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Original Research Article

Vancomycin intermediate and vancomycin resistant *Staphylococcus aureus*: an upcoming threat

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ABSTRACT

Background: Either community or hospital settings, *Staphylococcus aureus* is a significant pathogen that causes mild localized infections of the skin to potentially fatal systemic infections. The increasing evidence of reduced vancomycin susceptibility (RVS) and vancomycin resistance in clinical MRSA isolates is troubling. There aren't many therapeutic options available for such isolates. We have identified the most current pattern of antimicrobial resistance and specifically evaluated *Staphylococcus aureus's* susceptibility profile to vancomycin. vancomycin-intermediate *Staphylococcus aureus* and isolates of *Staphylococcus aureus* that are resistant to vancomycin.
Methods: Non-duplicate, consecutive isolates of *S. aureus* obtained from January 2021 to June 2022 were subject to antimicrobial susceptibility testing using standard disk diffusion tests or epsilometer tests according to the clinical laboratory standards institute 2021 requirements.
Results: The total of 315 *S. aureus* were isolated during study period. Swab and pus sample shows highest isolation followed by other sample types. A total of 202 (64.1%) isolates were MRSA, while 111 (35.2%) were Inducible clindamycin positive (ICR Positive). Antibiotic resistance observed is, penicillin (303/315, 96.1%), Ofloxacin (266/315, 84.4%), levofloxacin (255/315, 80.9%), Azithromycin (190/315, 60.3%) followed by other class of antibiotic groups. In our study Vancomycin , Linezolid and Teicoplanin are 100% sensitive. Vancomycin resistance is not noted in any isolates but we have 7 Vancomycin intermate isolates.
Conclusions: Gate keeping in advent use of antibiotic is paramount importance to control the antibiotic resistance. As well as continuous laboratory monitoring of various antibiotic resistance pattern is needed.

Keywords: Methicillin-resistant *Staphylococcus aureus*, *Staphylococcus aureus*, Vancomycin, Vancomycin-intermediate *Staphylococcus aureus*, Vancomycin-resistant *Staphylococcus aureus*

INTRODUCTION

One important pathogen that can be found in both clinical and community settings is *Staphylococcus aureus* ranging in intensity from mild localized infections of the skin and skin structure to potentially lethal systemic infections such osteomyelitis, sepsis, necrotizing pneumonia, septic arthritis and endocarditis.[1]

MRSA (Methicillin Resistant *Staphylococcus aureus*) is widespread in hospitals today and the rise of community-associated (CA) MRSA has raised yet another significant issue.[2] The first found glycopeptide antibiotic vancomycin, offers one of the empiric therapies and continues to be a cornerstone for treating MRSA (Methicillin Resistant *Staphylococcus aureus*) infections.[3]

From Japan, the first vancomycin intermediate *S. aureus* (VISA) with a MIC of 8 ug/ml was reported in 1997.[4] In 2002, the first instance of Vancomycin resistant *S. aureus* (VRSA) was accounted for in a diabetic patient in the USA.[5]

Vancomycin discovery and action mechanism

Vancomycin was isolated from Amycolatopsisorientalis.[6] The Clinical and Laboratory Standards Institute has divided the *S. aureus* isolates with decreased vancomycin susceptibility into three categories. Vancomycin-intermediate *S. aureus* (VISA) has a MIC of 4–8 ug/ml, vancomycin-susceptible *S. aureus* (VSSA) has a MIC of less than 2 ug/ml and VRSA has a MIC greater than 16 ug/ml.

Molecular techniques should be used to demonstrate the presence of vanA or other van resistance determinants in order to determine whether an isolate is a member of the VRSA.[6-8]

VISA strains are generally believed to be initiated from heterogeneous vancomycin-intermediate *S. aureus* (hVISA), which is defined as *S. aureus* strain with a vancomycin MIC within the susceptible range determined by conventional methods, while a cell subpopulation is in the vancomycin-intermediate range (1-4 ug/ml). The exact mechanism of resistance is unknown.[6]

Comparative genomics has, however, been used extensively to find genetic factors linked to vancomycin-intermediate resistance. The analysis of the transcriptome and proteome of VISA and its isogenic VSSA revealed several alterations in the genes involved for VISA production.[9,10] Out of all important genes involved in regulatory systems WalKR, GraSR and VraSR.[11-16] Despite having different genetic backgrounds, VISA strains often exhibit similar characteristics, such as thicker cell walls, decreased autolytic activity, and a reduction in virulence.[17]

Vancomycin resistance in vancomycin resistance Enterococi was mediated mostly by transposons discovered on plasmids, which prompted serious concerns regarding the potential of Vancomycin-resistant traits in medically significant, universally susceptible bacteria, particularly *S. aureus*.[18]

These isolates usually have a high MIC of >16 ug/ml. The mechanism of resistance in VRSA is target modification because of transferable van A gene, possibly of enterococcal in origin.[6]

According to the centers for disease control and prevention (CDC), From Michigan a 40-years-old woman became the first known individual in the world to contract a strain of *Staphylococcus aureus* that was resistant to the antibiotic vancomycin in the summer of 2002.[19] Since then, reporting of VRSA isolates from different part of world have been continuously noted.

So, the present study is conducted aiming to i) evaluate antibiotic susceptibility pattern of *Staphlococcus aureus*. ii) To identify vancomycin intermediate and Vancomycin resistant *Staphylococcus aureus*.

METHODS

This laboratory based retrospective observational study between January 2021 to June 2022. The study was conducted after ethical clearance from institutional ethics committee. Inclusion and exclusion criteria. All samples came for bacteriological culture and antibiotic susceptibility testing received in to microbiology department in the last one and a half year would be included. Sample for fungal culture, duplicate sample are excluded.

Various samples including blood, pus, smear, body fluid and urine were collected during the study period and subjected to bacterial culture on culture media followed by biochemical reaction and antibiotic susceptibility identification by Mueller-Hinton agar (MHA) disk diffusion method. The latest CLSI recommendations were followed.

All disks were purchased from HiMedia, Mumbai, Maharashtra, India. MRSA were identified by disk diffusion testing with cefoxitin (30 µg). Inducible resistance to clindamycin in isolates with erythromycin resistance was detected using the D test. Vancomycin testing was performed using the E test. Interpretation of the antibiotic susceptibility profile was based on the CLSI of the corresponding year. *S. aureus* strains ATCC 25923, ATCC 29213 and ATCC 43300 were used as quality control strains for disk diffusion testing, MIC testing and MRSA testing, respectively. Total 29388 samples were received during the study period. Out of that 6800 are positive samples. Total of 315 *S. aureus* were identified during the study period.

Data extraction and definitions–The collection of data and analysis was done after ethical approval, which was after April 2023.Forvancomycin-susceptible *S. aureus* (VSSA) with MIC<2 ug/ml, vancomycin-intermediate S. aureus (VISA) with MIC of 4–8 ug/ml and VRSA with MIC>16 ug/ml.

Statistical analysis

Data was entered in Microsoft excel windows 10 and analysis was done by using Microsoft excel including frequency distribution and percentage.

RESULTS

Total 29388 samples were received during the study period. Out of that 6800 are positive samples. Total of 315 *S. aureus* were identified during the study period. Out of 6800 positive isolates, 315 were *S. aureus*.

Their sample-wise distribution as follows: swab (194, 61.5%), pus (60, 19%), blood culture (25, 7.9%), body fluid (9, 2.8%), sputum (8, 2.5%) and tissue (6, 1.9%), Endotracheal tube (4, 1.2%), urine (3, 0.9%), tip (2, 0.6%), Cerebro-spinal fluid (2, 0.6%), drain (2, 0.6%). Out of total

isolates two hundred and forty-one (76.5%) isolates were from male patients, whereas 74 (23.4%) were from females. Male to female ratio is 3.2:1. Figure 1 shows age-wise distribution of all cases.

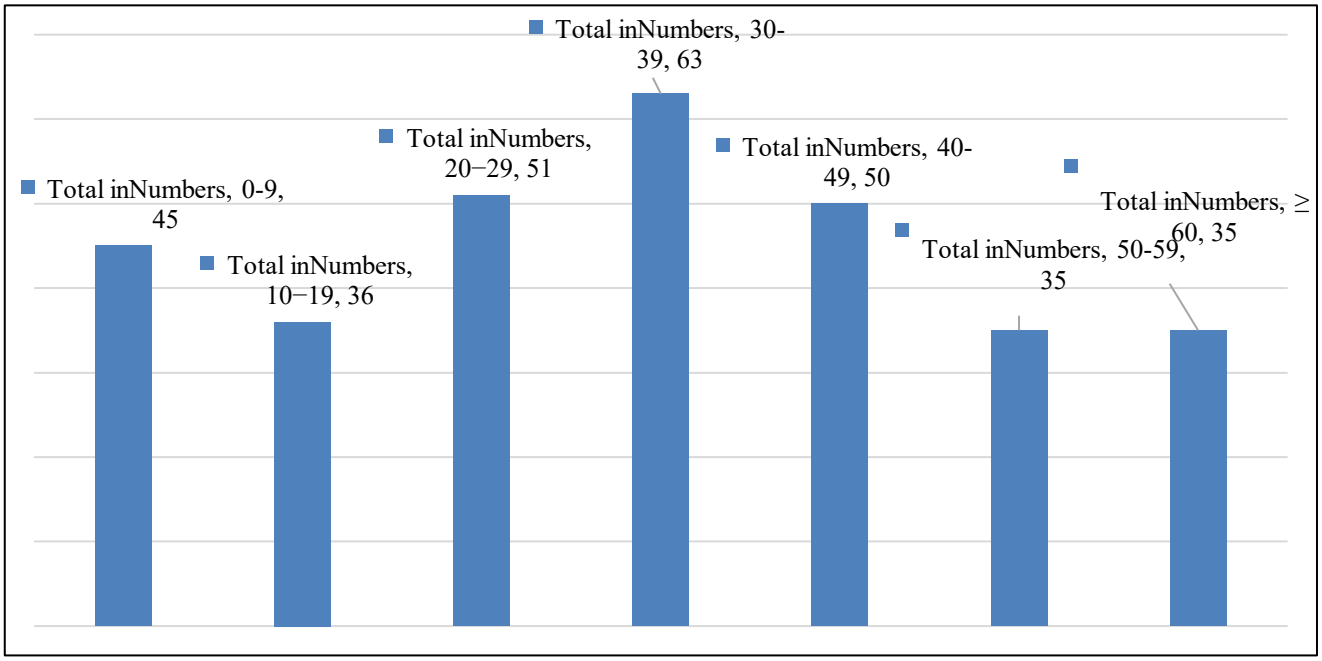

Figure 1: Age-wise distribution.

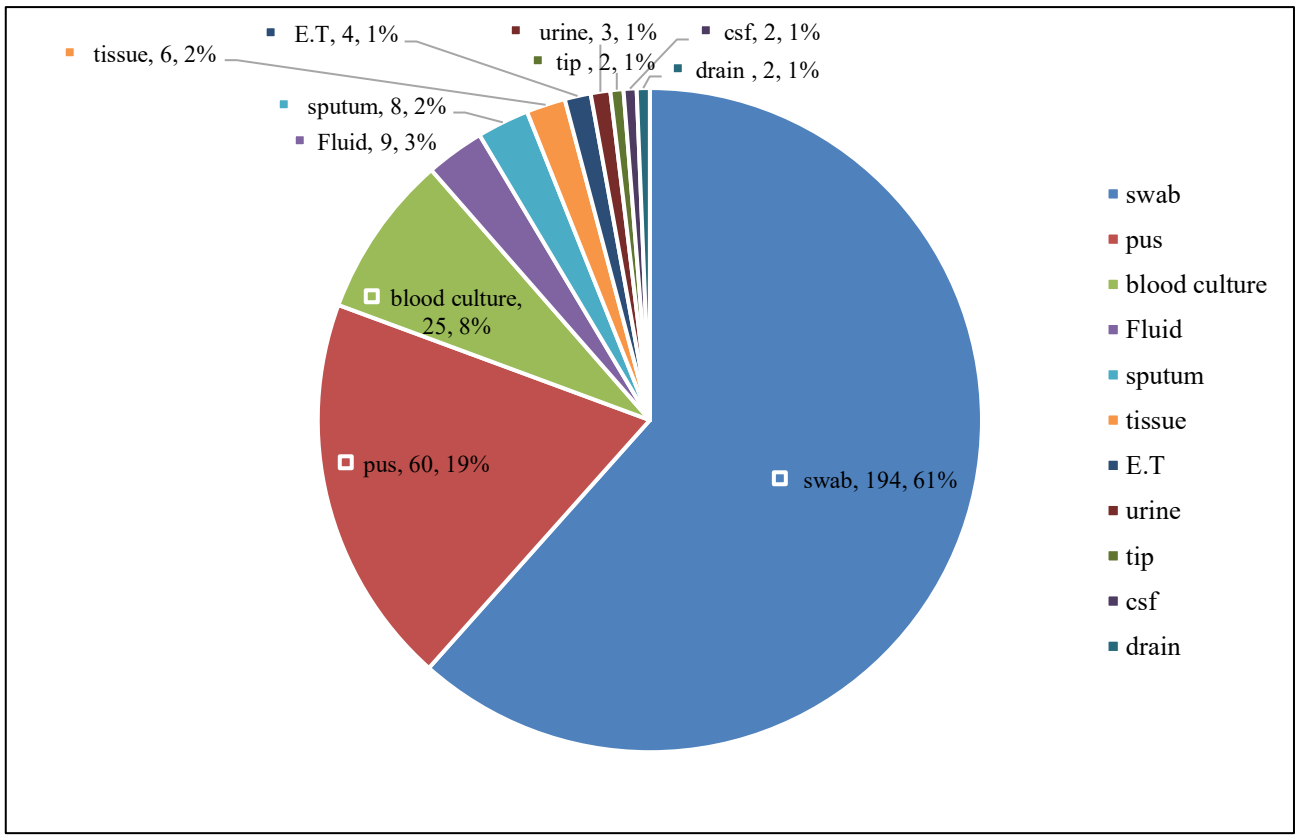

Figure 2: Sample-wise distribution.

When we look at the sample-wise distribution, top three sample types were swab sample highest 194 (61.5%) followed by Pus 60 (19 %) and Blood culture 25 (7.9%). Looking at detailed distribution of samples we can say that *Staphylococcus aureus* can do almost all system infection. Figure 2 shows Sample-wise distribution.

A total of 202 (64.1%) isolates were MRSA, while 111 (35.2%) were Inducible clindamycin positive (ICR Positive). The MRSA isolates recovered from the OPD patients was 13% (41), whereas that from the admitted patients was 50.7% (160). Overall, high resistance was observed to penicillin (303/315, 96.1%), ofloxacin (266/315, 84.4%), levofloxacin (255/315, 80.9%), azithromycin (190/315, 60.3%), erythromycin (189/315, 60%), ciprofloxacin (150/315, 47.6%), clindamycin (136/315, 43.1%) and resistance was low to Tetracycline (25/315, 7.9%), rifampicin (13/284, 4.1%) and doxycycline (17/284, 5.3%), isolates shows no resistance to Vancomycin, Linezolid and Teicoplanin I observe. Table 2 shows the distribution of MRSA and MSSA MICs to vancomycin, revealing that 308 (97.7%) isolates were susceptible to vancomycin and 7 (2.2%, 1 MRSA and 6 MSSA) had intermediate resistance. The maximum number of isolates (53.0%) had vancomycin MICs of 1.5 µg/ml, followed by 1.0 µg/ml (27.6%). Of the 7 VISAs, 2 (28.5%) had vancomycin MICs of 3 µg/ml, 3 (42.8%) had MICs of 4 µg/ml and 2 (28.5%) had vancomycin MICs of 6 µg/ml.

Table 1: Antibiotic profile of *Staphylococcus aureus* isolates (n=315) to various antimicrobials.

Antibiotic	Resistant isolates (%)
Penicillin-G (10 ug)	303 (96.1)
Ofloxacin (5 ug)	266 (84.4)
Levofloxacin (5 ug)	255 (80.9)
Azithromycine (15 ug)	190 (60.3)
Erythromycin (15 ug)	189 (60)
Clarithromycine (15 ug)	166 (52.6)
Ciprofloxacin (5 ug)	150 (47.6)
Clindamycin	136 (43.1)
Gentamycin (10 ug)	59 (18.7)
Chloramphenicol (30 ug)	30 (9.5)
Co-trimoxazole (1.25/23.75 ug)	26 (8.2)
Tetracycline (30 ug)	25 (7.9)
Doxycycline (30 ug)	17 (5.3)
Rifampicin (5 ug)	13 (4.1)
Vancomycin	0 (0.0)
Linezolid (30 ug)	0 (0)
Teicoplanin (30 ug)	0 (0)

Table 2: Minimum inhibitory concentration distribution of methicillin-resistant *Staphylococcus aureus* and methicillin-susceptible *Staphylococcus aureus* to vancomycin.

S. aureus isolates	MIC to vancomycin (µg/ml) by E-test								
	0.5	**0.75**	**1**	**1.5**	**2**	**3**	**4**	**6**	**Total**
MRSA	1	5	61	108	26	0	0	1	202
MSSA	0	5	26	59	17	2	3	1	113
Total (%)	1	10	87	167	43	2	3	2	315

S. aureus=*Staphylococcus aureus*, MRSA=Methicillin-resistant *S. aureus*, MSSA=Methicillin-susceptible *S. aureus*, MIC=Minimum inhibitory concentration.

DISCUSSION

The study presents comprehensive data on MRSA and MSSA in a tertiary care hospital in eastern India that receives patients not only from local areas on a primary basis but also through referrals from neighbouring districts and states. The top three isolates in the study included smear samples with the highest number of 194 (61.5%), followed by pus 60 (19%) and blood cultures 25 (7.9%). The study also revealed a prevalence of MRSA among S. aureus isolates of 64.1% (202 of 315), which is comparable to previously published studies from India in recent times with a prevalence of 38.4% to 54.8%.[20-22]

Antibiotics such as Penicillin, ofloxacin, levofloxacin, Azithromycin, erythromycin, ciprofloxacin, clindamycin shows highest resistance while Tetracycline, rifampicin and doxycycline shows low resistance.

As regards vancomycin susceptibility demonstrated a vancomycin MIC of 1.5 µg/ml, followed by 1.0 µg/ml (27.6%). Among 7 VISA, 2 (28.5%) had vancomycin MIC 3 µg/ml, 3 (42.8%) had MIC 4 µg/ml and 2 (28.5%) had vancomycin MIC 6 µg/ml.[23] Apart from these, two studies from North India have observed the presence of VISA and hVISA in their setup.[24,25]

Limitation of study is we wanted genome level of research to explore all possible genes involved or other new information detected for better understanding of this upsurging resistance.

CONCLUSION

Staphylococcus is most common micro-organism causing disease. Increasing MRSA as well as presence of VISA strains put current scenario to alarm. Looking at our antibiotic susceptibility Vancomycin, Linezolid and Teicoplanin are 100% sensitive for future management. But our study shows VISA isolates which means we need to monitor the usage of antibiotic and continuous testing monitoring of different antibiotic by laboratories.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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