Original Article

IRANIAN JOURNAL OF PHARMACOLOGY & THERAPEUTICS

Iranian J Pharmacol Ther. 2018 (June);16:1-11.

Evaluation of resistance to aminoglycosides among clinical isolates of *Acinetobacter baumannii*: A systematic review and meta-analysis

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Please cite this article as:
Nazari A, Alikhani2 MY, Sayehmiri K, Sayehmiri F, Karami M, Ghaderkhani J. Evaluation of resistance to aminoglycosides among clinical isolates of *Acinetobacter baumannii*: A systematic review and meta-analysis. Iranian J Pharmacol Ther. 2018 (June);16: 1-11.

ABSTRACT

In past decades, aminoglycosides have been commonly used to treat gram-negative infections as well as multi-drug resistant tuberculosis strains. However, in recent years, intrinsic, adaptive and acquired resistances have been raised against aminoglycosides which limits the uptake of these antibiotics. Acquired resistance to *Acinetobacter baumannii* responsible for nosocomial infection against aminoglycosides, has been led to a medical dilemma. In the present study, we aimed to investigate the prevalence rate of *A. baumannii* resistance to aminoglycosides using a meta-analysis and systematic review. International databases of Scopus, PubMed, Web of Science and Google Scholar, as well as national databases, include SID, Magiran, IranDoc, and IranMedex, were searched carefully and 62 articles published during years 1993 and 2016 were selected. After data extraction, random-effects model was used for analysis. Also, data heterogeneity was assessed using the I2 index and the final statistical analysis was done using STATA and R software. The total sample size of 28,055 extracted from the chosen articles and entered the meta-analysis process. The drug resistance value of *A. baumannii* isolates to various antibiotics was determined as follows: Amikacin 69% (57% to 81%), Tobramycin61% (52% to 71%), Netilmicin 35% (11% to 59%) and Gentamicin 68% (57% to 80%). The highest and lowest sensitivity of *A. baumannii* was considered against Netilmicin 57% (32% to 82%) and Gentamicin 26% (12% to 39%), respectively. According to our findings, the drug-resistance rate of *A. baumannii* clinical isolates to aminoglycosides, especially Amikacin, Tobramycin, and Gentamicin are relatively high. So, Gentamicin and Amikacin are not recommended as first-line treatment of *A. baumannii* isolates.

Conflicts of Interest: Declared None
Funding: None

Keywords
Drug- resistance,
Aminoglycosides,
Acinetobacter baumannii,
Meta-analysis

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Received: 12 Dec 2017
Revised: 5 Feb 2018
Accepted: 9 Apr 2018

INTRODUCTION

Acinetobacter baumannii is a gram-negative, non-fermentative and immobile bacilli which could lead to opportunistic nosocomial infections, especially in hospital intensive care units [1, 2]. Acinetobacter related organisms are almost ubiquitous in the nature; however, *A. baumannii* targets are exposed areas of the skin as well as mucosal membranes or moist tissues. These bacteria have low dietary requirements for growth and can survive a long time in adverse conditions, dry surfaces and the also aquatic environment. Also, this bacteria has not been identified as normal flora and can cause severe infections in immunocompromised individuals [3, 4]. *A. baumannii* is primarily associated with hospital-borne infections and pose a great threat to those patients who are hospitalized in the intensive care unit [5] or who had a prolonged hospital stay and are receiving wide spectrum antimicrobial treatment or anti-cancer therapy. Various hospital-acquired infections such as bacteremia, urinary tract infection, secondary meningitis, as well as upper respiratory tract pneumonia has been reported to be associated with *A. baumannii*. It is also one of the most common bacterial cause of sepsis in immunodeficient patients [6] and has been evidenced as the most common bacterial species isolated from blood, sputum, skin, pleural fluid and urine of hospital admitted patients [7, 8]. Many studies have been conducted to investigate the mortality rate associated with *A. baumannii* infection; however, there is still debate to actual impact of this infection on patient's mortality. In this regard, the result of some studies indicated that *A. baumannii* infection has a detrimental effect on patient's outcome.

Family of aminoglycoside antibiotics (such as Gentamicin, Amikacin, Netilmicin, Tobramycin) is prescribed as the first-line therapy against *A.baumannii* isolates. The bactericidal activity of AGs are almost because of their ability to disrupt mRNA reading frame which results in incomplete protein production [9]. It has been reported that microorganisms can cause treatment associated problems by obtaining the multi-faceted resistance to a wide range of antibiotics [4]. Accordingly, many studies have suggested that *A.baumannii* could acquire drug resistance against aminoglycoside antibiotics. Considering this, it is difficult to control the infection, and as a result, patients with *A. baumannii* infection may face critical problems [10]. Nowadays, a global concern is related with nosocomial infections which are of considerable importance especially in intensive-care units of hospitals. Acquired drug resistance by *A.baumannii* could pose a major threat to patients with prolonged hospital stays. Several studies have been conducted worldwide to investigate the prevalence of antibiotic resistance in the clinical isolates of *A. baumannii*. Soroush and colleagues in 2010 found 81% of *A.baumannii* isolates with multi-drug resistance pattern at Children's Medical Center in Tehran [11]. Zerrily and colleagues (Aril et al. 2008) in Lebanon, found 50% of *A.baumannii* isolates with drug-resistance to at least 64 mg/l and 125 mg /l concentrations of Amikacin and Gentamicin, respectively [12]. Kooti et al. 2015 (Kooti et al. 2015) also showed 84.5% and 86.5% of *A.baumannii* isolates are resistant to Gentamicin and Amikacin, respectively [13]. Carretto and colleagues (Italy, 2011) investigated 277 species of *A.baumannii* in which sensitivity and resistance to Amikacin was determined to be 18.9% and 80.3%, respectively [14]. Given to that, the prevalence of antibiotics resistance in *A. baumannii* isolates are gr owing up and are associated with patient's mortality. Therefore, considering the prevalence of *A. baumannii* resistance to AGs is a global necessity. Here in the present study, we have tried to investigate the prevalence rate of *A. baumannii* resistance to aminoglycosides using a meta-analysis and systematic literature review. The data of such study could definitely help decision makers to take appropriate measurements in order to prevent the increasing spread of antibiotic resistance.

MATERIALS AND METHODS

The current study is a systematic review and meta-analysis aimed to review, collect, analyze, and interpret information on the prevalence rate of aminoglycoside antibiotic resistance among *A. baumannii* clinical isolates between the years 1993 and 2016 in Iran and other countries in the world. To this end, international and national databases, including Google Scholar, PubMed, Web of Science, Scopus, SID, Magiran, IranDoc, and IranMedex were searched carefully and the studies pertaining to antibiotic resistance of *A.baumannii* to aminoglycosides were obtained.

The titles, abstracts and full texts of the selected articles were examined thoroughly to exclude unrelated works and maintain possible related articles. Searching was mainly performed using the systematic search keywords such as prevalence of drug resistance, antibiotics, antibiotic resistance, aminoglycosides, and *A.baumannii* with all possible combinations keywords, original and sensitive. In addition, relevant studies which were referenced or listed in the selected articles were also evaluated for further inclusions in this study.

Inclusion and exclusion criteria

Herein, all cross-sectional studies or studies in relation to the "prevalence of antibiotic resistance in clinical isolates of *Acinetobacter baumannii*" were considered carefully. To enter the study, selected articles were examined in three stages: title, abstract and full text and the studies related to the prevalence of antibiotic resistance in *A.baumannii* isolates were included in present study.

Also some articles were excluded from the meta-analysis because of the following criteria; articles with insufficient information, articles without epidemiological methodologies, studies which was not cross-sectional, studies that related to other Acinetobacter isolates, the studies were related to antibiotic resistance other than the aminoglycoside group, review articles, abstracts of congresses, studies published in languages other than Persian and Latin, as well as meta-analysis studies and repetitive publications.

Data Extraction

Initially, 112 articles including phrases "the prevalence of resistance "and "Acinetobacter baumannii" and "aminoglycosides" in their titles were listed based on their

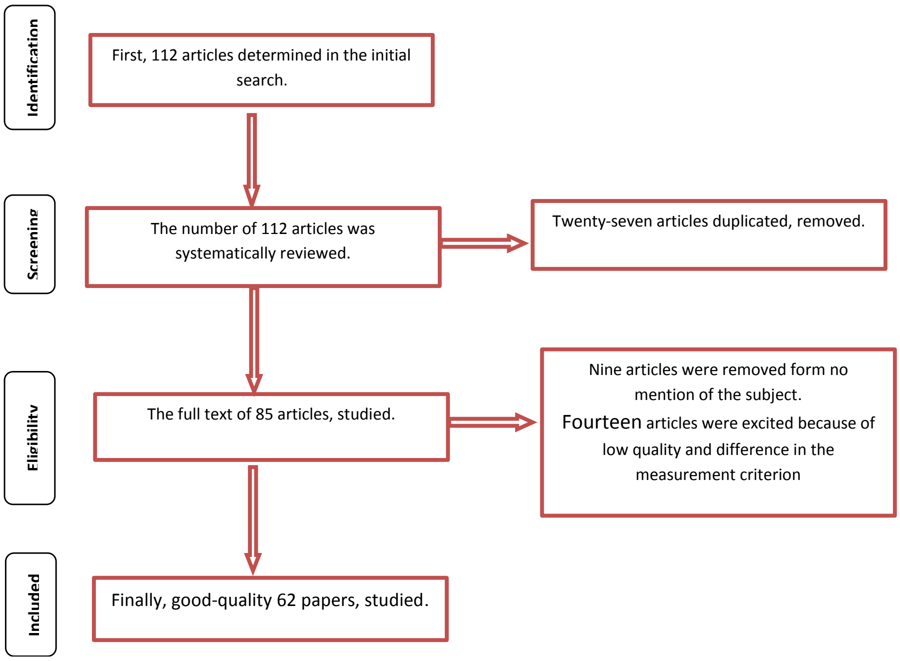

Figure 1. Data flowchart entered to the meta-analysis

abstracts**.** The primary list was assessed and 27 out 112 articles that were found to be duplicated, were excluded. Also, 23 out of the remaining 85 studies were further excluded due to lack of relevance to subjected matter or different measurement criteria (Fig. 1). Finally, 62 were found to be appropriate to enter the meta-analysis. A checklist consisting of multiple sections with necessary information of each study (researcher name, the year of study, study location, the number of samples, the prevalence of resistance to any aminoglycoside antibiotics, sensitivity rate for each of antibiotics, method of resistance and sensitivity measurement to antibiotics) was prepared. General specifications and main data needed to investigate are shown in Table 1.

Statistical analysis

The prevalence of antibiotic resistance and number of samples were collected from each study. For calculating the variance of each study, the weighted average values of the binomial distribution and the prevalence rate reported in the considered studies were obtained. Due to the differences in the prevalence rate reported in each study (heterogeneity of studies), heterogeneity index (I^2) of random-effects model was used.

RESULTS

In the present study, a number of 62 articles on the prevalence of aminoglycoside antibiotics resistance among *A.baumannii* clinical isolates between that are reported between the years 1993 and 2016 were collected and examined in detail. General features of all included articles in this meta-analysis are summarized in Table 1. The total

Table 1. General features and data of selected articles in the meta-analysis, the prevalence of resistance to aminoglycoside antibiotics in clinical isolates of *A. baumannii*

Author	*Year*	*Location*	*Sample Number*	*Amikacin*		*Tobramycin*		*Netilmicin*		*Gentamicin*	
				Sensitivity	*Resistance*	*Sensitivity*	*Resistance*	*Sensitivity*	*Resistance*	*Sensitivity*	*Resistance*
Kooti.S[11]	2015	Iran	200	8.5	86.5	-	-	-	-	-	-
Kwan. S.K[13]	2007	Korea	214	-	30.2	-	-	-	-	-	-
Aygun.G[14]	2002	France	170	45.5	54.5	36.4	63.6	95.2	4.8	4.8	95.2
Gur. D[40]	2008	Turkey	321		-	43.9		-	-	-	25.6
Hamez[42]	2012	Syria	260	21.7	-			-	-	-	17.3
Elabd. F.M[20]	2014	Saudi Arabia	108	-	75	-	79.6	-	-	-	81.5
Chen.C.M[21]	2014	Taiwan	87	44	87	-	-	-	-	50	98
Mohamed.H.A[43]	2014	Egypt	40	32.5	45	-	-	-	-	-	-
Carretto.E[22]	2011	Italy	277	18.9	80.3	-	-	-	-	-	-
Livermore.D.M[44]	2010	London	166	15.5		13.9	-	-	-	4.9	-
Vafaii.S[45]	2014	Iran	130	-	95	-	56	-	-	-	63
Mirzaii.E[46]	2015	Iran	100	-	95	-	56	-	-	-	63
Farahani.N[47]	2013	Iran	50	10	90	28	28	-	-	30	64

Table 1. Cntd

Caroline.J.H[37]	2002	UK	443		21	-	-	-	-	-	7.5
Mostofi.S[48]	2011	Iran	50	10	85	72	26	-	-	36	61
Hashemizadeh. Z[49]	2010	Iran	147		81	-	-	-	-	-	78
Anguti.G[50]	2015	Iran	61	50	38	50		-	-	-	77
Cisneros.J.M[23]	2016	Spanish	79	20	80	10	60	61	39	2	97
Scheetz.M.H[51]	2007	USA	93	38	-	-	-	-	-	-	-
Song.J.Y[52]	2007	Korea	43		-	-	-	-	-	-	-
Noormohamady .Z[15]	2014	Iran	100	21	66	30	67	-	-	9	89
Karlowsky.JA[38]	2003	USA	7394	80.2	13.8			-	-	49.3	47.9
Liu.JY[53]	2015	Taiwan	378	4	96	5	94	-	-	0	100
Reguero.MT[24]	2013	Columbia	51	-	68			-	-		82
Dinh Van.T[30]	2014	Vietnam	66	-		31.7	42.9	-	-	17.5	1
Aliakbarzade.K[54]	2014	Iran	103	17	81	37	63	-	-	11	86
Karbasizadeh.V[18]	2013	Iran	456		64			-	-	-	-
HernandezTorres. A[29]	2012	France	77	57	13	57	31	-	-	-	-
Talebi Taher.M[19]	2013	Iran	51	38	65	-	-	-	-	5	94.2
Vila.J[55]	1993	Spain	54	72		50		66		33	-
Sadeqifard.N[56]	2007	Iran	66	44	56	48.5	50	18.2	78.8		-
Nazari Monazam.A[57]	2014	Iran	100	30	95	10	56	-	-	-	63
Sinirtas.M[58]	2009	Europe	100	-	100	-	100	-	-	-	100
Higgins.PG[59]	2010	Europe	515	35.7	-	-	-	-	-	-	-
Dizbay.M[25]	2008	Turkey	66	30.3	63.6	-	-	51.5	30.3	-	-
Yau.W[26]	2009	Africa	30	20	80	26.7	73.3	-	-	6.7	93.3
Saderi.H[60]	2016	Iran	106	2.8	96.2	22.6	73.6	-	-	-	79.2
Jasemi.S[7]	2016	Iran	2382	53.4	40	-	-	-	-	60	33.4
Japooninejad.A R[61]	2014	Iran	56	-	77	-	-	-	-	-	85.5
Mirnejad.R[62]	2012	Iran	500	-	90	-	28	-	-	-	64
Hosainijazani.N[63]	2010	Iran	48	-	52	-	-	-	-	-	70.8
McGowan.JE[41]	2006	USA	433	56	14	-	-	-	-	-	-
Shrestha.S[64]	2015	Nepal	122	-	98	-	-	-	-	-	-
Amin Shahidi.M[65]	2015	Iran	86	-	66.3	-	72.1	-	-	-	-
Shokri.D[36]	2015	Iran	43	65.7	28.6	-	-	-	-	34.3	62.8
Lowings. M[66]	2015	Africa	100	-	7	-	-	-	-	-	-
Fazeli. H[67]	2014	Iran	121	-	87.6	-	86.8	-	-	-	-
Ahmadi. KH[68]	2014	Iran	43	14	86	-	-	-	-	-	-
Shahcheragi.F[69]	2009	Iran	95	-	75.7	-	-	-	-	-	-
Kalaatbari Farahani.R[70]	2008	Iran	48	6.7	80	10	68.3	-	-	58.3	30
Afshar Yavari.SH[31]	2016	Turkey	150	22	72	48	52	46	54	32	62
Alaee. N[33]	2013	Iran	84	-	-	52	43	41	36	-	-
Ardebili.A[71]	2012	Iran	65	-	94		62	-	-	-	86
Mirnejad. R[72]	2013	Iran	400	5	95	37	56	-	-	27	63
Farshadzadeh. Z[73]	2015	Iran	92		86		66	-	-	-	93
Moammadi.F[28]	2014	Iran	100	5.1	85.6	19.6	80.4	-	-	10.3	89.7
Baran. G[32]	2008	Turkey	1100	54.4	86.4	35.1	74.2	36.8	32.1	73.7	78.8
Nasrolahei M[74]	2014	Iran	100	-		-	83	-	-		83
Bayram Y[75]	2013	Turkey	377	-	64	-	-	-	-		94
Morkel G[76]	2014	Africa	14	14	86	-	-	-	-	14	86
Noreen H[77]	2011	USA	-	-	-	-	33.9	-	-	-	-
Kumar A[78]	2014	India	65	32.4	-	-	-	-	-	20.3	-

sample size 28,055 was obtained. Drug-resistant rate of *A. baumannii* was obtained to Amikacin (69%), Tobramycin (61%), Netilmicin (35%) and Gentamicin (68%). Clinical isolates of *A.baumannii* showed the most and least sensitivity to Netilmicin antibiotic (57%) and Gentamicin (26%), respectively.

According to Tables 2 and 3, the mean value of prevalence rate of drug resistance to Amikacin in world obtained to be 69% (0.57%-81%) and the highest intercontinental drug-resistance rates of *A. baumannii* to Amikacin were observed in Asia (76%), Tobramycin in Africa (73%), and Gentamicin in Africa (93%). However, the lowest rates of resistance were reported to Amikacin in America (14%), to Tobramycin in Europe (63%) and to Gentamycin in America (48%). Considering Iran, *A. baumannii* drug resistance to Amikacin in Iran was reported

Table 2. The total rate of resistance and sensitivity *of A. baumannii* to aminoglycosides, according to the studies were included in the meta-analysis.

P for Heterogeneity	*Homogeneity Index I^2 (%)*	*Confidence interval 95% (CI%95)*	*Prevalence*	*Study number*	*Sensitivity or Resistance*	*Aminoglycoside antibiotics*
0.000	99.9	0.57 – 0.81	0.69	49	R	Amikacin
0.000	99.7	0.18 – 0.43	0.30	36	S	
0.000	98.3	0.52 – 0.71	0.61	30	R	Tobramycin
0.000	96.8	0.25 – 0.40	0.33	23	S	
0.00	99.2	0.11 – 0.59	0.35	7	R	Netilmicin
0.000	99.2	0.32 – 0.82	0.57	8	S	
0.000	99.8	0.57 – 0.80	0.68	38	R	Gentamicin
0.000	99.8	0.12 – 0.39	0.26	23	S	

Table 3. The frequency distribution of *A. baumannii* resistance to aminoglycosides according to the study location and continent in the meta-analysis.

P value	*Homogeneity index I^2(%)*	*Confidence interval 95% (CI%95)*	*Prevalence*	*Sensitivity or Resistance*	*Continent*	*Aminoglycoside antibiotics*
0.000	98.0	-0.03 - 0.90	0.44	R	Africa	Amikacin
0.252	27.4	0.12 - 0.34	0.23	S		
0.907	0.00	0.13 - 0.15	0.14	R	America	
0.000	98.8	0.36 - 0.81	0.58	S		
0.000	98.9	0.69 - 0.83	0.76	R	Asia	
0.000	99.1	0.16 - 0.36	0.26	S		
0.001	99.8	0.19 - 0.98	0.59	R	Europe	
0.000	96.1	0.22 - 0.49	0.36	S		
–	0	0.57 - 0.89	0.73	R	Africa	Tobramycin
–	0	0.11- 0.43	0.27	S		
–	–	–	–	R	America	
–	–	–	–	S		
0.000	97.2	0.53 - 0.72	0.63	R	Asia	
0.000	97.3	0.24 - 0.42	0.33	S		
0.000	99.1	0.18 - 1.10	0.64	R	Europe	
0.000	96.1	0.12 - 0.53	0.32	S		
0.000	99.5	0.84 - 1.02	0.93	R	Africa	Gentamicin
	0	-0.02 - 0.16	0.07	S		
0.000	0.00	0.47 - 0.49	0.48	R	America	
–	0	0.48 - 0.50	0.49	S		
0.000	99.8	0.57 - 0.84	0.70	R	Asia	
0.000	99.0	0.18 - 0.47	0.32	S		
0.000	99.7	0.00 -1.00	0.50	R	Europe	
0.000	86.6	0.02 - 0.13	0.07	S		

to be 77% (68% to 85%) which is very high in comparison to other studied countries. Also, according to the results, the highest sensitivity to Amikacin has been recorded in America, while the lowest sensitivity to Gentamicin was obtained in Europe and Africa.

DISCUSSION

The objective of this work was to determine the prevalence rate of antibiotic resistance among clinical isolates of *A. baumannii* to the group of aminoglycoside antibiotics in Iran and rest of the world using a systematic review method and meta-analysis. According to our results, the drug resistance rate of *A. baumannii* to Amikacin was obtained to be high (69%), which was almost similar in Iran and other countries (Table 1). The results of different studies conducted in Iran are as follows: Noormohammady (66%) [15], Kooti (86.5%) [11], Vafaee (95%) [16], Farahani (90%) [17], Karbasizadeh (64%) [18], Talebi Taher (65%) [19]). Also, the similar results were obtained in countries other than Iran as follows: Aygün in Turkey (54.4%) [14], Elebd in Saudi Arabia (75%) [20] Chen in Taiwan (87%) [21], Carretto in Italy (80.3%) [22], Cisnoros in Spain (80%) [23], Reguero in Colombia (68%) [24], Dizbay in (63.6 %) [25], Yau in Africa (80%) [26] (Diagram 1). In addition, the rate of antibiotic resistance to Amikacin in Iran (77%) compared to developed countries in America (28%), was obtained to be considerably high. Different factors may influence such a difference such as self-medication by patients, incomplete period of treatment, uncontrolled prescribing of antibiotics by physicians and health providers, receiving high or inadequate drug doses, unavailability of high quality drugs, reliance on empirical treatment, poor

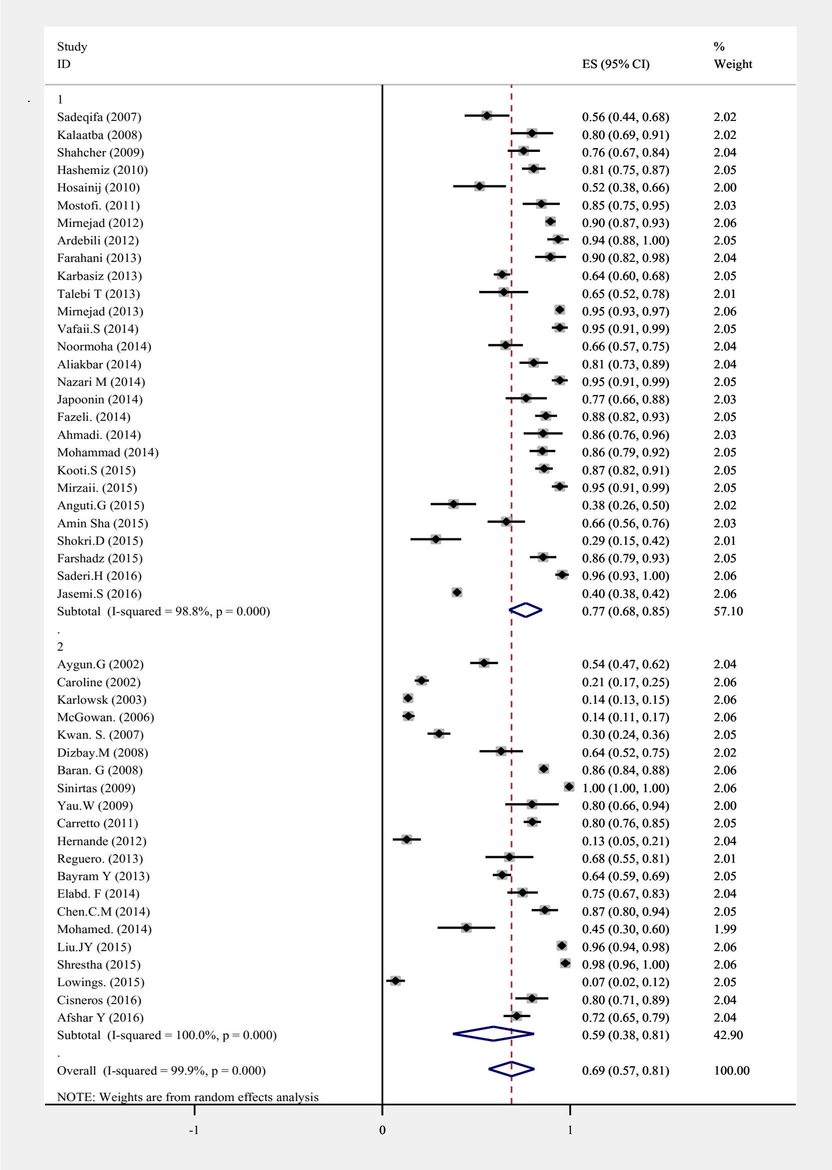

Diagram 1. Prevalence of resistance to Amikacin in clinical isolates of *A. baumannii* according to the location study (code 1: Iran and code 2: other parts of the world) based on the random-effects model. The midpoint of each line segment represents the estimate of the prevalence. The length of the segment indicates the 15% confidence interval in each study. Rhombic mark indicates the prevalence rate for all the studies.

hygiene conditions, low socioeconomic level and etc. which are most prevalent in developing countries. Given to these results it seems that the rate of *A. baumannii* resistance to aminoglycosides is rapidly increasing. Thus, it is necessary to take strict measurements in order to prevent and combat drug-resistance. Our findings also show that the drug-resistant rate of *A.baumannii* to Tobramycin (Diagram 2) was 61% worldwide, while this rate in Iran was obtained to be 59%. Accordingly the finding of studies in Iran were reported by Vafaii (56%) [16], Mizrahi (56%) [27], Noor Mohammady (67%) [15] and Mohammad (80.4%) [28], and in other countries the results of the studies are as follows: Amgun in Turkey (63.6%) [14], Hernandez Torres in France (31%) (31%) [29], Cisnoros in Spain (60%) [23], Dinah Van in Vietnam (42.9%) [30], Afsharyavari in Turkey (52%) [31]. The drug resistance rate of *A.baumannii* to Netilmicin was found to be 35% worldwide, while this rate is estimated to be 27% in Iran Similar results were obtained in other studies by Baran in Turkey (62.1 %) [32], Alaei in Iran (36%) [33], Afsharyavari in Turkey (54%) [31], Dizbay in Turkey (30.3%) [25] and Cisnoros in Spain (39%) [23].

The drug resistance rate of *A.baumannii* clinical isolates in terms of Gentamicin is reported to be 68.5% (57%-80%) in worlwide), which is similar to those reported in Iran and rest of the world (Diagram 4). These results were obtained from the studies from Vafaii (63%) [16], Mirzaii (63%)

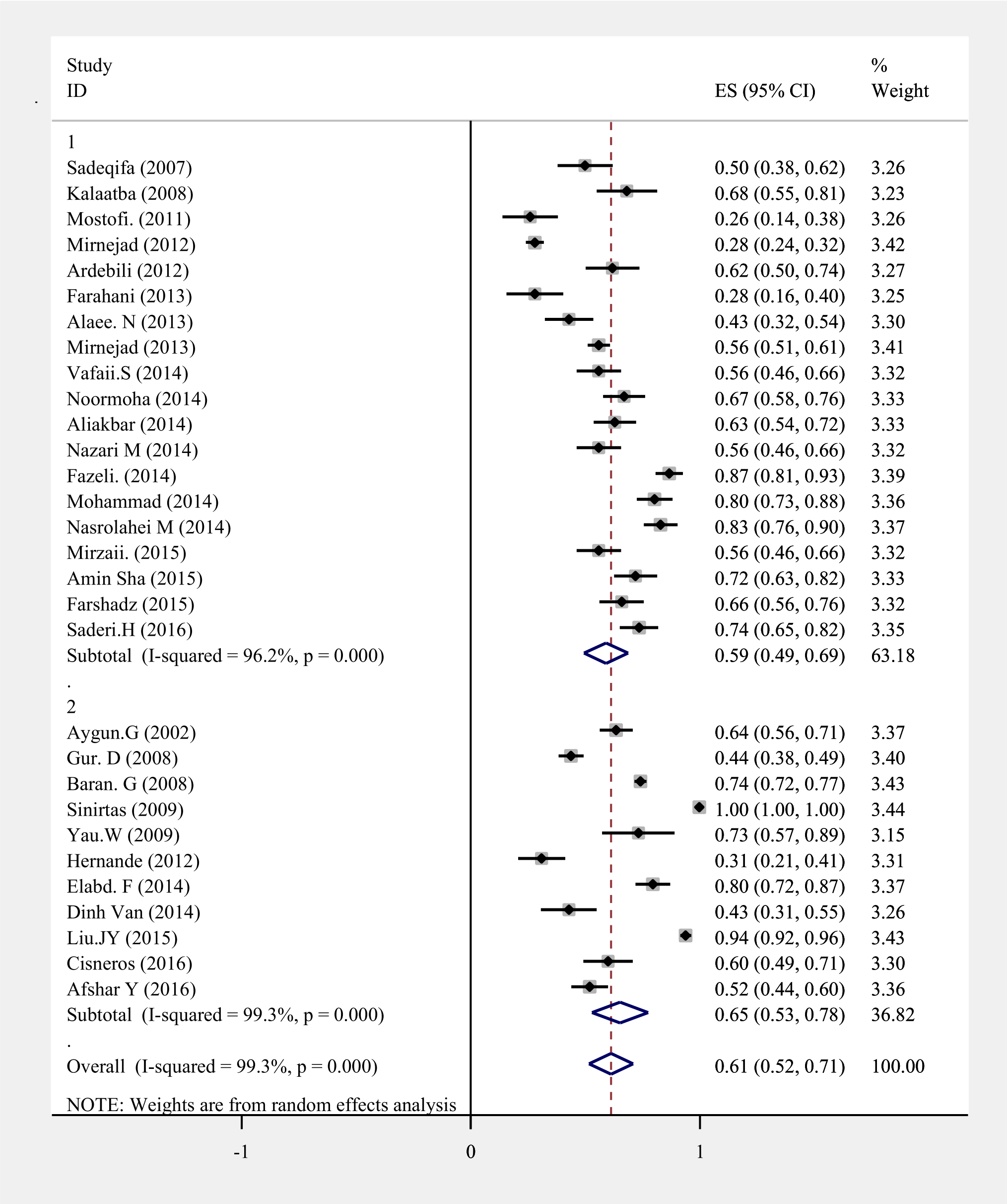

Diagram 2. Prevalence of resistance to Tobramycin in clinical isolates of *A. baumannii* according to the location study (code 1: Iran and code 2: other parts of the world) based on the random-effects model. The midpoint of each line segment represents the estimate of the prevalence. The length of the segment indicates the 15% confidence interval in each study. Rhombic mark indicates the prevalence rate for all the studies.

[27], Farahani (64%) [17], Saderi (79.2%) [34], Hosseini jazani (70.8%) [35] and Shokri in Iran (62.5%) [36], and Caroline in America (43%) [37], Karlowsky in America (47.9%) [38], Yau in Africa (93.3%) [26], Aygün in Turkey (95.2%) [14], Afsharyavari (62%) [31], Baran in Turkey (78.8%) [32], Reguero in Colombia (82%) [24], and Elebd in Saudi Arabia (81.5%) [20]. Due to high resistance of *A.baumannii* to Amikacin, Tobramycin, and Gentamicin, prescribing these antibiotics to treat *A. baumannii* is not recommended. Although, studies by Khalat Barry Farahani in Iran [39] and Gur Goor in Turkey [40] reported this rate 30% and 25.6% respectively, but the resistance rate is still high.

According to the results, clinical isolates of *A. baumannii* showed the highest sensitivity to Netilmicin (57%), while this sensitivity was the least to Gentamicin (26%) (Diagram 3). In addition, the highest and lowest resistance to Amikacin was observed in countries from Asia (77%) and America (28%), respectively. Considering Tobramycin, the highest resistance rate was reported in Africa (73%) and Europe (41%), respectively, while the lowest resistance rate are found to be Gentamicin in Africa (93%) and Europe

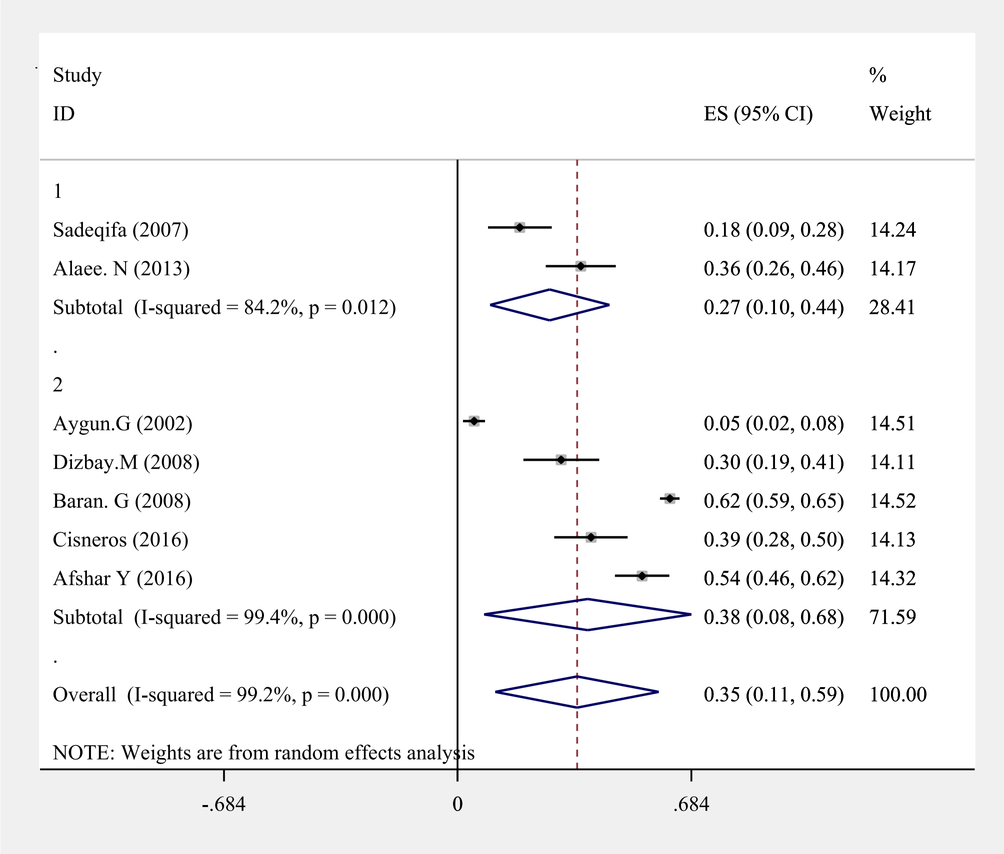

Diagram 3. Prevalence of resistance to Netilmicin in clinical isolates of *A. baumannii* according to the location study (code 1: Iran and code 2: other parts of the world) based on the random-effects model. The midpoint of each line segment represents the estimate of the prevalence. The length of the segment indicates the 15% confidence interval in each study. Rhombic mark indicates the prevalence rate for all the studies.

(61%), respectively. Putting the results together, the highest drug sensitivity is reported for Amikacin in clinical isolates from America continent and the least sensitivity to Gentamicin in Europe and Africa continents. In contrast to the results obtained by most of the studies, low resistance rate of *A. baumannii* to Netilmicin, Amikacin, Tobramycin, and Gentamicin have been reported only in few studies of Kwan in Korea [13], Caroline in the Kingham State [37], Karlwosky in America [38], Mc Gowan in America [41] and Herna´ndez-Torres in France [29]. We assume that this low resistance rate may be due to low consuming amount and minor amount prescription of these antibiotics and/or because of the few numbers of studies has been conducted in these regions.

CONCLUSION

Altogether, in all conducted studies the resistance rate of A. baumannii to aminoglycosides have been reported to be high all around the world. Thus, our findings strongly suggest that new strategies should be implemented in order to prevent acquiring drug resistance by *A. baumannii*. Also, prescription of aminoglycosides to treat this infection should be revisited.

ACKNOWLEDGMENTS

The authors would like to thank Deputy of Research and Technology of Ilam University of Medical Sciences, Iran.

CONFLICT OF INTEREST

Authors want to declare that they have no conflict of interests.

REFERENCES

1. Opazo A, Domínguez M, Bello H, Amyes SG, González-Rocha G. OXA-type carbapenemases in Acinetobacter baumannii in South America. J Infect Develop Countr 2011;6(04):311-6.
2. Peleg AY, Seifert H, Paterson DL. Acinetobacter baumannii: emergence of a successful pathogen. Clin Microbiol Rev 2008;21(3):538-82.
3. Murray PR BE, Pfaller MA. Manual of Clinical Microbiology. ed t, editor. Washington,D.C: ASM Press; 1999.
4. Bauernfeind A, Kljucar S, Jungwirth R. Overview of antibiotic resistance problems in Acinetobacter spp. J Med Microbiol 1997;46:726-8.
5. Fagon JY, Chastre J, Domart Y, Trouillet JL, Gibert C. Mortality due to ventilator-associated pneumonia or colonization with Pseudomonas or

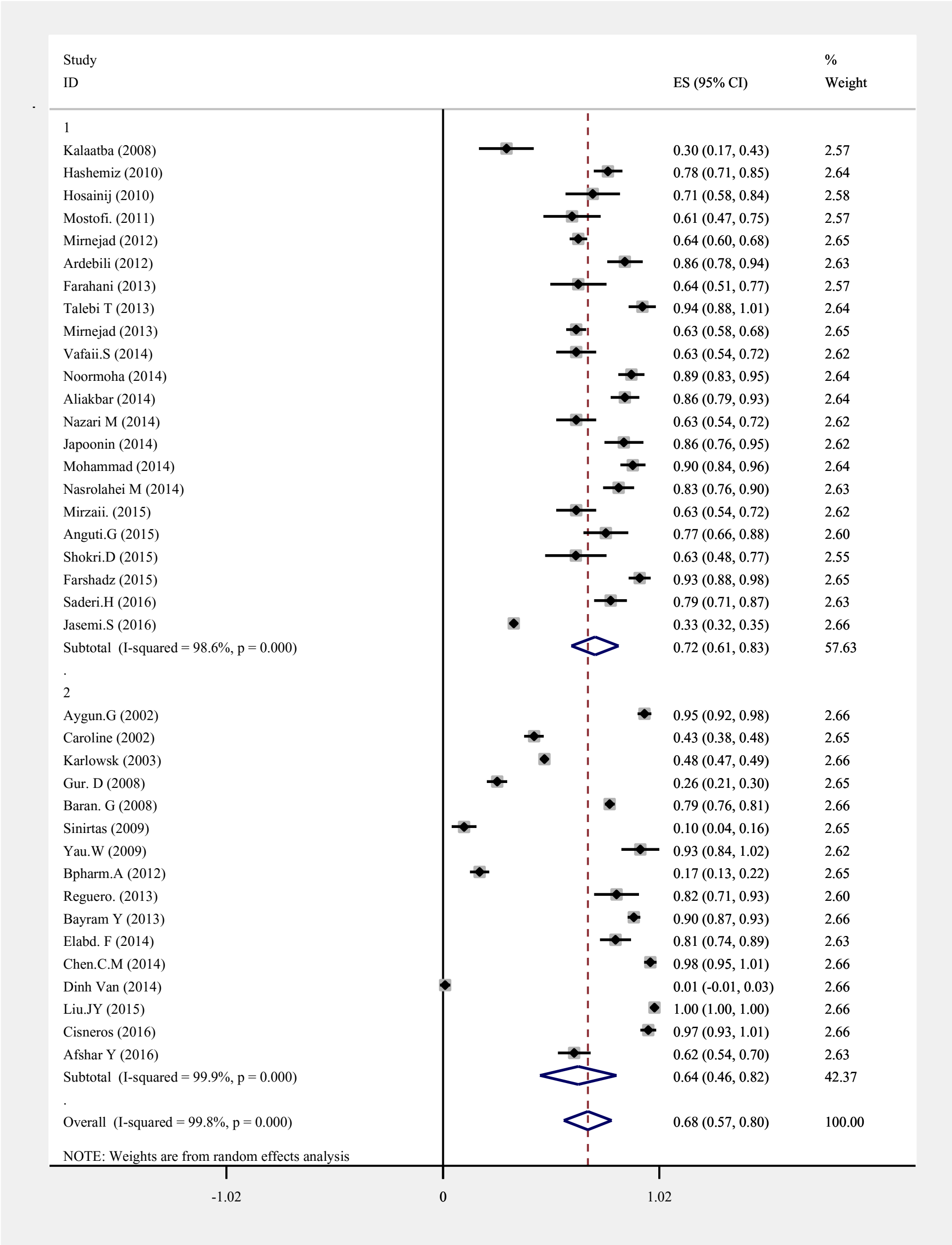

Diagram 4. Prevalence of resistance to Gentamicin in clinical isolates of *A. baumannii* according to the location study (code 1: Iran and code 2: other parts of the world) based on the random-effects model. The midpoint of each line segment represents the estimate of the prevalence. The length of the segment indicates the 15% confidence interval in each study. Rhombic mark indicates the prevalence rate for all the studies.

Acinetobacter species: assessment by quantitative culture of samples obtained by a protected specimen brush. Clin Infect Dis 1996;23(3):538-42.

6. Murray PR BE, Pfaller MA. Manual of Clinical Microbiology. In: 7, editor. Washington,D.C: ASM Press; 1999.
7. Jasemi SS, Alipour F, Dehbashi S, Mardaneh J. Isolation pseudomonas and acinetobacter from blood specimens in patients hospitalized in emam khomeini Hospital (Kermanshah). ISMJ. 2015;18(2):323-33.
8. Hanlon G. The emergence of multidrug resistant Acinetobacter species: a major concern in the hospital setting. Lett Appl Microbiol 2005;41(5):375-8.
9. Podnos YD, Cinat ME, Wilson SE, Cooke J, Gornick W, Thrupp LD. Eradication of multi-drug resistant Acinetobacter from an Intensive Care Unit. Surg Infect 2001;2(4):297-301.
10. Soroush S, Haghi-Ashtiani MT, Taheri-Kalani M, Emaneini M, Aligholi M, Sadeghifard N, et al. Antimicrobial resistance of nosocomial strain of Acinetobacter baumannii in Children's Medical Center of Tehran: a 6-year prospective study. Acta Med Iran 2010;48(3):178-84.
11. Kooti S, Motamedifar M, Sarvari J. Antibiotic resistance profile and distribution of oxacillinase genes among clinical isolates of Acinetobacter baumannii in Shiraz teaching hospitals, 2012-2013. Jundishapur J Microbiol. 2015;8(8).

12. Zarrilli R, Domenico V, Popolo A.D, Bagattini M, Daoud Z, Khan AU, et al. A Plasmid-Borne bla OXA-58 Gene Confers Imipenem Resistance toAcinetobacterbaumanniiIsolates from a Lebanese Hospital. Antimicrob Agents Chemother 2008:4115-20.
13. Ko KS, Suh JY, Kwon KT, Jung SI, Park KH, Kang CI, et al. High rates of resistance to colistin and polymyxin B in subgroups of Acinetobacter baumannii isolates from Korea. J Antimicrob Chemother 2007;60(5):1163-7.
14. Aygün G, Demirkiran O, Utku T, Mete B, Ürkmez S, Yılmaz M, et al. Environmental contamination during a carbapenem-resistant Acinetobacter baumannii outbreak in an intensive care unit. J Hosp Infect 2002;52(4):259-62.
15. Normohamady Z, Zamanzad B, Shavarzi A, Kiani P. Evaluation antimicrobial resistance of Acinetobacter baumannii isolated from Shahrekord teaching hospitals in 2013. J Shahrekord Uni Med Sci 2015;16(6):1-8.
16. Vafaii S, Mirnejad R, Mzafari NA, ImaniFuladi AA. Antibiotic Resistance Pattern and the prevalence of beta-lactamases of broad spectruminA. baumannii strains isolated from clinical samples phenotypicmethods. Infect Dis 2013; 1811):39-44.
17. Farahani N, Mirnejad R, Ahmadi Z, Mozafari NA, Masjedian F. Molecular typing of Clinical isolates ofA. baumanniiin Tehran with the methodpulsedfield gel electrophoresis. Med Sci 2013;2(4):259-66.
18. Karbasizade V, Heidari L. Antimicrobial Resistance of Acinetobacter Baumannii Isolated from Intensive Care Units of Isfahan Hospitals, Iran. J Isfahan Med School. 2012;30(191).
19. Talebi-Taher M, Latifnia M, Javad-Moosavai SA, Adabi M, Babazadeh Sh. Risk factors and antimicrobial susceptibility in ventilator associated pneumonia: a brief report. Tehran Uni Med Sci 2012;70(9).
20. Elabd FM, Al-Ayed MS, Asaad AM, Alsareii SA, Qureshi MA, Musa HAA. Molecular characterization of oxacillinases among carbapenem-resistant Acinetobacter baumannii nosocomial isolates in a Saudi hospital. J Infect Public Health 2015;8(3):242-7.
21. Chen CM, Ke SC, Li CR, Chang CC. The comparison of genotyping, antibiogram, and antimicrobial resistance genes between carbapenem-susceptible and-resistant Acinetobacter baumannii. Compar Immunol Microbiol Infect Dis 2014;37(5):339-46.
22. Carretto E, Barbarini D, Dijkshoorn L, van der Reijden T, Brisse S, Passet V, et al. Widespread carbapenem resistant Acinetobacter baumannii clones in Italian hospitals revealed by a multicenter study. Infect Gene Evolu 2011;11(6):1319-26.
23. Cisneros JM, Reyes MJ, Pachon J, Becerril B, Caballero FJ, Garmendia JLG, et al. Bacteremia due to Acinetobacter baumannii: epidemiology, clinical findings, and prognostic features. Clin Infect Dis 1996;22(6):1026-32.
24. Reguero MT, Medina OE, Hernández MA, Flórez DV, Valenzuela EM, Mantilla JR. Antibiotic resistance patterns of Acinetobacter calcoaceticus–A. baumannii complex species from Colombian hospitals. Enfermedades Infecc Microbiol Clin 2013;31(3):142-6.
25. Dizbay M, Altuncekic A, Sezer BE, Ozdemir K, Arman D. Colistin and tigecycline susceptibility among multidrug-resistant Acinetobacter baumannii isolated from ventilator-associated pneumonia. Int J Antimicrob Agents 2008;32(1):29-32.
26. Yau W, Owen RJ, Poudyal A, Bell JM, Turnidge JD, Heidi HY, et al. Colistin hetero-resistance in multidrug-resistant Acinetobacter baumannii clinical isolates from the Western Pacific region in the SENTRY antimicrobial surveillance programme. J Infect 2009;58(2):138-44.
27. Mirzaii E, Hosayni Dost R, Mirnejad R, Haqiqat S, HR R. Molecular typing of Clinical isolates ofA. baumanniiin Tehran with the methodpulsedfield gel electrophoresis. Med Sci 2014;19(67):61-9.
28. Moammadi F, Arabestani MR, Safari M, Roshanaii G, Alikhani MY. Prevalence of class1, 2 and 3 integrons among extensive drug resistance Acinetobacter baumanii strains isolated from intensive care units in Hamadan, west province, Iran. Iran J Med Microbiol 2014;8(3):8-14.
29. Hernández-Torres A, García-Vázquez E, Gómez J, Canteras M, Ruiz J, Yagüe G. Multidrug and carbapenem-resistant Acinetobacter baumannii infections: factors associated with mortality. Med Clin 2012;138(15):650-5.
30. Van TD, Dinh Q-D, Vu PD, Nguyen TV, Van Pham C, Dao TT, et al. Antibiotic susceptibility and molecular epidemiology of Acinetobacter calcoaceticus–baumannii complex strains isolated from a referral hospital in northern Vietnam. J Global Antimicrob Resist 2014;2(4):318-21.
31. Afsharyavari Sh, Seyyal Rota , Kayahan Caglar, Fidan I. Determination of resistance pattern of isolated acinetobacter baumannii from intensive care units (ICUS) in Gazi hospital, Ankara. J Urmia Nurs Midwif Faculty 2016;13(10):912-8.
32. Baran G, Erbay A, Bodur H, Öngürü P, Akıncı E, Balaban N, et al. Risk factors for nosocomial imipenem-resistant Acinetobacter baumannii infections. Int J Infect Dis 2008;12(1):16-21.
33. Alaee N, Bahador A, N H. Molecilar epidemiology & antibacterial resistance of Acinetobacter baumannii isolated from Namazi hospital, in Shiraz by modified AFLP analysis. J Microb World 2013;6(2):91-104.
34. Saderi H, P O. Pattern of resistance to different antibiotic groups among clinical isolates of Acinetobacter baumannii in two hospitals in Tehran. J Shahed Uni 2015;22(118):11-9.
35. Hosseini-Jazani N, Babazadeh H, Khalkhali H. An assessment of the sensitivity of Acinetobacter spp Burn isolates to Ciprofloxacin and some other antibiotics used for treatment. J Jah Univ Med Sci 2009;7:48-58.
36. Shokri D, Mobasherizadeh S, Fatemi M, Moayedinia R, Sadeghinaeini M. Hospital based surveillance of carbapenem resistance in multidrug-resistance(MDR) strain Entrobacter and Escherichia coli in Isfahan. J Microb World 2015;8(1):64-75.
37. Henwood CJ, Gatward T, Warner M, James D, Stockdale MW, Spence RP, et al. Antibiotic resistance among clinical isolates of Acinetobacter in the UK, and in vitro evaluation of tigecycline (GAR-936). J Antimicrob Chemother 2002;49(3):479-87.
38. Karlowsky JA, Draghi DC, Jones ME, Thornsberry C, Friedland IR, Sahm DF. 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. 2003;47(5):1681-8.
39. Farahani Kheltabadi R, Moniri R, Shajari GR, Shirazi N, Hossein M, Musavi SGA, et al. Antimicrobial Susceptibility patterns and the distribution of resistance genes among Acinetobacter species isolated from patients in shahid Beheshti hospital, Kashan. KAUMS J (FEYZ). 2009;12(4):61-7.
40. Gur D, Korten V, Unal S, Deshpande LM, Castanheira M. Increasing carbapenem resistance due to the clonal dissemination of oxacillinase (OXA-23 and OXA-58)-producing Acinetobacter baumannii: report from the Turkish SENTRY Program sites. J Med Microbiol 2008;57(12):1529-32.
41. McGowan JE, Carlet J. Antimicrobial resistance: a worldwide problem for health care institutions. Am J Infect Control 1998;26(6):541-3.
42. Hamzeh AR, Al Najjar M, Mahfoud M. Prevalence of antibiotic resistance among Acinetobacter baumannii isolates from Aleppo, Syria. Am J Infect Control 2012;40(8):776-7.
43. Al-Agamy MH, Khalaf NG, Tawfick MM, Shibl AM, El Kholy A. Molecular characterization of carbapenem-insensitive Acinetobacter baumannii in Egypt. Int J Infect Dis 2014;22:49-54.
44. Livermore DM, Hill RL, Thomson H, Charlett A, Turton JF, Pike R, et al. Antimicrobial treatment and clinical outcome for infections with carbapenem-and multiply-resistant Acinetobacter baumannii around London. Int J Antimicrob Agents 2010;35(1):19-24.
45. Somayeh Vafaei RM, Noor Amirmozafari. Determining the Patterns of Antimicrobial Susceptibility and the Distribution of blaCTX-M Genes in Strains of Acinetobacter Baumannii Acinetobacter Baumannii Isolated from Clinical Samples. J Isfahan Med School 2013;31(252, 2nd Week):1443-51.
46. Mirzaii E HDR, Mirnejad R, Haqiqat S, Rabii HR. The frequency of beta-lactamases of broad spectrum KPC and NDM in Acinetobacter baumannii isolated of patients in Tehran molecular methods PCR. Infect Dis 2015(67):61-9.
47. Farahani N, Mirnejad R, Ahmadi Z, Amirmozafari N, Masjedian F. Molecular typing of Acinetobacter Baumannii clinical strains in Tehran by pulsed-field gel electrophoresis. J Fasa Uni Med Sci 2013;2(4):259-65.
48. Mostofi S, Mirnejad R, Masjedian F. Multi-drug resistance in Acinetobacter baumannii strains isolated from clinical specimens from

three hospitals in Tehran-Iran. Afr J Microbiol Res 2011;5(21):3579-82.

49. Hashemizadeh Z, Bazargani A, Emami A, Rahimi M. Acinetobacter antibiotic resistance and frequency of ESBL-producing strains in ICU patients of Namazi Hospital (2008-2009). J Qazvin Univ Med Sci 2010;14(2):47-53.
50. Anguti G GH, Besharat M, Hajizadeh M, zarin ghalam moghadam.M. Acinetobacter baumannii strains in isolated from patients admitted to study drug resistance In Imam Reza Haspital of (AS) Tabriz, 2013. J Med Shahid Beheshti Uni Med Sci. 2014;28(2):106-10.
51. Scheetz MH, Qi C, Warren JR, Postelnick MJ, Zembower T, Obias A, et al. In vitro activities of various antimicrobials alone and in combination with tigecycline against carbapenem-intermediate or-resistant Acinetobacter baumannii. Antimicrob Agents Chemother 2007;51(5):1621-6.
52. Song JY, Kee SY, Hwang IS, Seo YB, Jeong HW, Kim WJ, et al. In vitro activities of carbapenem/sulbactam combination, colistin, colistin/rifampicin combination and tigecycline against carbapenem-resistant Acinetobacter baumannii. J Antimicrob Chemother 2007;60(2):317-22.
53. Liu JY, Wang FD, Ho MW, Lee CH, Liu JW, Wang JT, et al. In vitro activity of aminoglycosides against clinical isolates of Acinetobacter baumannii complex and other nonfermentative Gram-negative bacilli causing healthcare-associated bloodstream infections in Taiwan. J Microbiol Immunol Infect 2015.
54. Aliakbarzade K, Farajnia S, Nik AK, Zarei F, Tanomand A. Prevalence of aminoglycoside resistance genes in Acinetobacter baumannii isolates. Jundishapur J Microbiol 2014;7(10).
55. Vila J, Marcos A, Marco F, Abdalla S, Vergara Y, Reig R, et al. In vitro antimicrobial production of beta-lactamases, aminoglycoside-modifying enzymes, and chloramphenicol acetyltransferase by and susceptibility of clinical isolates of Acinetobacter baumannii. Antimicrob Agents Chemother 1993;37(1):138-41.
56. Noor khoda sadeghifard RR, Amir Ghasemi, Iraj Pakzad, Javad zaemi yazdi, Ahmad Zaheri, Ali Hemmatian, Sobhan Ghafoorian. Evaluation of drug resistance of Acinetobacter baumannii and other Acinetobacter species isolated from three hospitals in Tehran. J Ilam Uni Med Sci 2006;14(3):29-36.
57. Nazari Monazam A, Hosseini Doust SR, Mirnejad R. Prevalence PER and VEB beta-lactamase Genes among Acinetobacter baumannii Isolated from Patients in Tehran by PCR. Iran J Med Microbiol 2015;8(4):28-35.
58. Sınırtaş M, Akalın H, Gedikoğlu S. Investigation of colistin sensitivity via three different methods in Acinetobacter baumannii isolates with multiple antibiotic resistance. Int J Infect Dis 2009;13(5):e217-e20.
59. Higgins PG, Dammhayn C, Hackel M, Seifert H. Global spread of carbapenem-resistant Acinetobacter baumannii. J Antimicrob Chemother 2010;65(2):233-8.
60. Saderi H OP. Pattern of resistance to different antibiotic groups among clinical isolates of Acinetobacter baumannii in two hospitals in Tehran. J Shahed Uni 2015;22(118):11-9.
61. Japoni-Nejad A, Sofian M, van Belkum A, Ghaznavi-Rad E. Nosocomial outbreak of extensively and pan drug-resistant Acinetobacter baumannii in tertiary hospital in central part of Iran. Jundishapur J Microbiol 2013;6(8).
62. Mirnejad R, Mostofi S, Masjedian F. Antibiotic resistance and carriage class 1 and 2 integrons in clinical isolates of Acinetobacter baumannii from Tehran, Iran. Asia Pacific J Tropic Biomed 2013;3(2):140-5.
63. Hosseini Jazani N, Babazadeh H, Khalkhali H. An assessment of the sensitivity of Acinetobacter sp. burn isolates to Ciprofloxacin and some other antibiotics used for treatment. J Jahrom Univ Med Sci 2009;7(2):48-58.
64. Shrestha S, Tada T, Miyoshi-Akiyama T, Ohara H, Shimada K, Satou K, et al. Molecular epidemiology of multidrug-resistant Acinetobacter baumannii isolates in a university hospital in Nepal reveals the emergence of a novel epidemic clonal lineage. Int J Antimicrob Agents 2015;46(5):526-31.
65. Amin Shahidi M, Anvarinejad M, Abbasian A, Abbasi P, Rafaatpour N, Dehyadegari MA, et al. Characterization of multi-drug resistant ESBL producing nonfermenter bacteria isolated from patients blood samples using phenotypic methods in Shiraz (Iran). J Birjand Uni Med Sci 2015;22(3):256-65.
66. Lowings M, Ehlers MM, Dreyer AW, Kock MM. High prevalence of oxacillinases in clinical multidrug-resistant Acinetobacter baumannii isolates from the Tshwane region, South Africa–an update. BMC Infect Dis 2015;15(1):1.
67. Fazeli H, Taraghian A, Kamali R, Poursina F, Esfahani BN, Moghim S. Molecular Identification and Antimicrobial Resistance Profile of Acinetobacter baumannii Isolated From Nosocomial Infections of a Teaching Hospital in Isfahan, Iran. Avicenna J Clinical Microbiol Infect 2014;1(3).
68. Ahmadi K, Mardaneh J, Saadat S. Determination antimicrobial resistance profile of Acinetobacter strains isolated from hospitalized patients in Different Part of Taleghani Hospital (Ahvaz, Iran). Iran South Med J 2014;17(4):620-8.
69. Shahcheraghi F, Abbasalipour M, Feizabadi M, Ebrahimipour G, Akbari N. Isolation and genetic characterization of metallo-β-lactamase and carbapenamase producing strains of Acinetobacter baumannii from patients at Tehran hospitals. Iran J Microbiol 2011;3(2):68-74.
70. Farahani Kheltabadi RM, Shajari GR, Nazem Shirazi MH, Musavi SGA, Ghasemi A, Haj Aghazadeh S. Antimicrobial susceptibility patterns and the distribution of resistance genes among Acinetobacter species isolated from patients in Sshahid Beheshti Hospital, Kashan. Feyz J Kashan Uni Med Sci 2009;12:61-7.
71. Ardebili A, Azimi L, Mohammadi-Barzelighi H, Beheshti M, Talebi M, Jabbari M, et al. Determination of resistance pattern of isolated acinetobacter baumannii from hospitalized burned patients in Motahari Hospital, Tehran. Zabol Uni Med Sci J 2012;20(83):112-9.
72. Mirnejad R, Vafaei S. Antibiotic resistance patterns and the prevalence of ESBLs among strains of Acinetobacter baumannii isolated from clinical specimens. J Gene Microb Immun. 2013;2:1-8.
73. Farshadzadeh Z, Hashemi FB, Rahimi S, Pourakbari B, Esmaeili D, Haghighi MA, et al. Wide distribution of carbapenem resistant Acinetobacter baumannii in burns patients in Iran. Frontiers Microbiol 2015;6.
74. Nasrolahei M, Zahedi B, Bahador A, Saghi H, Kholdi S, Jalalvand N, et al. Distribution of bla OXA-23, IS Aba, Aminoglycosides resistant genes among burned & ICU patients in Tehran and Sari, Iran. Ann Clin Microbiol Antimicrob 2014;13(1):1.
75. Bayram Y, Gültepe B, Bektaş A, Parlak M, Güdücüoğlu H. Çeşitli klinik örneklerden izole edilen Acinetobacter baumannii suşlarının antibiyotiklere direnç oranlarının araştırılması. Klimik Dergisi 2013;26(2):49-53.
76. Morkel G, Bekker A, Marais B, Kirsten G, van Wyk J, Dramowski A. Bloodstream infections and antimicrobial resistance patterns in a South African neonatal intensive care unit. Paediatr Int Child Health 2014;34(2):108-14.
77. Chan-Tompkins NH. Multidrug-resistant gram-negative infections. Critic Care Nurs Quart 2011;34(2):87-100.
78. Kumar A, Randhawa VS, Nirupam N, Rai Y, Saili A. Risk factors for carbapenem-resistant Acinetobacter baumanii blood stream infections in a neonatal intensive care unit, Delhi, India. J Infect Develop Countr 2014;8(08):1049-54.