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Impact of elevated vancomycin minimum inhibitory concentrations on the outcome of catheter-related bloodstream infection due to methicillin-resistant *Staphylococcus aureus*

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Contact information:

Mario Fernández-Ruiz, MD

Unit of Infectious Diseases
University Hospital "12 de Octubre"
Avda. Córdoba, s/n. 28041. Madrid, Spain

E-mail: mario_fdezruiz@yahoo.es

Mario Fernández-Ruiz[a], Rafael San-Juan[a], José María Aguado[a], Oriol Gasch[b], Mariana Camoez[c], Francisco López-Medrano[a], María Ángeles Domínguez[c], Benito Almirante[d], Belén Padilla[e], Miquel Pujol[f]

on behalf of REIPI/GEIH Study Groups

[a]Unit of Infectious Diseases, Hospital Universitario "12 de Octubre", Instituto de Investigación "12 de Octubre" (i+12), Madrid; [b]Department of Infectious Diseases, Corporació Sanitària Parc Taulí, Sabadell; [c]Department of Microbiology, Hospital Universitari de Bellvitge, IDIBELL, Barcelona; [d]Department of Infectious Diseases, Hospital Universitari Vall d'Hebron, Barcelona; [e]Department of Clinical Microbiology and Infectious Diseases, Hospital General Universitario Gregorio Marañón, Madrid; [f]Department of Infectious Diseases, Hospital Universitari de Bellvitge, IDIBELL, Barcelona, Spain.

INTRODUCTION

- The increased risk of clinical failure and mortality in episodes of methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infection (BSI) treated with vancomycin in isolates showing high vancomycin minimum inhibitory concentrations (MICs) is well established.
- A recent meta-analysis reported an increased risk of failure in the high vancomycin MIC group compared to the low MIC group (relative [RR]: 1.40, 95% confidence interval [CI]: 1.15-1.71). The overall mortality risk was also greater in the high vancomycin MIC group than in the low MIC group (RR: 1.42, 95% CI 1.08 - 1.87).
- However, most of the previous studies have analyzed the different sources of MRSA-BSI as a whole. Evidence on the impact of the vancomycin MIC on the outcome of low-risk sources of BSI (i.e., catheter-related) is still scarce.
- On the other hand, it has been demonstrated a correlation between the phenotype of reduced susceptibility to vancomycin and the reduced expression of the accessory gene regulator *(agr)* quorum-sensing system , particularly in association with the *agr* II genotype. The *agr* dysfunction is associated with a longer duration of BSI and, eventually, a higher risk of hematogenous seeding and complications.
- The present study was aimed at analyzing the impact of higher vancomycin MICs on the outcome of MRSA catheter-related BSI (CR-BSI) not only in terms of overall mortality but also of complicated BSI.

METHODS

- ***Study design and setting:*** A multicentre study on MRSA BSI diagnosed in patients 18 years old or older was conducted in 21 Spanish hospitals from June 2008 to December 2009. A standardized protocol with demographic and clinical information was applied. Strains were sent to a central laboratory for further studies. The first isolate of each episode was used for the analysis. We assessed the predictors for clinical and microbiological outcome in 218 episodes of CR-BSI out of a total of 579 episodes of MRSA BSI originally included in the study.
- ***Susceptibility testing and molecular epidemiology:*** Antimicrobial susceptibility testing of all MRSA isolates was carried out in a central laboratory using broth microdilution (results interpreted following the guidelines of the CLSI) and E-test (BioMérieux) methods. Pulsed-field gel electrophoresis (PFGE) was performed after SmaI restriction of chromosomal DNA. To determine the multilocus sequence type (MLST) and the staphylococcal chromosome cassette *mec* (SCC*mec*) types, we studied representative isolates of each PFGE type and subtype. Accordingly, MLSTs and SCC*mec* types were further inferred for all the strains. The *agr* polymorphism and the presence of genes in all the isolates were examined by PCR.
- ***Clinical definitions:*** Initial antibiotic therapy was that administered in the first 48 hours after CR-BSI onset. Definitive therapy was that administered once the results of susceptibility tests were available. Hematogenous seeding was diagnosed in presence of a focal infection different than intravascular catheter. Persistent BSI was defined as growth of MRSA in blood cultures after more than 48 hours of appropriate antibiotic therapy. Endocarditis was diagnosed according to modified Duke criteria.

Table 1. Clinical characteristics of patients (n = 218).

Variable	
Age, years [mean ± SD]	66.9 ± 14.2
Gender (male) [n (%)]	136 (62.4)
Charlson comorbidity index [median (IQR)]	4 (2 - 6)
Pitt bacteremia score [median (IQR)]	1 (0 - 3)
McCabe-Jackson score [n (%)]	
Non-fatal	107 (49.3)
Ultimately fatal	85 (39.2)
Rapidly fatal	25 (11.5)
Acquisition [n (%)]	
Nosocomial non-ICU	123 (56.4)
Nosocomial ICU	34 (15.6)
Health care-associated	16 (7.3)
Community	11 (5.0)

ICU: intensive care unit; IQR: interquartile range; SD: standard deviation.

Table 2. Microbiological studies (n = 207).

Variable	
agr type [n (%)]	
II	107 (49.3)
I	85 (39.2)
III	25 (11.5)
Clonal complex [n (%)]	
5	156 (77.2)
22	19 (9.4)
8	14 (6.9)
Other	13 (6.4)
PGFE type [n (%)]	
2	132 (63.8)
4	20 (9.7)
5	16 (7.7)
12	13 (6.3)
Other	26 (12.6)
Panton-Valentine leukocidin [n (%)]	2 (1.0)
Microdilution vancomycin MIC ≥1 mg/L [n (%)]	44 (21.3)
E-test vancomycin MIC ≥1.5 mg/L [n (%)]	97 (46.9)

MIC: minimum inhibitory concentration; PGFE: pulsed-field gel electrophoresis; PVL: Panton-Valentine leukocidin.

RESULTS

Table 3. Treatment.

Variable	
Catheter withdrawal in the first 48 hours [n (%)]	147 (67.4)
Appropriate initial therapy [n (%)]	167 (76.6)
Time to appropriate therapy, days [median (IQR)]	1 (0 - 2)
Initial antibiotic therapy [n (%)]	
Vancomycin	106 (48.6)
Daptomycin	25 (11.5)
Linezolid	18 (8.3)
Other	18 (8.3)
Definitive antibiotic therapy [n (%)]	
Vancomycin	104 (48.1)
Daptomycin	60 (27.8)
Linezolid	28 (12.8)
Other	18 (8.3)

Table 4. Clinical and microbiological outcome.

Variable	
Hematogenous seeding [n (%)]	43 (19.7)
Endocarditis [n (%)]	10 (4.6)
Persistent BSI [n (%)][a]	42 (24.3)
Relapse [n (%)]	8 (3.7)
30-day all-cause mortality [n (%)]	53 (24.3)
Early (48 hours) mortality [n (%)]	7 (3.2)

[a] Data available for 173 patients.

Table 5. Incidence of hematogenous complications according to vancomycin CMI (E-test) and type of initial antibiotic therapy.

Variable [n (%)]	E-test CMI <1.5 mg/L	E-test CMI ≥1.5 mg/L	*P*-value
Initial therapy with vancomycin			
Hematogenous seeding	6/46 (13.0)	16/53 (30.2)	0.041
Endocarditis	0/46 (0.0)	6/53 (11.3)	0.020
Initial therapy with daptomycin			
Hematogenous seeding	6/19 (31.6)	2/6 (33.3)	0.651
Endocarditis	1/19 (5.3)	2/6 (33.3)	0.133

Figure 1. Clinical and microbiological outcome according to the E-test vancomycin MIC in the overall cohort (n = 207).

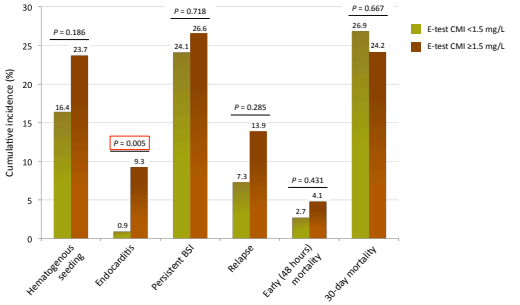

Table 6. Logistic regression model of risk factors for endocarditis in the overall cohort.

	Univariate analysis OR	(95% CI)	*P*-value	Multivariate analysis OR	(95% CI)	*P*-value
Prior hospital admission	5.04	(1.05 - 24.32)	0.027	6.01	(1.34 - 31.75)	0.035
Appropriate initial therapy	2.85	(0.35 - 23.03)	0.306	-	-	-
Catheter withdrawal in the first 48 hours	1.99	(0.41 - 9.60)	0.385	-	-	-
Persistent BSI	5.29	(1.42 - 19.77)	0.007	5.36	(1.29 - 22.5)	0.021
E-test vancomycin MIC ≥1.5 mg/L	11.15	(1.39 - 89.68)	0.005	14.91	(1.73 - 128.30)	0.014

BSI: bloodstream infection; CI: confidence interval; MIC: minimum inhibitory concentration; OR: odds ratio.

CONCLUSIONS

The phenotype of decreased susceptibility to vancomycin was a predictor for the development of complicated CR-BSI due to MRSA in form of hematogenous seeding, mainly endocarditis. This association appeared to be evident when vancomycin was used as initial therapy, although might be also present in episodes treated with other antistaphylococcal agents.