Jundishapur J Microbiol. 2019 April; 12(4):e85819. doi: 10.5812/jjm.85819.
Published online 2019 April 23. **Research Article**

Seven-Year Trend of Antimicrobial Resistance of *Acinetobacter* and *Pseudomonas* spp. Causing Bloodstream Infections: A Retrospective Study from Shiraz, Southern Iran

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Received 2018 October 27; **Revised** 2019 April 06; **Accepted** 2019 April 07.

Abstract

Background: Antimicrobial resistance is a growing healthcare system threat of huge concern worldwide.
Objectives: This study aimed to report the seven-year trend of antimicrobial resistance of *Acinetobacter* and *Pseudomonas* spp. causing bloodstream infections (BSIs) in Shiraz, southern Iran, during 2010 - 2016.
Methods: This retrospective study was conducted on the recorded blood cultures during 2010 - 2016. The susceptibility testing of isolates was performed by the agar diffusion test. Data were grouped into three episodes: 2010 to 2011, 2012 to 2013, and 2014 to 2016. The chi-square test was used to determine the significance of antimicrobial resistance trends.
Results: The rates of resistance to antibiotics such as amikacin, cefepime, cefotaxime, ceftazidime, ciprofloxacin, and piperacillin-tazobactam were high within 2014 - 2016, with a statistically significant increasing trend over the abovementioned three periods. The resistance rates of *Pseudomonas* spp. to the antibiotics such as amikacin, tobramycin, gentamicin, cefepime, ceftazidime, and ciprofloxacin were high in 2014 - 2016 with a statistically significant increasing trend over the three periods.
Conclusions: The increasing trend of antimicrobial resistance of *Acinetobacter* and *Pseudomonas* spp. to almost all the conventional antibiotics over the seven-year period of this study is alarming.

Keywords: Bacteremia, Cross-Infection, Drug Resistance, Gram-Negative Aerobic Rods and Cocci, Iran

1. Background

Antimicrobial resistance is a growing healthcare concern worldwide. Gram-negative, non-fermenter, rod-shaped bacteria including *Acinetobacter* spp. and *Pseudomonas* spp. are significant causes of nosocomial infections. These bacteria are a serious challenge to health care systems because they are optimally successful pathogens to develop antimicrobial resistance. *Acinetobacter* spp. are opportunistic organisms that can cause several infections ranging from superficial skin and soft-tissue infections to more severe diseases such as pneumonia and bloodstream infection (BSI) (1-3). The results of a cohort study in the United States showed that the mortality rate of bloodstream infections caused by *Acinetobacter* spp. was 49.6% (4). *Pseudomonas* spp., especially *Pseudomonas aeruginosa*, as renowned opportunistic bacteria, was the sixth cause of healthcare-associated infections and the third most common Gram-negative bacterium causing BSI among 11,282 patients in 183 hospitals of the United States (5).

The report from India revealed that the overall prevalence rates of *Acinetobacter* and *Pseudomonas* spp. were respectively 1048 (5.6%) and 828 (4.4%) among 18,695 isolates from blood samples between 2008 and 2014 (6). In a multicenter study in Iran by Poorabbas et al. among all 858 isolates obtained from positive sterile body fluid cultures, 95 (11.07%) and 67 (7.80%) of them were *Pseudomonas* and *Acinetobacter* spp., respectively (7). Currently, these pathogens have turned out to be a "red-alert" because of their rapid emergence of resistance following the overuse and misuse of antibiotics and the increased incidence and the worldwide spread of multidrug-resistant (MDR) isolates (8).

Antimicrobial resistance surveillance is crucial for timely administration of the proper empirical antibiotics to reduce the unfavorable complications, the length of

hospital stay, mortality, and health care costs (9). Antimicrobial resistance surveillance should be carried out and carefully observed in each area. Unfortunately, there are no sufficient data from developing countries on the trend of antimicrobial resistance of such microorganisms causing BSIs.

2. Objectives

In this study, we aimed to report the seven-year trend of antimicrobial resistance of *Acinetobacter* and *Pseudomonas* spp. causing BSIs in Shiraz, southern Iran, during 2010 - 2016.

3. Methods

3.1. Design, Period and Location of the Study

This retrospective descriptive study was conducted at Professor Alborzi Clinical Microbiology Research Center (PACMRC), a referral microbiology laboratory in Shiraz, southern Iran, on the recorded blood cultures from 2010 to 2016. We investigated the antimicrobial resistance of all *Acinetobacter* and *Pseudomonas* spp. isolated from blood specimens submitted for culture in an automated blood culture system (BACTEC® BD).

The blood samples were sent from Nemazee Teaching Hospital and four other teaching hospitals (Shahid Dastghaib, Rajaiee, Chamran, and Zeinabieh hospitals) affiliated to Shiraz University of Medical Sciences, and eight other nonteaching hospitals (Amir, Dena, Markazi, Ghadir, Kowsar, Ghotbedin, Ordibehesht, and Moslemin hospitals) in Shiraz. The majority of the samples were from Nemazee teaching hospital, a tertiary hospital with more than 1000 beds including surgical and medical wards, emergency room, and intensive care units.

3.2. Identification and Confirmation of the Isolated Bacteria

The identification and confirmation of the isolated bacteria were performed using biochemical methods (7). The biochemical characterization was done by performing oxidase reaction, pigmentation or mucoidity, growth at 42°C, growth on MacConkey agar, and using two commercially available miniaturized multi-test identification systems, i.e., API (bio Merieux SA, Marcy-1, Etoile, France) and Microgen (Microbiology International, UK).

3.3. Antimicrobial Susceptibility Testing

The disk diffusion method was used to assess susceptibility to 19 antimicrobial agents including amikacin (30 μg), ampicillin-sulbactam (10/10 μg), aztreonam (30 μg), cefepime (30 μg), cefotaxime (30 μg), ceftazidime (30 μg), ceftriaxone (30 μg), ciprofloxacin (5 μg), trimethoprim and sulfamethoxazole (1.25/23.75 μg), colistin (10 μg), gentamicin (10 μg), levofloxacin (5 μg), Imipenem (10 μg), meropenem (10 μg), piperacillin-tazobactam (100/10 μg), tetracycline (30 μg), ticarcillin (75 μg), tigecycline (30 μg), and tobramycin (10 μg).

All the isolates were tested by using cation-adjusted Mueller-Hinton agar (Merck Co., Germany). The results were interpreted according to the clinical and laboratory standards institute (CLSI) guideline (10). To determine the resistance of *Acinetobacter* spp. to colistin, we used the disk diffusion test based on provisional zone diameter breakpoints suggested by Galani et al. (11). We considered inhibition zone diameter breakpoints of $\geq$ 14 mm as susceptible. Extended-spectrum beta-lactamases (ESBL) production was determined according to the CLSI guideline using cefotaxime, cefotaxime-clavulanic acid (30/10 μg), ceftazidime, and ceftazidime–clavulanic acid disks (30/10 μg) (10).

3.4. Statistical Analysis

We merged the intermediate resistant pathogens into resistant ones to report the susceptibility rate, on the ground that the clinical approach to both is the same. For the purpose of analysis, data were grouped into three episodes: 2010 to 2011, 2012 to 2013, and 2014 to 2016. The statistical analyses were done by SPSS version 16 software. The chi-square and Fisher's exact tests were used to determine the significance of antimicrobial resistance trends over the three periods of study. The P values of $\leq$ 0.05 were considered statistically significant.

4. Results

The number and percentage of microorganisms in each period are shown in Table 1. In the first episode (2010 - 2012), *Acinetobacter* spp. and *Pseudomonas* spp. were ranked as the fourth and fifth common bacteria causing BSIs. In 2012 - 2013, *Pseudomonas* spp. and *Acinetobacter* spp. were the third and fourth prevalent isolated bacteria, respectively. In the last episode, *Pseudomonas* spp. was the most frequent bacteria and *Acinetobacter* spp. was ranked third.

The total number of isolated *Acinetobacter* spp. was 439. There was a statistically significant increase in the antibacterial resistance trend of *Acinetobacter* spp. against amikacin (P = 0.011), cefepime (P = 0.011), cefotaxime (P = 0.029), ceftazidime (P = 0.001), ciprofloxacin (P = 0.048), and piperacillin-tazobactam (P < 0.001). The pattern of resistance to the frequently used anti-*Acinetobacter* antibiotics is shown in Table 2 and Figure 1. The resistance of

Table 1. The Number and Percentage of Bacterial Pathogens Isolated from Patients with Bloodstream Infection in 2010 - 2016[a]

Bacteria	2010 to 2011		2012 to 2013		2014 to 2016		Total	
***Acinetobacter* spp.**	91	6.64	180	11.05	177	11.71	448	9.93
***Brucella* spp.**	14	1.02	18	1.10	5	0.33	37	0.82
***Citrobacter* spp.**	18	1.31	5	0.31	5	0.33	28	0.62
Escherichia coli	249	18.16	225	13.81	146	9.66	620	13.74
***Enterobacter* spp.**	66	4.81	47	2.89	59	3.90	172	3.81
***Enterococcus* spp.**	122	8.90	175	10.74	181	11.97	478	10.59
***Klebsiella* spp.**	72	5.25	109	6.69	100	6.61	281	6.23
***Pseudomonas* spp.**	90	6.56	194	11.91	198	13.10	482	10.68
***Salmonella* spp.**	14	1.02	9	0.55	17	1.12	40	0.89
***Serratia* spp.**	65	4.74	36	2.21	30	1.98	131	2.90
Staphylococcus aureus	283	20.64	351	21.55	150	9.92	784	17.38
Stenotrophomonas maltophilia	39	2.84	34	2.09	175	11.57	248	5.50
Streptococcus pneumoniae	27	1.97	22	1.35	12	0.79	61	1.35
***Streptococcus* spp.**	86	6.27	93	5.71	121	8.00	300	6.65
Others	135	9.85	131	8.04	136	8.99	402	8.91
Totals	1371	100	1629	100	1512	100	4512	100

[a] Methicillin-resistant coagulase-negative *staphylococci* (MRCoNS) is a remarkable sample contaminant; therefore, the results are reported in this table excluding these bacteria.

Acinetobacter spp. to colistin increased from zero percent in both 2010 - 2011 and 2012 - 2013 periods to 0.7% in 2014 - 2016.

The total number of isolated *Pseudomonas* spp. was 473. There was a statistically significant increase in the antibacterial resistance trend of *Pseudomonas* spp. to amikacin (P = 0.008), tobramycin (P = 0.039), gentamicin (P = 0.003), cefepime (P = 0.008), ceftazidime (P = 0.011), and ciprofloxacin (P = 0.017). Table 3 and Figure 2 show the trend of resistance rate of *Pseudomonas* spp. to the antibiotics, with the resistance to colistin being zero percent throughout the three periods.

5. Discussion

In this study, we surveyed the antimicrobial resistance patterns of *Acinetobacter* and *Pseudomonas* spp. isolates causing BSIs in Shiraz, southern Iran, over a seven-year period. The main finding of this study is the growing trend of antimicrobial resistance of *Acinetobacter* and *Pseudomonas* spp. to the most popular antimicrobials, e.g., aminoglycosides, fluoroquinolones, and third-generation cephalosporins. Moreover, colistin was found to be the most effective antibiotic against *Acinetobacter* and *Pseudomonas* spp. *Acinetobacter* and *Pseudomonas* spp. are recognized for their capability to develop resistance rapidly against most antibiotics that is why knowledge of the best antibiotic against these pathogens is very crucial.

The effect of ciprofloxacin on *Pseudomonas* spp. (sensitivity of 45.2%) was relatively superior to the effect on *Acinetobacter* spp. (sensitivity of 17.5%); however, for both organisms, there was a statistically significant increase in the rate of resistance to ciprofloxacin over the seven-year period. A previous report from our center showed that 83% of *Pseudomonas* spp. were sensitive to ciprofloxacin within 2005 - 2006 (12), indicating a growing trend. The resistance rate to levofloxacin, which was determined only in the last episode, was more than that to ciprofloxacin. Carbapenem has been the treatment of choice for the infections caused by MDR Gram-negative bacilli, but unfortunately, the resistance to carbapenem compromises the treatment options. The results of the present study indicate that *Acinetobacter* spp. had a high resistance rate to this group of antibiotics in 2014 - 2016. A study from southern Iran demonstrated oxacillinases (OXA-type β-lactamases) had become a principal carbapenem resistance determinant in *Acinetobacter* baumannii clinical isolates (2).

The resistance of *A. baumannii* to carbapenems was reported as 23% in 2007 - 2008 in our center (13). At present, nearly 92% - 76% of *Acinetobacter* isolates are resistant to imipenem in different regions (14). Our results revealed that a statistically significant decreasing

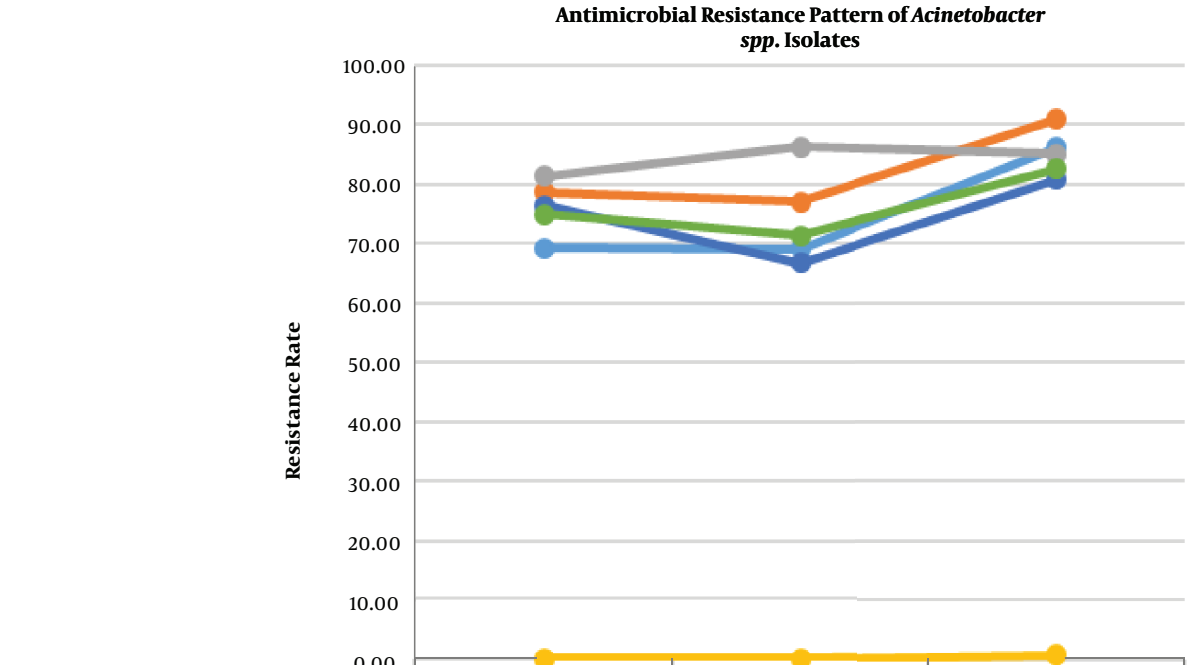
Table 2. Antimicrobial Susceptibility Pattern of 439 *Acinetobacter* spp. Clinical Isolates[a]

Antibiotics	Susceptibility						P Value
	2010 to 2011 (N = 90)		2012 to 2013 (N = 194)		2014 to 2016 (N = 189)		
	Sensitive	Resistant	Sensitive	Resistant	Sensitive	Resistant	
Penicillins							
Piperacillin	ND	ND	27 (20.5)	105 (79.5)	7 (12.5)	49 (87.5)	0.220
Ticarcillin	12 (14.6)	70 (85.4)	31 (18.1)	140 (81.9)	13 (16.3)	67 (83.8)	0.792
Beta-lactam/beta-lactamase inhibitors combinations							
Ampicillin-sulbactam	ND	ND	ND	ND	27 (17.5)	127 (82.5)	-
Piperacillin-tazobactam	24 (30.8)	54 (69.2)	54 (30.9)	121 (69.1)	23 (13.9)	142 (86.1)	< 0.001
Cephalosporins							
Cefepime	9 (10.5)	77 (89.5)	37 (22.6)	127 (77.4)	19 (11.7)	144 (88.3)	0.011
Cefotaxime	ND	ND	20 (11.8)	150 (88.2)	8 (4.8)	157 (95.2)	0.029
Ceftazidime	19 (21.3)	70 (78.7)	40 (22.9)	135 (77.1)	15 (9.1)	149 (90.9)	0.001
Ceftriaxone	6 (7.6)	73 (92.4)	20 (11.4)	82 (89.1)	12 (7.3)	152 (92.7)	0.447
Carbapenems							
Imipenem	17 (18.9)	73 (81.1)	34 (19.4)	141 (80.6)	27 (16.2)	140 (83.8)	0.720
Meropenem	17 (18.7)	74 (81.3)	24 (13.7)	151 (86.3)	25 (14.9)	143 (85.1)	0.527
Aminoglycosides							
Amikacin	20 (23.5)	65 (76.5)	58 (33.3)	116 (66.7)	32 (19.3)	134 (80.7)	0.011
Tobramycin	26 (31.7)	56 (68.3)	48 (28.4)	121 (71.6)	39 (24.1)	123 (75.9)	0.412
Gentamicin	16 (17.6)	75 (82.4)	50 (29.4)	120 (70.6)	34 (20.6)	131 (79.4)	0.058
Trimethoprim- sulfamethoxazole	ND	ND	40 (25.6)	116 (74.4)	31 (18.7)	135 (81.3)	0.141
Fluoroquinolones							
Ciprofloxacin	22 (25.0)	66 (75.0)	49 (28.7)	122 (71.3)	29 (17.5)	137 (82.5)	0.048
Levofloxacin	ND	ND	ND	ND	8 (11.3)	63 (88.7)	-
Tetracyclines							
Tetracycline	11 (12.2)	79 (87.8)	29 (17.4)	138 (82.6)	17 (10.4)	146 (89.6)	0.176
Tigecycline	ND	ND	ND	ND	28 (25.0)	84 (75.0)	-

Abbreviation: ND, not determined.
[a] Values are expressed as No. (%).

trend exists for the resistance of *Pseudomonas* spp. to both imipenem and meropenem (29.6% for imipenem and 30.9% for meropenem in 2014 - 2016). These results were similar to the resistance rate of *Pseudomonas* spp. to imipenem in our center from 2005 to 2006, which was 23% (12).

We did not investigate the exact cause of the diminished resistance to carbapenems, but previous studies propose some mechanisms to explain how resistance rate of *Pseudomonas* spp. can be reduced. Controlling the use of one antibiotic can lead to a significant decrease in the rate of resistance (15). The restriction to ciprofloxacin at a large teaching hospital in the United States revealed a decline in the percentage rate of *P. aeruginosa* resistance to ciprofloxacin, carbapenems, and cefepime (16). Another study reported a significant decreasing trend in the resistance rate of *P. aeruginosa*, isolated from wound swabs, to ciprofloxacin, ceftazidime, meropenem, and imipenem. They suggested that it can be due to the reduction in the use of ciprofloxacin (17). Another study from China reported the same trend for the resistance of *P. aeruginosa* to carbapenems. The rate of resistance decreased during 2006 - 2014 (18). Exposure to ciprofloxacin causes selective mutations that upregulate the MexEF-OprN efflux system, decrease the levels of outer membrane porin protein D (OprD), and cause resistance to both fluoroquinolones



	2010 to 2011	2012 to 2013	2014 to 2016
Piperacillin Tazobactam	69.20	69.10	86.10
Ceftazidime	78.70	77.10	90.90
Meropenem	81.30	86.30	85.10
Colistin	0.00	0.00	0.70
Amikacin	76.50	66.70	80.70
Ciprofloxacin	75.00	71.30	82.50

Figure 1. Antimicrobial susceptibility pattern of *Acinetobacter* spp. against common antibiotics between 2010 and 2016

and carbapenems (19).

Therefore, one of the possible reasons for the reduction of resistance is the decrease in the prescription of imipenem and meropenem in the last episode for the treatment of patients with suspected MDR *Pseudomonas* spp. BSIs, because of the high resistance rate between 2012 and 2013. We could not demonstrate any association between the use of carbapenems and resistance to it because this study was designed retrospectively and the data regarding antibiotics usage were lacking in our centers. In our study, more than 90% of *Acinetobacter* and *Pseudomonas* spp. were ESBL producers, which explains resistance to cephalosporins, penicillins, and monobactams (20). In a previous report from our center, among the organisms isolated from hospitalized patients, the ESBL producer rates were 81.4% (70 of 86) for *Acinetobacter* spp. and 71.7% (71 of 99) for *Pseudomonas* spp. (21).

Colistin, with proven efficacy in the treatment of bloodstream, urinary tract, and wound infections caused by *Acinetobacter* and *Pseudomonas* spp., belongs to lipopeptide antibiotics. In our study, the most effective antibiotic against *Acinetobacter* and *Pseudomonas* spp. was colistin. The resistance rates of *Acinetobacter* spp. to tetracycline and tigecycline, a minocycline derivative, were high (89.6% and 75%, respectively). An investigation from China on 121 *Acinetobacter* spp. demonstrated a tigecycline susceptibility rate of 74.5% (22). Although the prescription of tigecycline was not listed in the pharmacopeia of the hospitals of this study, the rate of resistance was high, which could be explained by the cross-resistance by multisubstrate efflux

Table 3. Antimicrobial Susceptibility Pattern of 473 *Pseudomonas* spp. Clinical Isolates[a]

Antibiotics	Susceptibility						P Value
	2010 to 2011 (N = 90)		2012 to 2013 (N = 194)		2014 to 2016 (N = 189)		
	Sensitive	Resistant	Sensitive	Resistant	Sensitive	Resistant	
Penicillins							
Piperacillin	9 (30.0)	21 (70.0)	72 (44.7)	89 (55.3)	37 (50.0)	37 (50.0)	0.174
Ticarcillin	25 (34.2)	48 (65.8)	67 (36.0)	119 (64.0)	42 (44.7)	52 (55.3)	0.292
Beta-lactam/beta-lactamase inhibitors combinations							
Piperacillin-Tazobactam	36 (64.3)	20 (35.7)	116 (60.1))	77 (39.9)	136 (72.7)	51 (27.3)	0.031
Cephalosporins							
Cefepime	33 (39.8)	50 (60.2)	73 (40.8)	106 (59.2)	49 (26.3)	137 (73.7)	0.008
Ceftazidime	44 (50.0)	44 (50.0)	94 (49.2)	97 (50.8)	67 (35.4)	122 (64.6)	0.011
Monobactams							
Aztreonam	23 (34.3)	44(65.7)	41 (21.5)	150 (78.5)	40 (21.6)	145 (78.4)	0.085
Carbapenems							
Imipenem	51 (58.0)	37 (42.0)	88 (46.3)	102 (53.7)	133 (70.4)	56 (29.6)	< 0.001
Meropenem	49 (55.1)	40 (44.9)	71 (37.6)	118 (62.4)	130 (69.1)	58 (30.9)	< 0.001
Lipopeptides							
Colistin	22 (100.0)	0 (0.0)	143 (100.0)	0 (0.0)	178 (95.7)	0 (0)	-
Aminoglycosides							
Amikacin	45 (61.6)	28 (38.4)	86 (45.5)	103 (54.5)	76 (40.4)	112 (59.6)	0.008
Tobramycin	32 (48.5)	34 (51.5)	64 (33.9)	125 (66.1)	58 (31.0)	129 (69.0)	0.039
Gentamicin	47 (52.8)	42 (47.2)	71 (38.2)	115 (61.8)	57 (31.0)	127 (69.0)	0.003
Fluoroquinolones							
Ciprofloxacin	52 (60.5)	34 (39.5)	110 (57.6)	81 (42.4)	84 (45.2)	102 (54.8)	0.017
Levofloxacin	ND	ND	ND	ND	33 (41.3)	47 (58.8)	-

Abbreviation: ND, not determined.
[a] Values are expressed as No. (%).

pump (23). This can explain the high rate of tigecycline resistance in our center among *Acinetobacter* spp.

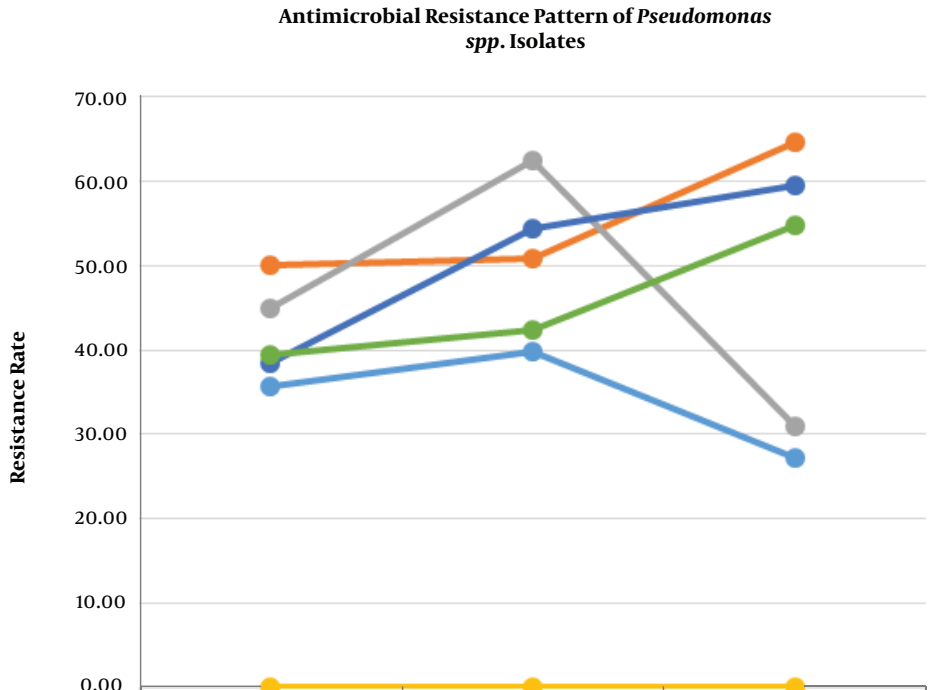
The present study has some limitations such as the lack of clinical data, as it was a retrospective laboratory-based study. According to the CLSI guideline, the disk diffusion method is accepted as a standard for reporting the resistance rate of *Acinetobacter* and *Pseudomonas* spp. to the reported antibiotics. The only exception is concerned with the resistance rate of *Acinetobacter* spp. to colistin. The disk diffusion method should be used cautiously to determine the resistance rate of *Acinetobacter* spp. to colistin. Since the present study focused on the two abovementioned pathogens, there might have been other pathogens causing BSI with an increasing trend of resistance.

5.1. Conclusions

According to the results, the resistance of *Acinetobacter* and *Pseudomonas* spp. to almost all antibiotic classes was high and increasing over the seven-year period of this study. Nowadays, a limited number of effective antibiotics are available for empirical therapy against *Acinetobacter* and *Pseudomonas* spp. The results emphasize the need for developing and intensifying infection control programs and antibiotics stewardship for proper prescription of antibiotics in hospitals to curb the increasing trend of resistance.

Acknowledgments

Our thanks go to Dr. Hassan Khajehei for language editing of the manuscript.



	2010 to 2011	2012 to 2013	2014 to 2016
Piperacillin Tazobactam	35.70	39.90	27.30
Ceftazidime	50.00	50.80	64.60
Meropenem	44.90	62.40	30.90
Colistin	0.00	0.00	0.00
Amikacin	38.40	54.50	59.60
Ciprofloxacin	39.50	42.40	54.80

Figure 2. Antimicrobial susceptibility pattern of *Pseudomonas* spp. against common antibiotics between 2010 and 2016

Footnotes

Authors' Contribution: Study concept and design: Amir Hossein Babaei, Gholamreza Pouladfar, and Bahman Pourabbas; acquisition of data: Amir Hossein Babaei, Zahra Jafarpour, Samin Ektesabi, and Pejman Abbasi; analysis and interpretation of data: Amir Hossein Babaei, Gholamreza Pouladfar, and Bahman Pourabbas; drafting of the manuscript: Amir Hossein Babaei, Bahman Pourabbas, Zahra Jafarpour, Samin Ektesabi, and Pejman Abbasi; critical revision of the manuscript for important intellectual content: Gholamreza Pouladfar and Bahman Pourabbas; statistical analysis: Amir Hossein Babaei, Zahra Jafarpour, and Samin Ektesabi; Administrative, technical, and material support: Gholamreza Pouladfar, Bahman Pourabbas, and Pejman Abbasi; study supervision: Gholamreza Pouladfar and Bahman Pourabbas.

Conflict of Interests: None to declare.

Ethical Approval: The study protocol was reviewed and approved by the Ethics Committee of Shiraz University of Medical Sciences (ethics code: IR.SUMS.REC.1397.886). The study was conducted according to the principles of the Declaration of Helsinki.

Financial Disclosure: None to declare.

Funding/Support: This paper was supported financially by the Professor Alborzi Clinical Microbiology Research Center and the Vice Chancellor for Research of Shiraz University of Medical Sciences (grant number: 97-01-14-18339).

Patient Consent: All subjects signed a general written in-

formed consent form on admission to hospitals to permit using the data of their medical records with consideration of their privacy.

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