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ORIGINAL ARTICLE

Antimicrobial resistance pattern in healthcare-associated infections: investigation of in-hospital risk factors

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ABSTRACT

Background and Objectives: Antimicrobial resistance (AMR) is an increasing threat for efficient treatment of infections. Determining the epidemiology of healthcare-associated infections and causative agents in various hospital wards helps appropriate selection of antimicrobial agents.
Materials and Methods: This retrospective study was performed by analyzing antibiograms from March 2017 to March 2018 among patients admitted to the different wards of Imam Khomeini Hospital Complex in Tehran, Iran.
Results: Among 2440 hospital acquired infections, 59.3% were Gram-negative bacilli: *E. coli* (n = 469, 22.2%), *K. pneumoniae* (n = 457, 21.7%), *Acinetobacter* spp. (n = 282, 13.4%), *P. aeruginosa* (n = 139, 6.6%) and important Gram-positive bacteria were *Enterococcus* spp. (n = 216, 10.2%), *S. aureus* (n = 148, 7%), *S. epidermidis* (n = 118, 5.6). Generally, there was a high antimicrobial resistance in bacterial isolates in this study. Methicillin resistant *Staphylococcus aureus* (MRSA) was 56.3 % and MRSE 62.9 %. Vancomycin resistant enterococci (VRE) was 60.7%. *K. pneumoniae*- ESBL was 79.6% and its resistance to carbapenem was 38.4%. *E. coli*-ESBL was 42% and its resistance to carbapenems was 2.3%. *P. aeruginosa* resistance to ceftazidime was 74.4%, to fluroquinolones 63.3%, to aminoglycosides 64.8%, to piperacillin tazobactam 47.6% and to carbapenems 62.1%. *Acinetobacter baumannii* resistance to ceftazidime was 98.7%, to fluroquinolones 97%, to aminoglycosides 95.9%, to ampicillin sulbactam 84%, to carbapenems 96.4% and to colistin 4%.
Conclusion: The study revealed an alarming rate of resistance to the commonly used antimicrobial agents used in treating HAIs. Also the relationship between AMR and some risk factors and thus taking steps towards controlling them have been shown.

Keywords: Drug resistance; Cross infection; Methicillin-resistant *Staphylococcus aureus*; Vancomycin resistant *Enterococci*; *Klebsiella pneumoniae*; *Escherichia coli*

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INTRODUCTION

Antimicrobial resistance (AMR), is an ecological problem that is characterized by complex interactions involving various microbial populations affecting the health of humans, animals and the environment. Most bacteria and their genes can move easily within and between humans, animals and the environment (1, 2). Antimicrobial resistance is an increasing threat to healthcare systems and is resulting in reduced efficacy of antimicrobial therapy and increased morbidity and mortality rates. It is estimated that AMR causes 21 to 34 billion dollars to health care expenditure and also 8 million days of inpatient admission in USA per year (3).

Over the recent decades, bacteria have become resistant to most clinically relevant antibiotics (4). Almost all the *S. aureus* isolates are resistant to penicillin in USA and England and resistance to methicillin is more than 50% in some populations. Taking appropriate measures in the 2000s controlled growth of MRSA and also VRE worldwide (5). In the contrary Gram- negative AMR is growing especially in HAIs which require imperative attention (6). One of the most important causes of antimicrobial resistance is the overuse of antibiotics (7). Despite the increase in awareness against AMR, basic steps like hand washing are still overlooked in many centers. Isolation of patients with resistant organism are not done efficiently due to late detection and high costs (8). "Health tourism" is another factor which contributes to transfer of resistant organisms among different countries (9).

Hospital acquired infections (HAIs) is an infection that occurs after admission to the hospital (48 to 72 hours after admission to 10 -30 days after discharge in some cases); the patient should not have the infection at the time of admission and should not be in incubation period (10). There are four main groups of these infections: pneumonia, bloodstream infections, urinary tract infections, and surgical site infections (11, 12).

Therefore, this study was designed to investigate AMR in hospital-acquired infections and probable associations between antimicrobial resistance and different variables, at Imam Khomeini Hospital Complex in Tehran, Iran.

MATERIALS AND METHODS

This retrospective study was performed from March 2017 to March 2018 (one year period) by examining all the antibiograms obtained from cultures on samples from nosocomial infections in different wards of Imam Khomeini hospital. Infections case-definitions were based on CDC/NHSN2016 (11). In this study, antibiograms were primarily based on disk diffusion techniques, except for the colistin and vancomycin that E-tests were used. What antibiotics to use for each microbe in the antibiogram were based on the standard table extracted from the CLSI2016 (13) and the recommended table from the Iranian Ministry of Health Reference Laboratory. Our study is approved by Ethics Committee of Tehran University of Medical Sciences and Iran National Committee for Ethics in Biomedical Research with Ethics code IR.TUMS.IKHC.REC.1397.141.

Statistical analysis. Data was entered into excel and then exported to be analyzed in SPSS version 22 software. Data was described as number (%) and proportion for all categorical variables. Significance of relationship between dependent and independent variables was analyzed using Chi-square (or Fisher exact) test. A p-value of <0.05 was considered as statistically significant.

RESULTS

In this study 2440 samples were taken and categorized as different HAIs. 49.8% were males and 50.2% were females. Most patients were 15-65 years old (65.7%, n = 1602).

HAIs were categorized into 506 (20.6%) blood stream infections (BSI), 443 (18.2%) pneumonias, 551 (22.6%) surgical site infections (SSI), 871 (35.7%) urinary tract infections (UTI), and 69 (2.8%) other infections. The crude mortality rate was 20.4% among HAIs.

HAI rates were 11.76% in ICU wards, 3.62% in surgery wards, 6.37% in internal wards and 13.79% in transplant wards.

Gram positive isolates were 502 (20.6%), Gram negative 1447 (59.3%), fungal (*Candida* spp.) 159 (6.5%) and unknown isolates 332 (13.6%).

Among Gram-negative organisms most important were: *E. coli* (n = 469, 22.2%), *Klebsiella pneumoniae* (n = 457, 21.7%), *Acinetobacter* spp. (n = 282, 13.4%), *P. aeruginosa* (n = 139, 6.6%). Among Gram-positive bacteria most important were: *Enterococcus* spp. (n = 216, 10.2%), *S. aureus* (n = 148, 7%), *S. epidermid-*

is (n = 118, 5.6%).

Most common type of infection caused by Gram-positive bacteria was BSI (46%) of which, 36% was caused by *Enterococcus* spp. Most common type of infection caused by Gram negative bacteria was UTI (43%), most commonly caused by *E. coli* (53%). Most common type of infection caused by *Candida* spp. was also UTI (69%).

Generally, there was a high antimicrobial resistance in bacterial isolates in this study. Among Gram-positive bacteria, *S. aureus* and *S. epidermidis* were resistant to oxacillin or cefoxitin 56.3 % and 62.9%, respectively (which are known as MRSA and MRSE). *Enterococcus* spp. resistance to vancomycin was 60.7% (VRE). *K. pneumoniae* resistance to 3rd or 4th generation cephalosporins and beta lactamase inhibitors was 79.6% and its resistance to carbapenems was 38.4% (KPC). *E. coli* resistance to 3rd or 4th generation of cephalosporins and beta lactamase inhibitors was 42% and its resistance to carbapenems was 2.3%. *P. aeruginosa* resistance to ceftazidime was 74.4%, to fluroquinolones 63.3%, to aminoglycosides 64.8%, to piperacillin tazobactam 47.6% and to carbapenems 62.1%. *A. baumannii* resistance to ceftazidime was 98.7%, to fluroquinolones 97%, to aminoglycosides 95.9%, to ampicillin sulbactam 84%, to carbapenems 96.4% and to colistin 4%.

In this study we chose some of the most important organisms among Gram positive and Gram negative organism and their most important antibiotic resistance patterns to analyze association between AMR and different variables. Results are shown in Table 1.

For ESBL-producing *K. pneumonia*, there was a significant relationship between the resistance and the time of detection (days after admission when the HAI was detected) (P=0.02) and also the ward (P<0.001). For *Acinetobacter* and its resistant to carbapenem, there was a difference in wards (P=0.06) but was not significant. In patients infected with MRSA, a significant difference was shown for wards (P=0.02) and a non-significant difference for length of stay (P=0.08).

Table. 1. Association between antimicrobial resistance and different variables.

Variables		ESBL *K. pneumoniae*			*Acinetobacter* res to Carbapenems			ESBL* *E. coli*			MRSA**		
		S n (%)	R n (%)	p. value	S n (%)	R n (%)	p. value	S n (%)	R n (%)	p. value	S n (%)	R n (%)	p. value
Age (year)		46.14 (23.06)	47.67 (24.12)	0.65	50.43 (21.75)	54.22 (21.06)	0.64	48.69 (24.3)	56.45 (18.53)	0.004	51 (19.17)	54 (17.48)	0.41
Time of detection		15.44 (23.47)	23.25 (25.72)	0.02	25 (34.24)	20.51 (18.49)	0.54	13.76 (24.69)	14.35 (25.30)	0.85	13.63 (14.22)	19.2 (22.63)	0.18
Length of stay		33.15 (52.78)	37.66 (29.6)	0.37	38.43 (30.34)	35.4 (20.93)	0.71	27.63 (46.05)	24.5 (25.09)	0.48	27.34 (13.34)	35.54 (27.85)	0.08
Gender	Male	26 (40.6)	126 (50.6)	0.15	4 (57.1)	114 (60.6)	0.85	41 (36.9)	56 (36.8)	0.98	27 (71.1)	32 (65.3)	0.56
	Female	38 (59.4)	123 (49.4)		3 (42.9)	74 (39.4)		70 (63.1)	96 (63.2)		11 (28.9)	17 (34.7)	
Ward	Internal medicine wards	34 (53.1)	52 (20.9)	0.00	3 (42.9)	20 (10.6)	0.06	52 (46.8)	63 (41.4)	0.44	15 (39.5)	17 (34.7)	0.02
	Surgery wards	16 (25)	39 (15.7)		0	15 (8)		30 (27%)	35 (23)		13 (34.2)	7 (14.3)	
	ICUs wards	9 (14.1)	120 (48.2)		4 (57.1)	134 (71.3)		18 (16.2)	35 (23)		7 (18.4)	23 (46.9)	
	Transplant wards	5 (7.8)	38 (15.3)		0	19 (10.1)		11 (9.9)	19 (12.5)		3 (7.9)	2 (4.1)	
Outcome	Discharged	92 (82.9)	126 (82.9)	0.95	5 (71.4)	90 (47.9)	0.44	92 (82.9)	126 (82.9)	0.95	32 (84.2)	38 (77.6)	0.29
	Deceased	16 (14.4)	21 (13.8)		2 (28.6)	90 (47.9)		16 (14.4)	21 (13.8)		6 (15.8)	8 (16.3)	
	Still hospitalised	3 (2.7)	5 (3.3)		0	8 (4.3)		3 (2.7)	5 (3.3)		0	3 (6.1)	

*Extended spectrum beta-lactamases (ESBL) ; S: Susceptible; R: Resistant

**Methicillin-resistant *S. aureus* (MRSA)

DISCUSSION

This study was conducted to determine the epidemiology of bacterial pathogens and antimicrobial resistance associated with HAIs. Based on the findings, Gram-negative bacteria were the most ones isolated, and UTI was the most site of infection. A multi-center study in ICUs of teaching hospitals in Tehran showed a similar trend (14). *Enterococcus* spp. was the most Gram-positive bacteria. In previous study in Iran, Peyvasti et al. reported that the highest number of enterococcal isolates was attributed to UTIs (66.7%) (15). Among Gram-negative bacteria, *E. coli* was the most prevalent, and the main positive cultures were for urine specimens. In Iran, Behzadi et al. reported that *E. coli* was one the most common uropathogenic bacteria causing UTI (16). In Northwest Ethiopia, among Gram-negative isolates, *E. coli* (63.6%) was predominant (17). Most common type of infection caused by *Candida* spp. was also UTI (69%). In Korea, Kim et al. reported that *Candida* spp. are the most common pathogens in UTIs (18).

AMR is an increasingly threatening emerging problem in majority of health care facilities. Multi-drug resistant HAIs are one of the major causes of deaths and morbidity amongst inpatients. The incidence of HAIs in developed countries has been reported to be 7%-10% based on recent World Health Organization updates (19). For example, in Chinese population during the 5-year surveillance period (2013-2017), 23361 HAI cases were identified, including 82.43% patients with one episode and 17.57% patients with more than one episode of HAI (20). This study found the rate of HAI to be 6.98%. In this study, there were a few positive blood culture specimens (20.7%), a finding which is in agreement with other studies that showed a low positive growth of blood cultures (21). Possibly this is because of antibiotic use prior to sampling, which hinders the detection of susceptible organisms (22). The majority of patients had been treated with antibiotics and then referred to our hospital. The bacterial spectrum observed from this study showed a high diversity of Gram-negative bacilli. This predominantly Gram-negative infection pattern also observed in other studies (23). The easy availability of antibiotic drugs made to be commonly used for treatment by medical practitioners as well as for self-medication, are factors which play a great role in drug resistance (24). Convincing percentages of resistant strains of *E. coli* and *Klebsiella* to 3rd and 4th generations of cephalosporins were broadly noted, 57.8% and 79.6%, respectively. In previous studies in other developing countries the same rate of resistance was reported (25). For *S. aureus*, more than half of the specimens were resistant to oxacillin or cefoxitin (MRSA) and also clindamycin. In Afghanistan, MRSA was found to be 56.2% (26). In some European countries, such as Belgium, Greece, Ireland, Italy, and the United Kingdom, MRSA rates varied from 40.2 to 45% (27). There were several limitations to this study needed to be addressed. It was a retrospective study, adequate data on clinical information was lacking. Hence, differentiating between a pathogen and a contaminant were sometimes difficult especially when it was isolated from endotracheal aspirate (ETA) specimen or urine (in a patient with urine-catheter).

CONCLUSION

The study revealed an alarming rate of resistance to the commonly used antimicrobial agents used in treating HAIs .also the relationship between AMR and some risk factors have been shown. This highlights the imperative of surveillance on antimicrobial susceptibility patterns in HAIs in each care center and also taking preventive steps to decrease high rates of AMR.

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