Article

BJPS

Brazilian Journal of
Pharmaceutical Sciences
vol. 52, n. 3, jul./sep., 2016
http://dx.doi.org/10.1590/S1984-82502016000300006

Antimicrobial susceptibility patterns among bacteria isolated from intensive care units of the largest teaching hospital at the northwest of Iran

Hadi Hamishehkar[1], Pegah Shadmehr[2], Ata Mahmoodpoor[3], Simin Ozar Mashayekhi[4], Taher Entezari-Maleki[1,5,*]

[1]Applied Drug Research Center, Tabriz University of Medical Sciences, Tabriz, Iran, [2]Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran, [3]Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran, [4]Tabriz Health Services Management Research Center, Tabriz University of Medical Sciences, Tabriz, Iran, [5]Cardiovascular Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

This study was conducted to determine the antimicrobial susceptibility patterns among common pathogens in the intensive care units (ICUs) of a university hospital in northwestern Iran. A retrospective study was done on laboratory records of patients with nosocomial infection who were admitted to five ICUs of Imam Reza Hospital during a 21-month period from March 2010 to January, 2012. A total number of 556 isolates from 328 patients were evaluated. The most common sites of infections included respiratory (51.7%), urinary (24.8%), and blood (10.4%). The most frequently isolated microorganisms were *Enterobacter aerogenes* (50.6%) followed by *Escherichia coli* (16.7%) and *Pseudomonas aeruginosa* (7.5%). *Staphylococcus aureus* was the most frequent pathogen among gram-positives (39.7%). The rate of methicillin-resistant *Staphylococcus aureus* (MRSA) was 87.5%. Multidrug-resistant (MDR) gram-negative bacteria were documented in 25.8% of *Acinetobacter*, 20% of *Klebsiella*, and 16.6% of *Pseudomonas*. The most active antimicrobials were vancomycin (93.5%) followed by amikacin (71.5%) and gentamicin (46%). The overall antibiotic susceptibility was as follows: 36% ciprofloxacin, 19% imipenem, 20% trimethoprim-sulfamethoxazole, 20.5% ceftazidime, and 12% ceftriaxone. Due to the high rate of antimicrobial resistance in the ICU setting, more surveillance and control of the use of antimicrobials is needed to combat infections.

Uniterms: Intensive care units/anti-infective agents/cross infection. Hospital University/Iran.

INTRODUCTION

Patients admitted to intensive care units (ICUs) are more vulnerable to various nosocomial infections because of their underlying illnesses and exposure to various invasive medical devices (Jatin, Mary, 2012; Archibald *et al*., 1997; Fridkin, 2001; Kollef, Fraser, 2001; Rhomberg *et al*., 2006).

Hospital infections affect approximately two million patients annually and lead to 90,000 deaths and a cost of $4.5 to $5.7 billion according to reports from the United States (Weinstein, 1998; Jarvis, 2001). They involve 5-10% of ICU patients (CDC, 1992; Stone, Larson, Kawar, 2002).

Antibiotics are the mainstay tools in the management of infections. Disappointingly, a number of studies have reported inappropriate uses of antimicrobials as well as the emergence of antibiotic resistance in most parts of the world (Tunger *et al*., 2009; Bergman *et al*., 2006). Today, the emergence of multidrug-resistant (MDR) gram-negative and methicillin-resistant *Staphylococcus aureus* (MRSA) pathogens has become a major public health concern. Moreover, they negatively influence patients' outcomes and increase the length of hospital stays and healthcare costs (Giske *et al*., 2008; De Kraker *et al*., 2011; Resch, Wilke, Fink, 2009; Mulvey, Simor, 2009).

Many studies have also showed that controlled use of antibiotics leads to improved microorganism sensitivity

***Correspondence:** T. Entezari-Maleki. Cardiovascular Research Center, Faculty of Pharmacy. Tabriz University of Medical Sciences, Tabriz, Iran, Daneshgah Street, 55617, Tabriz, Iran. E-mail: tentezari@gmail.com

to antimicrobial agents (Lee *et al.*, 2010; Takesue *et al.,* 2010). The emergence of resistant pathogens and their negative impact on patient survival and healthcare costs need the evaluation of antimicrobial susceptibility in each health center and hospital in order to control infection. Therefore, this study assessed antimicrobial susceptibility patterns in the ICUs of the largest teaching hospital in northwestern Iran. To the best of the authors' knowledge, this is the first report of bacterial resistance in ICUs at this location.

MATERIAL AND METHODS

Study Design and Setting

A retrospective study was done on laboratory records of the positive cultures patients with nosocomial infection who were admitted at the five ICUs of Imam Reza Hospital, a 500-bed tertiary care hospital affiliated to Tabriz University of Medical Sciences during a 21-month period (March 2010 to January 2012). This study was approved in the ethic committee of the university.

Data and Sample Collection

For doing the study a questionnaire form was designed in order to record patients' data included age, sex, file number, ward, culture results, site of infection, diagnostic species, and antibiogram test results. Prescribed drugs for ICU cultures were demonstrated using the hospital information system (HIS). All samples were taken in aseptic conditions. The sources of specimen included blood, urine, sputum, bronchial washing, wound, catheter, cerebrospinal fluid (CSF), tracheal, peritoneal, pleural, and synovial fluids.

Antimicrobial Susceptibility Testing

The Kirby-Bauer disk diffusion method was used to test antimicrobial susceptibility (in Mueller-Hinton agar medium, Merck, Germany) according to the guidelines of the National Committee for Clinical Laboratory Standards (NCCLS, 1997).

The performed antibiogram disks (Himedia laboratories, Mumbai, India) included vancomycin (V, 30 mcg), ciprofloxacin (CIP, 5 mcg), clindamycin (CD, 2 mcg), trimethoprim-sulfamethoxazole(SXT, 30 mcg), gentamicin (GM, 10 mcg), ofloxacin (OFX, 5 mcg), penicillin G (P, 10 mcg), oxacillin (OXA, 5 mcg), amikacin (AMK, 30 mcg), cefotaxime (CTX, 30 mcg), ceftazidime (CAZ, 30 mcg), ceftriaxone (CTR, 30 mcg), cefazolin (CZ, 30mcg), chloramphenicol (CHL, 30 mcg), piperacillin (PIP, 100 mcg), imipenem (IPM, 10mcg), nitrofurantoin (FM, 50 mcg), ampicillin (AM, 10 mcg) and rifampin (RIF, 5 mcg).

Determination of Pattern of Antibiotic Prescriptions

A clinical pharmacist and two intensive care sub-specialists evaluated the appropriateness of prescribed antibiotics based on result of each isolated cultures from ICU patients.

Patterns of antibiotic prescription based on culture results were divided into four groups: Group 1) Adherence with culture results, according to culture the drug is added or discontinued. Group 2) Not adherence with culture results as follows: 2-1) No change in medication; While, culture results showed resistance to antibiotics or following antibiotic therapy. We need to change the antibiotics but physician did not notice to culture results and antibiotics continued. 2-2) inappropriate changes in medication: the doctor noticed that you need to change the antibiotic, but changes were not accordance to protocols and appropriate drug that affect antibiotic therapy to improve patient has not chosen.

Group 3) rational change without culture result guide: due to the lack of laboratory antibiogram test for all antibiotics, a rationale prescription of drugs by doctors was made.

Group 4) No judgment: Because there was no complete transparency in the medical record for patient, judgment in this case considered impossible by experts.

Antibiotics utilization rates in ICUs were determined by Defined Daily Dose (DDD) per 100 bed-days.

Data Analysis

Data were processed in SPSS 16. Results were shown as standard deviation for quantitative variables and percentage for categorical variables.

RESULTS

A total number of 556 cultures isolated from 328 patients who were admitted at the five ICUs of the hospital were included in the study. Of which, 55.5% (n=182) were males and 44.5% (n=146) were females. The mean (SD) forage of the patients was 54± 19.5 years old. Data were collected from the five ICUs of the hospital as follows: 31.1% (n=102) from brain ICU, 22.6% (n=74) neurology ICU, 28.4% (n=93) lung ICU, 16.5% (n=54) surgery ICU and 1.5% (n=5) from the general ICU. As shown, the brain ICU has the greatest number of patients.

The most common sites of infection included respiratory (40.6%), urine (24.8%) and blood (10.4%) followed by sputum (4.7%), CSF (4.7%), plural (3.9%), bronchial washing (3.6%), catheter (2.7%), abscess (2.2%), wound (2%), peritoneal (0.4%) and synovial (0.2%) specimen. The result of Gram staining showed that the majority of cultured samples (86.8%, n=483) were Gram-negative bacteria as well as 13.2% (n=74) were Gram-positive.

The most frequently isolated microorganisms were *Enterobacter aerogenes* (50.7%, n= 282) followed by *Escherichia coli* (16.7%) and *Pseudomonas aeruginosa* (7.5%). The prevalence of isolated microorganisms is given in Table I.

TABLE I - Bacterial typing of ordered cultures Bacterial type

Gram Negative	*Enterobacter aerogenes*, n (%)	282 (50.7)
	Esherichia coli, n (%)	93 (16.7)
	Pseudomonas aeruginosa, n (%)	42 (7.6)
	Acintobacter spp. n (%)	31 (5.6)
	Unclassified Gram-negative bacteria, n (%)	25 (4.5)
	Klebsiella spp. n (%)	5 (0.9)
	Enterobacter + E.coli, n (%)	5 (0.9)
	Total, n (%)	483 (86.9)
Gram Positive	*Staphylococcu saureus*, n (%)	29 (5.2)
	Staphylococcus epidermidis, n (%)	24 (4.3)
	Enterococcus spp. n (%)	11 (2.0)
	Unclassified Gram-positive bacteria, n (%)	5 (0.9)
	Streptococcus spp. n (%)	3 (0.5)
	Streptococcus pnemoniae, n (%)	1 (0.2)
	Total, n (%)	73 (13.1)

Among Gram-positives, *Staphylococcus aureus* was the most frequently isolated pathogen (39.7%, n=29) followed by *Staphylococcus epidermidis*. Susceptibility rates of Gram-positive and Gram-negative microorganisms are shown in Table II and III respectively. Based on these findings, rate of methicillin resistance *Staphylococcus aureus* (MRSA) was 87.5%. However, all cases of *Staphylococcus aureus* and 90% of *Staphylococcus epidermidis* were sensitive vancomycin.

In the present study, multidrug resistant (MDR) Gram-negative bacilli were documented in 25.8% of *Acinetobacter*, 20% of *Klebsiella* and 16.6% of *Pseudomonas*. The susceptibility rate of *Enterobacter*, *Escherichia coli* and *Pseudomonas aeruginosa* to imipenem were 16.4%, 16.6% and 46% respectively. These rates for ciprofloxacin were 34.5%, 43.5%, and 56.5% and to amikacin were 64.5%, 88%, and 62.5% respectively. Regarding gentamicin, these susceptibility rates were 42.5%, 53.7%, and 38.5% respectively.

Overall susceptibility rates of the microorganisms isolated from the ICUs are also shown in table IV. The most active antimicrobials were vancomycin (93.5%) followed by amikacin (71.5%) and gentamicin (46%). The overall susceptibility of isolated microorganisms to regular important antibiotics was as follows: 36% for ciprofloxacin, 19% for imipenem, 20% for trimethoprim-sulfamethoxazole, 20,5%for ceftazidime, and 12% for ceftriaxone.

The most *Staphylococcus* strains were observed in lung and blood samples (31% and 17.2% respectively).

Enterobacter and *E.coli* were the most commonly isolated pathogens from urine samples (37.7% and 36.2% respectively as well as the most frequently isolated microorganisms from lung samples were *Enterobacter* (52.7%) followed by *Pseudomonas aeruginosa* (10.2%) and *Acinetobacter* (9.1%). *Entrobacter aerogenes* was the most common strain in all samples. *Entrobacter aerogenes* and *E.coli* was the most commonly detected microorganisms in most ICUs.

Pattern of antibiotic prescription showed that only 22.5% of prescriptions were in accordance with culture results and 34.5% were not adherence with culture results. Moreover, in 38% of prescriptions logical changes were made without culture result guide. In 5%, no judgment could be made.

The rate of antibiotics utilization included as follows: ciprofloxacin (8.7mg per 100 bed-days), meropenem (5.4 mg per 100 bed-days), cefepime (4.2 mg per 100 bed-days), imipenem (3.1 mg per 100 bed-days), ceftazidime (1.9 mg per 100 bed-days), amikacin (0.9 mg per 100 bed-days), gentamicin (0.8 mg per 100 bed-days), ceftriaxone (8 mg per 100 bed-days), vancomycin (4.3 mg per 100 bed-days), piperacillin-tazobactam (2.8 mg per 100 bed-days).

DISCUSSION

To the best of the authors' knowledge, this is the first report from the ICUs of the largest teaching hospital in northwestern Iran. The result of this study highlighted the important key role of rational prescription of antibiotics. This matter becomes more important when it concerns the emergence of antimicrobial resistance produced by gram-negative bacilli and MRSA strains (Giske *et al*., 2008; De

TABLE II - Susceptibility rates of the most common Gram-positive cocci isolated from the ICUs

		Organisms					
		S. aureus	*S. epidermidis*	*Enterococcus*	*Streptocococcus*	*S.pnemoniae*	*Unclassified Gram positive bacteria*
Disc n		29	24	11	3	1	5
AMP	S	2	–	–	–	1	–
	R	7	1	–	–	–	–
IPM	S	–	–	–	–	1	–
	R	3	1	–	–	–	–
AMK	S	2	1	–	–	–	–
	R	–	1	–	–	–	–
GEN	S	3	1	1	1	1	–
	R	10	4	–	1	–	–
CHL	S	13	1	1	1	–	–
	R	1	–	1	–	–	–
SXT	S	7	5	–	1	1	–
	R	8	1	3	2	–	–
NIT	S	1	3	2	–	–	–
	R	–	–	–	–	–	–
CIP	S	2	1	–	1	–	–
	R	8	4	1	–	–	–
CLI	S	4	1	1	–	–	–
	R	9	4	–	1	–	–
VAN	S	23	9	1	2	1	–
	R	–	1	1	–	–	–
RIF	S	1	–	–	–	–	–
	R	2	–	–	–	–	–
OXA	S	1	–	–	–	–	–
	R	15	6	–	1	1	–
PEN	S	–	–	–	–	–	–
	R	1	2	–	2	1	–
CEF	S	–	–	–	–	–	–
	R	1	–	–	–	–	–

R= Resistant, S= Sensitive, – = Not measured or not reported, AMP= Ampicillin, IPM= Imipenem, AMK= Amikacin, GEN= Gentamicin, CHL= Chloramphenicol, SXT= trimethoprim-sulfamethoxazole, NIT= Nitrofurantoin, CIP= Ciprofloxacin, CLI= Clindamycin, VAN= Vancomycin, RIF= Rifampine, A= Oxacillin, PEN= Penicillin, CEF= Cefazolin.

Kraker *et al*., 2011; Resch, Wilke, Fink, 2009; Mulvey, Simor, 2009). Hence, the detection of antimicrobial resistance patterns in every hospital plays an important role in the management of infections.

Hospital-acquired infections are life-threatening conditions that involve patients, especially those admitted to ICUs. Respiratory pathogens are responsible for about one-third of ICU infections (Garner *et al*., 1998; Flanders, Collard, Saint, 2006). In the present study, the most common site of infection was the respiratory tract (51.7 %); this result is in agreement with other studies conducted indifferent countries including Turkey (38.8 %) (Gunseren *et al*., 1999), India (29.7%) (Orrett, 2002), Oman (65%) (Al-Lawati, Crouch, Elhag, 2000), Italy (91%) (Bassetti *et*

TABLE III - Susceptibility rates of Gram-negative bacilli isolated from the ICU

		Organisms						
		P. aeruginosa	*E. coli*	*Klebsiella*	*Acintobacter*	*Enterobacter*	*Enterobacter+ E.coli*	Unclassified Gram negative bacteria
Disc n		42	93	5	31	282	5	25
CAZ	S	3	8	_	1	10	_	2
	R [b]	6	12	1	11	55	_	4
AMP	S	1	_	_	_	4	_	1
	R	10	19	1	15	49	1	4
CTX	S	4	4	_	_	5	_	1
	R	8	23	2	12	41	2	10
IPM	S	6	2	_	_	12	_	_
	R	7	10	1	4	61	1	1
AMK	S	20	66	3	20	111	3	11
	R	12	9	1	8	61	1	2
GEN	S	10	29	1	8	62	1	9
	R	16	25	1	8	84	1	_
CHL	S	1	16	2	_	24	_	1
	R	14	11	1	12	78	2	7
SXT	S	7	12	_	1	20	_	1
	R	17	47	2	18	109	3	9
NIT	S	_	33	1	_	16	_	_
	R	7	6	_	2	25	1	2
CIP	S	13	23	_	3	47	1	2
	R	10	30	1	13	89	3	_
CLI	S	_	_	_	_	_	_	_
	R	_	2	_	3	3	1	2
CET	S	3	1	_	1	8	_	1
	R	6	12	1	6	79	_	_
CEZ	S	3	6	_	_	9	_	1
	R	10	11	1	4	49	_	4
RIF	S	1	_	1	3	26	2	2
	R	3	11	_	_	15	_	2
OXA	S	_	_	_	_	1	_	_
	R	9	11	1	6	53	1	1
PEN	S	_	_	_	_	_	_	_
	R	_	_	_	_	_	_	_
PIP	S	_	_	_	_	_	_	_
	R	_	_	_	_	_	_	_

R= Resistant, S= Sensitive, – = Not measured or not reported, AMK= Amikacin, GEN= Gentamicin, SXT= trimethoprim-sulfamethoxazole, CIP= Ciprofloxacin, CHL= Chloramphenicol, CET= Ceftriaxone, CTX= Cefotaxime, CAZ= Ceftazidime, AMP= Ampicillin, IPM= Imipenem, OXA= Oxacillin, CEZ= Ceftizoxime, NIT= Nitrofurantoin, VAN= Vancomycin, CLI= Clindamycin, PEN= Penicillin, PIP= piperacillin.

TABLE IV - Overall susceptibility rates of the microorganisms isolated from the ICUs

Used discs	n (%)	Sensitive		Resistant	
		N	%	N	%
AMK	333 (59.8)	238	71.5	95	28.5
GEN	278 (50.0)	128	46.0	150	54.0
SXT	275 (49.4)	55	20.0	220	80.0
CIP	259 (46.5)	93	35.0	166	65.0
CHL	188 (33.8)	60	32.0	128	68.0
CET	123 (22.1)	15	12.2	108	87.8
CTX	117 (21.0)	15	12.8	102	87.2
CAZ	117 (21.0)	24	20.5	93	79.5
AMP	116 (19.8)	9	7.8	107	92.2
IPM	111 (20.0)	21	19.0	90	81.0
OXA	107 (19.3)	2	1.8	105	98.2
CEZ	100 (18.0)	19	19.0	81	81.0
NIT	99 (17.8)	56	56.5	43	43.5
VAN	39 (7.1)	36	92.3	3	7.7
CLI	31 (5.6)	6	19.4	25	80.6
PEN	6 (1.1)	-	-	6	100
PIP	1 (0.2)	-	-	1	100

AMK= Amikacin, GEN= Gentamicin, SXT= trimethoprim-sulfamethoxazole, CIP= Ciprofloxacin, CHL= Chloramphenicol, CET= Ceftriaxone, CTX= Cefotaxime, CAZ= Ceftazidime, AMP= Ampicillin, IPM= Imipenem, OXA= Oxacillin, CEZ= Ceftizoxime, NIT= Nitrofurantoin, VAN= Vancomycin, CLI= Clindamycin, PEN= Penicillin, PIP= piperacillin.

al., 2012), the United States (54.4%) (Streit *et al*., 2004), and a separate report from Iran (70.6%) (Mohammadtaheri *et al*., 2010).

The SENTRY Antimicrobial Surveillance Program which included 25 ICUs in Europe (1997-1998) and North America (2001) reported *S. aureus*as the most common pathogen in developed countries followed by *P. aeruginosa* and *E. coli* (Streit *et al*., 2004; Fluit *et al*., 2001). However, this pattern in developing countries such as Brazil (Mendes *et al*., 2005), Turkey (Kucukates, 2005), Iran (Mohammadtaheri *et al*., 2010), and other Middle Eastern countries were documented as *Pseudomonas* and *Acinetobacter* (Aly, Al-Mousa, Al Asar, 2008; Bayram, Balci, 2006). In the present study, *Enterobacter aerogenes* followed by *E. coli* and *P. aeruginosa* were the organisms most frequently recovered from ICUs. In a Serbian report, *Enterobacter* strains were the bacteria most commonly isolated from ICUs (Djordjevic *et al*., 2012).

In the current study, *Escherichia coli* (36.2%) and *Enterobacter aerogenes* (52.7%) were the isolates most commonly found in urinary and respiratory tracts. These findings are in agreement with those of the study conducted by Streit et al. in North America (Streit *et al*., 2004). However, in a report from Oman, *Escherichia coli* and *Pseudomonas aeruginosa* were the pathogens most commonly found in the urinary and respiratory tracts of ICU patients (Al-Lawati, Crouch, Elhag, 2000). Whereas, *Klebsiella* and *Pseudomonas* were the microorganisms most commonly found in the urine of patients admitted to the ICU of Imam Khomeini Hospital in Tehran (Hadadi *et al*., 2008).

In the current study, 86.2% of microorganisms isolated from urine were gram-negative bacteria. This finding is in line with a 2003 NNIS study that showed the highest rates of gram-negative infections to be in urine (Gaynes, Edwards, 2005).

The most common gram-positive organisms recovered from the ICUs in this study were *S. aureus* followed by *S. epidermidis*. This result is in agreement with the findings of Mohammadtaheri *et al*. (2010) and Khalili *et al.* (2012) in their studies conducted in ICU and infectious ward settings in Iran. ().

In the present study, MRSA made up 87.5% of all *S.aureus* isolates. This rate is higher than those reported from Canada (CAN-ICU study) (22.3%) (Zhanel *et al*., 2008), Europe (39%) (Fridkin, 2001), and the USA (55%) (Styers *et al*., 2006), but it is comparable with the report from Turkey (82%) (Bayram, Balci, 2006). Also, the rate of MRSA in the current study is lower than that report separately from Iran (96.2%) (Mohammadtaheri *et al*., 2010).

All MRSA isolates in the current study were susceptible to vancomycin; this is in line with the report from Iran and the CAN-ICU study (Mohammadtaheri *et al*., 2010; Khalili *et al*., 2012; Zhanel *et al*., 2008). The other active agent against MRSA was trimethoprim-sulfamethoxazole (46.7%); this result is similar to that of Mohammadtaheri *et al*. (51.9%) (Mohammadtaheri*et al*., 2010), but it is far from that of the CAN-ICU study (11.7%) (Zhanel *et al*., 2008).

Currently, MRSA is an emerging problem associated with a higher rate of mortality and increased durations of hospitalization and healthcare costs (Giske*et al*., 2008; De Kraker *et al.*, 2011).This higher rate of MRSA should raise the concerns of health authorities and lead to a larger battle against the propagation of infections.

In the present investigation, the resistance rate of pathogens to imipenem was documented in more than 80% of isolates; this rate is higher than those of Belgium (13%) (Glupczynski *et al*., 2001), Poland (8%) (Patzer, Dzierzanowska,Turner, 2002), and Turkey (20.8%) (Kucukates, 2005).

Recent data from Iran revealed that the resistance of microorganisms to imipenem has increased. The susceptibility rates of pathogens to imipenem in earlier studies from Iran were about 98% and 87.5% in 2006 and 2008, respectively (Vessal *et al*., 2006; Hadadi *et al*., 2008). In 2010, however, the authors of the current study reported the decline of these rates to 2-37% and 19%, respectively (Mohammadtaheri *et al*., 2010). Accordingly, it may be concluded that the appearance of pathogens resistant to imipenem is increasing in Iran with the passing of time and consumption of the drug.

Antimicrobial resistance to ciprofloxacin was documented in 65% of cases. This rate in reports from Iran, Turkey, and Belgium was 76%, 29%, and 21%, respectively (Kucukates, 2005; Hadadi *et al*., 2008; Glupczynski *et al*., 2001).

The overall resistance rate of antimicrobials was higher in the current study than in other reports (Gunseren *et al*., 1999; Mendes *et al*., 2005; Styers *et al*., 2006; Patzer, Dzierzanowska, Turner, 2002; Gonlugur *et al*., 2004; Karlowsky *et al*., 2003). Moreover, the resistance rate to cephalosporins (79.5%-87.8%) was comparable to that in Iran (Hadadi*et al*., 2008), but higher than reported in foreign studies (Gunseren *et al.,* 1999; Al-Lawati, Crouch, Elhag, 2000; Glupczynski *et al*., 2001; Patzer, Dzierzanowska,Turner, 2002; Gonlugur *et al*., 2004; Karlowsky *et al*., 2003; Meric *et al*., 2005).

Current results also showed that 25.8% of *Acinetobacter*, 20% of *Klebsiella*, and 16.6% of *Pseudomonas* were an MDR gram-negative pathogen. In one study from Turkey from 2000 to 2002, 45.4% of *Acinetobacters* and 37.7% of *P. aeruginosa* isolates were MDR (Yaman *et al.*, 2004). In another study conducted in Iran, 80% of *Acinetobacter* and 59% of *Klebsiella* isolates were MDR (Hadadi *et al*., 2008). In the Karlowsky *et al*. (2003) study, among *Acinetobacter* isolates, the MDR rate was 11.6-24.2%.

MDR gram-negative bacilli-related infections have become a major, rising problem (Thomson, Bonomo, 2005). Despite the growth of MDR strains, very few antimicrobials have been developed to combat these infections (Rubinstein, Vaughan, 2005). The growing body of evidence also proves the development of resistant gram-negative infections without adequate therapeutic options (Falagas *et al*., 2005). Moreover, MDR gram-negative infections are associated with increased mortality rates, extended durations of hospitalization, and higher healthcare costs (Bergman *et al*., 2006).

At the end, the results of the present study showed a higher rate of antimicrobial resistance patterns in the ICUs of the largest referral tertiary teaching hospital in northwestern Iran. The irrational use of antibiotics reported in this study may partially justify these results. Therefore, detecting and managing bacterial resistance should be given more attention by clinicians as an important part of any infection control program. Additionally, the development of antibiotic stewardship programs in hospitals, encouragement of rational antibiotic use, and national and local antibacterial surveillances and control programs are recommended to reduce the development of resistant strains and encourage the successful management of infections.

This study has some limitations. Because of its retrospective design, access to clinicians and a medical menu was not possible. Therefore, a clinical judgment about the administration of antibiotics in some cases was not applicable.

CONCLUSION

This study showed a higher rate of bacterial resistance in the ICUs of a tertiary teaching hospital in Iran. Due to the emergence of resistant microorganisms in ICUs and considering the critical condition of patients in such a setting, more surveillance and control of the use of antibiotics is needed to combat infections.

ACKNOWLEDGMENTS

The authors would like to thank Student Research Committee of Tabriz University of Medical Science and Imam Reza hospital staffs for supporting this study.

FINANCIAL DISCLOSURE

The authors declare no conflicts of interest.

FUNDING/SUPPORT

None declared.

AUTHOR ROLES

All authors contributed to the content, drafting, critical revision and approval of this manuscript.

We confirm all patient/personal identifiers have been removed or disguised so the patient/person(s) described are not identifiable and cannot be identified by analyzing the details of these cases.

REFERENCES

AL-LAWATI, A.M.; CROUCH, N.D.; ELHAG, K.M. Antibiotic consumption and development of resistance among gram-negative bacilli in intensive care units in Oman. *Ann. Saudi Med.*, v.20, n.3-4, p.324-7, 2000.

ALY, N.Y.A.; AL-MOUSA, H.H.; AL ASAR, E.S.M. Nosocomial infections in a medical-surgical intensive care unit. *Med. Princ. Pract.,* v.17, n.5, p.373-377, 2008.

ARCHIBALD, L.; PHILLIPS, L.; MONNET, D.; MCGOWAN, J.E.Jr.; TENOVER, F.; GAYNES, R. Antimicrobial resistance in isolates from inpatients and outpatients in the United States: increasing importance of the intensive care unit. *Clin. Infect. Dis.*, v.24, n.2, p.211-5, 1997.

BASSETTI, M.; DE GAUDIO, R.; MAZZEI, T.; MORACE, G.; PETROSILLO, N.; VIALE, P.; BELLO, G.; LA FACE, S.; ANTONELLI, M. A survey on infection management practices in Italian ICUs. *Crit. care*, v.16, p.R221, 2012.

BAYRAM, A.; BALCI, I. Patterns of antimicrobial resistance in a surgical intensive care unit of a university hospital in Turkey. *BMC Infect. Dis.*, v.6, p.155, 2006.

BERGMAN, M.; HUIKKO, S.; HUOVINEN, P.; PAAKKARI, P.; SEPPÄLÄ, H.; FINNISH STUDY GROUP FOR ANTIMICROBIAL RESISTANCE (FIRE NETWORK). Macrolide and azithromycin use are linked to increased macrolide resistance in Streptococcus pneumoniae. *Antimicrob. Agents Chemother.*, v.50, n.11, p.3646-3650, 2006.

DE KRAKER, M.E.; DAVEY, P.G.; GRUNDMANN, H.; BURDEN STUDY GROUP. Mortality and hospital stay associated with resistant Staphylococcus aureus and Escherichia coli bacteremia: estimating the burden of antibiotic resistance in Europe. *PLoS Med.*, v.8, n. 10, p.e1001104, 2011.

DJORDJEVIC, Z.; JANKOVIC, S.; GAJOVIC, O.; DJONOVIC, N.; FOLIC, N.; BUKUMIRIC, Z. Hospital infections in a neurological intensive care unit: incidence, causative agents and risk factors. *J. Infec. Dev. Countries*, v.6, n.11, p.798-805, 2012.

FALAGAS, M.E.; BLIZIOTIS, I.A.; KASIAKOU, S.K.; SAMONIS, G.; ATHANASSOPOULOU, P.; MICHALOPOULOS, A. Outcome of infections due to pandrugresistant (PDR) gram-negative bacteria. *BMC Infect. Dis.*, v.5, p.24, 2005.

FLANDERS, S.A.; COLLARD, H.R.; SAINT, S. Nosocomial pneumonia: state of the science. *Am. J. Infect. Control.*, v.34, n.2, p.84-93, 2006.

FLUIT, A.; VERHOEF, J.; SCHMITZ, F.; EUROPEAN SENTRY PARTICIPANTS. Frequency of isolation and antimicrobial resistance of gram-negative and gram-positive bacteria from patients in intensive care units of 25 European university hospitals participating in the European arm of the SENTRY Antimicrobial Surveillance Program 1997-1998. *Eur. J. Clin. Microbiol. Infect. Dis.*, v.20, n.9, p.617-625, 2001.

FRIDKIN, S.K. Increasing prevalence of antimicrobial resistance in intensive care units. *Crit. Care Med.*, v.29, p.N64-N68, Supl. 4, 2001.

GARNER, J.S.; JARVIS, W.R.; EMORI, T.G.; HORAN, T.C.; HUGHES, J.M. CDC definitions for nosocomial infections, 1988. *Am. J. Infect. Control.*, v.16, n.3, p.128-140, 1998.

GAYNES, R.; EDWARDS, J.R. Overview of nosocomial infections caused by gram-negative bacilli. *Clin. Infect. Dis.*,v.41, n.6, p.848-54, 2005.

GISKE, C.G.; MONNET, D.L.; CARS, O.; CARMELI, Y. Clinical and economic impact of common multidrug-resistant gram-negative bacilli. *Antimicrob. Agents Chemother*, v.52, n.3, p.813-21, 2008.

GLUPCZYNSKI, Y.; DELMEE, M.; GOOSSENS, H.; STRUELENS, M. Distribution and prevalence of antimicrobial resistance among gram-negative isolates in intensive care units (ICU) in Belgian hospitals between 1996 and 1999. *Acta Clin. Belg*., v.56, n.5, p.297-306, 2001.

GONLUGUR, U.; BAKICI, M.Z.; AKKURT, I.; EFEOGLU, T. Antibiotic susceptibility patterns among respiratory isolates of Gram-negative bacilli in a Turkish university hospital. *BMC Microbiol*., v.4, p.32, 2004.

GUNSEREN, F.; MAMIKOGLU, L.; OZTURK, S.; YUCESOY, M.; BIBEROGLU, K.; YULUG N.; DOĞANAY, M.; SÜMERKAN, B.; KOCAGÖZ, S.; UNAL, S.; CETIN, S.; CALANGU, S.; KÖKSAL, I.; LEBLEBICIOĞLU, H.; GÜNAYDIN, M. A surveillance study of antimicrobial resistance of gram-negative bacteria isolated from intensive care units in eight hospitals in Turkey. *J. Antimicrob. Chemother*., v.43, n.3, p.373-8,1999.

HADADI, A.; RASOULINEJAD, M.; MALEKI, Z.; YONESIAN, M.; SHIRANI, A.; KOURORIAN, Z. Antimicrobial resistance pattern of Gram-negative bacilli of nosocomial origin at 2 university hospitals in Iran. *Diagn. Microbiol. Infect. Dis*., v.60, n.3, p.301-305, 2008.

JATIN, M.V.; MARY, J.F. Overview of antibacterial susceptibility testing. *Up To Date,* 2012.

KARLOWSKY, J.A.; DRAGHI, D.C.; JONES, M.E.; THORNSBERRY, C.; FRIEDLAND, I.R.; SAHM, D.F. Surveillance for antimicrobial susceptibility among clinical isolates of Pseudomonas aeruginosa and Acinetobacter baumannii from hospitalized patients in the United States, 1998 to 2001. *Antimicrob. Agents. Chemother*. v.47, n.5, p.1681-8, 2003.

KHALILI, H.; DASHTI-KHAVIDAKI, S.; KARIMZADEH, I.; JAFARI, S.; ABDOLLAHI; A.; SHAHIDI, M.R.; JAHANGARD-RAFSANJANI, Z.; ENTEZARI-MALEKI, T. Changes in 4-year antimicrobial resistance pattern of gram-positive bacteria at the main referral teaching hospital, Tehran, Iran. *Acta. Med. Iran*., v.50, n.7, p.493-504, 2012.

KOLLEF, M.H.; FRASER, V.J. Antibiotic resistance in the intensive care unit. *Ann. Intern. Med*. v.134, n.4, p.298-314, 2001.

KUCUKATES, E. Antimicrobial resistance among Gram-negative bacteria isolated from intensive care units in a Cardiology Institute in Istanbul, Turkey. *Jpn. J. Infect. Dis.*, v.58, n.4, p.228-231, 2005.

LEE, Y.T.; TSAO, S.M; LIN, H.C.; HUANG, H.J.; LEE, M.C.; HSUEH, P.R. Decline in the incidence of healthcare-associated methicillin-resistant *Staphylococcus aureus* (HA-MRSA) correlates with deceased antimicrobial consumption at a tertiary care hospital in Taiwan, 2001-2009. *Int. J. Antimicrob. Agents*, v.36, n.6, p.523-530, 2010.

MENDES, C.; OPLUSTIL, C.; SAKAGAMI, E.; TURNER, P.; KIFFER, C. Antimicrobial susceptibility in intensive care units: MYSTIC Program Brazil 2002. *Braz. J. Infect. Dis*., v.9, n.1, p.44-51, 2005.

MERIC, M.; WILLKE, A.; CAGLAYAN, C.; TOKER, K. Intensive care unit-acquired infections: incidence, risk factors and associated mortality in a Turkish university hospital. *Jpn. J. Infect. Dis*., v.58, n.5, p.297-302, 2005.

MOHAMMADTAHERI, Z.; POURPAKI, M.; MOHAMMADI, F.; NAMDAR, R.; MASJEDI, M.R. Surveillance of Antimicrobial Susceptibility among Bacterial Isolates from Intensive Care Unit Patients of a Tertiary-Care University Hospital in Iran: 2006-2009. *Chemotherapy*, v.56, n.6, p.478-484, 2010.

MULVEY, M.R.; SIMOR, A.E. Antimicrobial resistance in hospitals: how concerned should we be? *CMAJ*, v.180, n.4, p.408-415, 2009.

NATIONAL COMMITTEE FOR CLINICAL LABORATORY STANDARDS. NCCLS.. *Performance standards for antimicrobial disk susceptibility tests*. Approved standard M2-A6. Wayne, Pa: National Committee for Clinical Laboratory Standards, 1997.

ORRETT, F.A. Nosocomial infections in an intensive care unit in a private hospital. *West Indian Med. J*., v.51, n.1, p.21-24, 2002.

PATZER, J.; DZIERZANOWSKA, D.; TURNER, P. Susceptibility patterns of Gram-negative bacteria from a Polish intensive care unit, 1997-2000. *Int. J. Antimicrob. Agents*., v.19, n.5, p.431-434, 2002.

CENTERS FOR DISEASE CONTROL. (CDC). Public health focus: surveillance, prevention, and control of nosocomial infections. *MMWR Morb. Mortal. Wkly. Rep.,*v.41, p.783-7, 1992.

RESCH, A.; WILKE, M.; FINK, C. The cost of resistance: incremental cost of methicillin-resistant Staphylococcus aureus (MRSA) in German hospitals. *Eur. J. Health Econ*.,v.10, n.3, p.287-297, 2009.

RHOMBERG, P.R.; FRITSCHE, T.R.; SADER, H.S.; JONES, R.N. Antimicrobial susceptibility pattern comparisons among intensive care unit and general ward Gram-negative isolates from the meropenem yearly susceptibility test information collection program (USA). *Diagn. Microbiol. Infect. Dis*., v.56, n.1, p.57-62, 2006.

RUBINSTEIN. E.; VAUGHAN, D. Tigecycline: a novel glycylcycline. *Drugs*, v.65, p.1317-1336, 2005.

STONE, P.W.; LARSON, E.; KAWAR, L.N. A systematic audit of economic evidence linking nosocomial infections and infection control interventions: 1990-2000. *Am. J. Infect. Control.,* v.30, n.3, p.145-152, 2002.

STREIT, J.M.; JONES, R.N.; SADER, H.S.; FRITSCHE, T.R. Assessment of pathogen occurrences and resistance profiles among infected patients in the intensive care unit: report from the SENTRY Antimicrobial Surveillance Program (North America, 2001). *Int. J. Antimicrob. Agents*., v.24, n.2, p.111-118, 2004.

STYERS, D.; SHEEHAN, D.J; HOGAN, P.; SAHM, D.F. Laboratory-based surveillance of current antimicrobial resistance patterns and trends among Staphylococcus aureus: 2005 status in the United States. *Ann. Clin. Microb. Antimicrob.*, v.5, p.2, 2006.

TAKESUE, Y.; NAKAJIMA, K.; ICHIKI, K.; ISHIHARA, M.; WADA, Y.; TAKAHASHI, Y.; TSUCHIDA, T.; IKEUCHI, H. Impact of a hospital-wide programme of heterogeneous antibiotic use on the development of antibiotic-resistant Gram-negative bacteria. *J. Hosp. Infec*., v.75, n.1, p.28-32, 2010.

THOMSON, J.; BONOMO, R.A. The threat of antibiotic resistance in gram-negative pathogenic bacteria: beta-lactams in peril! *Curr. Opin. Microbiol*., v.8, n.5, p.518-524, 2005.

TUNGER, O.; KARAKAYA, Y.; CETIN, C.B.; DINC, G.; BORAND, H. Rational antibiotic use. *J. Infect. Dev. Ctries*., v.3, n.2, p.88-93, 2009.

VESSAL, G.; AFHAMI, S.; GHOLAMI, K.; SHAFAGHI, B.; HEKMAT-YAZDI, S. Evaluation of antimicrobial resistance among Gram-negative isolates collected from intensive care units and reliability of routine disc susceptibility tests at a teaching hospital in Tehran. *Iran J. Pharm. Res*., v.5, p.89-100, 2006.

WEINSTEIN, R.A. Nosocomial infection update. *Emerg. Infect. Dis*., v.4, p.416-420,1998.

JARVIS, W.R. Infection control and changing health-care delivery systems. *Emerg. Infect. Dis.,* v.7, n.2, p.170-173,2001.

YAMAN, A.; TASOVA, Y.; KIBAR, F.; INAL, A.S.; SALTOGLU, N.; BUYUKCELIK, O.; KURTARAN, B.; DUNDAR, I.H. Investigation of the antibiotic susceptibility patterns of pathogens causing nosocomial infections. *Saudi Med. J*., v.25, n.10, p.1403-1409, 2004.

ZHANEL, G.G.; DECORBY, M.; LAING, N.; WESHNOWESKI, B.; VASHISHT, R.; TAILOR, F.; NICHOL, K.A.; WIERZBOWSKI, A.; BAUDRY, P.J.; KARLOWSKY, J.A.; LAGACÉ-WIENS, P.; WALKTY, A.; MCCRACKEN, M.; MULVEY, M.R.; JOHNSON, J.; CANADIAN ANTIMICROBIAL RESISTANCE ALLIANCE (CARA); HOBAN, D.J. Antimicrobial-resistant pathogens in intensive care units in Canada: results of the Canadian National Intensive Care Unit (CAN-ICU) study, 2005-2006. *Antimicrob. Agents Chemother*., v.52, n.4, p.1430-1437, 2008.

Received for publication on 18th July 2014
Accepted for publication on 17th May 2016