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Original Article

Prevalence and Antibiotic Susceptibility of Clinical Staphylococcus Aureus Isolates in Various Specimens Collected from a Tertiary Care Hospital, Hayatabad, Peshawar, Pakistan.

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ABSTRACT

Staphylococcus aureus is a notorious Gram-positive, non-spore-forming, opportunistic bacterium that causes a variety of infections including bacteremia, endocarditis, pneumonia, skin and soft tissue infections, and several others. Also, the overuse and misuse of drugs attributed to the crises of multidrug resistance especially in MRSA. **Objective:** Therefore, the aim of this study was to determine the prevalence rate of MRSA, antimicrobial susceptibility profiles of *S. aureus*, MRSA, and MSSA isolates to a variety of commonly used antibiotics, and its multidrug resistant patterns. **Methods**: Samples were collected from the microbiology department of HMC Peshawar, Pakistan. Antibiotic susceptibility patterns were determined under CLSI and EUCAST guideline, 2021 by following the Kirby-Bauer disc diffusion method. **Results:** Out of 106 *S. aureus* clinical isolates, 83(78.3%) isolates were identified as MRSA and 23 (21.7%) were MSSA. In MRSA high resistance was exhibited to Penicillin G and cefoxitin (100%), followed by erythromycin 84.34% and ciprofloxacin 79.52%. Meanwhile low resistance was observed to doxycycline 19.28% followed by chloramphenicol 14.46%, teicoplanin and linezolid 2.41% for each respectively. High sensitivity in MRSA isolates was exhibited to linezolid 97.59% followed by teicoplanin 95.18%, chloramphenicol 85.54%, doxycycline 80.72% and fusidic acid 74.70%. A total of n=94 (88.67%) isolates were characterized as MDR. **Conclusions:** In conclusion, the most effective antibiotics used to treat *S. aureus* infections were linezolid, teicoplanin, chloramphenicol, doxycycline, fusidic acid, and gentamycin. In addition, the current study also noticed a significant prevalence of resistance to several antibiotics, emphasizing the importance of antibiotic usage monitoring.

INTRODUCTION

Staphylococcus aureus (*S. aureus*) is a serious public health concern for both community and hospital-acquired individuals as it causes infections in humans that vary from wound abscesses to life-threatening diseases such as bacteremia, endocarditis, and several others [1]. In the 1960s, methicillin was first utilized as a human medication to treat *S. aureus* infections but within a year of its clinical usage, MRSA strains emerged [2]. The first case of MRSA was detected in United Kingdom in 1962 and United States (US) in 1968 [3,4]. Methicillin resistance in *S. aureus* is often associated with the *mec*A gene that encodes the low-affinity penicillin-binding protein (PBP2a) [5]. MRSA infections are highly prevalent around the world, largely vary among several European countries with a prevalence rate of more than 50% in Malta and Portugal, and less than 5% in Estonia, Denmark, Finland, Norway, Netherland, and Sweden [6]. In Asian countries, MRSA is quite prevalent, with a hospital-acquired prevalence of 67.4% and a community-acquired rate of 25.5% [7]. Every year in the US 80,000 invasive infections of humans are caused by MRSA, with a mortality rate of 11,000-18,000 people [8,9]. Antibiotic-resistant microorganisms are risking the efficacy of antibiotics as they rapidly increasing around the globe [3]. Due to excessive usage of antibiotics, antibiotic-

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resistant bacterial diseases are responsible for more than 35,900 deaths per year and is still a major public health issue in US, with 2.8 million antibiotic-resistant pathogenic infections [10]. Multi-drug resistant (MDR) bacteria are resistant to at least three or more antibiotic classes and are the most prominent trait of MRSA [11]. In Nigeria, β-lactam antibiotics are used for the treatment of MRSA infections, but they are highly (88%) ineffective against them. Even in India and Pakistan, 95% of adults carry β-lactam antibiotic-resistant pathogens [12]. In 2010, a study was conducted at a tertiary care hospital in Mangalore, South India, where a total of 237 isolates were studied, in which 29.1% were methicillin-resistant, while erythromycin, gentamicin, and chloramphenicol resistance were found in 40-50% of isolates. Inducible clindamycin resistance was observed in 18.8% of MRSA strains, with less than 30% resistance to ciprofloxacin and amikacin [13]. Another study from Rawalpindi, Pakistan aimed to determine the prevalence rate of MRSA. Out of 350 staphylococcal isolates, 60.40% were identified as MRSA isolates. All the β-lactam antibiotic drugs were 100% resistant to MRSA followed by nalidixic acid 89.18%, cotrimoxazole 86.48%, erythromycin 85.81%, levofloxacin 80.4%, gentamicin 76.35%, tetracycline 59.45%, ciprofloxacin 44.59%, chloramphenicol 18.24%, and rifampicin 10.13% [14]. Several reports had highlighted a significant proportion of nosocomial and community-acquired MRSA infections in Pakistan [15-18]. The first case of MRSA in Pakistan was discovered in 1989, and the prevalence has been steadily increasing since then. According to researches, the percentage of MRSA isolates grew from 5% in 1989 to 69% in 2020 [17-19]. Therefore, this study aimed to determine the prevalence rate of MRSA, antimicrobial susceptibility profile of *S. aureus*, MRSA and MSSA isolates to various antibiotics, and its MDR profile. These findings with respect to resistant phenotypes will help in the development of an appropriate hospital antibiotic stewardship policy to reduce the risk of *S. aureus*-associated infections. It would further highlight the importance of local surveillance in providing useful antibiotic-resistant data that can guide empiric therapy.

METHODS

A total of 106 samples were collected from the microbiology laboratory of HMC, Peshawar, Khyber Pakhtunkhwa (KPK), Pakistan. Various clinical samples including pus, fluids, blood, sputum, throat swab, and tracheal aspirate were collected from December 2020 to May 2021. The clinical isolates were randomly collected from patients who came to the hospital or were already admitted. The randomly collected clinical isolates were processed for bacterial culturing on Mannitol Salt Agar (OXOID CM0085, England), which is a selective and differential media with 7.5%-10% of salt concentration. Then followed by incubation for 24 hours at 37^{0}C. After the incubation, *S. aureus* isolates were identified through Gram-staining and isolated colonies were further subjected to biochemical tests including catalase, tube coagulase test and DNase test. *S. aureus* isolates were further processed for Antibiotic Susceptibility Testing (AST) through the Kirby-Bauer disc diffusion method [20]. Following 11 antibiotics were inoculated on Muller Hinton Agar (MHA) (OXOID CM0377, England) for antimicrobial testing: penicillin G (P) 10µg, chloramphenicol (C) 30µg, cefoxitin (FOX) 30µg, ciprofloxacin (CIP) 5µg, clindamycin (DA) 2µg, doxycycline (DO) 30µg, erythromycin (E) 15µg, fusidic acid (FD) 10µg, gentamicin (CN) 10µg, linezolid (LZD) 30µg and teicoplanin (TEC) 30µg. Results were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) guidelines, 2021 while for teicoplanin CLSI guidelines, 2016 were followed. The breakpoints of fusidic acid were interpreted according to European Committee on Antibiotic Susceptibility Testing (EUCAST) guidelines, 2021. The AST growth suspension was prepared in 5ml normal saline solution with the turbidity adjusted to match the 0.5 McFarland standards to obtain the estimated amount of organism number of 1x10^6 colony forming units (CFU) per milliliter. After 15 minutes of inoculation, antibiotics discs were placed on MHA, seeded with each isolate, and were cultured at 37^{0}C for 24 hours. After incubation, the antibiotics zones of inhibitions were measured using a ruler and the results were interpreted according to the CLSI and EUCAST guidelines, 2021. For the determination of MRSA, FOX discs of 30µg were used to screen all the *S. aureus* isolates. *S. aureus* isolates were grown on MHA agar at 37^{0}C for 18-24 hours with a growth suspension calibrated to 0.5 McFarland standards and inhibition zone equal to or less than 21mm on MHA was considered as MRSA while inhibition zone equal to or greater than 22mm on MHA was considered as MSSA by following CLSI guidelines, 2021. The D-test method was used to determine the inducible clindamycin resistance in MRSA isolates. Briefly, a 0.5 McFarland standards equivalent bacterial culture was seeded on MHA plates, followed by 15mm apart insertion of erythromycin (15µg) and clindamycin (2µg) discs. After that, the plate was incubated for an overnight period and positive inducible clindamycin resistance was determined by a "D" shaped clindamycin zone of inhibition towards an erythromycin disc. For the detection of MDR, Magiorakos *et al.*, [11]. definition of non-susceptibility to at least one antimicrobial agent out of three or more antimicrobial classes was used. The chi-square technique was used to establish statistical significance in the age, gender, and specimen type, using GraphPad Prism 9.1.2.226. A *p*-value

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<0.05 was considered statically significant.

RESULTS

Gram staining

All of the 106 bacterial isolates were identified as Gram-positive cocci under a light microscope.

Identification of isolates

The Gram-positive bacterial isolates on Mannitol Salt Agar plates changed the medium color from pink to yellow, confirming that the bacteria belong S. aureus species.

Biochemical tests

All the clinical isolates were tested positive for catalase test, tube coagulase test and DNase test.

Antibiotic susceptibility profiles of S. aureus isolates

All of the 106 strains were 100% resistant to Penicillin G. High resistance was observed among cefoxitin, ciprofloxacin, and erythromycin i.e., 78.3% (for each) whereas low resistance was found in linezolid 1.9% followed by teicoplanin 2.8% and chloramphenicol 13.2%. Two strains of clindamycin and erythromycin were intermediate while 3 strains (2.8%) were found intermediate to teicoplanin. For details follow Table 1.

Classes of Antibiotics	Antibiotics	Sensitive n(%)	Intermediate n(%)	Resistant n(%)
Penicillin's	Penicillin G			106 (100)
2nd generation cephalosporins	Cefoxitin	23 (21.7)		83 (78.3)
Phenicols	Chloramphenicol	92 (86.8)		14 (13.2)
Quinolones	Ciprofloxacin	23 (21.7)		83 (78.3)
Lincosamides	Clindamycin	41 (38.7)	2 (1.9)	63 (59.4)
Tetracycline	Doxycycline	89 (84)		17 (16)
Macrolides	Erythromycin	21 (19.8)		83 (78.3)
	Fusidic acid	80 (75.5)		26 (24.5)
Aminoglycosides	Gentamycin	69 (65)		37 (35)
Oxazolidinones	Linezolid	104 (98.1)		2 (1.9)
Polypeptides	Teicoplanin	100 (94.3)	3 (2.8)	3 (2.8)

Table 1: Antibiotic susceptibility profile of S. aureus isolates to various antimicrobial agents

Antibiotic susceptibility patterns of MRSA and MSSA isolates

All of the 83 MRSA and 23 MSSA strains were 100% resistant to Penicillin G. Clindamycin resistance in MSSA vs MRSA was 60.87% vs 59.04% respectively. Intermediate sensitivity i.e., 39.13% and 38.55% was exhibited to clindamycin in MSSA and MRSA isolates, respectively. One isolate of MRSA and 1 isolate of MSSA was observed intermediate to erythromycin. A single isolate of MSSA was found intermediate to teicoplanin while in the case of MRSA, there were 2 intermediate isolates. The D-test results showed that 10 (12.04%) of MRSA isolates were tested positive for inducible clindamycin resistance. For detailed descriptions of antibiotic susceptibility patterns of MSSA and MRSA follow Table 2.

Classes of Antibiotics	Antibiotics	Drug Susceptibility	MSSA n(%)	MRSA n(%)	p-value
Penicillin's	Penicillin G	Sensitive	0	0	1
		Resistant	23 (100)	83 (100)	
Phenicols	Chloramphenicol	Sensitive	21 (91.30)	71 (85.54)	0.470
		Resistant	2 (8.70)	12 (14.46)	
Quinolones	Ciprofloxacin	Sensitive	6 (26)	17 (20.48)	0.564
		Resistant	17 (74)	66 (79.52)	
Lincosamides	Clindamycin	Sensitive	9 (39.13)	32 (38.55)	0.974
		Resistant	14 (60.87)	49 (59.04)	
Tetracycline	Doxycycline	Sensitive	22 (95.65)	67 (80.72)	0.084
		Resistant	1 (4.35)	16 (19.28)	
Macrolides	Erythromycin	Sensitive	9 (39.13)	12 (14.46)	0.006
		Resistant	13 (56.52)	70 (84.34)	
	Fusidic acid	Sensitive	18 (78.26)	62(74.70)	0.725
		Resistant	5 (21.74)	21 (25.30)	
Aminoglycosides	Gentamycin	Sensitive	21 (91.30)	48 (57.83)	0.003
		Resistant	2 (8.70)	35 (42.17)	
Oxazolidinones	Linezolid	Sensitive	23 (100)	81 (97.59)	0.452
		Resistant	0	2 (2.41)	
Polypeptides	Teicoplanin	Sensitive	21 (91.30)	79 (95.18)	0.608
		Resistant	1 (4.35)	2 (2.41)	

Table 2: Antibiotic susceptibility patterns of MRSA and MSSA isolates to various antimicrobial agents

Frequencies of MRSA and MSSA

The frequency of MRSA and MSSA was n=83 (78.3%) and n=23 (21.7%) respectively. MRSA prevalence in males and females were almost the same, n=39 (79.6%) in males and n=44 (77.2%) in females. On the other hand, the prevalence of MSSA in males and females were n=10 (20.4%) and 13 (22.8%) respectively. According to the numbers of specimens, MRSA was most frequent in pus n=56 (80%), followed by fluids n=22 (75.9%), blood n=4 (100%) and tracheal aspirate n=1 (100%). On the other hand, MSSA was most frequently found in pus n=14 (20%) followed by fluids n=7 (24.1%), sputum n=1 (100%) and throat swab n=1 (100%). Age-wise distribution showed that MRSA vs MSSA between ages 51-60 years was 81% vs 19%, 41-50 was 80% vs 20%, 11-20 and 21-30 was 70% vs 30% for both respectively. For detailed descriptions of the frequencies of MRSA and MSSA strains, follow Table 3.

Variables	S. aureus (N)	MSSA n(%)	MRSA n(%)	X2	p-value
Age					
0-12 Months	2		2 (100)	0.565	0.452
1-10 Years	11	1 (9.1)	10 (90.9)	1.148	0.284
11-20 Years	20	6 (30)	14 (70)	1.000	0.317
21-30 Years	20	6 (30)	14 (70)	1.000	0.317
31-40 Years	9	3 (33.3)	6 (66.6)	0.783	0.376
41-50 Years	15	3 (20)	12 (80)	0.030	0.863
51-60 Years	21	4 (19)	17 (81)	0.108	0.742
61-69 Years	8		8 (100)	2.398	0.121
Gender					
Male	49	10 (20.4)	39 (79.6)	0.089	0.765
Female	57	13 (22.8)	44 (77.2)		
Specimen					
Pus	70	14 (20)	56 (80)	0.350	0.554
Fluids	29	7 (24.1)	22 (75.9)	0.140	0.708
Blood	4		4 (100)	1.152	0.283
Sputum	1	1 (100)		3.643	0.056
Throat Swab	1	1 (100)		3.643	0.056
Tracheal Aspirate	1		1 (100)	0.280	0.597

Table 3: Frequencies of MRSA and MSSAN (Total number of S. aureus isolates), X2 (Chi-square), p-value <0.05 is considered

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statically significant

Resistant phenotype of S. aureus

Ninety-four (88.67%) of the isolates were MDR. MDR strains ranged from resistance to three classes of antibiotics (n=10, 9.43%) to 9 classes of antibiotics (n=1, 0.94%). The high resistance rate for MDR was observed among s4-5 classes of antibiotics (n=25, 23.58%). The detailed resistance of the MDR pattern is given in Table 4.

Antibiotics	No. of resistant strains	Percentage of resistant strains
P	3	2.83
P, CIF	4	8.50
P, FOX	5	
P, DA, E	2	8.50
P, CIF, DA	1	
P, FOX, FD	2	
P, FOX,CIP	4	
P, CIP, E, FD	1	21.70
P, C, CIP, FD	1	
P, DA, E, CN	1	
P, CIP, DA, E	7	
P, FOX, DO, E	1	
P, FOX, DA, E	4	
P, FOX, CIP, E	6	
P, FOX, CIP, CN	2	
P, FOX, CIP, E, FD	1	21.70
P, FOX, CIP, E, CN	6	
P, FOX, DA, E, CN	2	
P, CIP, DA, E, FD	1	
P, FOX, DA, E, FD	1	
P, FOX, CIP, DA, E	11	
P, FOX, CIP, DO, E	1	
P, FOX, C, CIP, DA, E	2	18.86
P, FOX, DA, DO, E, FD	1	
P, FOX, CIP, DA, E, FD	2	
P, FOX, CIP, E, FD, CN	2	
P, FOX, CIP, DA, E, CN	10	
P, FOX, CIP, DA, DO, E	2	
P, FOX, CIP, DO, E, TEC	1	
P, C, CIP, DA, E, FD, CN	1	12.26
P, FOX, C, CIP, E, FD, CN	1	
P, FOX, C, CIP, DA, E, FD	1	
P, FOX, C, CIP, DO, E, FD	1	
P, FOX, C, CIP, DA, E, CN	1	
P, FOX, C, CIP, DO, E, CN	1	
P, FOX, C, CIP, DA, DO, E	1	
P, CIP, DA, DO, E, FD, TEC	1	
P, FOX, CIP, DA, DO, E, FD	1	
P, FOX, CIP, DA, E, FD, CN	3	
P, FOX, CIP, DA, DO, E, CN	1	
P, FOX, C, CIP, DA, E, FD, CN	1	2.83
P, FOX, C, CIP, DA, DO, E, CN	1	
P, FOX, CIP, DA, DO, E, FD, CN	1	
P, FOX, C, CIP, DA, DO, E, FD, CN	1	1.88
P, FOX, DA, DO, E, FD, CN, LZD, TEC	1	
P, FOX, C, CIP, DA, DO, E, FD, CN, LZD	1	0.94
Total	106	100

Table 4: Percentages of resistance pattern of S. aureus isolates to various antibiotics

P (Penicillin G), FOX (Cefoxitin), E (Erythromycin), FD (Fusidic acid), CIP (Ciprofloxacin) C (Chloramphenicol), DO (Doxycycline), DA (Clindamycin), CN (Gentamycin), TEC (Teicoplanin), LZD (Linezolid)

DISCUSSION

S. aureus is one of the most leading causes of hospital and community-acquired infections around the world due to its enhanced virulence and continuous development of antibiotics resistance [17,21]. The major findings of current study were MDR-MRSA, MRSA resistance in the age group of 2 and 9 months, and teicoplanin intermediate strains. Multi-drug resistance in MRSA has been a major issue around the world, resulting in ineffective therapy and higher treatment costs [6]. The current study highlighted a high (88.67%) number of MDR S. aureus isolates which was in line with the recent reports of 68% from Karachi, Pakistan [18], 83.8% from Kabul, Afganistan and an earlier report of 71.7% from Zaria, Nigeria [22,23]. Among 106 S. aureus isolates, MRSA was observed in 78.3% of samples which was a little high compared to the reports of 66.7% from Rahim Yar Khan-Punjab, Pakistan and 65% from Islamabad, Pakistan [24,17]. Gender-wise distribution showed that MRSA were highly prevalent in both males and females i.e., 79.6% and 77.2% respectively which was in correspondence with another study from Rawalpindi, Pakistan [25]. There were no statistically significant differences observed in MRSA prevalence by age, gender, and specimen type. A high (100%) prevalence of MRSA were found in the age group of 61-69 years. One strain (1.2%) of MRSA was isolated from the blood of the age group 2 months and one (1.2%) from the 9 months. According to the number of isolates, the current study reported that MRSA was most frequent in pus (80%) which was high compared to a study of 36.7% from Peshawar, Pakistan [26]. The antibiotic resistance rate demonstrated by S. aureus isolates to Penicillin was 100% which was in line with the previous findings from Pakistan [14,26], Afghanistan [22] and India [13]. Resistance exhibited to cefoxitin by S. aureus isolates in this study was 78.3% which was quite greater than the previous reports of 47.54% from Islamabad, Pakistan [16] and 66.7% from Rahim Yar Khan-Punjab, Pakistan [24]. Several reports of 100% resistance to cefoxitin antibiotics were also been previously observed in various cities (Rawalpindi, Karachi and Peshawar) of Pakistan [14,18,24]. The current study documented 25.30% resistance to MRSA against fusidic acid which was lower than several other studies of 40.6% [24], 53.1% [27] and 66.7% [28] from Pakistan. In the present study, MRSA resistance exhibited by ciprofloxacin was 79.52% which was quite greater compared to 44.59% [14] and 48% [24]. This study indicates a lower rate of MRSA resistance to doxycycline i.e., 19.28% which was very low compared to the previous studies of 41.6% [24] and 46.8% [27] from Pakistan, and 81.4% from Afghanistan [22]. In the current study, MRSA resistance to clindamycin was 59.04% which correlated with the findings of 60.1% [15] and 51% [27] from Pakistan. Two (2.41%) isolates of MRSA were found intermediate to clindamycin. Interestingly 84.34% of MRSA strains were resistance to erythromycin in the present study which were quite higher compared to the previous

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reports of 28.90% [25] and 46% from Pakistan [24], and 23% from Afghanistan [22] but lower compared 99.01% [26] from Pakistan. This study reported 12.04% of inducible clindamycin resistance in MRSA isolates which was almost in line with one of the study from Peshawar Pakistan that reported 15.84% of inducible clindamycin resistance strains in MRSA isolates [26]. The present study documented that MRSA was highly sensitive to linezolid and teicoplanin which can be used as a drug choice to treat MDR-MRSA infections. Resistance exhibited by MRSA to teicoplanin was 2.41% which was quite lower compared to 25% [18]. Zero percent resistance to teicoplanin has also been observed in various reasearches from Pakistan [15,27] and Turkey [29] while 2.41% resistance to linezolid was exhibited to MRSA isolates which was very low compared to 21.1% [25] and 24.1% [16]. Several reports of 0% resistance to linezolid were also been observed in Pakistan [15,26], India [30,31] and Turkey [29].

CONCLUSIONS

The current study found a high prevalence rate of MRSA in the patients of HMC Peshawar, KPK, Pakistan. The MDR-MRSA is a major public health concern in Peshawar. This bacterium can disseminate in the community and as well as in health facilities and can cause severe infectious diseases. Linezolid and teicoplanin were highly susceptible to MRSA and could be the drugs of choice for treating MRSA infections. To further understand the epidemiology and molecular causes of antibiotic resistance in MRSA, more research is needed in different regions of Pakistan.

Conflicts of Interest

The authors declare no conflict of interest.

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