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Full Length Research Paper

Antibiotic susceptibility profile of methicillin-resistant staphylococci isolated from nasal samples of hospitalized patients

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The aim of this study was to evaluate the prevalence rate and antibiotic resistant pattern of methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *Staphylococcus epidermidis* (MRSE). A prospective study was conducted at Holy Family Hospital Rawalpindi, Pakistan and Microbiology Research Laboratory, Quaid-i-Azam University, Islamabad, Pakistan during the period from December 2007 to August 2008. The antibiotic resistance pattern was studied for MRSA and MRSE isolated from nasal samples from patients admitted in medical and surgical intensive care units. The study was conducted on 283 isolates. The results depicted that 25% isolates of *S. aureus* were MRSA and 29.78% isolates of *S. epidermidis* were MRSE. All MRSA and MRSE were susceptible to vancomycin and quinopristin/dalfopristin while all isolates of MRSE were susceptible to teicoplanin. All the isolates of MRSA and MRSE were multidrug-resistant. The susceptibility of the isolates to the drugs varied greatly. The resistance rate of MRSA to various antibiotics was found to be as follow: cephalaxin (90%), cephalothin (58%), cephradine (86%), ciprofloxacin (80%), gentamicin (34%), imipenum (42%), levofloxacin (75%), tetracycline (49%), rifampicin (14%) and teicoplanin (3%). The resistance rate of MRSE to various antibiotics was found to be as follow: cephalaxin (64%), cephalothin (29%), cephradine (64%), ciprofloxacin (50%), gentamicin (21%), imipenum (7%), levofloxacin (21%), tetracycline (21%) and rifampicin (29%). The minimum inhibitory concentration (MIC) value for MRSA and MRSE in case of vancomycin ranged 1-4 g/ml, for tetracycline 4-128 g/ml, for rifampicin 0.5-32 g/ml and for gentamicin 0.5 – 64 g/ml. Both MRSA and MRSE showed variable susceptibility with different antibiotic groups but high susceptibility with streptogramin and glycopeptide antibiotics.

Key words: Antibiotic resistance, *staphylococcus aureus, staphylococcus epidermidis*, minimum inhibitory concentration.

INTRODUCTION

Staphylococcus aureus is one of the most virulent organisms and is considered as the most important cause of hospital-acquired infections (HAI) and community-acquired infections (CAI) (Lowy, 1998). The widespread use of antimicrobial agents to treat staphylo-coccal infections has resulted in the emergence of resistant forms of these organisms. To date most MRSA have become resistant to number of antimicrobial agents like -lactams (Kim et al., 2004). Like MRSA large number of coagulase negative staphylococci (CoNS) which not only have high rate of methicillin resistance but also resistant to other multiple antibiotics (Petinaki et al., 2001; Spencer, 1996; Tacconelli et al., 2001). *Staphylo-coccus epidermidis* is usually non-pathogenic but can cause infections in immune- compromised individuals (Jarlov, 1999; Kleeman et al., 1993). Presently MRSA and MRSE isolates have been uniformly susceptible only to glycopeptides. But recently, numbers of isolates resistant to glycopeptides have been reported

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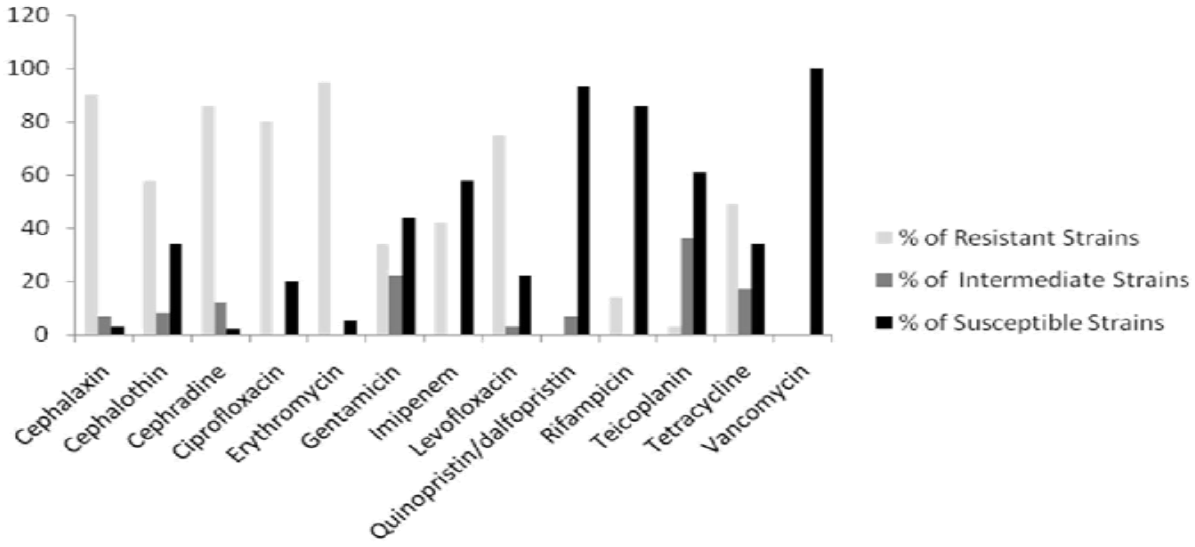

Figure 1. Percentage of resistance pattern of MRSA isolates from patients admitted in medical and surgical intensive care units.

(Goldstein et al., 1990; Hanaki et al., 1998; Hiramatsu et al., 1997a, b; Huang et al., 2006; Sieradzki et al., 1998; Wilson et al., 1986). For clinical microbiologists and public health official's knowledge of the local antimicrobial susceptibility pattern of bacterial pathogens is essential to guide empirical and pathogen specific therapy.

The aim of this study was to evaluate the prevalence rate and antibiotic resistant pattern of MRSA and MRSE isolated from patients admitted in medical and surgical intensive care units in teaching hospitals at Rawalpindi and its is assume that this study may help health care professionals to select best antibiotics for the treatment of MRSA and MRSE infections.

MATERIALS AND METHODS

The present study was carried out in the Microbiology laboratory, Holy Family Hospital, Rawalpindi, Pakistan and Microbiology Research Laboratory, Quaid-i-Azam University, Islamabad, Pakistan during the period from December 2007 to August 2008. The study was conducted on 283 isolates, collected from the patients admitted in the Medical Intensive Care Unit (MICU) and Surgical Intensive Care Unit (SICU). The samples were collected once from anterior nares (nostrils) with the help of sterile swabs. There was no duplication of samples. All these non-duplicate MRSA and MRSE isolates, irrespective of the age and sex of the patient were included in the study.

Each sample was inoculated onto sheep blood agar and mannitol salt agar plates and incubated at 37°C for 24 h. The characteristic isolates were aseptically isolated and identified as *Staphylococcus* by standard methods, including colonial morphology, Gram's staining and catalase test. The isolates with coagulase and DNAse test positive were considered as *S. aureus* and those negative were considered as *S. epidermidis.* Final identification was done by API-Staph kit and results were interpreted with the help of API web software. Oxacillin (1 µg) and methicillin (10 g) disks were used to assess the susceptibility of the isolates to methicillin. The isolates were taken as methicillin resistant if the zone of inhibition was <10 mm for oxacillin and <9 mm for methicillin.

Antibiotic susceptibility of the isolates as MRSA and MRSE was done by Kirby-Bauer disc diffusion method as recommended by the National Committee for Clinical Laboratory Standards (1997). The following antibiotic disks (Oxoid-UK) were used: cephalaxin (30 µg), cephalothin (30 µg), cephradine (30 µg), ciprofloxacin (5 µg), quinopristin/dalfopristin (15 µg), gentamicin (30 g), erythromycin (15 g), imipenem (10 µg), levofloxacin (5 µg), tetracycline (30 g), rifampicin (5 g), teicoplanin (30 g) and vancomycin (30 g). The isolates were inoculated on Mueller Hinton Agar (Oxoid-UK) containing 5% NaCl and incubated at 35 °C for 24 h.

Agar dilution method was used to determine the lowest concentration of antimicrobial agents (MICs) required inhibiting the growth of microorganism against vancomycin, tetracycline, rifampicin and gentamicin.

RESULTS

Out of 283 isolates under investigation, 236 (83.39%) isolates were *S. aureus* and 47 (16.61%) were *S. epidermidis.* Out of 236 *S. aureus* 59 (25%) were methicillin resistant (MRSA), and out of 47 *S. epidermidis,* 14 (29.79%) were methicillin resistant (MRSE).

Antibiotic susceptibility profile of MRSA

All MRSA were susceptible to vancomycin and quinopristin/dalfopristin. The resistance pattern among MRSA to other antibiotics was cephalaxin (90%), cephalothin (58%), cephradine (86%), ciprofloxacin (80%), gentamicin (34%), erythromycin (95%), imipenem (42%), levofloxacin (75%), tetracycline (49%), rifampicin (14%) and teicoplanin (3%) (Figure 1).

The MIC for vancomycin ranged from 1 - 4 g/ml; 87%

Table 1. MICs of different antibiotics for MRSA

Antibiotics	Range (g/ml)	% inhibited	MIC (g/ml)
Vancomycin	1-4	87	<2
		13	4
Tetracycline	4-128	45	16
		15	32
		40	64
Rifampicin	0.5-32	59	0.5
		27	<8
		14	32
Gentamicin	0.5-64	24	0.5
		59	32

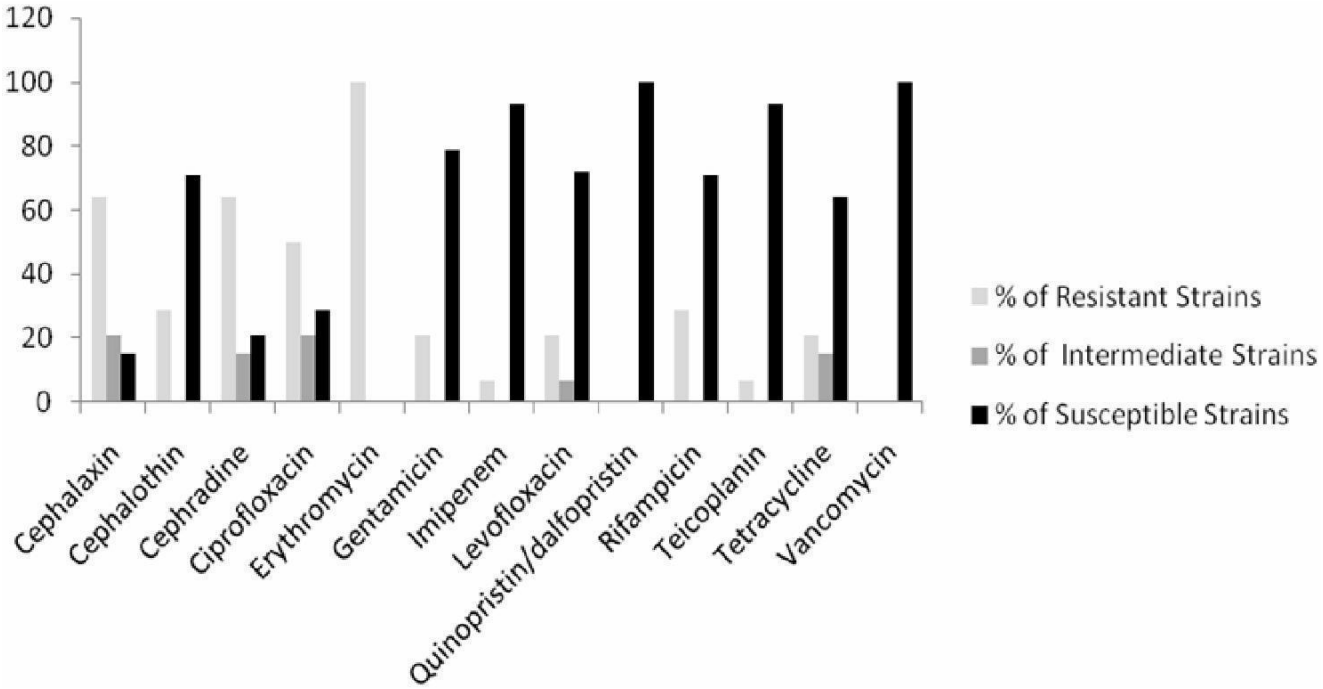

Figure 2. Percentage of resistance pattern of MRSE isolates from patients admitted in medical and surgical intensive care unit.

solates were inhibited at concentration of ≤2 g/ml, and 13% at 4 g/ml. For tetracycline the MIC ranged from 4-128 g/ml; 45% isolates were inhibited at ≤16 g/ml, 15% at 32 g/ml and 40% at ≥64 g/ml. For rifampicin the MIC value ranged from 0.5-32 g/ml; 59% isolates were inhibited at 0.5 g/ml, 27% at 8 g/ml, and 14% at 32 g/ml. For gentamicin the MIC value ranged between 0.5-64 g/ml; 24% of isolates were inhibited at concentration 0.5 g/ml, 59% at ≥32 g/ml. (Table 1).

Antibiotic susceptibility profile of MRSE

All MRSE isolates were resistant to erythromycin and but susceptible to vancomycin, teicoplanin and quinopristin/ dalfopristin. The resistance pattern among MRSE to other antibiotics was cephalaxin (64%), cephalothin (29%), cephradine (64%), ciprofloxacin (50%), gentamicin (21%), imipenum (7%), levofloxacin (21%), tetracycline (21%), erythromycin (100%) and rifampicin (29%) (Figure 2).

For MRSE, MICs of vancomycin ranged from 1-4 g/ml; 50% of isolates were inhibited at ≤2 g/ml, 50% at 4 g/ml. For tetracycline the MIC ranged from 4- 128 g/ml; 78% at ≤16 g/ml, and 21% at 128 g/ml. The MIC value of rifampicin ranged between 0.5-32 g/ml; 71% at 0.5 g/ml, and 29% at ≥8 g/ml. In case of gentamicin the MIC value ranged between 0.5-64 g/ml, 29% at 0.5

Table 2. MICs of different antibiotics for MRSE.

Antibiotics	Range (g/ml)	% inhibited	MIC (g/ml)
Vancomycin	1-4	50	<2
		50	4
Tetracycline	4-128	78	≤16
		21	128
Rifampicin	0.5-32	71	0.5
		29	>8
Gentamicin	0.5-64	29	0.5
		71	>16

g/ml, and 71% at ≥16 g/ml. (Table 2).

DISCUSSION

The present study was conducted to determine the resistant pattern among MRSA and MRSE isolated from patients admitted in surgical and medical ICUs. In this study 236 isolates of *S. aureus* and 47 isolates of *S. epidermidis* were used for the determination of drug resistance. 25% of isolates of *S. aureus* were methicillin resistant which shows that the prevalence of methicillin resistance is lower than previous reports in major cities in South Africa such as Johannesburg and Cape Town, which ranged between 33 and 43% (Bouchillon et al., 2004; Diekema et al., 2001; Zinn et al., 2004). Sader et al. (2002) and Qureshi et al. (2004) reported 28.4% occurrence of MRSA. Several surveys confirmed that the incidence of MRSA and MRSE varies from region to region. Our study shows that the prevalence rate of MRSA and MRSE is 25 and 29.78% respectively.

In our study all of the isolates of MRSA and MRSE were resistant to multiple antibiotics tested. Isolates showed resistance towards various antibiotics such as cephalosporins, tetracycline and gentamicin which is almost similar to previous reports (Archer, 1991; Foster, 1996; Gales et al., 2000). James and Reeves (1996), found MRSA strains resistant to first, second, third and fourth generation of cephalosporins. In this study 86% of the MRSA isolates showed resistance against cephradine. Mahmood et al. (2001), reported 29% resistance in *S. aureus* against first generation cephalosporins.

Gentamicin is an aminoglycoside most often used because of its low cost and reliable activity against gram-positive bacteria. In the present study 34% of MRSA showed resistance towards gentamicin which is higher than reported earlier 30% (Siddiqi et al., 2002). Another drug considered suitable for treatment of MRSA infection is rifampicin. However, rifampicin should be reserved and never used alone (Bayer et al., 1985; Chambers et al., 1995; Zavasky et al., 1998). Our study showed that the resistance of rifampicin is 14% which is significantly lower than 73.8% as reported by Shittu and Lin, (2006).

In this study 95% of MRSA were resistant to erythromycin, which is comparable to previous reports (Huang et al., 2006; Qureshi et al., 2004).

Among fluoroquinolones, ciprofloxacin and levofloxacin were tested in this study. The percentage resistance found in MRSA and MRSE was 80 and 50% for ciprofloxacin and 75 and 21% for levofloxacin respectively. This shows more susceptibility of levofloxacin than ciprofloxacin which might be due to less frequent usage of levofloxacin. Previously reported resistance of ciprofloxacin shows the same type of pattern (Auckenthaler et al., 2000; Visser et al., 1991). Since the emergence of methicillin resistant *S. aureus* and *S. epidermidis,* the glycopeptides vancomycin has been the only effective treatment for MRSA and MRSE infections (Paradisi et al., 2001). In the present study all the isolates were susceptible to vancomycin. Mitchell et al. (1996), reported that all the isolates of MRSA were susceptible to vancomycin and 84.6% were susceptible to teicoplanin. Higher resistance pattern of MRSE as compare to MRSA documented the rates of resistance to teicoplanin (6.5%) but in this study no isolate is resistant to teicoplanin (Bouchami et al., 2007).

Quinopristin/dalfopristin which is an injectable streptogramin antibiotic, is a new agent which possesses *in vitro* activity against Gram-positive pathogen (Barriere et al., 1992). It is the first streptogramin antibiotic suitable for parenteral use (Dowziky et al., 1998). In the present study no isolate of MRSA and MRSE were resistant to this drug. Auckenthaler (2000), reported that the drug was highly effective against MRSA and MRSE.

MIC values of MRSA and MRSE were determined against antibiotics which includes vancomycin, tetracycline, rifampicin and gentamicin. MIC for vancomycin was 87% at concentration ≤2 g/ml of vancomycin and 13% at 4 g/ml in MRSA, Where as in case of MRSE an average of 50% of isolates were inhibited at concentra-tion ≤2 g/ml and remaining 50% of isolates at concentration 4 g/ml. These ranges are higher than the previously reported ranges. Denis et al. (2006) reported

that 100% inhibition at concentration of 1 g/ml and Lozniewski et al. (2001) reported MRSA and MRSE inhibition at concentration of 0.5-1 g/ml. Higher MICs for vancomycin in case of MRSA is an alarming sign of development of infections with vancomycin resistant *S. aureus* (VRSA).

In case of gentamicin 24% of MRSA isolates were inhibited at concentration 0.5 g/ml. However, 59% of isolates were inhibited at concentration ≥32 g/ml. Denis et al. (2006), showed that 95% of MRSA were inhibited at 0.5 g/ml and total 4% of isolates showed inhibition at concentration ≥32 g/ml. High MICs is also an alarming sign to resistance of pathogen for available options.

In this study rifampicin inhibited 59% of isolates of MRSA at concentration of 0.5 g/ml and 24% of isolates showed inhibition at 8 g/ml. 24% of isolates were inhibited at concentration of 32 g/ml. Denis et al. (2006), showed that 99% of isolates were inhibited at concentration of 2 g/ml.

In conclusion most of the clinical isolates of MRSA and MRSE were resistant to cephalosporins, gentamicin, fluoroquinolones and even to imipenem, so these are less effective in the treatment of MRSA and MRSE infections, however vancomycin and teicoplanin remain the good treatment option available. This rise in resistance may be due to frequent and irrational use of antimicrobials. This alarming increase in resistance demands development of new antimicrobial drugs for future treatment regime.

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