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Worrisome trends in rising minimum inhibitory concentration values of antibiotics against methicillin resistant *Staphylococcus aureus* – Insights from a tertiary care center, South India

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ABSTRACT

Introduction: Appearance of isolated reports of resistance to anti-methicillin-resistant *Staphylococcus aureus* (MRSA) drugs is worrisome underscoring the need to continuously monitor the susceptibility of clinical MRSA isolates to these drugs. Hence, the present study is conducted to determine the susceptibility of MRSA isolates to various classes of anti-MRSA drugs such as vancomycin (glycopeptide), daptomycin (lipopeptide), tigecycline (glycylcycline), and linezolid (oxazolidinone) to determine the MIC_{50} and MIC_{90} values, and to observe MIC creep over a three year period, if any, with respect to these drugs.

Methods: A total of 200 isolates of MRSA obtained from clinical specimens were included. MIC was determined by *E*-test for anti-MRSA antibiotics vancomycin, linezolid, daptomycin, and tigecycline. Non-parametric methods (Kruskal–Wallis and Chi-square test) were used to assess MIC trends over time. In addition, MIC_{50} and MIC_{90} values were also calculated.

Results: No isolate was found resistant to vancomycin, daptomycin, or linezolid; five isolates were resistant to tigecycline. Seven VISA isolates were encountered with the MIC value for vancomycin of 4 μg/mL. MIC values for vancomycin, tigecycline, linezolid showed a definite increase over a 3-year period which was statistically significant with *p*-values <0.0001, 0.0032, 0.0242, respectively. When the percentage of isolates with a median MIC value less than or equal to that of the index year was calculated, the change was most striking with vancomycin. The proportion of isolates with higher MIC values was greater in 2014 than 2012 and 2013.

Conclusion: MIC creep was notably observed with vancomycin, and to some extent with tigecycline and linezolid. Selection pressure may result in creeping MICs, which may herald the emergence of resistant organisms.

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Introduction

Vancomycin has been the mainstay of therapy for serious infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), because of its relatively good safety profile, its low potential to induce resistance, and for many years, the lack of other approved alternatives.[1] However, its efficacy has become uncertain, because of its slow bactericidal activity, the emergence of isolates with reduced susceptibility and possible "MIC creep" among susceptible strains.[2]

In the last few years, newer antibiotics such as linezolid, daptomycin, tigecycline, dalbavancin, telavancin, oritavancin, ceftobiprole, ceftaroline, and iclaprim have been added to the arsenal of anti-MRSA drugs with many of them already in clinical use and some on the horizon. Linezolid is a synthetic oxazolidinone that inhibits the initiation of protein synthesis at the 50s ribosome and has bacteriostatic activity against MRSA. It is currently approved by the United States Food and Drug Administration (US FDA) for the treatment of complicated skin and skin-structure infections (SSSIs) and nosocomial pneumonia caused by susceptible pathogens, including MRSA.[1] Daptomycin is a cyclic lipopeptide that causes depolarization of the bacterial cell membrane and has bactericidal activity. It is recommended for treatment of skin and skin structure infections, bacteremia, and right-sided endocarditis caused by MRSA, as well as patients with prolonged MRSA bacteremia, who are at high risk for metastatic complications and death.[3] Tigecycline is the first glycylcycline class of antibiotic which has bacteriostatic activity against MRSA, has been approved by US FDA for the treatment of complicated skin and skin structure infections (cSSSI) and complicated intra-abdominal infections.[4] Tigecycline can overcome the two common mechanisms that are associated with tetracycline resistance – ribosomal protection and efflux pumps.[5]

Appearance of isolated reports of resistance to these alternative drugs is worrisome underscoring the need to continuously monitor the susceptibility of clinical MRSA isolates to these drugs. The present study was conducted to determine the susceptibility of MRSA isolates to various classes of anti-MRSA drugs such as vancomycin (glycopeptide), daptomycin (lipopeptide), tigecycline (glycylcycline) and linezolid (oxazolidinone) to determine the MIC_{50} and MIC_{90} values and to observe MIC creep, if any, with respect to these drugs.

Materials and methods

A total of 200 isolates of MRSA obtained from clinical specimens (pus – 119; blood – 12; tissue bit – 9; pleural fluid – 2; tracheal aspirate – 4; wound swab – 40, and 14 from other specimens) submitted to Department of Microbiology, JIPMER, Puducherry from January 2012 to December 2014. The isolates were almost equally distributed over the three-year period – 2012 (62), 2013 (63), and 2014 (75). Only one isolate per patient was included in the analysis. In case of multiple isolates, the first isolate was included. Minimum inhibitory concentration (MIC) was determined by *E*-test for anti-MRSA antibiotics vancomycin, linezolid, daptomycin, and tigecycline, according to manufacturer's instructions (bioMérieux,) and the results were interpreted as per CLSI guidelines[6] and EUCAST guidelines[7] for tigecycline. For quality control, *Staphylococcus aureus* ATCC 29213 was employed. Methicillin resistance was confirmed by PCR for *mec*A gene.

The percentage of isolates with a median MIC value less than or equal to that of the index year (2012) was calculated for each antibiotic in the three years under study, to observe changes in the proportion of isolates with lower MIC values, which would suggest an "MIC creep". In addition, MIC_{50} and MIC_{90} values of vancomycin, linezolid, daptomycin, and tigecycline were also calculated.

Statistical analysis

Chi-square test was employed for the assessment of significant change, if any, among the MIC values of isolates in three years in comparison with the median MIC value of the index year (2012). MIC trends over the three years and the significance of changes in MIC values were assessed using non-parametric Kruskal–Wallis test with the help of Graphpad prism 6.0 software. p-Value <0.05 was considered significant.

Results

The MIC values for vancomycin ranged from 0.125 to 3 mg/L, for linezolid from 0.016 to 2 mg/L, for daptomycin from 0.016 to 0.5 mg/L, and for tigecycline from 0.016 to 1 mg/L. MIC_{50} and MIC_{90} values are depicted in Table 1.

Table 1 – MIC_{50} and MIC_{90} of anti-MRSA drugs.

Antibiotics	MIC values	2012 ($n=62$)	2013 ($n=63$)	2014 ($n=75$)	Total ($n=200$)
Vancomycin	MIC_{50}	0.75	1	1.5	1
	MIC_{90}	2	2	2	2
Daptomycin	MIC_{50}	0.125	0.125	0.125	0.125
	MIC_{90}	0.25	0.38	0.38	0.38
Tigecycline	MIC_{50}	0.094	0.094	0.19	0.094
	MIC_{90}	0.38	0.38	0.5	0.5
Linezolid	MIC_{50}	0.19	0.25	0.5	0.38
	MIC_{90}	1	1.5	1.5	1.5