Vancomycin minimum inhibitory concentrations and lethality in *Staphylococcus aureus* bacteremia

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Abstract

Background **After the dissemination of penicillin and oxacillin resistance in *Staphylococcus aureus*, vancomycin-intermediate and vancomycin resistant isolates have been reported. Even between isolates with minimum inhibitory concentrations (MICs) within the susceptible range, some authors have demonstrated that higher MICs correlate with higher lethality.**

Methods **To test this hypothesis in our setting, we compared vancomycin MICs evaluated by two methods and clinical outcomes in hospitalized patients with *S. aureus* bacteremia.**

Results **We compared lethality in patients infected with isolates that had MICs under or over 2 mg/L. Among patients infected with isolates that had microdilution MICs <2 mg/L, the lethality was 25%; among patients infected with strains that had microdilution MICs ≥2 mg/L, 33% died.**

Among patients infected with isolates that had Etest MICs <2 mg/L, 23% died; in comparison, patients infected with strains that had Etest MICs ≥2 mg/L had a lethality of 44%.

Conclusion **Our results showed a slight tendency of higher lethality when higher MICs were present. However, this difference did not reach statistical significance, possibly due to the relatively small number of patients included in the study. Future prospective studies are needed to further evaluate this correlation and to help clinicians guide antimicrobial therapy.**

Keywords ***S. aureus*, vancomycin, susceptibility**

Introduction

Staphylococcus aureus is a common colonizing and infecting agent in humans.[1] In the 1940s, the advent of penicillin overwhelmingly changed the prognosis of staphylococcal infections, but resistance rose and spread fast. Semisynthetic penicillins, resistant to staphylococcal penicillinases, such as methicillin and oxacillin became an option for the treatment of penicillin-resistant strains. History repeated itself and a few years later oxacillin resistance was reported. As with penicillin, resistance spread first in hospitals and peaked in the 1990s with reports of community-acquired resistant strains.[2-4] In the past two decades, vancomycin became the main treatment option for resistant strains, especially in the hospital, even though partial and full resistance to this antimicrobial have already been spotted.[5,6]

Even amongst vancomycin susceptible isolates, which are those that present minimal inhibitory concentrations (MIC) ≤2 mg/L, studies have shown less favorable response to treatment when MICs are ≥1.5 mg/L. This

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correlation was not found by other authors, and its authenticity is hard to be verified because of the diverse results achieved by various methods for susceptibility evaluation of *Staphylococcus aureus* to vancomycin, including Etest, microdilution, and disk diffusion.[7-13]

There currently are no studies in our area which evaluate the clinical and laboratory outcomes of invasive staphylococcal infections caused by isolates with different vancomycin MICs, and this data would be very important for antimicrobial treatment guidance.

Methods

We performed a study to evaluate clinical and laboratory outcomes in patients with invasive staphylococcal infections, according to the vancomycin MICs of the isolates.

We included 125 *S. aureus* isolates from blood cultures of patients hospitalized in a large tertiary-care hospital in São Paulo, Brazil, from July 2011 to June 2012. We confirmed the identification of the isolates using biochemical methods and included only one isolate per patient. Susceptibility to vancomycin was determined in all isolates with Etest (bioMérieux, Marcy l'Étoile, France) and broth microdilution (Probac do Brasil, São Paulo, Brasil). ATCCs 25923, 29213, 43300 (*S. aureus*), 29212 and 51299 (*E. faecalis*) were used as controls and results were interpreted according to the recommendations of the Clinical and Laboratory Standards Institute (CLSI).[14]

The authors who were blind to the laboratory results (FS, DTB and FA) retrospectively analyzed the charts of patients included in this laboratory-based study, collecting data related to clinical and laboratory outcome, including the following variables: age; treatment unit; hospitalization period; hospitalization period prior to discovery of *S. aureus*; hospitalization period after positive blood culture; period spent in the intensive care unit (ICU, 0 if the patient did not go to the ICU at any point); antimicrobial used after detection of *S. aureus*; period of antimicrobial use; clinical outcome (death or discharge). Unfortunately, only in 39 patients all the clinical data were available in the charts. The results were analyzed critically and using statistical tools, including Chi-square and Fisher tests. A multivariable analysis was not performed because of the intense heterogeneity of the clinical data available.

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Results

Age

Sixty-one percent (24 patients) were over 50 years old; 10% (4) were between 40 and 50 years old; 12% (5) were between 30 and 40 years old; and 2% (1) were between 20 and 30 years old. The same value (2%) was found for the intervals of 15 to 20 and 1 to 15 years old. Only 7% (3) of the patients were under 1 year old. The average age was 49.4 years and the median age was 51.5 years.

Treatment unit

Blood samples were collected from the following hospital units: 41% (16) in the emergency room; 13% (5) in the medical ward; 10% (4) in the surgical ward; 5% (2) in the orthopedic ward; 23% (9) in the ICU; 8% (3) in the pediatric ward.

Hospitalization period before the isolation of *Staphylococcus aureus*

S. aureus confirmation occurred in a timespan of under 10 days in 61% of cases (24 patients), and in over 10 days in 39% (15 patients). The average hospitalization period before laboratory confirmation was 9.5 days and the median was 8 days.

Hospitalization period after positive blood culture

Concerning the period of hospitalization after the first positive blood culture, the results were the following: 43.6% (17) stayed another 10 days; 28.2% (11) 11 to 20 days; 15.4% (6) 21-30 days; 2.6% (1) 31 to 40 days; 5.1% (2) 41 to 50 days; and another 5.1% 60-90 days. This variable had an average of 17.7 days and a median of 12 days.

Total hospitalization period

Regarding the total period that the patients spent in the hospital, from admission to death/discharge, 20.5% (8) spent up to 10 days;

33.3% (13) spent 11 to 30 days; 33.3% (13) spent 31-50 days; 10.3% (4) spent 51-70 days; there were no patients in the 71-90 days range; and 2.6% (1) spent over 90 days (105). The average period of total hospitalization was 30 days and the median for was 8 days.

Period spent in the intensive care unit

This variable had the following distribution: 49% (19) did not spend any time in the ICU; 20% (8) spent up to 10 days; 20% (8) spent 11-20 days; 5% (2) spent 21-30 days; 2.5% (1) spent 31-40 days; and 2.6% (1) spent over 40 days. The average time spent was 9.7 days and the median 7 days.

Antibiotic therapy

The use of antibiotics in the studied cases varied widely. The six major outlines of treatment plans after the isolation of the *S. aureus* strain were: only beta-lactam in 33% (13) of patients; only vancomycin in 23% (9) of patients; vancomycin associated with another antibiotic class in 8% (3) of patients; only macrolides in 3% (10) of patients; beta-lactam and macrolide association in 13% (5) of patients; beta-lactam and vancomycin association in 13% (5) of patients; and vancomycin, beta-lactam and macrolide association in 2.6% (1) of patients. The most used beta-lactams included oxacillin, ceftriaxone, ceftazidime and meropenem.

Period of antibiotic use

Analyzing the period of antibiotic use in the 39 patient charts that composed this study, the results were the following: 11 (28%) patients used antibiotics from 0 to 4 days; 11 (28%) patients used the drugs 5 to 8 days; 5 (13%) patients used antibiotics 9 to 12 days; 2 patients used antibiotics between 13 and 16 days, 5 (13%) patients used antibiotics 17 to 20 days; and 2 (5%) patients used antibiotics for over 20 days. For two of the patients in the study there was no record regarding the duration of antibiotic therapy.

Deaths

Among the 39 patients in the study 28% (11) died before being discharged. In this group of 11, 6 had ages between 41 and 50 years old and 5 were over 50 years old. No patients under the age of 40 died.

Oxacillin resistance

The strains collected from the patients presented oxacillin resistance in 56% of cases (22 strains), while 44% (17 strains) were shown to be susceptible to oxacillin.

Vancomycin MIC by microdilution

Among the 39 strains, 61% (24) had vancomycin MICs <2 mg/L when measured by the method of microdilution. The other 39% (15 patients) had MICs ≥2 mg/L.

Vancomycin MIC by Etest

Using the Etest method to determine MICs, 77% (30) of patients had strains with MICs <2 mg/L and the other 23% (9) of patients had MICs ≥2 mg/L. The highest MIC found was 4 mg/L (vancomycin-intermediate), identified in a single isolate. This isolate had an MIC of 2 mg/L when tested by microdilution.

Microdilution MIC versus lethality

We compared lethality in patients infected with isolates that had microdilution MICs under or over 2 mg/L. Among patients infected with isolates that had MICs <2 mg/L, 75% (18 cases) were discharged and 25% (6 cases) died, from a total of 24 isolated cases. Among patients infected with strains that had MICs ≥2 mg/L, 66% (10) were discharged, while 33% (5) died. The p value by Fisher's method was 0.718 and 0.844 by the Chi-squared test.

Etest MIC versus lethality

We compared lethality in patients infected with isolates that had Etest MICs under or over 2 mg/L. Among patients infected with isolates that had MICs <2 mg/L, 77% (23) were discharged and 23% (7) died, from a total of 30 patients. Among patients infected with strains that had MICs ≥2 mg/L, 56% (5) were discharged and 44% (4) died, from a total of 9 cases. The p value by Fisher's method was 0.238 and 0.417 by the Chi-squared test.

Discussion

The comparison between the obtained test results and the clinical outcome, one of the aims of this study, was shown not to have statistical significance, probably because of the small number of patient charts with all the information necessary. Nevertheless, even with a small number of cases, there was a tendency of higher

lethality with higher MIC values measured by Etest. Van Hal et al., in a recently published meta-analysis, unmistakably presented this tendency.[10]

Of the isolated strains, 55% were oxacillin-resistant, showing the spread of oxacillin resistance in our area. We had only one isolate with intermediate resistance to vancomycin (MIC by Etest equal to or higher than 4 mg/L), demonstrating that vancomycin resistance is still rare in our setting. Of note, this isolate had a MIC of 2 mg/L when evaluated by microdilution. Other authors have also found different results between Etest and microdilution when evaluating vancomycin susceptibility in *S. aureus*.[7,8,15] Although CLSI still recommends dilutions as the reference methods, most reports correlating higher MICs with poorer outcomes used Etest as the vancomycin susceptibility test.

Future prospectively designed studies are paramount to better evaluate and further corroborate the correlation between vancomycin MICs and lethality, and to analyze all of the factors beyond the bacterial infection that can influence clinical outcomes, such as tracheal intubation and presence of central vascular catheter, among others, as well as the heterogeneous results between different antimicrobial susceptibility tests, helping clinicians to guide antimicrobial therapy.

Conclusion

Our results showed a slight tendency of higher lethality when higher MICs were present. However, this difference did not reach statistical significance, possibly due to the relatively small number of patients included in the study. Future prospective studies are needed to further evaluate this correlation and to help clinicians guide antimicrobial therapy.

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