Meta-analysis to evaluate the vancomycin MIC Creep in *Staphylococcus aureus* infections

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Introduction: Vancomycin is currently the primary treatment option for methicillin-resistant *Staphylococcus aureus* (MRSA) (1, 2). However, an increasing number of MRSA isolates with high minimum inhibitory concentrations (MICs), within the susceptible range (vancomycin MIC creep) are being reported worldwide (3). Recent studies reported reductions in efficacy of vancomycin against MRSA strains, suggesting that subtle changes in MIC may explain clinical failures (3). Recurring to a meta-analysis approach, we comprehensively assess the evidence of vancomycin MIC creep, between 2006 and 2018 and the importance of monitoring this phenomenon lead to an update of the results from our previous published meta-analysis (4) and a new research was performed to include recent reports on vancomycin MIC.

Methods: The studies included in the first meta-analysis approach were retrieved from Pubmed database with a defined search query, from January 2006 to January 2016. The abstracts of the collected articles were reviewed and a study was considerable to be eligible for inclusion if it was written in English, the values of vancomycin MIC are known, details of the applied MIC methodologies, number of studied isolates, year of study and country. The studies to be included in the meta-analysis update were retrieved from Pubmed database, from December 2016 to September 2018 with the search query previously defined in first meta-analysis. All articles were reviewed and selected if they match the inclusion criteria.

Homogeneity among studies was computed using the Cochran's Q statistic and the I^2 statistic. On the other hand, I^2 provides an estimate of the proportion of the variance in the aggregate effect size that is attributable to study heterogeneity, with values of 0.25, 0.50 and 0.75 indicating low, moderate and high degrees of heterogeneity.

To compare the pooled effect size in different groups (sub- groups) the Z-test was used and for simultaneous statistical tests the Sidak correction was applied.

MetaXL 5.3, a tool for meta-analysis, was used to pool individual prevalence from each study.

Results: In first meta-analysis, the literature search identified 980 studies. After title and abstract analysis, 880 were excluded and 100 full-text articles were reviewed. Of these, 55 studies were included in the meta-analysis.

Considering all the studies included in the pool, the mean of vancomycin MIC was 1.20 mg/L and 1.19 mg/L, when determined by the BMD and Etest method, respectively. The analysis of the distribution of MRSA isolates with vancomycin MIC ≥ 2 mg/L showed a decrease over time, either with BMD or Etest methods. The Spearman's correlation coefficient results (-0.95 to BMD and -0.75 to Etest) showed no evidence of MIC creep (Table I).

In the meta-analysis update, 11 new studies were selected based on the same inclusion and exclusion criteria. These studies were added to the studies already included in the first meta-analysis (n=66).

Considering all the studies included, the pool mean of vancomycin MIC was now 1,14 mg/L and 1,23 mg/L, when determined by the BMD and Etest method, respectively. The analysis of the distribution of MRSA isolates with vancomycin MIC ≥ 2 mg/L showed a decrease over time, either with BMD or Etest methods. The Spearman's correlation coefficient results (-0,89 to BMD and -0.78 to Etest) showed no evidence of MIC creep (Table II).

The pool mean of vancomycin determined by BMD decreased from 1,20 mg/L (95% [CI] = 1,13–1,28) to 1,14 mg/L (95% [CI] = 1,08 – 1,14). Even with these values, the updated results did not show significant differences, since the 95% CI overlaps the previous one. The pool mean of vancomycin determined with Etest remains the same.

Table I: Pooled mean vancomycin MICs determined resorting to different MIC testing methodologies.

	MIC testing methodologies	Pooled mean	Confidence Interval (95%)		Spearman correlation [1]	I^2
			Lower bound	Upper bound		
MRSA 1st meta-analysis	BMD	1.20	1.13	1.28	-0.82	98.69
	Etest	1.23	1.13	1.33	-0.57	99.61
MRSA 2nd meta-analysis	BMD	1,14	1,08	1,20	-0,86	98.72
	Etest	1,23	1,14	1,33	-0,57	99,57

[1] Spearman correlation: correlation between time strata and pooled mean.

Table II: Pooled proportion of MRSA MIC ≥ 2 mg/L determined resorting to different MIC testing methodologies

	MIC testing methodologies	Pooled proportion	Confidence Interval (95%)		Spearman correlation [1]	I^2
			Lower bound	Upper bound		
MRSA 1st meta-analysis	BMD	0.18	0.12	0.25	-0.89	98.48
	Etest	0.14	0.10	0.19	-0.64	96.86
MRSA 2nd meta-analysis	BMD	0,16	0,11	0,22	-0,89	98,29
	Etest	0,13	0,09	0,17	-0,78	96,76

[1] Spearman correlation: correlation between time strata and pooled mean.

Conclusions: The first meta-analysis was the first study evaluating the trends of vancomycin MIC determined with different MIC methods, in a worldwide perspective, including single and large multicenter studies. The performed meta-analysis evaluated the trend of vancomycin MIC over time, and no statistically evidence of MIC creep phenomenon was detected. The meta-analysis updated results showed similar values when compared with the results obtained in the first meta-analysis but is important to highlight the slight decreased of vancomycin MIC determined by BMD.

The performed meta-analysis update evaluated the trend of vancomycin MIC over time and no statistical evidence of MIC creep phenomenon was detected. These findings must be considered when interpreting vancomycin susceptibility and during the discussion of the need to find alternative antistaphylococcal agents for patients with elevated but susceptible vancomycin MIC values. Monitoring possible changes in vancomycin MIC is fundamental to adequate treatment decisions when managing MRSA infections (4).

References:

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