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NOSOCOMIAL VANCOMYCIN RESISTANT STAPHYLOCOCCUS AUREUS (VRSA) IN A TERTIARY CARE TEACHING HOSPITAL; AN EMERGING TREND.

Medical Science

Shaika Farooq* Associate professor, Department of microbiology. Government medical college, Srinagar.J&K.India. *Corresponding Author

Afshan Shabir Senior Resident, Department of Medicine, Government Medical College, Srinagar. J&K.India.

Saqib Reshi Post graduate scholar, Department of Microbiology. Government Medical College. Srinagar. J&K.India.

Nahida Nahvi Professor. Department of Microbiology. Government Medical College. Srinagar. J&K.India.

ABSTRACT

Introduction. Methicillin resistant *Staphylococcus aureus (*MRSA) is a common pathogen in hospital and community acquired infections worldwide. Vancomycin, teicoplanin, linezolid, tigecycline are the chemotherapeutic agents mostly used in treatment of such infections. Clinical failures due to resistance to these drugs have been reported in recent years from various parts of the world. We felt a need to evaluate the in vitro antimicrobial resistance profile of MRSA strains isolated from our tertiary care teaching hospital in Kashmir, India.

Methodology.We investigated retrospectively,185 non- duplicate *staphylococcus aureus* isolates obtained from pus samples submitted to the Bacteriology laboratory , Department of Microbiology, Government Medical College, Srinagar, Kashmir, India .Isolates had been subjected to identification and in-vitro antimicrobial susceptibility testing on VITEX 2 compact system(Biomerieux) using CLSI criteria

Results. A high prevalence of MRSA(59.46%) than MSSA(40.54%) was observed.MRSA isolates had 94.66% and 95.45% resistance to ciprofloxacin and levofloxacin respectively. In the present study an alarmingly high prevalence (9.09%) Vancomycin Resistant *Staphylococcus aureus* (VRSA) was observed. Maximum numbers of VRSA isolates were yielded from surgical site infections (SSI).1.92% and 6.06% isolates were found resistant to linezolid and daptomycin. All isolates were sensitive to tigecycline.

Conclusion.Vancomycin Resistant *Staphylococcus aureus*(VRSA) infections in hospital setting are on the rise. Adequate infection control measure and screening for vancomycin resistant enterococci (VRE) in hospitalized patients should be done. Tigecycline and linezolid should be considered the drugs of choice in such infections.

KEYWORDS

VRSA SSI Tigecycline Daptomycin

INTRODUCTION

Among pathogenic microorganisms, Staphylococci are a leading cause of pyogenic infections worldwide. A small percentage of such infections remain sensitive to penicillin, but a high prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in nosocomial- and community-acquired infections is common around the globe.[1,2,3]Antibiotics such as the glycopeptides (vancomycin and teicoplanin), tigecycline, linezolid, daptomycin, and rifampin are the treatments used in our clinical settings, as they are elsewhere. However, in developing countries such as ours, the liberal use of antibiotics and the ensuing selection pressure has led this organism to more evolved mechanisms. Now, multidrug resistant MRSA is of increasing prevalence the world over.[2]With this, the antibiotic résistance profile of MRSA strains isolated from various clinical samples collected in our hospital, located in the great Himalayan belt, was evaluated.

MATERIALS AND METHODS

This retrospective observational study was conducted using data obtained from isolates collected over a period of one year (August 2015-August 2016) in a tertiary care teaching hospital in north India.

In total, 185 non-duplicate isolates of *S. aureus* were grown using standard methods[3]from pus samples collected from patients diagnosed with surgical site infections(SSIs,*n*=82), abscesses(*n*=60),acute osteomyelitis(*n*=35),chronic suppurative otitis media (*n*=4), or burn wound infections(*n*=4).A VITEK 2 Compact system(Biomerieux, Inc.)Was used to identify each. and the minimum inhibitory concentration (MIC) drug susceptibilities for penicillin, oxacillin, vancomycin,teicoplanin,linezolid,gentamycin, ciprofloxacin, levofloxacin, tigecycline,nitrofurantoin, tetracycline, daptomycin, erythromycin, clindamycin,co-trimoxazole, and rifampicin were determined using Clinical Laboratory Standards Institute (CLSI) software from 2016.[4]*Enterococcus faecalis* ATCC 29212 and *Enterococcus faecalis* ATCC 5129 were used as quality control strains for vancomycin susceptiblity and resistance respectively.

RESULTS

Of the 185 isolates, MRSA was found in 110 (59.5%), and MSSA was found in 75 (40.5%).A greater prevalence of MRSA, compared to MSSA,was found in SSIs (Fig. 1,Table1).The opposite was true in abscesses.

Using broth dilution and a VITEK 2 Compact system, MICs were determined to form the antimicrobial sensitivity profile of MRSA (Fig. 2, Table 2). It was most resistant to levofloxacin (95.5%) and ciprofloxacin (94.7%).Resistance to the commonly-used gentamycin was low (17%). It was clindamycin resistant and erythromycin resistant in 39.2% and 79.1% of the isolates, respectively.

Additionally, 96.6% of MRSA isolates were susceptible to daptomycin, and 50% were sensitive to co-trimoxazole. All showed *in vitro* susceptibility to tigecycline (MIC <=0.12µg/mL).

Of the 110 MRSA isolates, an alarming number (10; 9.09%) were resistant to vancomycin (MIC>=32µg/mL), of which seven were from SSIs following abdominal surgery, and one each were from a hip abscess, a breast abscess, and a burn wound.

All VRSA isolates were sensitive to tigecycline, and 20% were resistant to linezolid (Table 3). Additionally,30% were resistant to gentamycin, levofloxacin, tetracycline ,daptomycin, and rifampin, yielding MIC values greater than8,8,16,8, and 4µg/mL, respectively. Finally, 30% were resistant to co-trimoxazole(MIC>160µg/mL), 40% to nitrofurantoin (MIC>32µg/mL), and60% to ciprofloxacin (MIC>8 µg/mL). Heterogeneous resistance to vancomycin, daptomycin, and linezolid was found in one isolate from a breast abscess; it was found to be sensitive to tigecycline.

Two vancomycin-resistant isolates showed peculiar sensitivities to teicoplanin. All others (*n* =8) were resistant to that antibiotic. One strain of MSSA was resistant to ciprofloxacin and levofloxacin in addition to vancomycin.

DISCUSSION

Staphylococcal infections continue the world over because of this entity's evolving mechanisms of resistance to current antibiotics. In

our tertiary care hospital, we found, as have others in studies worldwide,[5]its antibiotic resistance profile includes a high percentage of MRSA(59.5%)compared to MSSA(40.5%). Among MRSA isolates, an alarming prevalence (9%) of VRSA strains was observed. The prevalence of VRSA has been documented by few studies in India in recent years. [6] This study shows that most MRSA and ensuing VRSA isolates can be found in SSIs. Similar findings[7] were observed elsewhere. These findings can be attributed to the survival and spread of highly-virulent strains of MRSA harboring the VAN-A[8]gene and genes for Panton–Valentine Leucocidin.[9]We, however did not evaluate the VRSA strains for VAN-A genes due to resource constraints and we strongly recommend that it should be performed. Nosocomial presence of these MRSA strains have been promoted by the ability to form biofilms,[10]antimicrobial pressure,[11] concurrent vancomycin-resistant *Enteroccoci* colonization,[12] and poor infection control practices.[13] The prevalence of VRSA at 9% could be an underestimate because routine automated antimicrobial sensitivity methods are known to overlook VRSA phenotypes.[14]In the present study, however, low prevalences of VISA(0.9%) and hVISA(1.6%) were observed. With this in mind, vancomycin is the gold standard treatment for MRSA infection.[15]Resistance to it should be critically evaluated, particularly because vancomycin is recommended as the chemo-prophylactic agent of first choice in SSIs by the Infectious Disease Society of America (IDSA).[16]

Daptomycin is considered an alternative to vancomycin for MRSA infections except in pulmonary cases.[17]In the present study, resistance to daptomycin in MRSA strains was lower (6.4%) than resistance to vancomycin. Of ten VRSA isolates, three were daptomycin-resistant .This strongly suggests that although daptomycin can be used as an alternative to vancomycin, antimicrobial susceptibility to daptomycin should be checked and must not be overlooked.[18] Furthermore, a correlation was observed between vancomycin resistance and reduced daptomycin susceptibility.[19]Interestingly, the sensitivities of VRSA strains to gentamicin, rifampin, tetracycline, and levofloxacin were found to be similar to that of daptomycin. Of all MRSA strains isolated in this study, resistance to daptomycin was lower than for gentamycin (17.3 %) or rifampin (11.8%).In light of these findings, a combination therapy of vancomycin and daptomycin could be better than one of vancomycin and gentamycin or vancomycin and rifampicin. However, combination therapies for MRSA infections are not adequately supported by clinical trial data.[20]

We also found a high percentage of MRSA isolates with flouroquinolone resistance. About 94.6% were resistant to ciprofloxacin, and95.6% were resistant to levofloxacin. Similar findings have been shown in India[21] (resistance to ciprofloxacin, 92.5% and to ofloxacin, 80.4%) and other parts of the world.[22]Once considered an alternative treatment in MRSA neither infection with β lactams or vancomycin, nowadays, neither second nor third generation flouroquinolones are alternatives for treating HA-MRSA infections.[23]

The linezolid resistance (1.92%) found in this study compares with other studies elsewhere.[24] Tigecycline was the most efficacious drug against all MRSA and VRSA isolates (MIC=< 0.12µg/mL), comparable to what has been found elsewhere.[25]

Tigecycline can be considered a good drug against VRSA infections. Other drugs such as ceftaroline, ceftoxalone, and ceftipirole are reportedly efficacious against *S. aureus* infections, but they are not currently well known or used in this part of the globe, and a new and remodeled vancomycin analogue recently developed by Scripps institute USA is claimed to be the most highly potent against VRSA. It has yet to undergo human trials.

CONCLUSION

Based on these findings, VRSA in SSIs must be contained by robust infection control measures, and hospitalized patients must be screened for vancomycin-resistant enterococci colonization. Tigecycline was found to be the best drug for treating VRSA and overall MRSA infections. It should be given as the drug of choice in VRSA infections. Other drugs, such as daptomycin or rifampicin, could be used in combination with vancomycin but with clinical outcomes must be monitored.

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Conflict of interest; none declared

DECLARATIONS

A. list of abbreviations;
MRSA; Methicillin resistant *Staphylococcus aureus*
MSSA; Methicillin sensitive *Staphylococcus aureus*
VRSA; Vancomycin resistant Staphylococcus *aureus*
CLSI; Clinical laboratory Standards Institute
MIC; Minimum Inhibitory Concentration
ATCC; American Type Culture Collection
SSI; Surgical Site Infection
CSOM; Chronic Suppurative Otitis Media
OM; Osteomyelitis

B. Ethics approval. The study was approved by the institutional ethics committee.

C. Consent for publication. Our manuscript does not contain any individual's personal data .Therefore consent for publication was not applicable.

D.Dataset ;Please contact author for data requests

E Funding; nil

F Authors contributions; SF carried out identification , antimicrobial susceptibility of isolates and drafted the manuscript.AS; conceived the study and participated in its design.SR and NN coordinated and helped draft the manuscript. All authors read and approved the manuscript.

G.Acknowledgements;not applicable

H. Competing interests; nil

Fig 1: Sample site wise distribution of MSSA and MRSA isolates;
Abbreviations; Surgical Site Infections (SSI) Abscess (abs) AcuteOsteomyelitis (OM), Chronic Suppurative Otitis Media (CSOM).

Fig 2; Showingpercentage (%) resistance of MRSA to various antimicrobials. Penicillin (PEN), oxacillin (OXA), vancomycin (VAN), teicoplanin (TEC), linezolid (lZ), gentamycin (GEN), ciprofloxacin (CIP),levofloxacin(LEV),tigecycline(TG),tetracycline (TET/TC),daptomycin(DAP), erythromycin(ERY),clindamycin(CD) ,cotrimoxazole (cot) and rifampicin(RMP)

Table 1; Sample Site wise distribution of MSSA and MRSA isolate

	MRSA	MSSA	TOTAL
Abscess	24	36	60
SSI	73	9	82
OM	6	29	35
CSOM	4	0	4
Burn	3	1	4
	110	75	185

Abbreviations=SSI=surgical site infections,OM=osteomyelitis, CSOM=chronic suppurative otitis media.

Table 2; In -vitro antimicrobial sensitivity profile of MRSA isolates to various antibiotics,asper CLSI MIC Broth micro dilution standards.

	GEN	CIP	LEV	LZ	DAP	TEC	VAN	TC	TGC	RMP	CD	ERY	COT
Sensitive	73.63%	1.82%	0.91%	98.18%	93.64%	95.45%	88.18%	85.45%	100%	88.18%	60.00%	12.73%	50.92%
Intermed	9.00%	3.64%	3.64%	0.00%	0.00%	0.00%	2.73%	0.00%	0.00%	0.00%	1.82%	11.82%	0.00%
Resistant	17.27%	94.55%	95.45%	1.82%	6.36%	4.55%	9.09%	14.55%	0.00%	11.80%	38.18%	79.09%	58.18%

Abbreviations;penicillin(PEN),oxacillin(OXA),vancomycin(VAN),teicoplanin(TEC),linezolid(lZ),gentamycin(GEN),ciprofloxacin(CIP),levofloxacin (LEV),tigecycline(TG),tetraycline(TET/TC),daptomycin(DAP),erythromycin(ERY),clindamycin(CD) ,cotrimoxazole(cot) and rifampicin(RMP)

Table 3; Description of VRSA (n=10) including antibiotic susceptibility profile as determined by MIC broth micro dilution. Penicillin

VRSA	SITE	WARD	RESISTENCE TO	SUSEPTIBILITY TO
VRSA 1	SSI	Post op surgery	GEN,CIP,LEV,VAN,TC, DAP,TEC,RMP,NIT	COT,TGC,LZ
VRSA 2	SSI	Post op surgery	GEN,LEV,CIP,VAN	LZ,DAP,TEC,TGC,TC NIT,RMP,COT
VRSA 3	SSI	Post op surgery	CIP,TEC,VAN, LZ ,COT	TGC,LEV,TC,NIT, RMP,DAP,GEN
VRSA4	SSI	postop surgery	CIP,DAP,TEC,VAN,NIT COT	GEN,LEV,LZ,TC,TGC, COT
VRSA 5	SSI	Burn	VAN,TEC	GEN,CIP,LEV,LZ,DAP,RMP.COT.NIT.TGC.TC
VRSA6	SSI	postop surgery	GEN,CIP,LEV,LZ,VAN, TC,TEC,RMP,COT	DAP,TGC
VRSA7	burn	burn	VA,TEC	GEN,CIP,LEV,LZ,DAP, RMP,COT,TGC,TC
VRSA 8	SSI	post op surgery	VAN,TEC,CIP, RMP LEV,LZ,TC ,COT	GEN,LZ,DAP,TGC, NIT
VRSA 9	hip pus	ortho	VAN,TEC,CIP,LEV, LZ RMP,COT,TC	GEN,TGC,DAP,NIT
VRSA 10	Breast abscess	surgery	CIP,LEV,VANC,RMP GEN,LZ,DAP,TEC	COT,TC,TGC,NIT

Abbreviations;Penicillin(PEN),oxacillin(OXA),vancomycin(VAN),teicoplanin(TEC),linezolid(lZ),gentamycin(GEN),ciprofloxacin(CIP),levofloxacin(LEV),tigecycline(TG),nitrofurantoin(NIT),tetracycline(TET/TC),daptomycin(DAP),erythromycin(ERY),clindamycin(CD) ,cotrimoxazole(cot) and rifampicin(RMP)

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