



ORIGINAL ARTICLE

Antibiotic Resistance of *Acinetobacter baumannii* in Iran: A Systemic Review of the Published Literature

Jale Moradi, Farhad B. Hashemi, Abbas Bahador*

Department of Microbiology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.

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Abstract

Objectives: *Acinetobacter baumannii* is a bacterium responsible for health care-associated infections, and it frequently develops multiple drug resistance (MDR). The prevalence of antibiotic-resistant *A. baumannii* in Iran has increased, and this may cause significant clinical problems. Therefore, in order to elucidate the development of antibiotic resistance, we performed a systematic review of the literature published on antibiotic-resistant *A. baumannii* reported in Iran.

Methods: Thirty-six publications that met the criteria for inclusion were reviewed from an initial 87 papers. Selected papers published between 2008 and September 2014, were categorized on the basis of the sample collecting year been between 2001 and 2013.

Results: Analysis of data revealed that, in general, there was an increase in antimicrobial resistance. During the initial time point of these studies (2001–2007) there was a high rate of resistance to all antibiotics, with the exception of carbapenems, lipopeptides, and aminoglycosides that had a low resistance rate in comparison with the others. Also, the resistance rate was increased in one group of these three antimicrobial groups from 2010 to 2013. In particular, there was an increase in resistance to carbapenems (imipenem and meropenem) from 2010–2011 and 2012–2013, whereas no significant change in the resistance rate of the other two antimicrobial groups (lipopeptides and aminoglycosides) during the study time was observed, although we did observe certain trends in amikacin (aminoglycoside group antibiotic) between 2011–2012 and 2012–2013.

Conclusion: These findings indicate that antimicrobial resistance of *A. baumannii* in Iran has increased, which may very well affect the antimicrobial resistance of this organism worldwide. Based on these results, novel prevention and treatment strategies against *A. baumannii* infections are warranted. Furthermore, these data may assist in revising treatment guidelines and regional policies in care units to slow the emergence of antimicrobial resistance.

*Corresponding author.

E-mail: abahador@tums.ac.ir, ab.bahador@gmail.com (A. Bahador).

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1. Introduction

Acinetobacter baumannii is a gram-negative, strictly aerobic, nonfermenting coccobacillus belonging to the Moraxellaceae family [1]. Species belonging to this genus are opportunistic pathogens with increasing relevance in both community-acquired and nosocomial infections, particularly among patients in intensive care units (ICUs) and high-dependency units (HDUs) [2–5]. These organisms have been implicated in various infections, including ventilator-associated pneumonia, endocarditis, meningitis, and infections of the skin, soft tissues, urinary tract, and those originating from prosthetic devices [4,6]. *A. baumannii* has been isolated from numerous sources such as soil, water, animals, and humans, while its presence in health care institutions and on environmental surfaces has been extremely difficult to control [6].

Three decades ago, *A. baumannii* infections were effectively treated with traditional antibiotics [7,8]. By contrast, it currently exerts resistance to nearly all major classes of antibiotics, including broad-spectrum penicillins, cephalosporins, carbapenems, most aminoglycosides, fluoroquinolones, chloramphenicol, and tetracyclines. In the past decade, multidrug resistant (MDR) clinical isolates have shown global distribution [3]. Therefore, this pathogen has become a “red-alert” for the following reasons: rapid emergence of resistance, increased incidence, and the worldwide spread of MDR isolates [7]. The rapid spread of MDR strains in nosocomial infections that exhibit resistance to most or all common antibiotics is a troubling evolution [3]. Thus, a study of the antibiotic resistance patterns both in individual hospitals and on countrywide levels may help to clarify the mode of *A. baumannii* antibiotic resistance spread and epidemiology worldwide [9]. The current review was performed to elucidate the mode of antibiotic resistance of *A. baumannii* in Iran.

2. Materials and methods

2.1. Database searches

Biomedical databases (Scopus, Medline, Web of Science, EBSCO, IranMedex) were searched in order to retrieve all related manuscripts published in English and Persian. The search identified publications of epidemiological studies in order to compile adequate information on *A. baumannii* antimicrobial resistance in Iran. The following key words were used: “*Acinetobacter baumannii* and Iran”, “antimicrobial resistance and *Acinetobacter baumannii* and Iran”, “antimicrobial resistance and either gram negative bacilli and Iran or Iran”, “nosocomial or hospital acquired and Iran”. Study publications were obtained through PubMed, MEDLINE, and IranMedex database searches. Also, references cited within these articles were used to find

additional relevant articles. In this review, *A. baumannii* susceptibility breakpoints based on Clinical Laboratory Standards Institute (CLSI)-relevant antibiotics were primarily those listed by the World Health Organization Recommended Surveillance Standards.

2.2. Study settings

From the first 87 papers, we identified a total of 36 that were written in English and considered to be eligible for inclusion in this review. The selected papers were published between 2008 and September 2014. We categorized studies on the basis of sample collection year, between 2001 and 2013; some papers collect samples during different years (Table 1). Two studies were performed in three regions of Iran, including central, north, and south. Twenty-two studies were performed north of Iran, with 18 in Tehran (capital of Iran). Two studies occurred in the south of Iran, three in the west, and three in the east. Although the studies used various methods, they were all approved by the CLSI and the National Committee for Clinical Laboratory Standards (NCCLS) and, therefore, suitable for trend analysis.

2.3. Microbiological methods

Clinical specimens in studies were collected from hospitalized patients with different disease and various sampling. Twenty of the studies obtained data from various clinical specimens, including blood, cerebrospinal fluid, urine, sputum, and respiratory tract samples. Data from eight studies were obtained from patients with burn wounds and seven from hospitalized patients in ICUs. Antibiotic susceptibility testing methodologies were declared in all studies, all of which were performed according to the CLSI breakpoints. Twenty-six studies used the Kirby-Bauer disk diffusion method, nine used the E-test, and two used broth microdilution. To identify resistance genes, 25 of the studies used one or more polymerase chain reaction-based molecular methods.

3. Results

3.1. Phenotypic resistance rates for different antibiotics

The susceptibility data for 3049 *A. baumannii* isolates are shown in Table 2. These data reflect the 12-year period from 2001 to 2013 of sampling time in the studies identified. The data demonstrate that, with the exception of carbapenems, lipopeptides, and aminoglycosides, there was a high rate of resistance to antimicrobial groups during the initial time point of this study (2001–2007). Also, the resistance rate was increased in one group of these three antimicrobial groups from 2010 to 2013. In particular, there was an increase in resistance to carbapenems (imipenem and meropenem) from 2010–2011 and 2012–2013, whereas no significant

Table 1. Characteristic of *Acinetobacter baumannii* antimicrobial resistance studies in Iran.

Year of publication (Refs)	Year of sample collecting	No. of studies	Total samples	Location of Iran (No. of studies)
2008 [10], 2010 [11], 2011 [12], 2014 [13]	2001–2007	4	383	Capital (4)
2011 [14], 2011 [15]	2007–2008	2	275	Capital (1), South (1)
2010 [16], 2010 [17], 2011 [14], 2011 [18], 2011 [12], 2012 [19], 2012 [20], 2013 [21]	2008–2009	8	680	Capital (1), North (3), West (2), South (1), East (1)
2011 [22], 2012 [23], 2013 [24]	2009–2010	3	276	Capital (3)
2012 [25], 2012 [26], 2013 [27], 2013 [28], 2013 [29], 2013 [30], 2013 [31], 2013 [32], 2013 [33], 2013 [34], 2014 [35], 2014 [36], 2014 [37]	2010–2011	12	970	Capital (6), North (4), East (1), West (1)
2013 [30], 2013 [32], 2013 [38], 2013 [39], 2014 [13], 2014 [40]	2011–2012	6	525	Capital (5), East (1)
2013 [41], 2013 [42], 2014 [43], 2014 [44]	2012–Sep 2014	4	308	Capital (3), North (1)

change in the resistance rate to other two antimicrobial groups (lipopeptides and aminoglycosides) during the study time was observed, although we did observe certain trends in amikacin (aminoglycoside group antibiotic) between 2011–2012 and 2012–2013.

There are data regarding resistance to penicillins from 2001 to 2011. There was a remarkable increase in piperacillin resistance (from 63.9% in 2001–2007 to 93.4% in 2010–2011). The resistance rate to the β -lactam/ β -lactamase combination group was high early in the study, with no substantial change to the study endpoint. The highest level of antimicrobial resistance throughout the study was noted among the cepheps group (>90%), including ceftazidime, cefepime, cefotaxime, and ceftriaxone. Resistance to carbapenems was low at the study start point (51.1% imipenem, 64.3% meropenem) and increased by the end of the study (76.5% imipenem, 81.5% meropenem), thus demonstrating the most drastic increase in resistance rate. A low level of resistance at the starting point was also observed for lipopeptides (polymyxin B and colistin), with no significant trends as the study progressed. The resistance rate to aminoglycosides was low, with the exception of amikacin (from 58.4% in 2001–2007 to 95% in 2012–2013). At the beginning of the study, there were no data for tetracyclines, whereas there was a high level of resistance to this group at the study endpoint. Resistance to fluoroquinolones was high during the study period with no remarkable pattern change. Finally, an increased resistance rate to folate pathway inhibitors, including trimethoprim sulfamethoxazole, was observed (from 76.6% in 2001–2007 to 99% in 2012–September 2014). In summary, these data demonstrate a high resistance rate to all antimicrobial agents except lipopeptides.

3.2. Genotypic resistance rate

Genotyping of a total of 1717 *A. baumannii* isolates was performed in 17 studies. Table 3 shows the

mechanisms of resistance that were studied for the different antibiotic classes from 2001 to 2013. The genotyping methods in all studies were polymerase chain reaction- and sequence-based. Among the 17 studies, 14, three, three, and one of them were focused on β -lactams, tetracyclines, aminoglycosides, and quinolones, respectively. These genotypic studies demonstrated that isolates harboring resistance genes have increased from 2001 to 2013, which is most remarkable for carbapenem.

3.3. Distribution of multidrug resistance

By definition, MDR *A. baumannii* isolates are resistant to three or more agents of different antibiotic classes. In total, seven studies revealed the presence of MDR isolates. Among these seven studies, this analyzed 584 *A. baumannii* isolates, MDR rates ranged from 32.7% to 93%. Chronologically, these rates can be broken down as follows: 2001–2007 (1 study, 50%), 2008–2009 (1 study, 66%), 2009–2010 (1 study, 83%), and 2010–2011 (4 studies, 32.7%, 74.9%, 93%, 94.4%, respectively). In general, the prevalence of MDR increased throughout the duration of the study.

4. Discussion

A. baumannii infection has become a critical challenge to health care systems. To become an optimally successful pathogen, an organism must develop antimicrobial resistance. Although there is debate regarding the definitions of “multidrug” and “pandrug” resistance [45], an understanding has been reached in that resistance to all common antimicrobial agents is currently a common problem in health care institutions [46,47]. The emergence of MDR isolates has become a serious problem that has made it difficult to select an empirical antimicrobial for the treatment of *A. baumannii* infections. Therefore, monitoring the antibiotic resistance

Table 2. Phenotypic antibiotic resistance rates in *Acinetobacter baumannii* isolate from Iran.

Antibiotic agents	Mean resistance rate (%) in different studies						
	2001–2007 <i>n</i> = 383 (4 studies) [10–13]	2007–2008 <i>n</i> = 275(2 studies) [14,15]	2008–2009 <i>n</i> = 620(7 studies) [12,14,17–21]	2009–2010 <i>n</i> = 276(3 studies) [22–24]	2010–2011 <i>n</i> = 907(12 studies) [25,26,29–37]	2011–2012 <i>n</i> = 280(4 studies) [13,38–40]	2012–Sep 2014 <i>n</i> = 308(4 studies) [41,43]
PIP	69.9	88.2	93.75	98	93.4	—	—
MZ	—	—	—	—	81.7	—	—
TIC	100	—	100	—	94	—	—
SAM	83.3	27.8	63.5	48.39	33.7	—	77.5
TZP	52.9	35.3	88.6	71.5	97.3	82.5	70
TIM	100	—	82.6	—	94	80	—
CAZ	93.5	90.7	92	93	92.6	—	97
FEP	—	94.1	89	96.6	88.6	—	97
CTX	95	100	94	99	96.1	98	97
CRO	89.1	100	93.6	97.3	95.6	—	97.5
IPM	51.1	32	57.75	52.4	81.9	80.5	76.5
MEM	64.3	27.8	59.25	72	85.2	81.5	81.5
PB	8.8	—	16	3	13.5	3	9.5
CST	—	1.3	19	12	9.3	—	16
GEN	76.85	81.9	83.75	40.6	82.9	63	78.5
TOB	63.2	39.2	—	28	60.9	56	70
AMK	58.4	79.4	82.7	69.5	75	89.5	95
NET	80.5	—	—	—	69.6	—	—
TET	—	—	—	34.78	83.82	51	56
DOX	—	—	—	—	25	—	42.9
MIN	—	—	—	—	25.6	—	34
CIP	83.9	67.6	83.75	92	85.2	97	72
LVX	83.3	—	81.75	—	81.25	—	99
GAT	—	—	—	—	43.3	—	—
SXT	76.6	82.4	87.3	—	94.3	—	99

AMK = amikacin; CAZ = ceftazidime; CIP = ciprofloxacin; CRO = ceftriaxone; CST = colistin; CTX = cefotaxime; DOX = doxycycline; FEP = cefepime; GAT = gatifloxacin; GEN = gentamicin; IPM = imipenem; LVX = levofloxacin; MEM = meropenem; MIN = minocycline; MZ = mezlocilli; NET = netilmicin; PB = polymyxin B; PIP = piperacillin; SAM = ampicillin/sulbactam; SXT = trimethoprim/sulfamethoxazole; TET = tetracycline; TIC = ticarcillin; TIM = ticarcillin/clavulanic acid; TOB = tobramycin; TZP = piperacillin/tazobactam.

Table 3. Genotypic resistance rate in *Acinetobacter baumannii* isolate from Iran.

Antimicrobial class	Resistance mechanism	Genes	Mean Resistance rate (%) in different studies						References	
			2001--2007 <i>n/N</i> = 2/208	2007-2008 <i>n/N</i> = 0/0	2008-2009 <i>n/N</i> = 3/360	2009-2010 <i>n/N</i> = 2/226	2010-2011 <i>n/N</i> = 7/602	2011-2012 <i>n/N</i> = 1/31		2012-Sep 2014 <i>n/N</i> = 2/302
β-lactams	β-lactamases	PER-1			51	54.3	27.6		78.03	21,27,23,45
		PER-2			0					21
		VEB-1			10				39.5	21,45
		TEM-1				47.2	13.1			27,23
		SHV				5.6				23
		IS <i>Aba</i> 1/ampC			46		63.1			27,20
		IS <i>Aba</i> 25/ampC					7.8			27
	Carbapenemases	OXA ₂₃ -like	25,		55	24.58,84	30,67,77.9,	80	70.1	28,30,27, 23,20,22, 12,37,44
		OXA ₄₀ -like					17.1,47		35.8	28,27,44
		OXA ₅₈ -like	21.2							12
		OXA ₂₄ -like	15,				19.2			12,34
		OXA ₅₁ -like	96			94	14.4			28,22,10
		IMP			19				3.48	18,45
		VIM			9				17.44	18,45
Tetracyclines	Efflux pump	Tet A					11		36	
		Tet B					99,86.1		19.4	36,37,44
Aminoglycosides	Enzymatic degradation	<i>aph</i> (3')-IIb					61.8			29
		<i>aac</i> (6')-Ib					60.5		16.4	29,44
		<i>aph</i> (3')-Ia					46.1		19.4	29,44
		<i>ant</i> (2'')-Ia					14.5		56.7	29,44
		<i>ant</i> (3'')-Ia					10.5			29
		<i>aph</i> (3')-Via					9.2,		95.5	29,44
		<i>aac</i> (3')-Ia					5.3		32.8	29,44
		<i>aacC1</i>			63.3					16
		<i>aadA1</i>			41.7					16
		<i>aadB</i>			3.3					16
		<i>aphA6</i>			65				16	
	16s rDNA methyltransferases	<i>armA</i>						9	44	
Quinolones	DNA gyrase/topoisomerase mutations	<i>gyrA/parC</i>					100			37

patterns of this organism over time may provide useful information regarding its treatment policy. This systematic review considered the distribution of antibiotic-resistant *A. baumannii* in CLSI-approved studies published in Iran between 2001 and September 2014.

According to the results, some level of resistance to all antibiotic classes existed in the beginning of our study. However, we revealed that the distribution of antimicrobial resistance to all agents was high at the endpoint, with the exception of the lipopeptides. Currently, the antibiotics of choice for treatment of *A. baumannii* infections include the aminoglycosides, fluoroquinolones, and carbapenems [48]. Thus, it is concerning that our data demonstrate that *A. baumannii* resistance to these agents increased over the time course of this study, with a resistance rate in excess of 90% in 2013. As such, these antibiotics may not be appropriate empirical therapy in many cases. For example, carbapenems are one of the most clinically important classes of antibiotics used against life-threatening *A. baumannii* infections in Iran [10]. Our results showed that this group of antibiotics had low-level resistance in 2001–2007 (51.1% imipenem, 64.3% meropenem), which increased in 2012–2013 (76.5% imipenem, 81.5% meropenem). The data also showed that the most drastic increase in resistance is associated with this antibiotic class, possibly due to its frequency of use in health care units. This is an alarming finding that strongly suggests the possibility of treatment failures in life-threatening *A. baumannii* infections due to carbapenem-resistance strains.

As mentioned previously, our data show that resistance to lipopeptides is lower compared with that of other antimicrobial groups. One of the antibiotics of this class is polymyxin B, which, despite previous concerns regarding its toxicity, has been implemented in treatment more frequently [49]. Another lipopeptide antibiotic is colistin, which has proven effective in the treatment of wound, urinary tract, and bloodstream infections [50], although its nephrotoxicity is a disadvantage to its use [51]. Although use of this antibiotic class has limitations due to toxicity, they are often used for the treatment of life-threatening infections.

In addition to an increase in antibiotic-resistant *A. baumannii* strains from 2001 to 2013, the prevalence of MDR strains also increased (from 50% in 2001–2007 to 74% in 2010–2011), with a mean prevalence of 71.2%. Treatment of MDR strains is usually difficult, thus creating critical challenges for health care consultants [52,53]. The antibiotic choice for the treatment of MDR *A. baumannii* infections is also limited and includes the lipopeptides, [52,54] which the results of this study suggest is the best class of antibiotics to use for MDR because of the lower prevalence of resistance.

In summary, our results demonstrate the need for effective surveillance of antimicrobial resistance in *A. baumannii* in Iran and suggest that it is essential to use

antibiotics with the most caution to prevent the emergence of drug-resistant strains. Furthermore, these findings indicate that the prevalence of antibiotic-resistant *A. baumannii* is high in Iran, especially for the antibiotics of choice. This is an emerging concern to public health, particularly in the clinical management of persons with life-threatening *A. baumannii* infections. We strongly suggest the implementation of a country-wide surveillance system. This would facilitate the active monitoring of resistance frequency and distinguish antibiotic resistance trends and prevalence, all of which would be effective tools in antibiotic treatment programs.

Conflicts of interest

None to declare.

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