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Antimicrobial resistance pattern among intensive care unit patients

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Nosocomial Infections (NIs) are an important cause of morbidity, mortality and economic problems especially in intensive care units (ICUs). This study aim was to investigate antimicrobial resistance pattern of the regional microorganisms in ICU patients. In a cross sectional study, 500 specimens from patients admitted in the ICU who had signs or symptoms of nosocomial infection were collected (2005 - 2006). For each patient, samples of blood, urine, sputum, foley catheters, nasogastric tubes and endotracheal tubes were obtained, cultured, dyed and analyzed with antibiogram. The most common locations for infection were respiratory tract (54.2%). The most frequent gram negative microorganisms derived from samples were *Pseudomonas aeruginosa* (43.2%) and *Klebsiella* spp (33.7%) as well as *Staphylococcus aureus* (39.2%) among gram positive microorganisms. Amikacin and imipenem were the most active antibiotics against gram-negative microorganisms (54% and 46% respectively) and most of these microorganisms were resistant to cephepime and tobramycin (77% and 75%, respectively). *Staphylococcus* species were sensitive to vancomycin (83.3%) and high resistant to cloxacillin (96.6%). As gram-negative pathogens acquired from ICU patients in our settings show high resistance to antibiotics. Regular monitoring of the pattern of resistance of common pathogens in the ICUs is critical in planning the best routines for empirical treatment of infectious patients.

Key words: Antibiotic, microorganism, nosocomial infection, gram positive, gram negative, antimicrobial resistance.

INTRODUCTION

Healthcare Associated Infections (HAIs) are an important health problem in terms of morbidities, mortalities and economic consequences, world- wide (Meric et al., 2005). They are especially important in intensive care units (ICUs) where they have a five-fold higher incidence rate compared to the general inpatient population (Ewans et al., 1999). This is due to the increased use of medical instruments such as mechanical ventilators, monitoring devices, blood and urine catheters and also high resistance of the microorganisms isolated from ICUs patients to most commonly used antibiotics, which in turn is a result of overt use of broad-spectrum antibacterial agents (Wenzel et al., 1983).

Pseudomonas aeruginosa and Enterobacteriaceae species are the major cause of HAIs, associated with significant morbidity and mortality. They are also subjected to multi-drugs resistance (Carmeli et al., 1999). Approximately 2 - 10% of *P. aeruginosa* are resistant to all available treatments (Carmeli et al., 1999; Babay, 2007). The most common HAIs in ICUs include Urinary Tract Infections (UTIs), bacteremia and pneumonia (Richards et al., 2000), the latter being the leading cause of death in ICUs patients. Vincent et al., 1995; Eggimann and Pittet, 2001).

Because of importance of HAIs, it is critical to conduct surveillance studies to obtain the required data about the regional microorganisms and their susceptibility to antibiotics. This study is aimed to provide such information for our clinicians.

MATERIALS AND METHODS

In this cross-sectional study, from July 2006 to June 2007, we collected 500 specimens from patients with criteria of HAIs infection, admitted in the intensive care unit of a general hospital in south of

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Table 1. Standard indices of NCCLS for interpretation of Diffusion Disc results.

Antibiotic name	Abbreviation	Susceptible	Intermediate	Resistant
Gentamycin	Gm	>14	13 - 14	<13
Imipenem	Imp	>15	14 - 15	<14
Ofloxacin	Ofx	>15	13 - 15	<13
Tobramycin	Tob	>14	13 - 14	<13
Vancomycin	V	>16	15 - 16	<15
Amikacin	Am	>16	15 - 16	<15
Ciprofloxacin	Cp	>20	16 - 20	<16
Cloxacillin	Cx	>15	11 - 15	<11

Table 2. Frequency of different microorganisms of various locations.

Microorganism	Trachea	Urine	Blood	Ulcer	Cerebro spinal fluid
Pseudomonas spp	92 (33.9%)	23 (24.3%)	14 (20.9%)	16 (29.2%)	5 (41.7%)
Klebsiella spp	65 (23.3%)	15 (15.8%)	13 (10.5%)	14 (25.5%)	5 (41.7%)
Staphylococcus aureus	39 (14.4%)	8 (8.4%)	7 (10.5%)	6 (10.9%)	0
Acinetobacter spp	20 (7.3%)	13 (13.7%)	3 (4.4%)	8 (14.6%)	0
E. coli	6 (2.3%)	26 (27.4%)	6 (8.9%)	3 (5.4%)	0
Entrobacter spp	9 (3.3%)	3 (3.1%)	4 (6%)	0	0
Proteus spp	4 (1.5%)	2 (2.1%)	0	2 (3.6%)	0
Coagulase negative staphylococci	0	0	17 (25.4%)	3 (5.4%)	2 (16.6%)
Streptococcus -hemolytic	0	0	3 (4.4%)	3 (5.4%)	0

Iran. According to the definition of HAIs infections, patients with signs of infection during admission to ICU were excluded, as well as the patients within the incubation period of the infection. For each patient, a form was filled according to the National Guideline of Controlling HAIs infections (Masoomi, 2006).

Clinical specimens included blood, urine, pus and discharges from endotracheal tubes and post surgical wounds swabs, were collected and cultured on Eosin Methylen Blue (EMB), Blood agar, chocolate agar, thioglycollate and Trypticase Soy broth (TSB) media and incubated at 37°C for 24 - 48 h. Thioglycollate cultures and TSB bottles were reincubated for at least 7 days and subcultured on EMB and blood agar or chocolate agar plates, as necessary.

The pathogenic isolates were identified by Gram staining, biochemical reactions and diagnostic tests included catalase, tube-coagulase and Manitol Salt agar in order to identify *Staphylococcus aureus* from Coagulase Negative Staphylococci (CoNS). Reaction of the isolates in TSI, SIM, Urea and Simmon's citrate medium and oxidase tests were used for identification of gram negative bacteria. Antibiogram pattern of microorganisms was determined by Kirby Bauer method on Mueller Hinton agar medium (Baily and Scott, 1990). Results were recorded according to the standards provided by National Committee for Clinical Laboratory Standards (NCCLS, 2003) Table 1.

The study protocol was approved by research ethics committee of Hormozgan University of Medical Sciences and each patient's family gave informed consent before enrollment the study. The data was analyzed using Statistical Package for the Social Sciences (SPSS) version 12.

RESULTS

From the total 500 specimens obtained, 112(22.4%) were from female patients and 388 (77.6%) from males. The most common locations for infection were respiratory tract (54.2%), urinary tract (19%), blood (septicemia in 13.4%), surgical site (11%) and cerebrospinal fluid (2.4%). The most frequent microorganisms derived from samples included *P. aeruginosa* (30%), *Klebsiella* spp (22.4%), *S. aureus* (12%), *Acinetobacter* spp (8.8%), *Escherichia coli* (8.2%) and Coagulase-negative staphylococci (5.6%). Other microorganisms were detected in 13% of the samples. Table 2 categorizes this data according to the location of specimens.

The most frequent gram negative microorganisms derived from samples were *P. aeruginosa* (43.2%) and *Klebsiella* spp (33.7%) as well as *S. aureus* (39.2%) among gram positive microorganisms.

From the 347 samples which contained gram-negative bacteria *(Pseudomonas*, *Klebsiella* spp, *Escherichia* spp or *Acinetobacter* species), 160 (46%) were sensitive to imipenem, 178 (51.3%) were resistant to it and 9 (2.7%) were intermediate. Table 3 depicts the susceptibility of the different microorganisms to various antibiotics. Amikacin and imipenem were the most active antibiotics against gram-negative microorganisms, and most of these microorganisms were resistant to cephepime and tobramycin.

Table 4 explains the sensitivity of different microorganisms to common antibiotics. *Pseudomonas* spp was mostly sensitive to amikacin (54%) and imipenem (46.7%)

Table 3. Distribution of microorganisms according to resistance and susceptibility to antibiotics.

Name	Susceptible	Intermediate	Resistant
Imipenem			
Pseudomonas spp	70	-	80
Klebsiella spp	60	9	43
E. coli	9	-	32
Acinetobacter spp	21	-	23
Cephepime			
Pseudomonas spp	5	-	145
Klebsiella spp	28	-	84
E. coli	3	-	31
Acinetobacter spp	-	-	44
Ciprofloxacin			
Pseudomonas spp	50	17	83
Klebsiella spp	49	2	61
E. coli	8	-	33
Acinetobacter spp	13	-	31
Amikacin			
Pseudomonas spp	81	23	46
Klebsiella spp	63	11	38
E. coli	25	-	16
Acinetobacter spp	14	-	30
Gentamycin			
Pseudomonas spp	43	7	100
Klebsiella spp	38	6	68
E. coli	5	-	36
Acinetobacter spp	3	-	41
Tobramycin			
Pseudomonas spp	36	14	100
Klebsiella spp	27	7	78
E. coli	0	-	41
Acinetobacter spp	3	-	41

and mostly resistant to cephepime (96.6%) and tobramycin and gentamycin (66.6%) . *Klebsiella* spp showed highest sensitivity to amikacin (56.2%) and imipenem (53.5%) and highest resistance to cephepime (75%) and tobramycin (69.6%). The most effective antibiotics for *Acinetobacter* spp were imipenem (47.7%) and amikacin (31.8%), while complete resistance existed to cephepime. *E. coli* was mostly susceptible to amikacin (60.9%) and imipenem (22%), and fully resistant to tobramycin. *Staphylococcus* species were very sensitive to vancomycin (83.3%) and very resistant to cloxacillin (96.6%). Finally, the most effective antibiotic for coagulase-negative staphs was vancomycin (82.2%) and ofloxacin was the least effective (82.2% resistance).

DISCUSSION

This study provides an analysis of epidemiology and microbiology of infections in the ICU patients of a general hospital in south of Iran. Consistent with other studies, pneumonia was the leading form of infection in the subjects of our study. *Pseudomonas* spp is the number one cause of pneumonia based on samples gathered from the trachea and shows approximately 50% resistance to amikacin. This is consistent with the results of a similar study conducted in India (Kumari et al., 2007)

Several studies have investigated the risk factors of hospital acquired pneumonia (HAP). These include age, gender and a history of prior hospitalization emergency

Table 4. Pattern of common antibiotic susceptibility of microorganism.

Microorganism	Frequency			Percent		
	S	I	R	S	I	R
Pseudomonas spp **(n = 150)**						
Imipenem	70	-	80	46.7	-	53.3
Cephepime	5	-	145	3.4	-	96.6
Ciprofloxacin	50	17	83	34	11.3	55.3
Amikacin	81	23	46	54	30.6	15.4
Gentamycin	43	7	100	28.6	4.8	66.6
Tobramycin	36	14	100	24	9.4	66.6
Klebsiella spp **(n = 112)**						
Imipenem	60	9	43	53.5	8.1	38.4
Cephepime	28	-	84	25	-	75
Ciprofloxacin	49	2	61	43.7	1.8	54.5
Amikacin	63	38	11	56.2	9.8	34
Gentamycin	38	68	6	34	5	61
Tobramycin	27	7	78	24	6.4	69.6
Escherichia coli **(n = 41)**						
Imipenem	9	-	32	22	-	78
Cephepime	3	-	38	7.3	-	92.7
Ciprofloxacin	8	-	33	19.5	-	80.5
Amikacin	25	-	16	60.9	-	39.1
Gentamycin	5	-	36	12.2	-	87.7
Tobramycin	0	-	41	0	-	100
Acinetobacter spp (n **= 44)**						
Imipenem	21	-	23	47.7	-	52.3
Cephepime	0	-	44	0	-	100
Ciprofloxacin	13	-	31	29.5	-	70.5
Amikacin	14	-	30	31.8	-	68.2
Gentamycin	3	-	41	6.8	-	93.2
Tobramycin	3	-	41	6.8	-	93.2

S = Susceptible I = Intermediate R = resistant.

surgery, chronic obstructive pulmonary disease, reintubation, coma, steroid treatment, intra-aortic balloon counter pulsation, enteral feedings, tracheostomy, APACHE II score, prior antibiotics and intermittent positive-pressure ventilation hours (Pawar et al., 2003; Erbay et al., 2004).

A recent study suggested that further advancements in development of risk models for HAP are required (Wolkewitz et al., 2008).

In our investigation, *E. coli* was the second most frequent pathogen obtained from patients with urinary tract infection. This is similar to previous studies in terms of how frequent this pathogen was detected, but not in regards to its pattern of antimicrobial susceptibility (Kiffer et al., 2005). In that study, *E. coli* species were fully susceptible to imipenem and amikacin, while our results show a relatively smaller susceptibility to amikacin and significant resistance to imipenem. Similarly, our results show a lower susceptibility of *P. aeruginosa* and *Klebsiella* species to imipenem and amikacin compared to that study. All together, this difference can be due to different routines in use of these antibiotics in our settings, or may be attributed to an alteration in the resistance pattern of these pathogens over time (that study was conducted in Brazil in 2005) (Kiffer et al., 2005) . In a more recent study conducted in Turkey in 2005, the values recorded for susceptibility of primary gram-negative pathogens acquired from ICU patients was more congruent with the results of our study (Kucukates, 2005). This further fortifies our theory about the effect of differences in time and settings of studies on their outcomes.

Although less prevalent than respiratory and urinary in-

fections, bacteremia is a major cause of morbidities and morality in ICU patients (Maldini et al., 2007). In this regard, attention should be given to the high level of resistance of CoNS – as the primary cause of septicemia in ICU – to ofloxacin. *S. aureus* was the second common gram positive microorganism in patients with a positive blood culture in our study.

A previous study combining the data from 25 UK hospitals has shown that this microorganism is resistant to ofloxacin and ciprofloxacin in 59% and 62% of the cases, respectively (Johnson et al., 2003). Similar to our results pertaining coagulase-negative staphylococci, in that study vancomycin was very effective on staphylococcus spp. similar result for vancomycin was achieved in Italy (Allegranzi et al., 2002). In their study a change in the routine interventions used for empirical therapy of *S. aureus* yielded a decline in resistance of this species against Ciprofloxacin from 91.3% to 78.6%, suggesting that a modification of routine antimicrobial treatments can effectively alter the pattern of resistance of this pathogen to these drugs.

In general, pathogens acquired from ICU patients in our settings show the least resistance to amikacin and imipenem, because these antibiotics are not commonly used in our settings. Ironically, high levels of resistance to cephepime are seen; although this antibiotic is usually reserved for complicated patients, this is the cross -resistance of other cephalosporins that results to high resistance to cephepime. Resistance of ICU-acquired pathogens against ciprofloxacin can be attributed to its high usage in inpatient and outpatient settings. We believe regular monitoring of the pattern of resistance of common pathogens in the ICUs is critical in planning the best routines for empirical treatment of infectious patients.

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