eP170

Vancomycin MIC creep: A fact or an artifact?

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Introduction

Resistance to vancomycin in MRSA (MIC of >2mg/L) remains infrequent, but there is growing evidence in the literature that vancomycin may be ineffective against an increasing proportion of isolates with MICs between 1 and 2 mg/L. This has been demonstrated by the emergence of strains of intermediate resistance, i.e., hetero-VISA (vancomycin-intermediate *S. aureus*) and VISA strains, and of increasing proportions of MRSA isolates with high MICs within the susceptible range, the so-called vancomycin MIC "creep". The creep phenomenon has not been reported consistently, but it is concerning because vancomycin still remains the cornerstone of therapy for many serious MRSA infections.

Some studies have found that vancomycin MIC creep is an unstable phenomenon that is not necessarily reproducible in stored isolates or even between different testing methods at the time of isolation. In this study we evaluated the impact of a variety of laboratory factors that could potentially influence this phenomenon.

Methods

From April 2012 to May 2013, 30 hospitals in Greece (18 in Athens Metropolitan area and the rest in other cities) provided all consecutive single-patient clinical isolates of *S.aureus* to the Infectious Diseases Research Laboratory of Hygeia Hospital in Athens to be submitted to susceptibility testing (see ePoster 181). Vancomycin MIC was tested using Vitek 2 automated system (bioMérieux,Marcy-l'Etoile, France) and by Etest® (AB Biodisk, Solna, Sweden) upon arrival for all isolates and retested again after a minimum of 6 months of storage at -80 °C for a subgroup of blood isolates.

Results

- A total of 1005 *S.aureus* isolates were collected and tested
- Vancomycin MIC distribution for the whole collection, evaluated by VITEK 2 and Etest simultaneously, when the isolates were received at the central laboratory are shown in Table 1. The MIC distribution of 171 bloodstream isolates that were retrieved from storage and retested 6 months later are shown in Table 2.
- Using the VITEK, vancomycin $MIC_{50/90}$ (range) were 1/1 (≤0.5-2) mg/L for the total as well as for the MRSA and the MSSA subgroups and 3.1% of isolates exhibited an MIC>1 mg/L. Using the Etest, vancomycin $MIC_{50/90}$ (range) were 1.5/1.5 (≤0.5-3) mg/L for the total as well as for the MRSA and the MSSA subgroups, 58.5% exhibited a MIC >1 and 8.8% a MIC of 2 mg/L. A discrepancy between the two methods (a difference >1 two-fold dilutions) was noted for 208 (23.2%) isolates. One hundred and seventy one blood isolates were retrieved from storage after at least 6 months and were resubmitted to susceptibility testing using the Etest. $MIC_{50/90}$ (range) were 0.75/1 (≤0.5-2) mg/L whereas 6.4% of isolates showed MIC >1 mg/L and 0.6% a MIC of 2 mg/L. A discrepancy between the two measurements (a difference >1 two-fold dilutions) was noted for 23 (13.5%) isolates. On the contrary, a discrepancy between VITEK and the second Etest measurement was found for 3.5% of isolates.

Results

Table 1. MIC distribution, MIC_{50}, MIC_{90} and percentage of vancomycin susceptibility for 1005 *S.aureus*, including 393 MRSA isolates. Vancomycin was tested by VITEK 2 and by E-test simultaneously when isolates were received at the central laboratory.

Antimicrobial agent /Methicillin- resistance phenotype	MIC (mg/L) range tested/No of isolates with indicated MIC										MIC_{50} (mg/L)	MIC_{90} (mg/L)	Susceptible %
Vancomycin (VITEK 2)	≤0.5	1	2	4	8	16	≥32						
S.aureus	277	697	31								1	1	100
MSSA	166	427	19								1	1	100
MRSA	111	270	12								1	1	100
Vancomycin (Etest)	≤0.5	0.75	1	1.5	2	3	4	8	16	≥32			
S.aureus	16	68	333	500	87	1					1.5	1.5	99.9
MSSA	9	42	200	307	54	1					1.5	1.5	100
MRSA	7	26	133	193	33						1.5	1.5	99.8

Table 2. MIC distribution, MIC_{50}, MIC_{90} and percentage of vancomycin susceptibility for 171 bloodstream *S.aureus*, including 76 MRSA isolates. Vancomycin was tested by VITEK 2 and by E-test simultaneously when isolates were received at the central laboratory and 6 months later.

Antimicrobial agent /Methicillin- resistance phenotype	MIC (mg/L) range tested/No of isolates with indicated MIC										MIC_{50} (mg/L)	MIC_{90} (mg/L)	Susceptible %
Vancomycin (VITEK 2)	≤0.5	1	2	4	8	16	≥32						
S.aureus	29	131	11								1	1	100
MSSA	18	71	6								1	1	100
MRSA	11	60	5								1	1	100
Vancomycin (Etest)	≤0.5	0.75	1	1.5	2	3	4	8	16	≥32			
S.aureus	1	5	59	91	14	1					1.5	1.5	99.4
MSSA	1	3	30	53	8	1					1.5	1.5	100
MRSA		2	29	38	6						1.5	1.5	98.7
Vancomycin (Etest, 6 months later)	≤0.5	0.75	1	1.5	2	3	4	8	16	≥32			
S.aureus	31	84	45	10	1						0.75	1	100
MSSA	16	50	26	3	1						0.75	1	100
MRSA	15	34	19	7							0.75	1.5	100

Conclusions

Several technical issues may account for the apparent MIC creep of vancomycin. This phenomenon was dependent on the MIC testing method and the measurement used for reporting the results (modal MIC or percentage of isolates with a higher MIC). In general, Etest results were 1 dilution higher whereas the VITEK significantly underestimated the proportion of isolates with a MIC >1 mg/L. Storage of isolates resulted in reduction of the modal MIC by 2 two-fold dilutions and attenuation of the phenomenon of "creep". There is a need to standardize susceptibility testing of vancomycin against *S.aureus*.

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