

RESEARCH ARTICLE

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## Tracking Vancomycin MIC Creep: A Five Year Analysis

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### Abstract

Methicillin resistant *Staphylococcus aureus* (MRSA) is a known human pathogen capable of causing community and hospital acquired infections worldwide. Treatment options available for MRSA infections are limited, with vancomycin being one of the most common drugs used. It is described in the literature that vancomycin can be ineffective against MRSA isolates with MIC values between 1-2 mg/litre. This slow and steady shift of vancomycin MIC values towards higher side over a period of time is known as "MIC creep". The present retrospective study was carried out over five year period from January 2019 to June 2023. *Staphylococcus aureus* isolates from all clinical samples isolated during study period were included in the study. MIC50, MIC90, geometric mean MIC values were determined and analysed using Microsoft Excel. In the present study, the prevalence of MRSA was high (79.6%) in pus and tissue samples followed by blood sample (9.7%). Most of the MRSA isolates (55.80%) in present study exhibited vancomycin MIC of 1 µg/ml, there is no increasing trend of MIC values over a five year period. MIC creep is a slow and steady process which is multifactorial in origin. Regular monitoring of vancomycin MIC trend is advisable as vancomycin is the first-line treatment for culture proven severe infection with MRSA.

**Keyword:** Treatment Failure, MIC Creep, Clonal Dissemination, Antimicrobial Stewardship, Hospital Infection Control

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## INTRODUCTION

Methicillin resistant *Staphylococcus aureus* (MRSA) is a known human pathogen capable of causing community and hospital acquired infections worldwide.<sup>1</sup> MRSA infections are associated with extended antibiotic therapy, increased duration of hospitalization, increased morbidity and mortality.<sup>2,3</sup> Treatment options available for MRSA infections are very few vancomycin being one of the commonest drug used.<sup>3,4-10</sup>

Various studies are conducted globally showing therapeutic failure in patients with MRSA infections with higher vancomycin MIC for the isolate though within susceptible range.<sup>8,11</sup> It is described in the literature that vancomycin can be ineffective against MRSA isolates with MIC values between 1-2 mg/litre.<sup>12-14</sup> This slow and steady shift of vancomycin MIC values towards higher side over a period of time is known as "MIC creep".<sup>15</sup> MIC creep results in slow clinical response, increased morbidity, higher relapse rates and therapeutic failure.<sup>16</sup>

American Thoracic Society and Infectious Diseases Society of America addressed the issue of clinical failure in MRSA infections due to higher MIC values for vancomycin.<sup>17,18</sup> In some local institutions MIC creep can be attributed to the clonal dissemination of these MRSA strains with higher MIC values.<sup>1</sup> For the clinical management of MRSA infections in particular geographic area it is important to study the susceptibility profile and MIC distribution pattern for the local MRSA isolates.<sup>19</sup> The present study was conducted to

assess the vancomycin MIC distribution for MRSA isolates in a tertiary care hospital in western Maharashtra, India.

## MATERIALS AND METHODS

The present retrospective study was carried out covering a five year period from January 2019 to June 2023 in the Microbiology diagnostic laboratory in a tertiary care centre. Ethical committee approval was obtained for this study.

*Staphylococcus aureus* isolates from all clinical samples isolated during study period were included in the study. Identification and antimicrobial susceptibility by microbroth dilution method of *Staphylococcus aureus* had been done by VITEK 2 automated system by Biomerieux, France. Methicillin resistance in *Staphylococcus aureus* was also determined by the automated system (VITEK 2) system by microbroth dilution method.<sup>1,15</sup>

MIC50, MIC90, geometric mean MIC values were determined and analysed using Microsoft Excel. Statistical significance was calculated using related samples Friedman's two-way analysis of variance by rank test.

## RESULTS

In the present study, total 900 MRSA isolates were obtained from all clinical samples over a period of five years. Sample wise distribution of MRSA isolates is shown in Table 1.

### MIC parameters for Vancomycin in MRSA isolates

MIC distribution of all MRSA isolates is shown in Figure 1. MIC range for vancomycin

**Table 1.** Showing sample wise distribution of MRSA isolates

Type of samples	No. of MRSA isolates (Total isolates=900)	Percentage MRSA
Pus and tissue	716	79.6%
Blood	87	9.7%
Respiratory samples (Sputum, ETT, BAL)	35	3.9%
Urine	45	5%
Body fluids (Ascitic fluid, CSF, Pleural fluid)	17	1.9%

**Table 2.** Year wise Vancomycin MIC distribution in MRSA isolates

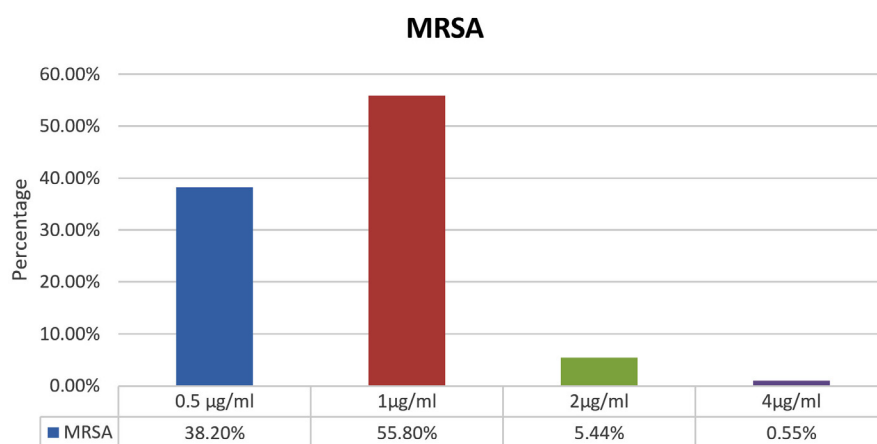
Year	Vancomycin MIC distribution in MRSA isolates			
	0.5 µg/ml	1 µg/ml	2 µg/ml	4 µg/ml
2019	32.9	58.4	7.56	1.03
2020	35.06	57.79	6.49	0.64
2021	40.78	55.86	2.79	0.55
2022	46.26	49.25	9.47	0
2023	37.33	58.66	4	0

in MRSA was from 0.5 to 4 µg/ml. Out of total 900 isolates of MRSA, 99.4% were vancomycin susceptible (VSMRSA) and 0.55% isolates were vancomycin intermediate (VISA). Vancomycin resistant MRSA (VRSA) strains were not observed in present study. Most of the MRSA isolates (55.8%) exhibited MIC value of 1 µg/ml. Year wise vancomycin MIC distribution is shown in Table 2. The percentage of VISA in 2019 were 1.03%, there after there was decreasing trend in 2020-2021 and VISA isolates were absent in 2022-2023. The vancomycin MIC related parameter analysis is shown in Table 3. The Vancomycin MIC50 value was 1 µg/ml in all five years. MIC90 value for vancomycin for 2019-2020 was 2 µg/ml after that it decreased to 1 µg/ml in 2021 to 2023. Geometric mean (GM) MIC value trend over a period of five years is shown in figure 2. Highest mean MIC values

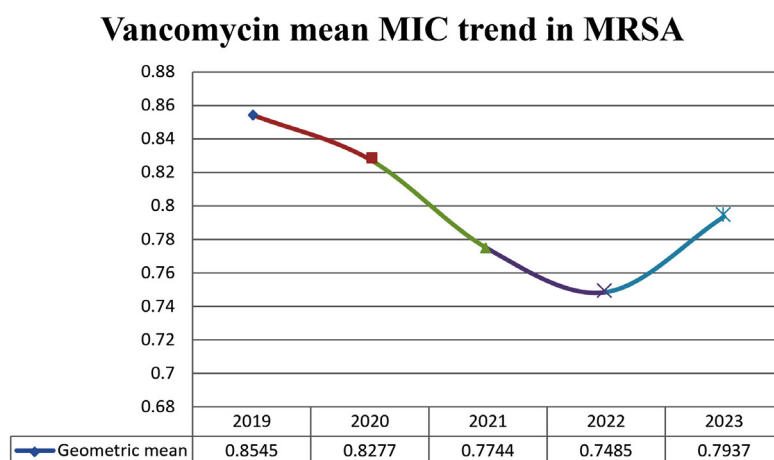
were observed in 2019 and lowest MIC values were seen in 2022. The declining trend of mean MIC values was observed from 2019-2022. This difference in the geometric mean MIC values over a period of 5 years was found to be statistically insignificant ( $p > 0.05$ ).

**Table 3.** Vancomycin MIC related parameters in MRSA

Year	MIC 50 µg/ml	MIC 90 µg/ml	Geometric mean µg/ml
2019	1	2	0.8545
2020	1	2	0.8277
2021	1	1	0.7744
2022	1	1	0.7485
2023	1	1	0.7937



**Figure 1.** Vancomycin MIC distribution in MRSA isolate



**Figure 2.** Vancomycin mean MIC trend in MRSA

## DISCUSSION

MRSA is a very important pathogen in both community and hospital set up.<sup>20</sup> In the present study prevalence of MRSA was high (79.6%) in pus and tissue samples. (Table 1) Lohan *et al.* (61.7%) and Mallick and Basak (61.4%) also showed similar finding in their studies.<sup>21,22</sup>

The present study is the first Indian study showing vancomycin MIC trend over a period of 5 years. In this study, MIC50 values for vancomycin were found to be constant over five year period. Studies conducted by Alos *et al.*<sup>23</sup> and Arshad *et al.*<sup>24</sup> have also not shown change in MIC 50 values over a period of four years. However, Steinkraus *et al.* have shown increase in MIC50 value from 0.75 µg/ml to 1 µg/ml over a period of five years.<sup>25</sup> The geometric MIC values showed decreasing trend from 2019-2022. Though most of the MRSA isolates (55.80%) in present study exhibited vancomycin MIC of 1 µg/ml, there is no increasing trend of MIC values over a five year period. Studies have reported that geometric MIC value is a sensitive marker to reflect the changes in MIC values as compared to other markers like MIC50, MIC90, percentage susceptible and percentage resistant.<sup>24-29</sup>

Vancomycin remains the mainstay of treatment for infections caused by MRSA. There is large numbers of work done describing vancomycin MIC creep, which means sustained increase in the MICs of vancomycin within susceptible range against *Staphylococcus aureus*.<sup>6,7,27</sup> But the results of these studies are conflicting. Various studies conducted globally have demonstrated MIC creep phenomenon.<sup>1,24,28-31</sup> Few studies have shown no change in vancomycin MICs over period of years.<sup>25,32,33</sup> On the contrary, studies conducted by Joana *et al.*, Haas *et al.* and Lu *et al.* have shown decreasing trend of vancomycin MICs in MRSA isolate.<sup>34-36</sup> Some authors have reported that pooling data from multiple centers can obscure the MIC trend that exists in individual set up. Also there can be variation in MIC values in two different institutes in the same geographic area.<sup>19</sup>

The present study did not show any vancomycin MIC creep phenomenon. The decreasing trend of vancomycin MICs in the present study was mainly associated with

decrease in percentage of MRSA isolates with MIC >1µg/ml over a period of 5 years. The development of vancomycin MIC creep is found to be multifactorial.<sup>1</sup> It is affected by drug over use, clonal spread, geographical area, methodologies used to detect vancomycin MIC, guidelines used for interpretation<sup>1,26</sup> and MIC parameters analysed.<sup>24</sup> Other important factors affecting the MIC creep are antimicrobial stewardship and hospital infection control practices in the institute.<sup>1,26,24</sup> Recognition of this creep phenomenon is important as it can be precursor of hVISA and VISA and can lead to therapeutic failure with poor outcome.<sup>4,5,7,8,37,38</sup> Joana *et al.* reported that MIC creep phenomenon is not generalised. So each institution should independently monitor vancomycin MICs in their set up.<sup>34</sup>

The present study had certain limitations. The MIC values were taken from the automated susceptibility testing system and were not confirmed by any other method. The performance of the automated system for detection of glycopeptide resistance are said to underestimate the MICs,<sup>37-39</sup> but still these results were useful for observing the trend of vancomycin MICs over a long period in present study.

## CONCLUSION

The “MIC creep” for vancomycin was not observed in present study. MIC creep is a slow and steady process which is multifactorial in origin. Regular monitoring of vancomycin MIC trend is advisable as vancomycin is the first-line treatment for culture proven severe infection with MRSA. An analysis of regional variation is essential as they may differ from global trends.

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None

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## AUTHORS' CONTRIBUTION

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

**FUNDING**

None.

**DATA AVAILABILITY**

All datasets generated or analyzed during this study are included in the manuscript.

**ETHICS STATEMENT**

This study was approved by the Institutional Ethics Committee, Bharati Vidyapeeth (Deemed to be University) Medical College, Pune, India, with reference number BVDUMC/IEC/127.

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