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RESEARCH ARTICLE

Increasing antimicrobial resistance in nosocomial pathogens; multidrug-resistant extensively drug-resistant and pandrug-resistant *Acinetobacter baumannii*

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ABSTRACT

Objective: The aim of this study was to determine the antimicrobial susceptibility of *Acinetobacter baumannii* strains, which were isolated from nosocomial infections and compare the changes in resistance rates of isolates over time.

Methods: *Acinetobacter* spp. strains isolated from hospitalized patients diagnosed with nosocomial infection at Cumhuriyet University Hospital between 2007 and 2011 were included in the study. Isolate identification and antibiotic susceptibility test were performed using an automated system according to the Clinical and Laboratory Standards Institute guidelines.

Results: In total, 454 *Acinetobacter spp*. strains were included in this study. *A. baumannii* was the most frequently isolated *Acinetobacter species*. Imipenem and meropenem resistance were determined to be 31.9% and 33.7%, respectively, and 74.4%, 78.0%, 76.7%, 46.6%, 62.4%, 66.8%, 61.3% and 53.9% of isolates were resistant to piperacillin-tazobactam, ceftazidime, cefepim, amikacin, gentamicin, ciprofloxacin, levofloxacin and tetracycline respectively. The resistance rates of multidrug-resistant (MDR), extensively drug-resistant (XDR), and pandrug-resistant (PDR) *A. baumannii* were 50.2%, 28.5%, and 14.0%, respectively. Changes in MDR, XDR and PDR rates over time were examined. Importantly, PDR *A. baumannii* have been reached dangerous levels over time.

Conclusion: *A. baumannii* is one of the most important pathogen, particularly in a nosocomial setting. Increasing resistance rates of this group to all antibiotics will likely lead to increased treatment failure in the future. *J Microbiol Infect Dis 2014;4(1): 7-12*

Key words: *Acinetobacter baumannii*, antimikrobial resistance, nosocomial infections.

Nozokomiyal patojenlerde artan antimikrobiyal direnç; çok ilaca dirençli, yaygın ilaç dirençli ve tüm ilaçlara dirençli *Acinetobacter baumannii*

ÖZET

Amaç: Bu çalışmada nozokomiyal enfeksiyonlardan izole edilen *Acinetobacter* spp. suşlarının antimikrobiyal duyarlılıkları tespit edilerek yıllar içerisindeki direnç değişimlerinin karşılaştırılması amaçlanmıştır.

Yöntemler: Çalışmamıza 2007-2011 tarihleri arasında Cumhuriyet Üniversitesi Hastanesinde tedavi gören ve nozokomiyal enfeksiyon tanısı konulan hastaların klinik örneklerinden izole edilen *Acinetobacter* spp. suşları alınmıştır. Suşların tanımlanması ve antimikrobiyal duyarlılık testleri Clinical and Laboratory Standards Institute önerilerine göre otomatize sistem kullanılarak yapılmıştır.

Bulgular: Klinik örneklerinden izole edilen toplam 454 *Acinetobacter spp.* suşu çalışmaya dahil edilmiştir. *A. baumannii* en sık izole edilen *Acinetobacter* türü olarak saptandı. İmipenem ve meropenem dirençli suş oranı sırası ile % 31.9 ve % 33.7 olarak saptanırken, piperasilin/tazobaktam, seftazidim, sefepim, amikasin, gentamisin, siprofloksasin, levofloksasin ve tetrasiklin direnç oranları sırası ile % 74,4, % 78.0, % 76.7, % 46.6, % 62.4, % 66.8, % 61.3 ve % 53.9 olarak saptandı. Çok ilaca dirençli (MDR), yaygın ilaç dirençli (XDR) ve tüm ilaçlara dirençli (PDR) *A. baumannii* oranları sırası % 50.2, % 28.5 ve % 14.0 olarak bulundu. Yıllar içindeki MDR, XDR ve PDR suş oranları değişimleri incelendiğinde, özellikle PDR *A. baumannii* oranının tehlikeli düzeylerde arttığı görüldü.

Sonuç: *A. baumannii* nozokomiyal enfeksiyonlarda en önemli patojenlerden biridir ve tüm antibiyotiklere karşı artan direnç oranları gelecekte daha çok tedavi başarısızlıklarına neden olacağı muhtemeldir.

Anahtar kelimeler: *Acinetobacter baumannii*; antimikrobiyal direnç, nozokomiyal enfeksiyon.

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INTRODUCTION

Nosocomial infections increase the length of hospitalization, raise overall health costs, and are a major cause of death worldwide. In the United States nosocomial infections cause or contribute to 1.7 million infections and 99.000 deaths annually.[1] *Acinetobacter* species are one of the most important factors in nosocomial infection as they are resistant to environmental influences and have developed resistance to various antibiotics,[2] including third-generation cephalosporins, aztreonam, piperacillin, and carbapenems.[3,4] Recent studies suggest that *Acinetobacter baumannii* is becoming increasingly antibiotic resistant and virulent, creating a major nosocomial threat.[5,6]

Efficient infection control strategies are needed to prevent *Acinetobacter* nosocomial infections.[2] Susceptibility to antimicrobials varies among countries, centers, and even hospital departments. These differences may reflect varying antibiotic usage patterns, epidemiological conditions, and antibiotic control policies. Thus, it is important to consider local surveillance data to choose antibiotics.[7] The main problem about *Acinetobacter* infections in hospitals is that, these infections could cause higher mortality among the critically ill patients and upward trend in multidrug resistance. In this study, we aimed to determine the antimicrobial resistance and susceptibilities of *Acinetobacter* spp. strains which were isolated from patients with nosocomial infections and to investigate the changes in resistance rates over years.

METHODS

We investigated *Acinetobacter* spp. strains which were isolated from patients with nosocomial infections at the Training and Research Hospital of Cumhuriyet University over a five-year period between May 2007 and December 2011. In total, 454 strains isolated from various patient specimens (165 respiratory tract, 99 urine, 76 blood, 70 wound site, 14 cerebrospinal fluid, nine drains, and 21 other) were included in this study.

Patient specimens sent to the Clinical Microbiology Laboratories of the Training and Research Hospital at Cumhuriyet University were planted in Columbia agar containing 5% sheep-blood (Salubris) and eosin methylene blue (EMB) agar (Salubris) media and then incubated at for 24-48 hours at 35°C. Colonies grown on Columbia and EMB agar media were transferred to Phoenix NMIC ID/82 and Phoenix UNMIC ID/82 panels (McFarland 0.5 BD Biosciences, Franklin Lakes, NJ, USA) according to the manufacturer's instructions, and then their identification and antimicrobial susceptibilities were determined using the BD Phoenix 100 (BD Biosciences) system.

The resistance and susceptibility of these strains to antimicrobials (amikacin, ceftazidime ciprofloxacin, cefepime, gentamicin, imipenem, meropenem, levofloxacin, piperacillin-tazobactam, trimethoprim-sulfamethoxazol, and tetracycline) were retrospectively examined based on laboratory records. While the strain that was first isolated from the patients was included in the study, repeat isolates with (the same) phenotype from the same patient were excluded from the study. Only one isolate (collected from the infected site, simultaneous growth of blood cultures were ignored) of the strains isolated from different specimens of the same patients was included in the analysis. Among the patients who showed no growth in other body fluids (i.e., urine, respiratory tract, and wound site) and had only positive blood culture was included as growth in the blood.

Multidrug-resistant (MDR) *A. baumannii* was defined as the strain having acquired non-susceptibility to at least one agent in three or more antimicrobial categories. Extensively drug-resistant (XDR) *A. baumannii* was defined as showing non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e., bacterial isolates remained susceptible to only one or two categories). Pandrug-resistant (PDR) *A. baumannii* was defined as non-susceptibility to all agents in all antimicrobial categories.[8]

The results were statistically analyzed using SPSS 15.0 (SPSS, Inc., Chicago, IL, USA) software and Epi Info 3.5.3 software programs (Centers for Disease Control and Prevention, Atlanta, GA, USA). Proportion comparisons for categorical variables were conducted using Chi-square tests, Fisher's exact test was used when data were sparse $P < 0.05$ was considered statistically significant. Chi-square test trend analyses were used to identify differences among resistance rates by year. Our study was conducted upon approval of the Ethics Committee of Cumhuriyet University Hospital.

In addition to the periodic control of bacteriology systems used in the Clinical Microbiology Laboratories of the Training and Research Hospital of Cumhuriyet University by internal quality control strains (ATCC 25922 *Escherichia coli*, ATCC 27853 *Pseudomonas aeruginosa*, ATCC 700603 *Klebsiella pneumoniae*, ATCC 25923 *Staphylococcus aureus*, and ATCC 29212 *Enterococcus faecalis*), systems were inspected by UK NEQAS between 2002 and

2008, they have been inspected by the College of American Pathologist (CAP) external quality control centers since 2008.

RESULTS

This study included 454 *Acinetobacter* spp. strains isolated from various clinical specimens of patients over a period of five years. While 196 (43.2%) of these strains were isolated from specimens of patients in the intensive care unit, 258 (56.8%) strains were isolated from patients hospitalized in other units. The numbers of strains isolated by year were found to be 63 in 2007, 84 in 2008, 90 in 2009, 124 in 2010, and 93 in 2011.

In total, 386 of the 454 strains (85%) cultured in clinical samples were defined as *A. baumannii* and 68 strains (15%) were defined as other *Acinetobacter* species. Resistance distributions of *A. baumannii* strains and *Acinetobacter* spp. other than *A. baumannii* are shown in Table 1. For all studied antibiotics, statistically significant (p<0.05) resistance rates were found in *A. baumannii* strains compared with species other than *A. baumannii.*

The resistance distributions of *A. baumannii* strains and changes in their distributions by year are shown in Table 2 and Figure 1. Resistance to gentamicin, ceftazidime cefepime, piperacillin-tazobactam, ciprofloxacin, levofloxacin, imipenem, meropenem, and tetracycline gradually increased over time. The annual changes in resistance rates against all antibiotics except amikacin were significant. While major changes were not observed in MDR rates and XDR rates over the years, for PDR rates; the pattern was unpredictable (the resistance rates were 4.7% and 3.1% in 2007 and 2008 which then increased to 20% in 2009 and 2011) (Figure 1).

Table 1. Resistance distributions of *Acinetobacter baumannii* strains and *Acinetobacter* species other than *Acinetobacter baumannii* between 2007-2011 years

Antibiotics	*A. baumannii* n (%)	*Acinetobacter spp.* n (%)	*p*
Amikacin	180/386 (46.6)	2/68 (2.9)	<0.001
Gentamicin	241/386 (62.4)	3/68 (4.4)	<0.001
Ceftazidime	301/386 (78.0)	17/68 (25.0)	<0.001
Cefepim	296/386 (76.7)	15/68 (22.1)	<0.001
Imipenem	123/386 (31.9)	1/68 (1.5)	<0.001
Meropenem	130/386 (33.7)	2/68 (2.9)	<0.001
Ciprofloxacin	258/386 (66.8)	7/68 (10.3)	<0.001
Levofloxacin	237/386 (61.3)	6/68 (8.8)	<0.001
PTZ	287/386 (74.4)	12/68 (17.6)	<0.001
TMP-SMZ	257/386 (66.6)	21/68 (30.9)	<0.001
Tetracycline	208/386 (53.9)	14/68 (20.6)	<0.001

PTZ= Piperacillin-tazobactam
TMP-SMZ = Trimethoprim-sulfamethoxazole

Table 2. The changes in the resistance distributions of *A. baumannii* strains by years (2007-2011) (n = 386)

Antibiotics/Years, n (%)	2007 (n=43)	2008 (n=64)	2009 (n=82)	2010 (n=112)	2011 (n=86)	*p**-value
Amikacin	23 (53.5)	16 (25.0)	48 (59.3)	54 (48.2)	39 (45.3)	0.554
Gentamicin	23 (53.5)	34 (53.1)	59 (72.8)	61 (54.5)	64 (74.4)	0.04
Ceftazidime	24 (55.8)	46 (71.9)	67 (82.7)	93 (83.0)	71 (82.6)	<0.001
Cefepim	20 (46.5)	48 (75.0)	70 (86.4)	89 (79.5)	69 (80.2)	<0.001
CIP	11 (25.6)	26 (40.6)	67 (82.7)	87 (77.7)	67 (77.9)	<0.001
LEV	10 (23.3)	21 (32.8)	57 (70.4)	83 (74.1)	66 (76.7)	<0.001
Imipenem	4 (9.3)	7 (10.9)	30 (37.0)	39 (34.8)	43 (50.0)	<0.001
Meropenem	2 (4.7)	9 (14.1)	32 (39.5)	42 (37.5)	45 (52.3)	<0.001
TMP SMZ	22 (51.2)	43 (67.2)	45 (55.6)	75 (67.0)	72 (83.7)	<0.001
Tetracycline	16 (37.2)	32 (50.0)	35 (43.2)	62 (55.4)	63 (73.3)	<0.001
PTZ	20 (46.5)	41 (64.1)	68 (84.0)	87 (77.7)	71 (82.6)	<0.001

CIP=Ciprofloxacin, LEV=Levofloxacin, TMP-SMZ=Trimethoprim-sulfamethoxazole, PTZ=Piperacillin/tazobactam
p*= Chi-square test trend analysis

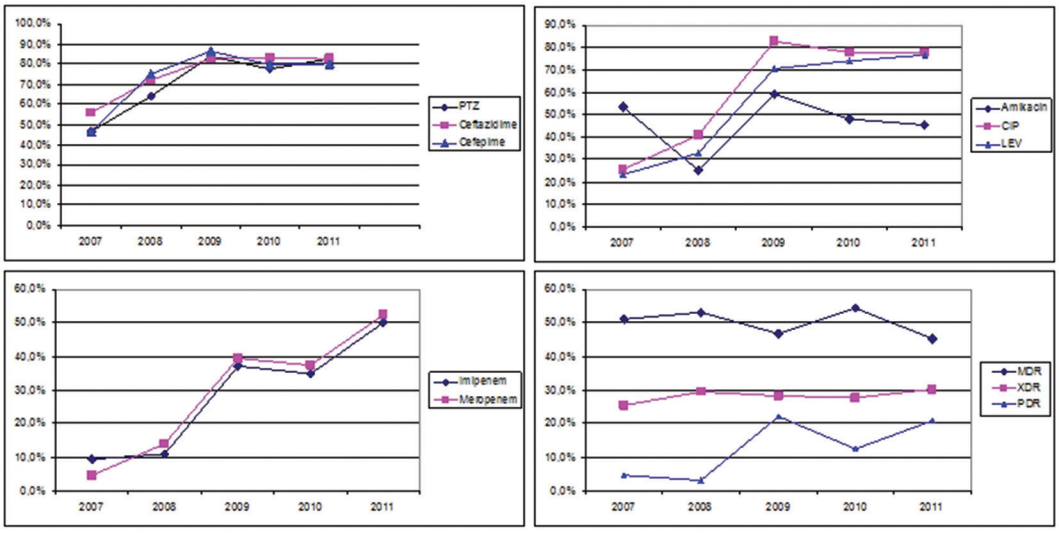

Figure 1. The changes in the resistance distributions of *A. baumannii* strains to several antibiotics which include most commonly used for treatment of nosocomial *Acinetobacter* infections and the distributions of MDR, XDR and PDR rates by years (2007-20011)

PTZ: Piperacillin/tazobactam, **CIP:** Ciprofloxacin, **LEV:** Levofloxacin, **MDR:** Multidrug resistant, **XDR:** Extensively drug resistant, **PDR:** Pandrug resistant

DISCUSSION

Antimicrobial resistance keeps increasing among hospital-acquired gram-negative pathogens. Particularly *A. baumannii*, *P. aeruginosa*, and *Stenotrophomonas maltophilia* display multiple resistances to various antibiotics; making therapy selection difficult.[9] *A. baumannii* has become a major nosocomial pathogen in many hospitals in various parts of the world. This infection is associated with considerable mortality, and no satisfactory results can be achieved using empirical therapies due to *A. baumannii*'s rapidly-increasing resistance to treatment.[10,11]

A. baumannii is one of the most common infection-causing isolate among *Acinetobacter* species limiting treatment options due to its high antibiotic resistance.[12] Our study showed that *Acinetobacter* strains, which were cultured from clinical samples, increased in number each year and that 85% of strains cultured in literature medium were found to be *A. baumannii*.

Clinical studies report increasing resistance rates of *A. baumannii*, which is a factor in nosocomial infections.[5,6] A worldwide study including 25 countries and 99 centers between 2002 and 2004 reported that resistance rates to *Acinetobacter* species were 24%, 25% 48%, 60%, 60%, and 72% for meropenem, for imipenem, gentamicin, ciprofloxacin, piperacillin-tazobactam, and ceftazidime respectively.[13] International studies have reported varying results from different centers. However, *Acinetobacter* species were shown to be highly resistant to antibiotics in all studies.[14-19] In a study conducted in our country, the authors reported resistance rates of 65%, 80%, 98%, 92%, 100%, and 86% for imipenem, amikacin, piperacillin-tazobactam, cefepime, ceftriaxone, tetracycline, and trimethoprim-sulfamethoxazol respectively.[20] Yuce et al.[21] reported resistance rates of 98%, 95%, 84%, 90%, and 100% for ceftazidime, cefepime, meropenem, imipenem, ciprofloxacin and piperacillin-tazobactam respectively. Resistance rates obtained in these studies which were conducted in our country are also high. In our study ,examining the five-year average antimicrobial resistance distributions of nosocomial *A. baumannii* strains, the lowest resistance was observed for imipenem and meropenem (31.9% and 33.7%) and with the highest resistance observed for cefepime and ceftazidime (76.7% and 78%). Relatively low resistance values were obtained for species other than *A. baumannii* (Table 1). The high resistance rates reported in studies may be associated with the efficiency of specific infection control programs and antimicrobial agent usage policies as well as more favorable environmental conditions in countries in which lower resistance rates were reported.

Carbapenems have been the first-line treatment for nosocomial gram-negative infections. However,

carbapenems have been showing reduced efficiency as a result of increasing worldwide resistance to carbapenems as well as the emergence of PDR strains resistant to all drugs other than MDR and colistin and due to the increase in their numbers.[6] In two European multi-center studies covering two different periods, imipenem resistance was shown to have increased from 25% to 40%, with meropenem resistance increasing from 24% to 35%.[13,22] Carbapenem resistance poses a major problem for Turkey compared with other European countries.[23] In a study by Alp et al.[24] in our country, imipenem and meropenem resistance were reported to be 51% and 54%, respectively, for *A. baumannii* strains. In our study, a review of the distributions by year revealed developed that resistance to carbapenems developed at an alarming rate. In 2007 the *A. baumannii* resistance to imipenem and meropenem was found to be 9.3% and 4.7%, respectively, while these resistance rates had respectively increased to 50.0% and 52.3% in 2011.

It is commonly known that MDR and PDR strain rates are high in nosocomial *A. baumannii* infections.[25,26] Joung et al.[27] found the MDR and PDR resistance rates to be 60.3% and 15.5%, respectively. Aimsaad et al.[28] reported these rates to be 67.5% and 21.1%, respectively. In a study conducted in our country, Eser et al.[20] reported the MDR *Acinetobacter* antibiotic resistance rate to be 41%. A review of resistance distributions of antibiotics used in our study over a period of five years showed increasing rates of MDR and PDR strains. Particularly, the 4.7% PDR strain rate in 2007 was found to be 20.9% in 2011. These resistance rates are considered indicators of a gradual increase in difficulties treating *Acinetobacter* infections.

Colistin is an older antibiotic that has recently been used for treating PDR microorganisms. Duenas et al.[29] reported that 98% of *Acinetobacter* strains were susceptible to colistin under in vitro conditions. Minimum inhibitory concentration levels should be determined when these drugs are used for treatment purposes. Clinical studies have revealed that colistin is efficient for treating many multidrug-resistant gram-negative bacterial infections, and that it is a reliable treatment option against MDR, XDR or PDR strains.[30-32] In our study, we did not conduct an antimicrobial susceptibility test for colistin that included broth microdilution and/or E-test methods.

There are some limitations of our study. First of all, the numerous studies have been investigating antibiotics such as colistin that were old but gained renewed importance in treatment of MDR *A. baumannii* isolates. Antimicrobial susceptibility results of colistin could not be given and we think that this condition compose the major deficiency of our study. Furthermore, although additional methods were used for antimicrobial susceptibility in some studies especially investigate MDR strains, we did not perform additional antimicrobial susceptibility test such as E-test due to our retrospective design.

Different antibiotic-resistance rates of *Acinetobacter* strains have been reported worldwide. Previous studies generally reveal high resistance rates which on the rise. These are raising concerns regarding the treatment of *Acinetobacter* infections. Our five-year local data can be used particularly in considering nosocomial *Acinetobacter* infections in order to create successful empirical treatment models and effectively prevent the spread of such microorganisms. Further studies are needed to examine colistin which found to be susceptible even in PDR strains under in vitro conditions, as well as new treatment options.

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REFERENCES

1. Curtis LT. Prevention of hospital-acquired infections: review of non pharmacological interventions J Hosp Infect 2008;69:204-219.
2. Sunenshine RH, Wright MO, Maragakis LL, et al. Multidrug-resistant *Acinetobacter* infection: mortality rate and length of hospitalization. Emerg Infect Dis 2007;13:97-103.
3. Nicoletti G, Schito G, Fadda G, et al. Bacterial isolates from severe infections and their antibiotic susceptibility patterns in Italy: a nationwide study in the hospital setting. J Chemother 2006;18:589-602.
4. Joshi SG, Litake GM, Satpute MG, et al. Clinical and demographic features of infection caused by *Acinetobacter* species. Indian J Med Sci 2006;60:351-360.
5. Doi Y, Husain S, Potoski BA, et al. Extensively drug-resistant *Acinetobacter baumannii*. Emerg Infect Dis 2009;15:980-982.
6. Towner KJ. *Acinetobacter:* an old friend, but a new enemy. J Hosp Infect 2009;73:355-363.
7. Saltoğlu N. Treatment of *Acinetobacter baumannii* infections. Klimik J 2007;20:204-207.
8. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug- resistant, extensively drug resistant and pandrug resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012;18:268-281.

9. Clark NM, Patterson J, Lynch JP: Antimicrobial resistance among gram-negative organisms in the intensive care unit. Curr Opin Crit Care 2003;9:413-423.
10. Falagas ME, Kasiakou SK, Rafailidis PI, et al. Comparison of mortality of patients with *Acinetobacter baumannii* bacteraemia receiving appropriate and inappropriate empirical theraphy. J Antimicrob Chemother 2006;57:1251-1254.
11. Karageorgopoulos DE, Falagas ME. Current control and treatment of multidrug resistant *Acinetobacter baumannii* infections. Lancet Infect Dis 2008;8:751-762.
12. Schreckenberger PC, Daneshvar MI, Weyant RS, Hollis DG. *Acinetobacter, Achromobacter, Chryseobacterium, Moraxella* and Other Nonfermantative Gram Negative Rods In: Murray PR, Baron EJ, Pfaller MA, Landry ML, Jorgensen JH. (Eds.). Manuel of Clinical Microbiology 9th ed. Washinghton ASM Pres 2007:770-802.
13. Ünal S, Rodriguez JAG. Activity of meropenem and comparators against *Pseudomonas aeruginosa* and *Acinetobacter s*pp. isolated in the MYSTIC Program, 2002-2004. Diagn Microbiol Infect Dis 2005;53:265-271.
14. Looveren MV, Goossens H, ARPAC Steering Group. Antimicrobial resistance of *Acinetobacter* spp. in Europe Clin Microbiol Infect 2004;10:684-704.
15. Broek PJ, Reijden TJK, Strijen E, et al. Endemic and epidemic *Acinetobacter* species in a university hospital: an 8-year survey J Clin Microbiol 2009;47:3593-3599.
16. Dent LL, Marshall DR, Pratap S, Hulette RB. Multidrug resistant *Acinetobacter baumannii*: a descriptive study in a city hospital BMC Infect Dis 2010; 10:196.
17. Gaur A, Garg A, Prakash P, et al. Observations on carbapenem resistance by minimum inhibitory concentration in nosocomial isolates of *Acinetobacter* species: An experience at a tertiary care hospital in North India J Health Popul Nutr 2008;26:83-188.
18. Lee K, Lee MA, Lee CH, et al. Increase of ceftazidime- and fluoroquinolone-resistant *Klebsiella pneumoniae* and imipenem-resistant *Acinetobacter* spp. in Korea: Analysis of KONSAR study data from 2005 and 2007. Yonsei Med J 2010;51:901-911.
19. Ko WC, Lee NY, Su SC, et al. Oligonucleotide array-based identification of species in the *Acinetobacter calcoaceticus-A. baumannii* complex in isolates from blood cultures and antimicrobial susceptibility testing of the isolates. J Clin Microbiol 2008;46:2052-2059.
20. Eser ÖK, Ergin A, Hasçelik G. Antimicrobial resistance and existence of metallo-beta-lactamase in *Acinetobacter* species isolated from adult patients. Mikrobiyol Bul 2009;43:383-390.
21. Yüce A, Yapar N, Kutsoylu OE. Evaluation of antibiotic resistance patterns of *Pseudomonas aeruginosa* and *Acinetobacter* spp. strains isolated from intensive care patients between 2000-2002 and 2003-2006 periods in Dokuz Eylul University Hospital, Izmir. Mikrobiyol Bul 2009;43:195-202.
22. Turner PJ. Meropenem activity against European isolates: report on the MYSTIC (Meropenem Yearly Susceptibility Test Information Collection) 2006 results. Diagn Microbiol Infect Dis 2008;60:185-192.
23. Metan G, Alp E, Aygen B, Sümerkan B. Carbapenem-resistant *Acinetobacter baumannii*: an emerging threat for patients with post neurosurgical meningitis. Int J Antimicrob Agents 2007;29:112-113.
24. Alp E, Esel D, Yıldız O, et al. Genotypic analysis of *Acinetobacter* bloodstream infection isolates in a Turkish university hospital. Scand J Infect Dis 2006;38:335-340.
25. Deveci A, Coban AY, Acicbe O, et al. In vitro effects of sulbactam combinations with different antibiotic groups against clinical *Acinetobacter baumannii* isolates. J Chemother 2012;24:247-252.
26. Zhang Y, Chen F, Sun E, et al. In vitro antibacterial activity of combinations of fosfomycin, minocycline and polymyxin B on pan-drug-resistant *Acinetobacter baumannii*. Exp Ther Med 2013;5:1737-1739.
27. Joung MK, Kwon KJ, Kong CI, et al. Impact of in appropriate antimicrobial theraphy on outcome in patients with hospital-acquired pneumoniae caused by *Acinetobacter baumannii*. J Infect 2010;61:212-218.
28. Aimsaad L, Diraphat P, Utrarachkij F, et al. Epidemiological characteristics of *Acinetobacter baumannii* infections at Phramongkutklao Hospital. J Med Assoc Thai 2009;92:164-172.
29. Duenas Diez AI, Bratos Perez MA, Eiros Bouza JM, et al. Susceptibility of the *Acinetobacter calcoaceticus-A.baumannii* complex to imipenem, meropenem, sulbactam and colistin, Int J Antimicrob Agents 2004;23:487-493.
30. Michalopoulos A S, Tsiodras S, Rellos K, et al. Colistin treatment in patients with ICU-acquired infections caused by multiresistant gram-negative bacteria: the renaissance of an old antibiotic Clin Microbiol Infect 2005;11:115-121.
31. Garnacho-Montero J, Ortiz-Leyba C, Jime´nez-Jime´nez FJ, et al. Treatment of multidrug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia (VAP) with intravenous colistin: a comparison with imipenem-susceptible VAP Clin Infect Dis 2003;36:1111-1118.
32. Oztoprak N. Intensive care units infections and antimicrobial drugs. Turkiye Klinikleri J Pulm Med-Special Topics 2010;3:55-62.