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Vancomycin Minimum Inhibitory Concentration Trend in Methicillin Resistant *Staphylococcus aureus* from a Tertiary Care Hospital in Central Kerala, India

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ABSTRACT

Background: Methicillin resistant *Staphylococcus aureus* (MRSA) is an important cause of nosocomial infections. Vancomycin is one of the mainstays for the cure of MRSA infections and vancomycin MIC creep have been reported from different parts of the world. This study evaluated the trends of vancomycin MIC among the MRSA and analysed its relationship with vancomycin consumption.

Methods: During the six years of this retrospective study, the MIC of Oxacillin and Vancomycin of all clinically relevant *Staphylococcus aureus* were retrieved from the automated Vitek-2 compact system. The consumption rate of vancomycin in our hospital as the defined daily doses (DDDs) per 1000 bed-days were collected from Pharmacy services. The data obtained were statistically analysed.

Results: Out of 1,19,112 total samples processed 2.02% were found as *Staphylococcus aureus* among which 44.7% were MRSA. Over the study period, all the MRSA isolates were susceptible to vancomycin and there was a statistically significant increase in isolates with vancomycin MIC =1 µg/ml depicting the MIC creep phenomenon in our isolates. But a significant correlation between DDDs/1000 bed days of vancomycin and increase in MIC range could not be established.

Conclusion: There is a dire need to identify the trend of vancomycin MICs in our local area to assess the existence of creep trend and warn the clinicians of these disastrous strains. Sensitization about this type of MRSA MIC creep among the primary health physician is also needed to implement the control measures and limit its spread in communities.

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Introduction

Antimicrobial resistance (AMR) is an expanding threat and this process gets accelerated with misuse and overuse of antimicrobials. Methicillin resistant *Staphylococcus aureus* (MRSA) is an important cause of nosocomial infections. Vancomycin has been the cornerstone in the treatment of patients with serious methicillin resistant *Staphylococcus aureus* (MRSA) infections. There are vancomycin-susceptible *S. aureus* (VSSA) with MIC ≤ 2 µg/ml, vancomycin-intermediate *S. aureus* (VISA) with MIC of 4–8 µg/ml, and VRSA with MIC ≥ 16 µg/ml. VISA strains are generally believed to be initiated from heterogeneous vancomycin-intermediate *S. aureus* (hVISA), which is defined as an *S. aureus* strain with a vancomycin MIC within the susceptible range (≤2 µg/ml) determined by conventional methods, while a cell subpopulation is in the vancomycin-intermediate range (≥4 µg/ml) (1, 2).

A reduction in the efficacy of vancomycin against MRSA strains with a high vancomycin MIC (1–2 µg/mL) has been described in many observational studies, suggesting that subtle changes in the MIC may lead to treatment failures (3). This phenomenon of gradual increase in the value of glycopeptide vancomycin MIC for *S. aureus* is known as MIC creep. Although the vancomycin MIC creep is a global scenario, regional evaluation of susceptibility profiles is important for the successful clinical management of MRSA infections locally. Monitoring antimicrobial usage remains a cornerstone of antimicrobial stewardship programme. So, this study was initiated with an objective of determining the vancomycin MIC trends of MRSA isolates over six years & to analyse the relationship between the vancomycin consumption in the hospital & vancomycin MIC trend.

Materials and Methods

The study was conducted retrospectively for a period of 6 years (January 2016 to December 2021) in the Department of Microbiology Jubilee Mission Medical College & RI, Thrissur. The specimens received in the Microbiology laboratory were processed as per routine microbiology techniques. The antibiotic susceptibility data of all clinically relevant non-repetitive *Staphylococcus aureus* isolates were retrieved from the automated Vitek-2 compact system. The MIC of Oxacillin and Vancomycin were analysed.

According to WHO Collaborating Centre for Drug Statistics Methodology (4). (http://www.whocc.no/atcddd/), the usage of vancomycin in hospital is described by the defined daily doses per 1000 bed-days (DDDs/1000 bed-days). The consumption of vancomycin in our hospital was obtained from the records of the Pharmacy Service. The number of in-patients every year was collected from the Medical Records Room.

Statistical Analysis

The data obtained were analysed using IBM SPSS system for statistical data analysis. Association between DDDs/1000 bed days for vancomycin and the MRSA susceptibility was assessed using Linear Regression Analysis.

Results

We received a total of 1,19,112 samples (Blood, Pus, Urine & Respiratory specimens) for culture and sensitivity in the Dept of Microbiology, Jubilee Mission Medical college during the study period of six years from Jan 2016 to Dec 2021. The specimen wise and year wise distribution of total samples received is depicted in Table 1.

Table 1. Specimen wise and year wise distribution of total samples.

YEAR	BLOOD	PUS	URINE	RESPIRATORY	TOTAL
2016	4490	3195	4650	1184	13519
2017	8076	3758	9945	3825	25604
2018	7713	3587	8953	3269	23522
2019	7229	3613	8461	2789	22092
2020	5659	2807	6462	1712	16640
2021	6389	2773	6576	1997	17735
TOTAL	39556	19733	45047	14776	119112

The percentage of clinically relevant *Staphylococcus aureus* isolated from the total samples is 2.02% (N=2410). The year wise distribution of clinically relevant *Staphylococcus aureus* in percentage is shown in Figure 1.

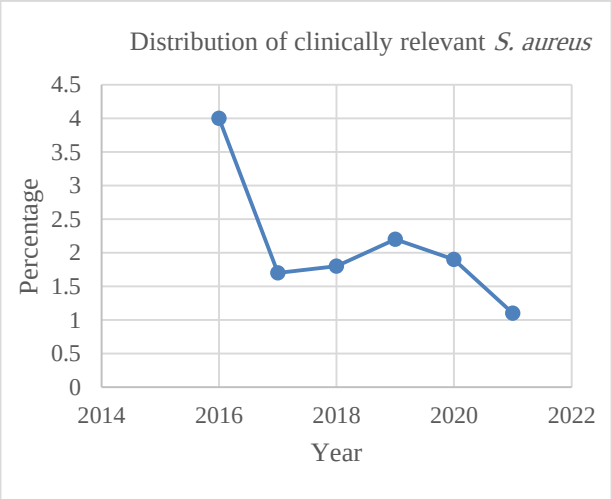

Fig 1. Year wise distribution of clinically relevant *Staphylococcus aureus* in percentage.

After analysing Oxacillin MIC, 1077 isolates (44.7%) among the 2410 clinically relevant *Staphylococcus aureus* (44.7%) isolates were found to be methicillin resistant *Staphylococcus aureus* (MRSA).

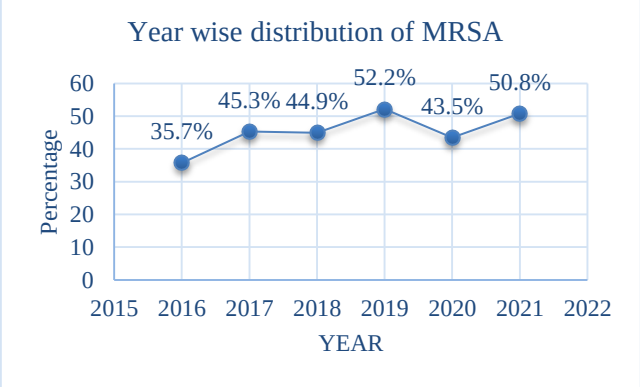

Fig 2. Yearwise distribution of MRSA.

The year wise, specimen wise, department wise distribution of MRSA isolates are detailed in Figure 2, 3 and 4.

All strains were susceptible to vancomycin using current CLSI guidelines. The vancomycin MIC distribution of MRSA over the six years are depicted in Figure 5. Vancomycin consumption during the study period in our hospital is shown in Figure 6.

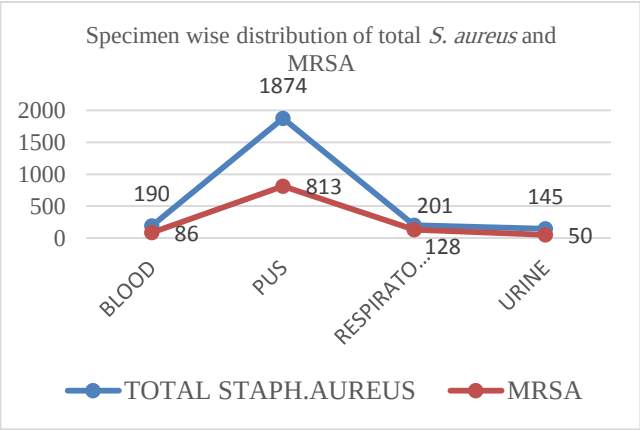

Fig 3. Specimen wise distribution of total *S. aureus* and MRSA.

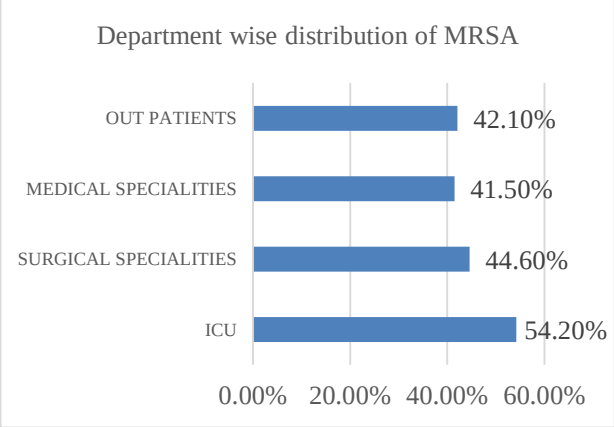

Fig 4. Department wise distribution of MRSA.

Over the study period, there was a significant reduction ($p < 0.001$) in the number of MRSA isolates with MIC < 0.5 mg/L ranging from 62.4% to 23.8%, and expected increase in the number of MRSA isolates with MIC = 1 mg/L (35.6% to 72.3%) and MIC = 2 mg/L (2.1% to 4%). Annual vancomycin consumption rates in our hospital ranged from 1.4 to 1.7 DDDs/1000 bed days during the study period. Correlation analysis between the consumption of vancomycin and the percentage of MRSA isolates with a vancomycin MIC = 1 mg/L revealed a statistically significant low positive correlation ($r = 0.302$, $p < 0.05$).

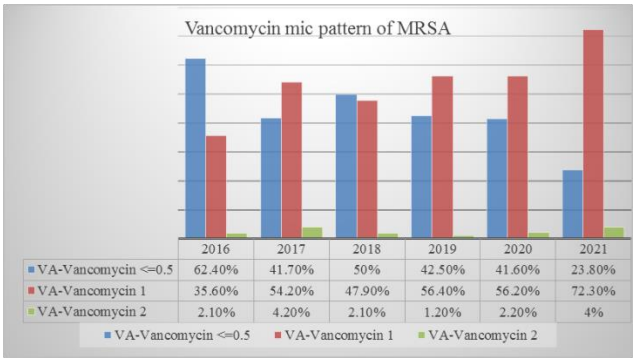

Fig 5. Yearwise vancomycin MIC pattern of MRSA.

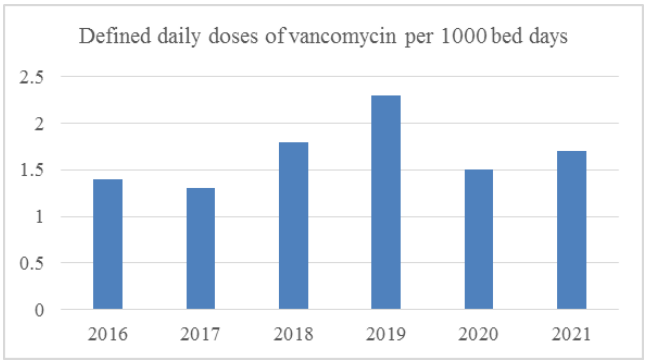

Fig 6. Year wise Vancomycin usage (DDD/1000 bed days).

Discussion

MRSA accounts for a sufficiently large proportion of hospital-acquired infection (HAI) disease, thus making it "worth" targeting. In a recent study, MRSA was identified to be a leader in global deaths as far as antimicrobial resistance is concerned (5). Despite ongoing development of new treatments, active surveillance efforts, and advancements in infection control, the incidence of MRSA has emerged as a major source of morbidity, higher costs of healthcare delivery services, and increased mortality in hospitals over the past decades along with organisms such as

carbapenem resistant *Enterobacteriaceae* (CRE), *Acinetobacter*, Extended Spectrum Beta-Lactamase (ESBL) producing bacteria, *Klebsiella* and *Clostridium difficile* (6,7). The prevalence of MRSA varies greatly between nations, as well as from one hospital to another within a single nation. The most recent data from the WHO on MRSA incidence showed rates surpassing 20% in all WHO regions and even as high as 80% in some countries (8).

Vancomycin has been one of the first line drugs to treat MRSA infections for decades (9). However, the clinical isolates of *S. aureus* with intermediate and complete resistance to vancomycin have emerged within the past two decades, and have become a serious public health concern (10, 11). The increase in the vancomycin MIC for MRSA in susceptible range over time (MIC creep) is a phenomenon reported in prior studies as a possible predictor of treatment failure and precursor to vancomycin-intermediate *S. aureus* and heterogeneous VISA (VISA and hVISA) (12, 13).

In the present study, clinically relevant *S. aureus* isolated accounts for a 2.02% over a six year period from 2016 to 2021. Among the 2410 clinically relevant *Staphylococcus aureus*, 1077 isolates (44.7%) were found to be MRSA. In India the MRSA prevalence ranges from 26.14% to 70%, with variations observed between hospital and community settings and many studies showed similar trend of MRSA as observed in our study (14, 15).

In the present study, from 2016 to 2021; continuous increase in MRSA isolates in the clinical specimen was observed from 35.7% (2016) to 50.8% (2021). In a similar study conducted in Wardha, India increasing trend was observed by Mallick and Basak (16). Similar rising trend were observed from Germany, United Kingdom, and Greece by Tiemersma et al. between 1999 and 2002 (17).

Several studies reported a higher detection of MRSA from pus aspirates and similar findings were present in our study (16, 18). This could be due to exposure of wound to microorganism in the environment and *S. aureus* present on skin as commensal makes the wound more prone for infection.

In the present study, MRSA were observed more in inpatients (IP) (73.6%) as compared to outpatients (OP) (26 %) cases which could be attributed to presence of MRSA strains in hospital environment mainly various Intensive Care Units (ICUs) and wards. It is similar to the findings by Lohan et al18 from North India in 2021.In the present study, highest number of MRSA (54.2%) isolates were from ICUs followed by surgical specialities. An obvious reason for this observation could be colonization of skin by MRSA and increased chances of invasion with use of invasive approach associated with surgical departments and indwelling devices in ICUs. Similar trends were observed by Mallick and Basak and Sanjana et al (16, 19).

The prevalence of MRSA strains, which have been shown to be resistant to vancomycin in earlier investigations, varies substantially depending on the study location, from none (0.0%) in Nepal (20) to 0.33% in India (21), and alarmingly higher (29.4%) in Ethiopia (22) and 62.5% in south-west Nigeria (62.5%) (23) Analysing the vancomycin susceptibility in the present study, all isolates were susceptible to vancomycin using current CLSI guidelines. This lack of resistance is encouraging because vancomycin is the treatment of choice for MDR MRSA infections and should only be used as a last resort for MRSA infections that have proven resistant to other classes of antibiotics, in view of the possibility of resistance emergence.

In the present study, there is a statistically significant increase ($p < 0.05$) in the vancomycin MIC 1 µg/mL (35.6% to 72.3%) during the study period. It was also noted that the percentage of MRSA isolates with MIC 2 µg/mL also had a shift from 2.1% to 4% over the six year period. From India, in 2020 a study by Ketaki et al showed the

phenomenon of Vancomycin MIC creep correlating with the results of our study (24). In a study by Golan et al., (25) authors reported a statistically significant increase in vancomycin MIC from 2001-2005 in a regional medical centre in the United States. In a study done by Afzal Husain, in 2014 to 2016 and in a study done by Chang et al, in 2010, in China, vancomycin MIC creep phenomenon was observed (13, 26).

The development of dynamic changes in the vancomycin MIC over time can be explained by many factors like clonal replacement of *S. aureus*, drug overuse, the availability of alternative drugs like linezolid, teicoplanin for MRSA and antibiotic restriction in stewardship programs. The annual vancomycin consumption rate analysis of our hospital based on defined daily doses per 1000 bed-days (DDDs/1000 bed-days) has not shown a significant increase from 2016 to 2021. In a study by Chang et al, (13) a correlation analysis between the vancomycin usage density and the percentage of MRSA isolates with a vancomycin MIC = 1 mg/L and MIC ≤0.5 mg/L unveiled a statistically significant association indicating the increase of vancomycin usage may have contributed to MIC creep. In the present study, correlation analysis between the consumption of vancomycin and the percentage of MRSA isolates with a vancomycin MIC = 1 mg/L revealed a very low positive correlation coefficient (r = 0.302) and a clear correlation between them could not be established.

Conclusion

Vancomycin "MIC creep" was detected in our dataset. MIC creep is a dynamic process that can be influenced by many factors. By looking at other factors and monitoring the MIC trend of vancomycin and its usage may help in providing insight into emergence of resistance. Other hospitals and healthcare providers in our state should monitor their local status of vancomycin MICs and screen for the possibility of MIC creep. Present study stress upon the need of continuous monitoring of MRSA and their antibiogram in tertiary care setting as well as hospital located in periphery. The most effective way to prevent MRSA infection is by performing regular MRSA surveillance of HCWs, strict compliance to hand hygiene, and formulation of antibiotics policies with effective infection control practices. The message needs to be spread loud and clear: We are running out of antibiotic armamentarium against *Staphylococcus aures*, if we do not stop antibiotic abuse, we will be left with no drug to deal with this dreaded organism.

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Ethics approval and consent to participate

Not needed.

Conflict of interest

None.

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