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The Prevalence of Antibiotic Resistance to Polymyxins in Clinical Isolates of *Acinetobacter baumannii* in Iran and the World: A Systematic Review and Meta-Analysis

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Abstract

Background: *Acinetobacter baumannii* is one of the most important opportunistic pathogens responsible for several nosocomial infections. A major problem in treatment is antibiotic resistance.

Methods: By searching international and national databases, including PubMed, Google Scholar, Web of Science, SID, Magiran, IranDoc and IranMedex, 38 articles between years 2002 to 2016 published world-wide were extracted and analyzed using the meta-analysis method and random effects model. The heterogeneity of studies was assessed using the I^2 index. Data were analyzed with the R and STATA (Ver 11/2) software.

Results: Forty-three articles were selected for this study. Drug-resistance of *Acinetobacter baumannii* towards Polymyxin was reported as 5%, yet for Colistin 4% was estimated. Resistance rates to Polymyxin and Colistin in the continent of America and Asia was 6% and Sensitivity rate to Polymyxin and Colistin was 96% and 80%, respectively.

Conclusions: Given that drug resistance rate of *Acinetobacter baumannii* to Polymyxin and Colistin in this study was 5% and 4%, respectively, thus indicating high sensitivity of *Acinetobacter baumannii* to these antibiotics, this group can be administered as appropriate therapeutic agents against these bacteria.

Keywords: Prevalence of Resistance, Antibiotics, Polymyxins, Colistin, *Acinetobacter baumannii*

1. Background

Acinetobacter baumannii are coccobacillus gram-negative, oxidase negative, strictly aerobic, non-motile, and non-fermentative bacteria that are widely spread in soil and water and also in hospital environments and survives in these environments for a long time and is readily transmitted among patients (1). Due to the significant clinical activity of this bacteria and its ability to acquire antibiotic resistance, it is considered as one of the threatening microorganisms towards antimicrobial drugs (2). The major problem in the treatment of *A. baumannii* is its ability to acquire resistance to major antibiotic classes (3). *Acinetobacter baumannii* infections, include nosocomial infections, bacteremia, urinary tract infection, and secondary meningitis, while it has an important role in hospital pneumonia, especially pneumonia in upper respiratory tract hospitalized patients at intensive care units around the world. *Acinetobacter baumannii* is one of the most common isolates causing sepsis in patients with immune deficiency and is associated with increased risk of mortality (4). It is the most common species from blood, sputum, skin, urine, and pleural fluid isolates (5). Therapeutic problems caused by these bacteria and the possibility of transfer between living and non-living objects and also long-lasting nature in hospital environments has caused enhancement in the appearance of the bacteria in hospital environments and its increasing infection. Therefore, mortality in patients with *A. baumannii* infections is estimated to be about 75%. Hospital infections are currently a major problem around the world (6). The major problem in the treatment of infections caused by *A. baumannii* is the ability of these bacteria to acquire antibiotic resistance towards a large class of antibiotics. The emergence and spread of drug-resistant *A. baumannii* capable of transferring genetic elements of

different antibiotic resistance has created a major threat in hospitals (7). One of the therapeutic agents effective against *A. baumannii* is polymyxin group antibiotics, including Polymyxin B and Colistin (Polymyxin E). Colistin is a cationic polypeptide composed of a circular decapeptide. These antibiotics show antimicrobial activity by two mechanisms, including initial connection and permeability of the outer membrane followed by re-establishment of the cytoplasmic membrane. Colistin has the wide antimicrobial spectrum of many gram-negative bacteria and is often considered as one of the last effective antibiotics against multi-resistant *A. baumannii* isolates. However, in the recent years, clinical isolates resistant to Colistin have also been reported (8, 9). Therefore, with regards to the importance of antibiotic resistance rate in clinical isolates of *A. baumannii*, the information on its statistics worldwide could help health planners in order to prevent the spread of antibiotic resistance and adopt appropriate strategies.

2. Methods

This systematic review and meta-analysis study was conducted to assess the prevalence rate of resistance to Polymyxins in clinical isolates of *A. baumannii* during years 2002 to 2016 in Iran and around the World. To collect the required data from published papers in national and international journals research in different databases was performed, including PubMed, Google Scholar, Scopus, SID, Magiran, and IranMedex. Keywords to search articles included prevalence of resistance, polymyxins, and *Acinetobacter baumannii* with all combinations possible. After reading the abstract of the articles, related articles were separated.

2.1. Study Selection Criteria and Data Extraction

The major inclusion criteria was that the study had to address "prevalence of resistance to the Polymyxin and Colistin in clinical isolates of *Acinetobacter baumannii*" and the exclusion criteria of the study was lack of referrence to the prevalence of resistance to antibiotics in clinical isolates of *A. baumannii*, unrelated studies, and low-quality articles. To begin with, a researcher collected all the articles related to antibiotic resistance and after finishing the search, a list of article abstracts was prepared. At this stage, 156 articles, which mentioned "prevalence of resistance to antibiotics" and "*Acinetobacter baumannii* and 'polymyxin and colistin' in their titles were entered in the initial list. Then, 46 articles were excluded because of repetition, 34 articles due to differences in the type of criteria used, 23 articles due to low quality, and 11 articles due to the unavailability of the full text. Finally, 43 appropriate articles in order to enter the stage of meta-analysis were selected (Figure 1). Then, for the final evaluation, a checklist of data was prepared. Accordingly, the selected 43 articles were studied. The following information was needed for the study, investigator's name, age, location, the number of samples, and the prevalence of resistance. The underlying data for this study were to interpret the chart insert.

2.2. Statistical Analysis

At first in this section, all the prevalence rates of antibiotic resistance were recorded, then to calculate the variance of each study, the binomial distribution formula was used. To combine the prevalence rate of different studies, average weight was used. Each study was weighted inversely proportional to its variance. Due to the large differences in the prevalence rates in various studies (heterogeneity of studies), significant heterogeneity index (I^2) of the random-effects model was used.

3. Results

In the present study to conduct a meta-analysis and systematic review, 43 reports were selected and related articles conducted between 2002 and 2016 were studied. Extracted data are shown in Table 1. Total specimen volume of the 43 articles was 5360 samples. Drug-resistance of *A. baumannii* towards polymyxins was reported as 5%, according to estimates of 11 papers (Tables 2 - 4 and Figures 2 and 3).

4. Discussion and Conclusions

According to results of this study, the prevalence of *A. baumannii* isolates resistant to polymyxins is increasing. According to previous studies, the spread of antibiotic-resistant *A. baumannii* isolates and associated therapeutic problems have been approved in Iran and the World. In this study, the resistance rate towards colistin was 4% and for polymyxin, this was 5%. In the study of Ardabili et al. the pattern of resistance in *A. baumannii* isolates from patients in Motahari Tehran Hospital Burn Unit was towards 17 antibiotics determined by disk diffusion agar (DDA), while the drug resistance rate towards Colistin was zero percent (39). Moreover, in other studies, this resistance has been reported as zero percent (13, 18, 26, 41, 43). In the studies of Shahcheraghi et al. studies (38), Yau et al. (32), Elebd et al. (16) and Al-Agamy et al. (17), this amount was less than 5%. While in other studies, resistance has been unusually high, such as Youssefian et al. (29) 53.1%, Vila-Farres et al. (33) 25.6%, Talebi-Taher et al. (44) (40%), Ahmadi et al. (37) 39.5%.

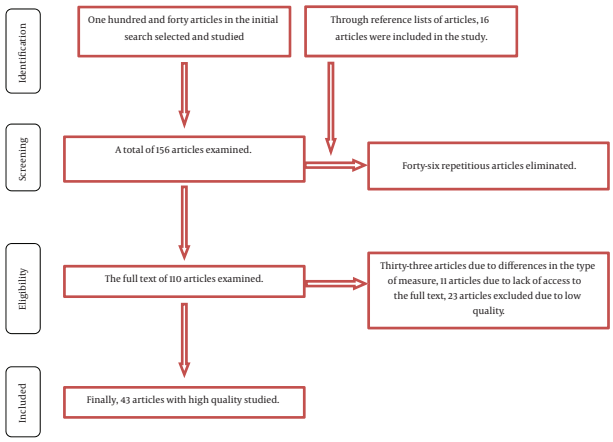
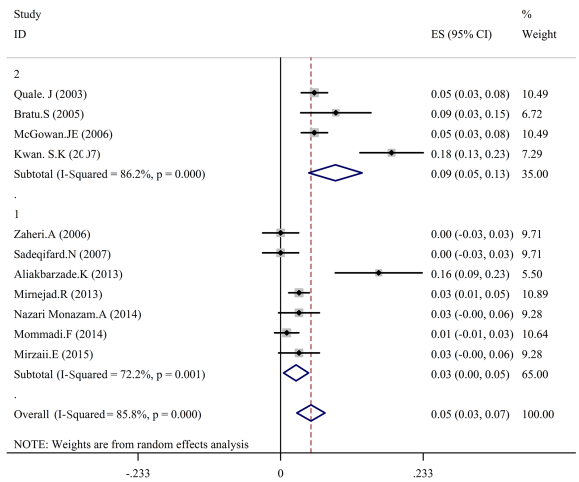


Figure 1. The Stages Entered Into the Systematic Review and Meta-Analysis

Figure 2. The Prevalence of Antibiotic resistance in *Acinetobacter baumannii* Clinical Isolates to Polymyxin Based on a Random-Effects Model



The midpoint of each segment is the estimation of prevalence rate and line length is a confidence interval of 15% per study and diamond mark shows prevalence rate for all studies (code 1: Iran, code 2: Other countries).

There has been large differences in the resistance rate of the organism towards Colistin. The study of Goudarzi et al. was done by the DDA method, and showed antibiotic resistance rate of *A. baumannii* in 243 samples to 19 antibiotics; all the samples were susceptible to colistin and tigecycline, so these two antibiotics were suggested for the treatment of *A. baumannii* (49).

In another study, 108 isolates of *A. baumannii* were isolated from 2 hospitals in Tehran. Resistance isolates to colistin were determined by DDA; 1.8% of the isolates were resistant to colistin (50). Polymyxin resistance to *A. baumannii* obtained in this study are almost consistent with the resistance obtained in other studies, including Moammadi et al. 1% (40), Ardebili et al. 3% (39), McGowan and Carlet 5.5% (36), Bratu et al. 9% (30), Nazari Monazam et al. 3% (27), Mirzaii 3% (20), and Quale et al. 5.5% (11). While in other studies, such as Aliakbarzadeh et al. (16%) (42) and Ko et al. (18%) (12) higher resistance rates were reported. Dispute in the findings with the results of this study could be attributed to differences in methods (51-54). The DDA method is a common method for determining susceptibility to antibiotics used, yet evaluation of susceptibility to antibiotics has shown DDA diverse methods compared to methods based on minimum inhibitory concentration

Table 1. General Information and Data Entered in the Meta-Analysis Studies

First Author	Study Location	Publication Year	The number of Samples	Study Type	The Sensitivity and Resistance Rate of *Acinetobacter baumannii* to Polymyxins, %			
					Polymyxin		Colistin	
					Sensitivity, %	Resistance, %	Sensitivity, %	Resistance, %
Kooti (10)	Iran	2015	200	Case study	100	0	100	0
Quale (11)	New York	2003	433	Case study	94.5	5.5		
Kwan (12)	Korea	2007	214	Cohort	18		30.6	
Lolans (13)	India	2006	94	Case study			100	0
Gur (14)	Turkey	2008	321	Cohort	99.3	0.7		
Bpharm (15)	Syria	2012	260	Cohort			93.1	
Elabd (16)	Saudi Arabia	2014	108	Case study			4.6	0
Mohamed (17)	Egypt	2014	40	Case study			95	5
Carretto (18)	Italy	2011	277	Case study			100	0
Livermore (19)	London	2010	166	Cohort			99.4	
Mirzaii (20)	Iran	2015	100	Case study	97	3		
Anguti (21)	Iran	2015	61	Cross sectional			89	
Scheetz (22)	USA	2007	93	Cohort	100			
Song (23)	Korea	2007	43	Cohort			100	0
Lim (24)	Singapore	2010	31	Case study	100	0		
Alaii (25)	Iran	2014	85	Cross sectional			71	16
Sadeqifard (26)	Iran	2007	66	Case study	84.8		100	0
Nazari Monazam (27)	Iran	2014	100	Cross sectional	97	3		
Noormohamad (28)	Iran	2014	100	Cross-sectional			7	24
Yosefiyan (29)	Iran	2015	96	Case study				53.1
Bratu (30)	USA	2005	96	Cohort	91	9		
Dizbay (31)	Turkey	2008	66	Cross sectional			100	0
Yau (32)	Africa	2009	30	Cohort			96.7	3.3
Vila-Farres (33)		2011	14	Case study			0.5	25.6
Japooninejad. (34)	Iran	2014	56	Cross-sectional				4
Mirnejad (35)	Iran	2014	400	Cross sectional	97	3		
McGowan (36)	USA	2006	433	Case study	94.5	5.5		
Ahmadi (37)	Iran	2014	43	Case study			60.5	39.5
Shahcheraghi (38)	Iran	2009	95	cross-sectional				4.2
Ardebili (39)	Iran	2012	65	Case study				0
Mohammadi (40)	Iran	2014	97	Case study	98.9	1		
Dinh Van (41)	USA	2014	63	Case study			100	0
Aliakbarzade (42)	Iran	2013	103	Case study	84	16	77	19
Hernandes-Torres (43)	Spain	2012	77	Case study			100	0
Sadeghifard (26)	Iran	2006	66	Case study	84.8	0	100	0
Talebi-Taher (44)	Iran	2012	35	Cross sectional			21	40
Nasrolahei (45)	Iran	2014	100				88.7	
Bayram (46)	Turkey	2013	377				100	0
Morkel (47)	Africa	2014	17	Retrospective			71	29
Kumar (48)	India	2014	65	Retrospective			100	0

(MIC), which have a higher error rate. On the other hand, the geographical differences in the area of sample isolation are also effective in the pattern of antibiotic resistant isolates; depending on the type of treatment strategy used, the resistance pattern changes. However, it should be noted that the results of epidemiological studies on antibiotic resistance of bacteria are not always predictable. Since Polymyxin is used as the last line of these bacteria, increasing resistance to these antibiotics is a dangerous alarm for health systems. Thus, the application of new therapeutic regimens, more sensitive diagnostic methods, and control of hospital infections seems essential.

Table 2. The Resistance of *Acinetobacter baumannii* Against Polymyxins in Terms of the Number Entered in the Study Meta-Analysis

Antibiotic		Study Number	Prevalence	Confidence Interval 95% (CI%95)	Heterogeneity IndexI^2, %	P Value
Polymyxin	Resistance	11	5	0.03 - 0.07	85.8	0.000
	Sensitivity	13	96	0.95 - 0.98	86.9	0.000
Colistin	Resistance	21	4	0.03 - 0.5	93.8	0.000
	Sensitivity	22	80	0.77 - 0.83	99.9	0.000

Table 3. *Acinetobacter Baumannii* Resistance to Polymyxins in Terms of Study Site Entered in the Meta-Analysis

Antibiotic	Continent		Prevalence	Confidence Interval 95% (CI%95)	Heterogeneity IndexI^2, %	P Value
Polymyxin	America	Resistance	6	0.03 - 0.09	20.6	0.262
		Sensitivity	96	0.91 - 1.00	89.1	0.000
	Asia	Resistance	5	0.02 - 0.08	87.8	0.000
		Sensitivity	97	0.95 - 0.99	84.4	0.000
	Europe	Resistance	5	0.03 - 0.08	0.0	0.000
		Sensitivity	94	0.92 - 0.97	0.0	0.000
Colistin	Africa	Resistance	3	0.03 - 0.10	0.0	-
		Sensitivity	86	0.61 - 1.11	80.1	0.025
	Asia	Resistance	6	0.04 - 07	94.9	0.000
		Sensitivity	73	069 - 0.77	95.1	0.000
	Europe	Resistance	1	-0.01 - 0.02	68.2	0.024
		Sensitivity	100	0.99 - 1.00	0.0	0.422

Table 4. *Acinetobacter baumannii* Resistance to Polymyxins in Iran and Other Countries

Antibiotic	Location		Prevalence	Confidence Interval 95% (CI%95)	Heterogeneity IndexI^2 (%)	P Value
Polymyxin	Iran	Resistance	3	0.00 - 0.05	72.2	0.001
		Sensitivity	95	0.92 - 0.98	88.2	0.00
	Other countries	Resistance	9	0.05 - 0.13	86.2	0.000
		Sensitivity	97	0.97 - 0.99	86.9	0.000
Colistin	Iran	Resistance	14	0.07 - 0.21	95.0	0.000
		Sensitivity	72	0.56 - 0.88	99.4	0.000
	Other countries	Resistance	1	0.00 - 0.02	91.0	0.000
		Sensitivity	83	0.80 - 0.87	99.7	0.000

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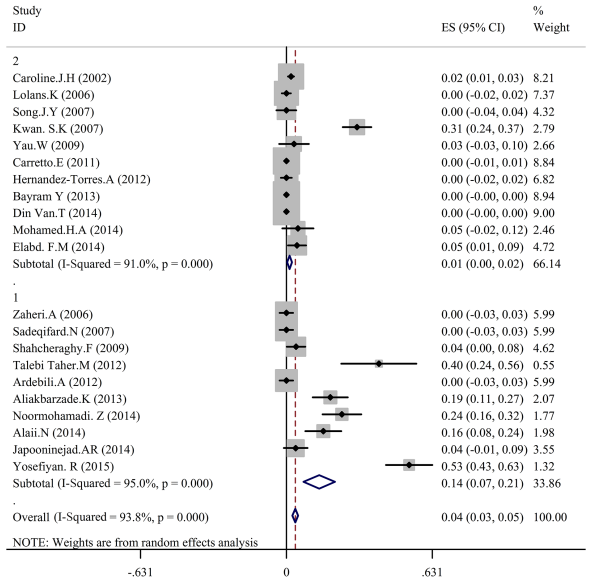

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