European Journal of Therapeutics

DOI: 10.58600/eurjther-28-4-0071

Original Research

Investigation of Antibiotic Resistance Profiles and Carbapenemase Resistance Genes in Acinetobacter Baumannii Strains Isolated From Clinical Samples

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ABSTRACT

Objective: Acinetobacter baumannii is an important pathogen that can develop multiple drug resistance. Here, we aimed to investigate the antibiotic resistance profiles of A. baumannii strains isolated from the various clinics of our hospital and determine the class D beta-lactamase resistance genes causing carbapenem resistance.

Methods: Between June-2016 and June-2017, 157 A. baumannii strains isolated from clinical specimens of our hospital were identified with automatic bacterial identification system and antibiograms were determined by the same system. Among the carbapenem resistant strains, bla_{OXA-51}, bla_{OXA-58}, bla_{OXA-23} and bla_{OXA-24} genes were also investigated by PCR method.

Results: When we analyze the resistance profiles of the strains, we observed that the lowest resistance rate was against colistin with 5 (3.2%) strains. OXA-51 and OXA-23 genes were found positive in all isolates, while OXA-24 was found positive in 16 (32%) strains; OXA-58 was not detected in any of the strains.

Conclusion: The most effective antibiotics for carbapenem resistant A. baumannii isolates were colistin, tigecycline and amikacin. Prevelance of OXA-24 enzyme gene was found higher than other similar studies. Monitoring antibiogram profiles and conducting molecular epidemiological studies may help us detect resistant bacteria at the source and reduce the development of resistance.

Keywords: Acinetobacter baumannii, OXA-23, OXA-24, OXA-51, OXA-58

INTRODUCTION

Acinetobacter baumannii is one of the the most important species in the Acinetobacter genus and has become one of the most important pathogens in hospital settings globally. In the last 15 years, its clinical importance has increased along with antibiotic resistance rates. These features have made it one of the main organisms threatening the current antibiotic use (1). A. baumannii generally targets patients who are most susceptible and have suppressed immune systems. Health-care associated pneumonia is accepted as the most common infection caused by A. baumannii; however, in recent times, infections involving the central nervous system, skin and soft tissue and bone have become very problematic for hospitals and health organizations (1). In A. baumannii strains, resistance to beta-lactam antibiotics involves production of beta-lactamase coded by chromosomes or plasmids. The reason for resistance against carbapenem group antibiotics is changes in proteins binding to porin and penicillin associated with acquiring genes coding class B or class D beta-lactamases. The most common beta-lactamase type acquired and causing carbapenem resistance in A. baumannii are some OXA-23, OXA-24, OXA-40, OXA-58 and OXA-143 enzymes from oxacillinases. Additionally, overproduction of OXA-51 type natural oxacillinase in conjunction with other OXA enzymes causes high levels of carbapenem resistance. Phenotypic tests are inadequate for identification of OXA enzymes and with the lack of reliability; these enzymes can be definitely identified using molecular methods (2, 3).

In this study, the aim was to research A. baumannii strains isolated during a one-year period from patient samples in a variety of clinics in Dr. Ersin Arslan Training and Research Hospital to determine antibiotic resistance status, and to determine the class D beta-lactamase (OXA-23, OXA-24, OXA-51, OXA-58) resistant genes causing carbapenem resistance in strains resistant to imipenem and meropenem with the real-time polymerase chain reaction (PCR) method.

METHODS

Sample Selection

The study included 157 A. baumannii strains isolated from patient samples sent under appropriate conditions to the Medical Microbiology laboratory of Dr. Ersin Arslan Training and Research

How to cite: Karabay O, Ekşi F, Yıldırım MS, Gazel D. Investigation of Antibiotic Resistance Profiles and Carbapenemase Resistance Genes in Acinetobacter Baumannii Strains Isolated From Clinical Samples. Eur J Ther 2022; 28(4): 252–9.

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Received: 30.06.2021 • **Accepted:** 22.09.2021

Hospital from June 2016 to June 2017. From these 157 strains, 50 A. baumannii strains resistant to imipenem and meropenem chosen randomly were researched for OXA-23 group, OXA-51 group and OXA-58 group genes with real-time PCR, while OXA-24 group resistant genes were researched with the optimized PCR method. Only one A. baumannii strain isolated from the same patient was included in the study.

Detection of Isolates and Antibiogram

Urine samples from patients were seeded on 5% sheep blood agar (RTA, Turkey) and EMB agar (GBL, Turkey) while other samples were seeded on 5% sheep blood agar, EMB agar and chocolate agar (RTA, Turkey) and left for 18-24 hours incubation at 37 °C. The blood culture samples were incubated in an automated culture system (BD BACTEC™ FX blood culture system, USA). Samples with proliferation in the automated blood culture system had seeding performed on 5% sheep blood agar and EMB agar after the device warning and were left for 18-24 hours incubation at 37 °C. Proliferating bacteria had smear preparate created from oxidase negative, non-hemolytic, catalase test positive colonies. Samples investigated with the microscope with gram negative coccobacillary appearance were defined at species level with a BD Phoenix™ (BD Phoenix™ ID & AST System, USA) automatic identification system and antibiotic susceptibility profiles were determined. The results of the susceptibility tests categorized samples as susceptible, moderately susceptible and resistant according to the Clinical and Laboratory Standards Institute (CLSI) criteria (4). The A. baumannii strains obtained from pure culture were stored at -20 °C in beaded storage media for use in advanced studies.

Determination of Carbapenem-Resistant Isolates

The randomized 50 A. baumannii strains from isolates which were resistant to imipenem and meropenem in the automated system were also susceptible to meropenem and imipenem via Kirby-Bauer disk diffusion method according to the CLSI recommendations. Additionally, the minimum inhibitory concentration (MIC) values for these two antibiotics were determined with the gradient strip test (Bioanalyse, Turkey). The Pseudomonas aeruginosa ATCC 27853 standard strain was used as quality control strain.

DNA isolation and molecular study:

A. baumannii DNA isolation was performed using a QIAamp DNA Mini Kit (Qiagen, Germany). The procedure was repeated according to the manufacturer's advice. Later the OXA-23 group, OXA-51 group and OXA-58 group genes were researched with real time PCR. The 50 A. baumannii strains determined to be resistant to meropenem and imipenem with the disc diffusion and gradient strip method and chosen randomly were researched for the presence of OXA-type carbapenemase groups (OXA-23 group, OXA-51 group and OXA-58 group). Four strains obtained from Gaziantep University were used as control strains. The first control strain was used as positive control for OXA-51 and OXA-58, the second control stain was used as positive control for OXA-51 and OXA-24 and the third control strain was used as positive control for the OXA-51 and OXA-23 gene regions. Additionally, a negative control strain was used without detection of these gene regions. To determine primers and probes, firstly some of the variant arrays for the OXA-51, OXA-23 and OXA-58 groups observed in A. baumannii were downloaded from the NCBI database. Alignment files were created using the ClustalW program. This file was opened with the jalview program and unchanging regions within the groups and regions displaying differences from other groups were observed and the primer and probe alternatives were determined with the aid of the Vector NTI program. As the multiplex PCR in the study can be optimized, the interactions of the relevant primers and probes were researched with the Vector NTI program and appropriate arrays were synthesized (care was taken that Tm degrees of primers were kept close to each other and Tm degrees of probes were at least 6-7 degrees more distant from primers). Differentiation of the proliferating regions was performed with the aid of probes synthesized with OXA 51-FAM, OXA 58-Cy5, and OXA 23-HEX stains. To check the synthesized primers and probes in the study, the experiments were designed with the same reaction program though samples were run independently for OXA-23, OXA-51 and OXA-58. All samples were trialed with a triple mix created in the same way with the Fluorion detection system (İontek, Turkey) and expected results were obtained. Then the multiplex reaction was optimized. Separate from these, PCR optimized with the primers designed with the method above for OXA-24 was used to study positive controls and other samples. Positive bands were checked with a gel imaging system.

Main Points:

- All isolates were positive for chromosomal-derived OXA-23 and OXA-51 enzymes.
- The OXA-24 enzyme had the rate of 32% which was higher when compared to other studies
- Monitoring antibiotic susceptibility patterns and performing molecular epidemiological studies may help reducing the infections by detecting the source of the bacterial isolate.

RESULTS

The samples containing the 157 A. baumannii strains included in the study comprised 64 samples from women (41%) and 93 from men (59%). The mean age of these patients was 53 years, with age interval from 1 to 91 years. Isolates produced from the samples were obtained from tracheal aspirate culture for 65 samples (41.4%), wound culture for 35 (22.3%), blood culture for 30 (19.1%), sputum culture for 17 (10.8%), urine culture for 5 (3.2%), CSF culture for 3 (1.9%) and catheter culture for 2 (1.3%). Among the patients with isolates obtained, 121 (77.2%) were intensive care patients, and 36 (32.8%) were ward patients. According to the distribution of units, A. baumannii strains were isolated from patient samples with 102 from the general ICU (65.1%), 15 from the wound care ward (6.4%), 10 from the chest diseases ward (6.4%), 7 from the additional building ICU (4.5%), 6 from the internal medicine ICU (3.8%), 4 from the cardiovascular surgery intensive care (2.5%), 4 from the orthopedics and traumatology ward (2.5%), 3 from the infectious diseases ward (1.3%), 2 from the neurology ICU (1.3%), and 1 each from the burns, nephrolo-

gy, brain surgery, oncology and rheumatology wards (0.6%). The distribution of the antimicrobial susceptibility profiles of 157 isolates are given in Table 1.

The susceptibility pattern of 50 A. baumannii isolates that were 100% resistant to imipenem and meropenem with genotyping performed found 37 strains (74%) were resistant, 1 strain (2%) was moderately susceptible and 12 strains (24%) were susceptible to amikacin. For cefepime 50 strains (100%) were resistant, for ceftazidime 50 strains (100%) were resistan, for ceftriaxone 50 strains (100%) were resistant and for ciprofloxacin 50 strains (100%) were resistant. For gentamicin, 47 strains (94%) were resistant and 3 strains (6%) were susceptible. For colistin, 3 strains (6%) were resistant, and 47 strains (94%) were susceptible. For netilmicin, 48 strains (96%) were resistant and 2 strains (4%) were susceptible. For piperacillin, 50 strains (100%) were resistant, while 50 strains (100%) were also resistant to piperacillin tazobactam. For tigecycline, 32 strains (64%) were resistant and 18 strains (36%) were susceptible. For trimethoprim sulfamethaxasole, 44 strains (88%) were resistant and 6 strains (12%) were susceptible. Results are summarized in Table 2.

In the chosen 50 A. baumannii isolates, the A. baumannii specific structural gene group of bla_{OXA-51} and the gene groups stated to be responsible for carbapenem resistance in the literature of bla_{OXA-23}, bla_{OXA-58} and bla_{OXA-24} gene groups were researched with real-time PCR. The structural gene group for A. baumannii of bla_{OXA-51} and the bla_{OXA-23} gene group were identified in 50 of the isolates (100%). None of the isolates had the bla_{OXA-58} gene group encountered, while 16 (32%) had bla_{OXA-24} gene group positivity identified. The bla_{OXA} gene distribution for the isolates identified with PCR is shown in Table 3 (Figure 1, 2 and 3). In terms of location, 10 isolates from the general ICU had bla_{OXA-24} gene identified, while 1 isolate each from the CVS ICU, wound service, internal medicine ICU, neurology ICU, infection and chest diseases wards had bla_{OXA-24} gene identified The other clinics did not have bla_{OXA-24} gene identified. The distribution of OXA beta lactamase genes according to clinic is shown in Table 4.

Table 1. Antibiotic susceptibilities of A. baumannii isolates with automated system

Antibiotic	Resistant	Intermediate	Susceptible
	n (%)	n (%)	n (%)
AK	113 (72)	2 (1.3)	42 (26.8)
FEP	148 (94.3)	0	9 (5.7)
CAZ	148 (94.3)	0	9 (5.7)
CRO	155 (98.7)	0	2 (1.3)
CIP	145 (92.4)	0	12 (7.6)
CN	139 (88.5)	0	18 (11.5)
CT	5 (3.2)	0	152 (96.8)
IPM	145 (9,4)	0	12 (7.6)
MEM	142 (9.4)	1 (0.6)	14 (8.9)
NET	153 (97.5)	0	4 (2.5)
PIP	149 (94.9)	0	8 (5.1)
TZP	149 (94.9)	0	8 (5.1)
TGC	89 (56.1)	0	68 (43.9)
SXT	126 (8.3)	0	31 (19.7)

AK: Amikacin, FEP: Cefepime, CAZ: Ceftazidime, CRO: Ceftriaxone, CIP: Ciprofloxacin, CN: Gentamicin, CT: Colistin, IPM: Imipenem, MEM: Meropenem, NET: Netilmicin, PIP: Piperacillin, TZP: Piperacillin tazobactam, TGC: Tigecycline, SXT: Trimethoprim–Sulfamethoxazole.

Table 2. Antibiotic Susceptibility Rates Of 50 Genotyped Isolates

Antibiotic	Resistant	Intermediate	Susceptible
	n (%)	n (%)	n (%)
AK	37 (74)	1 (2)	12 (24)
FEP	50 (100)	0	0
CAZ	50 (100)	0	0
CRO	50 (100)	0	0
CIP	50 (100)	0	0
CN	47 (94)	0	3 (6)
CT	3 (6)	0	47 (94)
IPM	50 (100)	0	0)
MEM	50 (100)	0	0
NET	48 (96)	0	2 (4)
PIP	50 (100)	0	8 (5.1)
TZP	50 (100)	0	8 (5.1)
TGC	32 (64)	0	18 (36)
SXT	44 (88)	0	6 (12)

AK: Amikacin, FEP: Cefepime, CAZ: Ceftazidime, CRO: Ceftriaxone, CIP: Ciprofloxacin, CN: Gentamicin, CT: Colistin, IPM: Imipenem, MEM: Meropenem, NET: Netilmicin, PIP: Piperacillin, TZP: Piperacillin tazobactam, TGC: Tigecycline, SXT: Trimethoprim-Sulfamethoxazole.

Table 3. blaOXA Gene Distribution In A. Baumannii Isolates

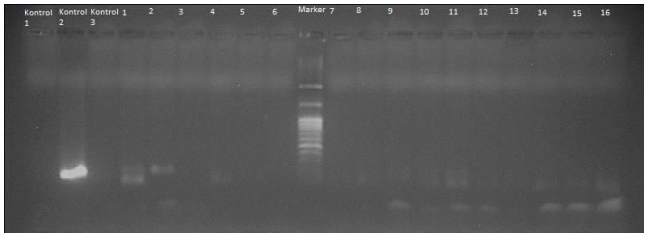
Isolate No	bla_{OXA-23}	bla_{OXA-51}	bla_{OXA-58}	bla_{OXA-24}
1	+	+	-	+
2	+	+	-	+
3	+	+	-	-
4	+	+	-	+
5	+	+	-	-
6	+	+	-	-
7	+	+	-	-
8	+	+	-	-
9	+	+	-	-
10	+	+	-	-
11	+	+	-	+
12	+	+	-	-
13	+	+	-	-
14	+	+	-	+
15	+	+	-	+
16	+	+	-	+
17	+	+	-	-
18	+	+	-	-
19	+	+	-	-
20	+	+	-	-
21	+	+	-	-
22	+	+	-	-

Isolate No	bla_{OXA-23}	bla_{OXA-51}	bla_{OXA-58}	bla_{OXA-24}
23	+	+	-	-
24	+	+	-	-
25	+	+	-	-
26	+	+	-	+
27	+	+	-	-
28	+	+	-	+
29	+	+	-	+
30	+	+	-	+
31	+	+	-	+
32	+	+	-	+
33	+	+	-	-
34	+	+	-	-
35	+	+	-	+
36	+	+	-	+
37	+	+	-	-
38	+	+	-	-
39	+	+	-	+
40	+	+	-	-
41	+	+	-	-
42	+	+	-	-
43	+	+	-	-
44	+	+	-	-
45	+	+	-	-
46	+	+	-	-
47	+	+	-	-
48	+	+	-	-
49	+	+	-	-
50	+	+	-	-

Table 4. Distribution of OXA beta-lactamase genes detected in A. baumanni isolates according to clinics

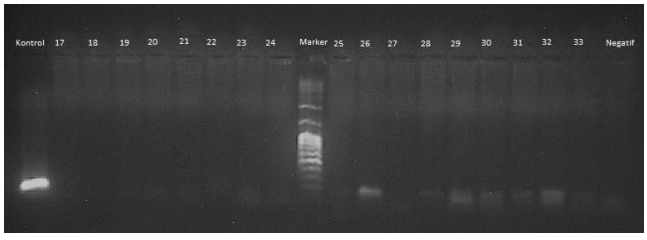
Departments	bla_{OXA-23}	bla_{OXA-51}	bla_{OXA-58}	bla_{OXA-24}
	n (%)	n (%)	n (%)	n (%)
General ICU	34 (68)	34 (68)	0	10 (67.5)
Wound Service	3 (6)	3 (6)	0	1 (6.25)
Pulmonology Unit	3 (6)	3 (6)	0	1 (6.25)
Internal Medicine ICU	3 (6)	3 (6)	0	1 (6.25)
Cardiovascular ICU	2 (4)	2 (4)	0	1 (6.25)
Neurology ICU	1 (2)	1 (2)	0	1 (6.25)
Infectious Diseases Unit	1 (2)	1 (2)	0	1 (6.25)
Burn Unit	1 (2)	1 (2)	0	0
Nephrology Unit	1 (2)	1 (2)	0	0
Neurosurgery Unit	1 (2)	1 (2)	0	0
Total	50 (100)	50 (100)	0	16 (100)

Figure 1. OXA-24 PCR gel image (From our study)



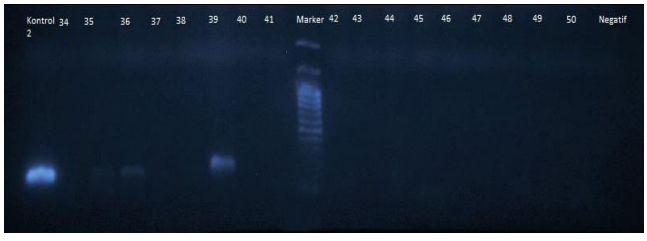
*Positive samples: 1, 2, 4, 11, 14, 15, 16.

Figure 2. OXA-24 PCR gel image (Continued)



*Positive samples: 26, 28, 29, 30,31, 32.

Figure 3. OXA-24 PCR gel image (Continued)



*Positive samples: 35, 36, 39.

DISCUSSION

In our study, A. baumannii strains were most frequently isolated from tracheal aspirate samples (n: 65/157, 41.4%). Previously, Özdem et al. (5) isolated 465 Acinetobacter isolates from 2007-2010 with 39.5% in tracheal aspirate culture, 19.8% in wound culture and 15.3% in blood culture. A study by Salih et al. (6) in a variety of provinces obtained most strains from tracheal aspirate culture at 42.5%. Our study generally appears to be consistent with these studies in terms of the units where strains were isolated.

In spite of identification of resistance rates from 72-88.5% in our study, amikacin was the most effective antibiotic after colistin and tigecycline. Altunok et al. (7) reported that among Acinetobacter isolates, amikacin resistance had a reducing trend through the years, while gentamicin resistance increased. A total of 124 Acinetobacter strains isolated from a variety of clinical samples in Hacettepe University detected 65.3% resistance to imipenem (8). A study in İzmir reported this rate was 86% for A. baumannii strains isolated from intensive care patients (9). Studies performed in 2014 observed that carbapenem resistance rate rose above 90% (7). A study in İstanbul by Barış et al. (10) reported the carbapenem resistance among the isolates was 96.3%. In our study, imipenem resistance was detected as 92.4% and was consistent with other studies showing an increase in resistance rates developing against carbapenem in recent years. The increase in carbapenem resistance in recent years may be explained by clonal association of isolates from A. baumannii strains obtained in excessive amounts from intensive care units due to the frequent use of carbapenem group antibiotics for empirical treatment.

Analyzing Acinetobacter baumannii isolates collected from different regions in Turkey (12 provinces), Beriş et al. (11) found 0.6% colistin resistance in a multicenter study. Research in 2019 by Çağlan et al. (12) with the broth microdilution method identified colistin resistance rate was 28% in Acinetobacter baumannii isolates. In recent years, colistin monotherapy was reported to cause problems like heteroresistance and resistance development; however, commonly used routine antimicrobial susceptibility tests cannot easily identify heterogeneous resistance against colistin. Two studies performed in Turkey in 2019 identified colistin heteroresistance at 34% and 21.4% rates in Acinetobacter baumannii isolates with carbapenem resistance (12, 13). In our study, colistin was identified as the most effective in vitro antimicrobial agent with 96.8% susceptibility, while tigecycline was in second place with 43.9% susceptibility. To prevent increasing resistance profiles and the spread of resistant strains, infection control precautions and smart antibiotic use policies should be applied. Additionally, the combined use of colistin for infections is important to prevent resistance development. Among the oxacillinases which can hydrolyze carbapenem acquired by Acinetobacter species, the bla_{OXA-23}, bla_{OXA-24}, bla_{OXA-48} and bla_{OXA-58} type enzymes were identified at various rates in different regions of the world. Al-Sultan et al. (14) reported 58% bla_{OXA-23}, 13% bla_{OXA-40}, and 0% bla_{OXA-58} in Saudi Arabia, while Mohajeri et al. (15) reported 77.9% bla_{OXA-23} and 19.2% bla_{OXA-24} positivity in Iran. When studies in our country are analysed, a study in Istanbul and Ankara by Gür et al. (16) investigated 321 A. baumannii strains and detected carbapenem resistance 44 out of 75 isolates (58.6%) in 2008. They reported that 26 of these isolates (59.1%) carried genes coding OXA-23 and 18 (40.9%) isolates carried genes coding OXA-58. Of 18 strains isolated in Ankara, 17 had OXA-23 and all had OXA-58, while all of the 26 strains isolated in Istanbul, bar one, had OXA-23 and one was identified to carry OXA-58 type genes (17). Again, in Turkey, the presence of bla_{OXA-58} genes from 0-23%, bla_{OXA-23} from 31-78% and low rates of bla_{OXA-24} gene were reported (18). Just as with different studies in our country, in our study the bla_{OXA-51} gene was identified in all isolates. Additionally, studies by Keskin et al. (19) reported 91.5% bla_{OXA-23}, 7% bla_{OXA-58} and 2% bla_{OXA-24}; Keyik et al. (17) reported 46.7% bla_{OXA-23} and 53.3% bla_{OXA-58}; Ertürk et al. (18) 94.5% bla_{OXA-23}; and Çiçek et al. (20) reported 78% bla_{OXA-23} gene presence. In our study, bla_{OXA-23} gene positivity rate was determined as 100%. All these results emphasize that the bla_{OXA-51} and bla_{OXA-23} gene regions comprise the dominant mechanism for imipenem resistance in A. baumannii isolates. Additionally, in our study, there was 32% positivity for the bla_{OXA-24} gene region. When other studies are examined, this rate was observed to be high. Additionally, the bla_{OXA-58} gene region was not identified in any sample. A multicenter study by Çiftçi et al. (21) reported that all isolates carried the bla_{OXA-51} gene, 74.4% of carbapenem-resistant isolates carried bla_{OXA-23}, and 17.3% carried the bla_{OXA-58} gene.

When 2008 isolates are compared with 2011 isolates, the bla_{OXA-23} gene was identified at 3 times higher rates (21).

In a research about molecular typing and carbapenemase in carbapenem-resistant A. baumannii, Özbey et al. (2) investigated the oxacillinase enzyme genes of bla_{OXA-23}, bla_{OXA-24}, bla_{OXA-51}, and bla_{OXA-58} gene regions and the metallo-beta-lactamase enzymes of IMP, VIM, SIM and SPM enzyme genes with multiplex PCR. While bla_{OXA-23} and bla_{OXA-51} positivity was identified in all isolates, it was stated that carbapenem resistance was due to excessive production of bla_{OXA-51} type natural oxacillinases and bla_{OXA-23} enzyme gene as samples were negative for bla_{OXA-24}, bla_{OXA-58}, IMP, VIM, SIM and SPM enzymes (2). Additionally, they reported variability in bla_{OXA} gene diversity in A. baumannii isolates between geographic regions with gene variations observed over time in the same geographic region (16). As a limitation of our study, the research isolates which were included in the study were obtained from only one center in Gaziantep. As another limitation, the MIC values for colistin drug were determined and screened by BD Phoenix™ (BD Phoenix™ ID & AST System, USA) automatic identification system which is not gold standard for antibiotic susceptibility testing. Further multi-center studies are necessary to obtain molecular epidemiology data from Acinetobacter baumannii clinical isolates.

CONCLUSION

In our study, 96.8% rate of susceptibility to colistin was reported, with colistin being the most effective antibiotic. This was followed by 43% susceptibility rates for tigecycline and 26% susceptibility rates for amikacin. To prevent the development of resistance or heteroresistance against these antibiotics, the combined use of these last-resort medications will be appropriate. According to real-time PCR results used to research oxacillinase enzymes causing carbapenem resistance, all strains were positive for chromosomal-derived OXA-23 and OXA-51 enzymes, with no isolate containing OXA-58 enzyme gene. The OXA-24 enzyme gene investigated with the optimized PCR method had the rate of 32% which was higher compared to other similar studies. We think that monitoring antibiotic susceptibility patterns and performing molecular epidemiological studies will detect the source of resistant bacteria and reduce the infections and resistance development.

Ethics Committee Approval: Ethics committee approval was received for this study from the Gaziantep University Clinical Researches Ethical Committee (Decision number: 2016/188, Date: 20.06.2016).

Informed Consent: All participants signed informed consent forms before study inclusion.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - O.K., F.E.; Design - O.K., F.E.; Supervision - F.E.; Resources - O.K., F.E., M.S.Y., D.G.; Materials - O.K., F.E., M.S.Y., D.G.; Data Collection and/or Processing - O.K., F.E., M.S.Y., D.G.; Analysis and/or Interpretation - O.K., F.E., M.S.Y., D.G.; Literature Search - O.K., F.E., M.S.Y., D.G.; Writing Manuscript - O.K., F.E., M.S.Y., D.G.; Critical Review - F.E., D.G.

Acknowledgements: The study was supported by the Gaziantep University Scientific Research Projects Committee with the project number YLT.16.31.

We would like to thank Dr. Zeynep GÜLAY and doctoral student Ayşe Nur SARI from Izmir Dokuz Eylül University Faculty of Medicine, Department of Medical Microbiology, who provided technical assistance in the study.

This study was presented as a poster presentation at the 5th National Clinical Microbiology Congress (KLİMUD-2019) held in Izmir on 28th October-1st November 2019.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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