Antibiotic Resistance Rates of *Acinetobacter Baumannii* Strains Isolated from Various Clinical Samples in Giresun Prof. Dr. Atilla ilhan Ozdemir State Hospital

Giresun Prof. Dr. Atilla İlhan Özdemir Devlet Hastanesinde Çeşitli Klinik Örneklerden İzole Edilen *Acinetobacter baumannii* Suşlarının Antibiyotik Direnç Oranları

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ABSTRACT

Objective: The aim of this study is to determine the types of specimens, distribution among clinics and antibiotic susceptibilities of 531 *Acinetobacter baumannii* strains isolated in our laboratory between January 2012-June 2014.
Methods: *Acinetobacter baumannii* isolates were identified by conventional methods and API 20 NE (bioMerieux, France), antibiotic susceptibility tests were performed according to the Clinical and Laboratory Standards Institute guidelines except tigecycline evaluated according to Food and Drug Administration guidelines.
Results: Strains were isolated from Anesthesiology and Reanimation Unit (36.9 %), Medical Intensive Care Unit (17.9 %), Neurological Intensive Care Unit (14.7 %), Surgical Intensive Care Unit (13.9 %), Coronary Intensive Care Unit (2.3 %), Internal Medicine Services (9.8 %) and Surgical Services (4.5 %). Specimen types were; 239 (45.0 %) tracheal aspirate, 92 (17.3 %) urine, 78 (14.7 %) blood, 55 (10.4 %) wounds, 38 (7.1 %) sputum and 29 (5.5 %) catheter. The antibiotic resistance rates were found as 99.1 % for nitrofurantoin, 98.9% for cefotaxime, 97.7 % for tetracycline, 97.4 % for piperacillin, 97.2 % for netilmicin, 94.9 % for ceftazidime, 94.7 % for cefepime, 92.8 % for piperacillin/tazobactam, 91.7 % for ampicillin/sulbactam and ciprofloxacin, 91.1 % for meropenem, 89.8 % for imipenem, 89.5 % for levofloxacin, 82.1 % for gentamicin, 81.2 % for trimethoprim/sulfamethoxazole, 79.3 % for amikacin, 69.5 % for cefoperazone-sulbactam, 25.4 % for tobramycin, 5.1 % for tigecycline and 0.8 % for colistin.
Conclusion: Our strains were found as sensitive to colistin, tigecycline, tobramycin and cefoperazone/sulbactam antibiotics. Resistance to carbapenems and other antibiotics were remarkable.

Key Words: *Acinetobacter baumannii*, antimicrobial drug resistance, intensive care units, colistin, tigecycline, multidrug resistance

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ÖZET

Amaç: Çalışmanın amacı laboratuvarımızda Ocak 2012-Haziran 2014 tarihleri arasında izole edilen 531 *Acinetobacter baumannii* suşunun gönderildiği klinikler, örnek tiplerine göre dağılımı ve in vitro antibiyotik duyarlılıklarının belirlenmesidir.
Yöntemler: *A.baumannii* suşları geleneksel yöntemlerle ve API 20 NE (bioMerieux, Fransa) sistemi ile tanımlanmış, antibiyotik duyarlılıkları, Food and Drug Administration standartlarına göre değerlendirilen tigesiklin hariç, Clinical and Laboratory Standards Institute standartları kullanılarak belirlenmiştir.
Bulgular: Suşların % 36.9'u Anesteziyoloji ve Reanimasyon Ünitesi, % 17.9'u Dahili Yoğun Bakım Ünitesi, % 14.7'si Nöroloji Yoğun Bakım Ünitesi, % 13,9'u Cerrahi Yoğun Bakım Ünitesi, % 2.3'ü Koroner Yoğun Bakım Ünitesi, % 9.8'i Dahili Servisler ve % 4.5'i ise Cerrahi Servisler'de yatan hastalardan izole edilmiştir. Örnek çeşitleri 239 (% 45.0) trakeal aspirat, 92 (% 17.3) idrar, 78 (% 14.7) kan, 55 (% 10.4) yara, 38 (% 7.1) balgam ve 29 (% 5.5) kateterden oluşmaktadır. İzole edilen suşların antibiyotik direnç oranları; % 99.1'i nitrofurantoin, % 98.9'u sefotaksim, % 97.7'si tetrasiklin, % 97.4'ü piperasilin, % 97.2'si netilmisin, % 94.9'u seftazidim, % 94.7'si sefepim, %92.8'i piperasilin/tazobaktam, %91.7'si ampisilin/sulbaktam ve siprofloksasin, % 91.1'i meropenem, %89.8'i imipenem, % 89.5'i levofloksasin, %82.1'i gentamisin, % 81.2'si trimetoprim/sülfametoksazol, % 79.3'ü amikasin, % 69.5'i sefoperazon/sulbaktam, % 25.4'ü tobramisin, % 5.1'i tigesikline ve % 0.8'i kolistine dirençli olarak bulunmuştur.
Sonuç: Suşlarımız in vitro olarak kolistin, tigesiklin, tobramisin ve sefoperazon/sulbaktama duyarlı bulunmuştur. Karbapenemler başta olmak üzere birçok antibiyotiğe yüksek oranda direnç görülmesi dikkat çekicidir.

Anahtar Sözcükler: *Acinetobacter baumannii*, antimikrobiyal ilaç direnci, yoğun bakım üniteleri, kolistin, tigesiklin, çoklu ilaç direnci

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INTRODUCTION

Acinetobacter bacteria are commonly found in nature. Members belonging to the genus *Acinetobacter* are emerging as opportunistic nosocomial pathogens. *Acinetobacter* species, can cause serious nosocomial infections such as ventilator-associated pneumonia, wound and urinary tract infections, endocarditis, sepsis and meningitis especially in intensive care units (ICU). As long as they can remain viable on moist surfaces such as the respiratory-related treatment equipments and on dry surfaces such as human skin, they may cause refractory health problems in patients with impaired host defense. In critical patients with ventilator-associated pneumonia and bloodstream infection who are infected with *Acinetobacter*, the mortality rate is quite high (1-4).

A. calcoaceticus, *A. baumannii*, *Acinetobacter* genomic species 3, and *Acinetobacter* genomic species 13TU, are very closely related and difficult to distinguish from each other by phenotypic properties. It has therefore been proposed to refer to these species as the *A. calcoaceticus-A. baumannii* complex (5). *A. calcoaceticus-A. baumannii* complex is located in the first row of opportunistic pathogens of medical importance as they include strains resistant to multiple antibiotics and are responsible for outbreaks particularly in intensive care units. Potential risk factors for *Acinetobacter baumannii* (*A. baumannii*) infections include use of broad-spectrum antimicrobial agents, prolonged hospital and intensive care unit stay, mechanical ventilation, burns, underlying diseases such as malignancy and immunodeficiency and various surgical and invasive procedures (6-8).

Sulbactam, carbapenems, aminoglycosides, polymyxins, tigecycline and tetracycline can be used in the treatment of *A. baumannii* infections. However, with the increase of antimicrobial resistance, new treatment protocols are to be identified (9). Especially "multi-drug resistant" (MDR) bacteria definition which is resistant to three or more antibiotics in the same therapeutic class has become increasingly important in recent years. The most important mechanisms of the development of resistance consist of broad-spectrum beta-lactamase production, aminoglycoside modifying enzymes, modifications in penicillin-binding proteins and outer membrane proteins. The treatment of these MDR *Acinetobacter* infections that emerged in recent years are challenging. Carbapenems have been widely used in the treatment of *Acinetobacter* since they are in clinical use. However, currently, a high rate of clinical carbapenem resistance in *Acinetobacter* strains is reported all over the world. On the ground that antibiotic resistance rates steadily increase against carbapenems, aminoglycosides, tetracyclines and sulbactam, polymyxin group and tigecycline are seen to be the most effective antibiotics in the treatment of multidrug resistant *A. baumannii* strains (1,10).

A. baumannii isolated from clinical specimens cause major problems in the treatment of infections due to high resistance to many antibiotics (10). The aim of this study is to determine resistance rates of *A. baumannii* strains which were isolated as a pathogen from various clinical specimens in Giresun Professor Dr. Atilla Ilhan Ozdemir State Hospital (GPDAIOSH) inpatient units retrospectively.

MATERIAL AND METHODS

Bacteria isolation

Acinetobacter strains which had been isolated in a two-and-a-half-year period (January 2012-June 2014) in Microbiology Laboratory of GPDAIOSH were included in the study. The *Acinetobacter* strains were isolated from various clinical samples (tracheal aspirates, urine, blood, wound, sputum, catheter) of 531 (287 male, 244 female) patients with the ages ranging from 4 to 108 who had been hospitalized in various clinics and intensive care units. If a patient had more than one sample with *A. baumannii* bacteria, only one of them were included in the study.

Bacteria identification

Clinical samples were inoculated in 5% sheep blood agar and "Eosin Methylene Blue" agar (Becton Dickinson, USA) and after the incubation at 37°C for 18-24 h, the colonies' growth in these mediums were evaluated. The identification of the isolated microorganisms was done via conventional methods and API 20 NE (bioMerieux, France) system.

Antibiotic susceptibility tests

Susceptibility of the strains to gentamicin, amikacin, netilmicin, tobramycin, cefepime, ceftazidime, imipenem, meropenem, ciprofloxacin, trimethoprim/sulfamethoxazole, piperacillin/tazobactam, cefoperazone/sulbactam and ampicillin/sulbactam, levofloxacin, cefotaxime, piperacillin, tetracycline (Oxoid, Thermo Scientific, UK) was evaluated via Kirby-Bauer disk diffusion method in accordance with the updated Clinical and Laboratory Standards Institute (CLSI 2012-2013-2014) guideliness (11-13).

Susceptibility of the strains to colistin and tigecycline was evaluated via E-test method (bioMerieux, France) by determining minimal inhibitory concentration (MIC). E-test MIC values for tigecycline were evaluated considering FDA interpretation criteria for Enterobacteriaceae (14). According to the breakpoints; ≥ 8 mg/ml is resistant, 4 mg/ml is intermediate, ≤ 2 mg/ml was considered as susceptible (14). E-test MIC values for colistin were evaluated according to the updated CLSI criteria; ≥ 4 mg/ml was resistant, ≤ 2 mg/ml was considered as susceptible (11-13).

Statistical analysis

Distribution of specimens in terms of clinics where they had been sent from was heterogeneous (x2: 124.4, P<0.0001). Similarly, distribution of the types of clinical specimens was not homogeneous. (x2: 144.4, P<0.0001). In making these comparisons, statistical tests of the Pearson chi-square test was used.

RESULTS

A total of 45.289 samples were sent to the Microbiology Laboratory of GPDAIOSH between January 2012-June 2014. Of these cultures 13.473 (29.7%) were positive and *A. baumannii* growth was observed in 1735 (12.9%) of them. Only one of *A. baumannii* isolate was included in this study from different samples of each patient. *A. baumannii* strains were isolated mostly in the samples sent from (36.9 %) anaesthesiology and reanimation intensive care unit. The isolates were mostly (45.0 %) isolated from tracheal aspirates and this accounts for nearly half of all samples. The distribution of the isolated strains and related clinics are shown in Table1.

Table 1. Distribution of A. *baumannii* strains according to clinics and clinical samples [n (%)].

Clinic \ Sample	Tracheal aspirate*	Urine	Blood	Wound	Sputum	Catheter	**Total** (%)
Anaesthesiology and Reanimation Intensive Care Unit (ARICU)	107	38	19	12	13	7	**196 (36.9)**
Medical Intensive Care Unit (MICU)	52	19	9	5	7	3	**95 (17.9)**
Neurological Intensive Care Unit (NICU)	9	12	17	20	3	5	**78 (14.7)**
Surgical Intensive Care Unit (SICU)	21	10	21	7	2	10	**74 (13.9)**
Coronary Intensive Care Unit (CICU)	7	2	2	-	1	-	**12 (2.3)**
Internal Services ** (IS)	19	9	5	7	10	2	**52 (9.8)**
Surgical Services *** (SS)	9	2	5	4	2	2	**24 (4.5)**
Total (%)	**239 (45.0)**	**92 (17.3)**	**78 (14.7)**	**55 (10.4)**	**38 (7.1)**	**29 (5.5)**	**531 (100)**

*Tracheal aspiration is performed from tracheostomy cannula.
***Internal Services (Infectious Diseases, Dermatology, Chest Diseases, Internal Medicine, Nephrology, Neurology)*
****Surgical Services (Urology, Plastic Surgery, Neurosurgery)*

Colistin was identified as the most sensitive antibiotic with a 0.8% resistance rate, which was observed in three strains. This was followed by tigecycline with a resistance rate of 5.1 %. A resistance rate over 90% has been observed against penicillins, cephalosporins, quinolones and carbapenems. Antibiotic susceptibility of isolated strains are shown in Table 2.

Table 2. Rates of antibiotic resistance in *Acinetobacter* strains.

Antibiotics	Susceptible strains / Resistant strains (Total strains)	Resistance rate (%)
Nitrofurantoin	5/526(531)	99.1
Cefotaxime	6/525(531)	98.9
Tetracycline	12/519(531)	97.7
Piperacillin	14/517(531)	97.4
Netilmicin	15/516(531)	97.2
Ceftazidime	27/504(531)	94.9
Cefepime	28/503(531)	94.7
Piperacillin/Tazobactam	38/493(531)	92.8
Ampicillin/Sulbactam	44/487(531)	91.7
Ciprofloxacin	44/487(531)	91.7
Meropenem	47/484(531)	91.1
İmipenem	54/477(531)	89.8
Levofloxacin	56/445(531)	89.5
Gentamicin	95/436(531)	82.1
Trimethoprim/Sulfamethoxazole	100/431 (531)	81.2
Amikacin	110/421 (531)	79.3
Cefoperazone/Sulbactam	162/369 (531)	69.5
Tobramycin	396/135 (531)	25.4
Tigecycline (MIC)	150/27 (177)	5.1
Colistin (MIC)	351/3 (354)	0.8

**Mid-susceptible strains were considered as resistant.*

When we compare nitrofurantoin, cefotaxime, tetracycline, piperacillin and netilmicin antibiotics (resistance ratio 99.1%-97.2%) resistance rates with ceftazidime, cefepime, piperacillin/tazobactam antibiotics (resistance ratio 94.9%-92.8%) there was a statistical difference ($p<0.05$). Additionally resistance rates of ampicillin/sulbactam, ciprofloxacin, meropenem, imipenem, levofloxacin, (resistance ratio 91.7%-89.5%) was significantly lower ($p <0.001$), and the lowest resistance rate was observed in gentamicin, trimethoprim/sulfamethoxazole amikacin, cefoperazone/sulbactam, tobramycin, tigecycline, colistin antibiotics (resistance ratio, 82.1%-0.8 %) ($p<0.0001$).

Among aminoglycosides, activity comparison between netilmicin, gentamicin, tobramycin and amikacin was statistically significant except for the relationship between amikacin and gentamicin ($p <0.0001$).

In addition, when we compare the cephalosporin group among its members, cefotaxime was significantly more active than the others ($p<0.0001$).

No significant difference was found between the activity of the carbapenem (imipenem, meropenem) and the quinolone (levofloxacin, ciprofloxacin) group antibiotics.

Colistin was found to be the most active antibiotic when compared to all antibiotics especially tigecycline ($p <0.0001$).

In making these comparisons, statistical tests of the Pearson chi-square test was used.

DISCUSSION

Nosocomial infections may cause prolonged hospital stay and large increases in treatment costs with high morbidity and mortality rates. Infectious agents are often antibiotic-resistant microorganisms due to high frequency of implementation of invasive procedures, underlying diseases, inadequate infection control and inadequate empirical therapies. Suppressed immune systems of ICU patients, and the overuse of broad-spectrum antibiotics increase resistance problems. In recent years, increasingly reported multidrug resistance made *Acinetobacter* species and especially *A. baumannii* become crucial again (3,10,15).

Outbreaks due to *A.baumannii* have been reported worldwide, especially in adult ICUs. When *Acinetobacter* strains were evaluated in terms of clinics from where the strains were isolated, ICU takes the first place with a ratio of 58-84% (2,16-21). In our study, 85.7% of *Acinetobacter* strains were isolated from ICUs also.

When distribution of clinical samples of *A. baumannii* isolates were analyzed, it can be seen that respiratory tract samples take the first place (2,4,19). Similarly, in our study respiratory tract samples especially 107 (20%) tracheal aspirate samples sent from ARICU took the first place.

When the resistance profile of the strains were evaluated, the strains isolated from tracheal aspirates were found to be more resistant than the isolates of other types of clinical samples. Moreover, the strains isolated from urine samples were found to be more sensitive than the other sample types. In addition, when clinical distribution of the resistance profile was evaluated, sensitive isolates are mostly isolated from internal medicine departments, and among intensive care units, the most resistant strains were isolated from ARICU.

Antibiotic susceptibility rates of nosocomial pathogens plays an important role especially in the determination of empirical therapy, in the creation of policies about the use of antibiotics and in directing control measures. Antibiotic resistance observed in *Acinetobacter* strains can vary from country to country, from city to city, from hospital to hospital and even in the same hospital from one clinic to another due to changing epidemiological conditions, different antibiotic usage patterns and the environmental factors (4,6,22). Therefore, consideration of local surveillance data and determination of resistance profiles of each hospital periodically are essential for accurate antimicrobial usage (22).

A. baumannii is naturally resistant to many antibiotics, and is also capable of developing resistance to different classes of antibiotics (6,22). Xu T et al. (4) reported that isolation rate of *A. baumannii* in the hospitals of China's Nanjing region raised from 7% to 18.8% between 2008 and 2011. In this four-year period, it was also reported that particularly respiratory specimens sent from geriatrics departments constituted about 80% of these *A. baumannii* strains. Significant resistance developed to 12 different types of antibiotics. Cefoperazone/sulbactam resistance raised from 12% to 67.4%, imipenem resistance raised from 14.8% to 90.8% and meropenem resistance raised from 23.3 % to 91.1%. In our Turkey, Ozdem et al. (2) also reported that between 2007 and 2010, a significant resistance developed against various antibiotics; cefoperazone/sulbactam resistance raised from 20.6% to 38.2%, imipenem resistance raised from 32.7% to 74% and meropenem resistance raised from 31.8% to 80.3%.

In our country, the studies conducted in various hospitals of different regions reported different susceptibility results and increasing levels of antibiotic resistance rates in *A. baumannii* strains (8,10,23). It is a fact that the rate of resistance in our country is quite high when compared to other European countries (3). Yurtsever et al. (22) reported that the most effective antibiotic was cefoperazone/sulbactam with a susceptibility rate of 87% against 120 *A. baumannii* strains isolated as nosocomial infectious agent. This was followed by netilmicin with a susceptibility rate of 76% and imipenem with a susceptibility rate of 65% in 2008. Again, in 2010,Aral et al. (17) reported in their study conducted on 130 strains that imipenem and amikacin were found to be susceptible with rates of 28% and 19%, respectively. In addition, they also reported a 92% resistance rate to ceftazidime, 91% resistance rate to levofloxacin, 85% resistance rate to trimethoprim/sulfamethoxazole, 85% resistance rate to gentamicin and 81% resistance rate to amikacin. In our study, *Acinetobacter* species have developed resistance to almost all antimicrobial agents including penicillins, aminoglycosides, quinolones, cephalosporins and extended spectrum beta-lactam antibiotics. Carbapenems are still the first choice in *Acinetobacter* infections, but the resistance to carbapenems has increased gradually in Turkey and throughout the world (24,25). In our study, resistance to carbapenems has been found to be as high as 89.8%. In the carbapenem group, no difference was found between meropenem and imipenem by the means of resistance.

In this study, it was seen that high rates of resistance had developed against the majority of antibiotics tested. Additionally, in our country the studies report that the imipenem resistance is between 60.8-92%, and the meropenem resistance is between 64-96% (6,15,17-19,21,24,26). In Kayseri, Alp et al. (16) reported an increase in resistance to imipenem from 45% to 92% in a surveillance study covering the years of 2000-2009. In Taiwan, Lee et al. (27) reported that imipenem susceptibility decreased from 82% to 15 % in *A. baumannii* strains isolated from intra-abdominal infections between the years 2006-2010 in five different medical centers. In Italy, Mezzatesta et al.(28) reported that imipenem resistance of 202 clinical strains determined according to the MIC values in two different periods (2004-2005 and 2008-2009) raised from 90.8% to 100%. Furthermore, the meropenem resistance was reported to be 100% in both periods. Jiang et al. (23) reported that all *A. baumannii* strains isolated in a 3-year period were resistant to imipenem in China. Although the resistance profile varies between countries and even regions, increase in the carbapenem resistance is attributed to clonal relationship of *Acinetobacter* strains isolated from ICUs and the common use of carbapenems in empiric treatment (19). However, in some areas it is seen that the resistance rate is still low.

In Korea, Huh et al.(29) reported resistance profiles of 158 *A. baumannii* strains isolated from blood cultures in 13 different institutions as follows; amikacin 16.9%, cefotaxime 23.1%, levofloxacin 36.1%, meropenem 37.5%, ceftazidime 37.7%, cefepime 39.2%, gentamicin 39.9%, piperacillin 40.7%, ciprofloxacin 41.7%, piperacillin/tazobactam 52.9%, imipenem 55.4%, trimethoprim/sulfamethoxazole 57.1% and aztreonam 68.9%. In a surveillance study, about 73.0% of *A. baumannii* isolates were found not to be susceptible to at least a carbapenem (doripenem, imipenem and meropenem) in the Asia-Pacific region (30).

High rates of antibiotic resistance in *A. baumannii* strains caused the search for alternative treatment modalities. Colistin, sulbactam and tigesklin are alternatives that can be used in the MDR *Acinetobacter* infections (3,24). But recently, studies in several European countries have begun to report a colistin resistance. While 2.7% polymyxin B resistance was seen in the European surveillance program, colistin resistance rates of 3% and 2 % have been reported in patients hospitalized in intensive care units in Greece and in the UK respectively. In a study conducted in Germany, while colistin resistance was reported as 2.8%, and tigecycline resistance was reported to be 6%, it was emphasized that tigecycline resistance in Turkey was 25% (3).

Microbial activity of tigecycline can be measured with the use of different methods. In the literature, of these methods, the disk diffusion method has been reported to have a lower sensitivity when compared to Etest in the determination of susceptibility of *A. baumannii* isolates to tigecycline (1). In various studies in Turkey and different countries, tigecycline susceptibility was reported to be between 61-100% and colistin susceptibility rate was reported to be between 91-100% (2,6,8,18,25,26,28). In our study, colistin was identified as the most effective antimicrobial agent with 99.2% in vitro susceptibility, and tigecycline was evaluated as an antimicrobial agent that can be used in the resistant *Acinetobacter* infections with a 94.9 % susceptibility. In line with with the results of our study, Kurtoğlu et al.(20) found colistin, tigecycline and cefoperazone/sulbactam to be the most effective antibiotics with the respective resistance rates of 5%, 16% and 28% against *A. baumannii* strains isolated from various clinical specimens between 2008-2010.

In the treatment of MDR Acinetobacter infections, rifampin, sulbactam, aminoglycosides, colistin, carbapenems and other agents are used in different combinations (7). Ni et al.(31) reported that tigecycline/colistin combination showed synergistic effects in 24.3% of strains, and the tigecycline/sulbactam combination showed synergistic effects in 64.3% of the strains.

It is possible to avoid more resistant strains by using broad spectrum antibiotics in a rational manner with appropriate doses and durations. Furthermore, following an empirical therapy, the rearrangement of antibiotherapy after culture results will prevent inappropriate use of antibiotics. The high prevalence of carbapenem- and other antibiotics-resistant MDR *A. baumannii*, which is an important nosocomial pathogen, will be decreased by rigorous infection control measures and appropriate antimicrobial use (2,21,30).

CONCLUSION

Consequently, high rates of resistance in *A. baumannii* strains against multiple antibiotics complicate the treatment of *A. baumannii* infections severely. In our study, *A. baumannii* strains which show multiple resistance to many antibiotics such as carbapenems were susceptible to colistin at a rate of 99.2%, tigecycline 94.9%, tobramcine 74.6% and cefoperazone/sulbactam 40.05%. However, this susceptibility should not mislead us. Because, as noted in many studies, resistance can develop to colistin in different consecutive periods in a short time as well as other antibiotics. Monitoring in vitro antibiotic susceptibility profiles of *Acinetobacter* strains with multiple antibiotic resistance at regular intervals will be useful. In addition, hand hygiene of the staff working in the ICUs is crucial to prevent the spread of nosocomial infectious agents such as *A. baumannii*. Evaluation of high resistance profile of *A. baumannii* strains belonging to a small state hospital increases the importance of our work. However for the detection of the resistance profile and the clonal relationship of *A. baumannii* strains in our geographic region further studies are needed.

Conflict of Interest

No conflict of interest was declared by the authors.

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