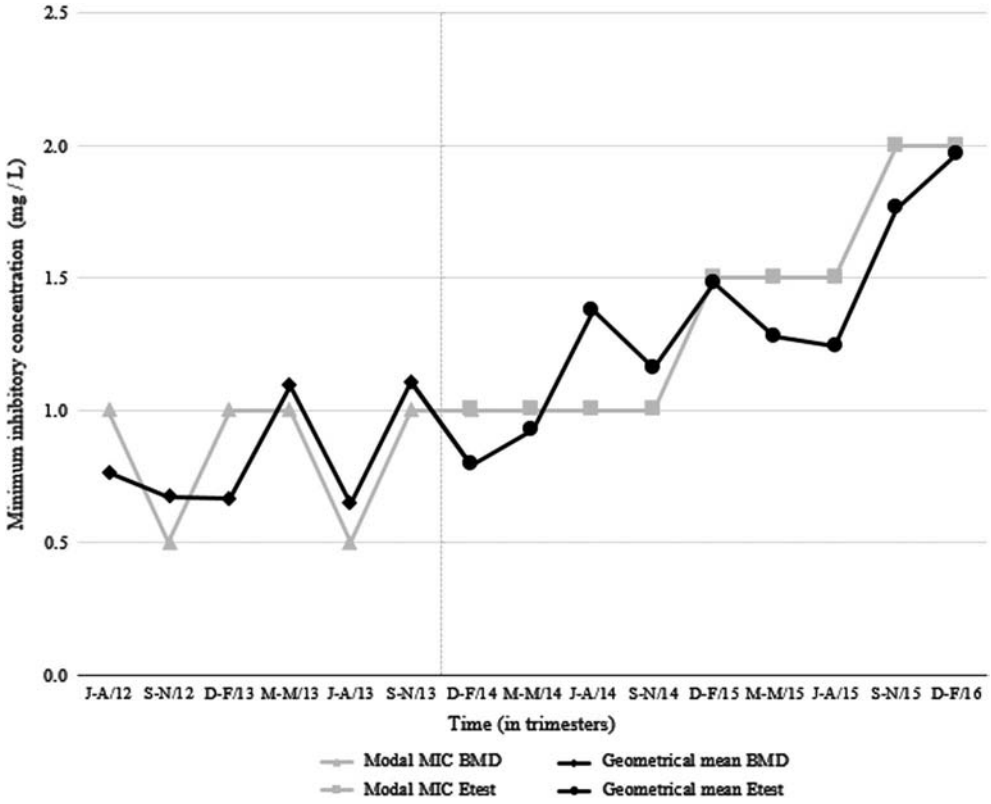

FIGURE 1. Evolution of vancomycin minimum inhibitory concentration (MIC) geometric mean and modal MIC through the time, considering both methodologies. For the data from the first period, June 2012 to November 2013, broth microdilution (BMD) was used; for the data from the second period, December 2013 to February 2016, Etest was performed.

We observed an increase in the vancomycin MIC geometric mean throughout the study period. Moreover, when the Etest period was considered separately, the same phenomenon was detected. Although there is probably an overestimation of MIC by the Etest method, when compared to BMD,[6] another study found that the MIC can be identical or may have just one discordant dilution.[7] Regardless of the change in methodology, our study revealed an increase in MIC that can be considered "MIC creep."

Modal vancomycin MIC increased significantly for the entire study period and also for the Etest period independently. The proportion of isolates with vancomycin MIC > 1 mg/L increased as well. These findings bring concerns about the high proportion of MRSA isolates with a high vancomycin MIC. Even though the mortality risk associated with this finding is the subject of ongoing debate,[1,8] the risk of failure with vancomycin therapy is an important problem. These data suggest the need to evaluate the suitability of vancomycin as the drug of choice, and they may also indicate a need to assess the antimicrobial susceptibility profile of other anti-MRSA antibiotics at this center (which are not routinely performed).

The absence of correlation between vancomycin consumption and MIC variation suggests that other factors are related to MIC increases. The correlation between consumption and antimicrobial resistance is difficult to demonstrate in studies that do not involve a large number of isolates or a prolonged period of evaluation.[5,9] The MIC creep phenomenon may not be associated with the emergence of de novo resistance caused by antimicrobial consumption, but it may be associated with clonal selection and the spread of isolates with higher vancomycin MICs.[6,10]

This study has some limitations, such as not evaluating the consumption of other anti-MRSA drugs. Another limitation, the change in the MIC determination methodology, might have interfered with MIC variation during the study due to possible overestimation by the Etest, but this possibility was circumvented by separating the analyses of the 2 different methodology periods.

Knowledge about the effect of selective pressure exerted by antimicrobial consumption is crucial. This study describes findings in accordance with the literature regarding the possible existence of vancomycin MIC creep among MRSA isolates,[3] and the results have revealed an absence of correlation with vancomycin consumption,[10] which suggests clonal dissemination. Genotyping of isolates are needed to confirm this hypothesis.

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