Multidrug Resistance Among *A. baumannii* Isolates from Intensive Care Unit: A Four Years Retrospective Study

Yoğun Bakım Ünitesinde İzole Edilen Çok İlaca Dirençli *A. baumanni* İzolatları: Dört Yıllık Retrospektif Çalışma

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ABSTRACT Objective: *Acinetobacter baumannii (A. baumannii)* is one of the major causes of nosocomial infections and these infections have been strongly associated with increased morbidity and mortality. In this study, we aimed to evaluate the general properties of cases with nosocomial lower respiratory tract infection (LRTI) caused by *A. baumannii* and to determine the factors which effect the mortality. **Material and Methods:** We investigated clinical data of cases with nosocomial LRTI caused by *A. baumannii* treated from 2009 to 2013 in a university hospital. **Results:** We evaluated 87 patients. All *A. baumannii* isolates were resistant to gentamicin, third and fourth generation cephalosporins, and quinolones. The resistance rates to carbapenems in 2009 and 2010 were 28.6% and 33.3%, respectively. Over the last 3 years the carbapenem resistance rate was 100%. Tigecycline and colimisin resistance were identified in 3 cases. The overall mortality was 64.4%. We determined that mortality was higher in patients more than 65 years old. **Conclusions:** Carbapenem resistance has increased over the years, and in recent years, an alarming resistance has been found in all *A. baumannii* isolates. Invasive procedures performed in the intensive care unit do not affect mortality. The low resistance rate of tigecycline and colistin is the most favourable result of this study.

Key Words: Acinetobacter infections; Acinetobacter baumannii; drug resistance, bacterial; drug resistance, multiple

ÖZET Amaç: Hastane kökenli enfeksiyonlar artmış morbidite ve mortalite ile ilişkilidir ve *Acinetobacter baumannii* hastane enfeksiyonlarının en önemli etkenlerinden biridir. Bu çalışmada *A. baumannii* ile gelişen hastane kökenli alt solunum yolu enfeksiyonu (ASYE) olan olguların genel özelliklerinin değerlendirilmesi ve mortalite üzerine etkili faktörlerin belirlenmesi amaçlanmıştır. **Gereç ve Yöntemler:** Bir üniversite hastanesinde 2009-2013 yıllarında *A. baumannii* ile gelişen hastane kökenli ASYE olan olguların dosyaları incelendi. **Bulgular:** Seksen yedi hastada saptanan tüm *A. baumannii* izolatları gentamisin, üçüncü ve dördüncü kuşak sefalosporinler ve kinolonlara dirençli idi. 2009 ve 2010 yıllarında karbapenem direnç oranları sırasıyla %28.6 ve %33.3, son 3 yılda %100 idi. Tigesiklin ve kolimisin direnci 3 olguda tespit edildi. Mortalite %64.4 idi ve 65 yaşından büyük hastalarda daha yüksekti. **Sonuç:** Karbapenem direnci yıllar içinde artmıştır ve son yıllarda tüm *A. baumannii* izolatlarında endişe verici bir direnç söz konusudur. Yoğun bakımda yapılan invaziv girişimlerin mortalite üzerine etkisi yoktur. Tigesiklin ve kolistine ait düşük direnç oranı bu çalışmanın en umut verici sonucudur.

Anahtar Kelimeler: Acinetobacter enfeksiyonları; Acinetobacter baumani; ilaç direnci, bakteriyel; ilaç direnci, çoklu

Nosocomial infections are related to prolonged hospitalization stays and increased mortality and morbidity.[1] Among microorganisms, *Acinetobacter ssp* plays an important role, and in recent years its prevalence in intensive care unit (ICU) patients has risen.[2,3] *A. baumannii* is an aerobic, Gram-negative, non-fermentative bacteria, which is the most

frequently seen microorganism among *Acineto-bacter ssp* caused nosocomial infections, especially in ICU patients. It is resistant to most broad-spectrum antibiotics and maintains viability in in vitro environment and dry surfaces. *A. baumannii* is an important agent of ICU infections.[4-7] This microorganism can cause many infections such as sepsis, urinary tract infections, wound infections, ventilatory associated pneumonia, meningitis, and endocarditis and these infections have been strongly associated with increased morbidity and mortality.[8-11]

Increasing resistance to broad-spectrum antibiotics including carbapenems has been reported.[12-14] Multidrug resistance is associated with high morbidity and mortality.[15-16] Increased multidrug resistant (MDR) isolates of *A. baumannii* are probably a consequence of the extensive use of antimicrobial agents.

Comorbid diseases and invasive procedures such as tracheostomy, intubation, parenteral nutrition or central venous catheterization, previous antibiotic usage, and prolonged length of ICU/hospital stay have been identified as major risk factors related to mortality.[17-19] Nosocomial LRTI other than pneumonia represented 15.5% of ICU-acquired infections. Nosocomial lower respiratory tract infection (LRTI) are found the third-most frequent ICU-acquired infection, following pneumonia (47%) and urinary tract infections (26%).[20]

In this study, we aimed to evaluate the general properties of cases with nosocomial LRTI caused by *A. baumannii* and to determine the factors which effect the mortality. Also we aimed to determine the incidence of broad spectrum antibiotic resistance of *A. baumannii* in our internal ICU. Centers for Disease Control (CDC) definitions are used for the diagnosis of nosocomial tracheobronchitis and pneumonia.[21]

MATERIAL AND METHODS

We retrospectively evaluated 87 internal ICU patients (male/female= 56/31) with LRTI caused by *A. baumannii* from January 2009 to December 2013 at a tertiary care hospital. We defined nosocomial pneumonia and tracheobronchitis as nosocomial

LRTI. Comorbidities (chronic renal failure, congestive heart failure, chronic obstructive pulmonary disease (COPD), cerebrovascular disease, diabetes mellitus), previous antibiotic usage and invasive procedures performed in the ICU (intubation, central venous catheterization, nasal/oral gastric feeding tubes, enteral/parenteral nutrition, and cardiopulmonary resuscitation) were all noted. Invasive procedures performed proceding two days of the diagnosis was adopted for evaluation

Laboratory evaluation is considered as the last two daily values before microbiological diagnosis. Levels of serum sodium (Na), blood urea nitrogen (BUN), creatinine, albumin, hemoglobin, white blood cell (WBC), C-reactive protein (CRP) and procalcitonin (PCT) were noted.

A. baumannii was isolated from samples taken from the endotracheal tube (in intubated patients) and sputum by using conventional methods and an automated system (Phoenix, Becton Dickinson ID, USA). Antibiotic resistance was analysed with an automated system (Phoenix, Becton Dickinson ID, USA) and the Kirby-Bauer disc diffusion method. The susceptibility of isolates was determined according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI).[22]

STATISTICAL ANALYSIS

According to the Kolmogorov-Smirnov normality test, two independent sample t-test were used to compare the continuous data between the two groups. Continuous data were expressed as mean ± standard deviation (SD). For comparison to the categorical data, the chi-square test and Mann-Witney U test were used. Categorical data were expressed as counts and percentages. A univariate logistic regression model was implemented to determine the risk factors associated with mortality and carbapenem resistance. P values < 0.05 were considered statistically significant. Statistical analysis was performed using commercial software (IBM SPSS Statistics 19, SPSS Inc., an IBM Co., Somers, NY).

RESULTS

Eighty-seven ICU cases were evaluated. The mean age of the cases was 67.0 ± 12.3 years and 56

(65.1%) of them were male. The most common co-morbid diseases were COPD (n= 28), cerebrovascular disease (n= 22), diabetes mellitus (n= 16), and congestive heart failure (n = 14).

A. baumannii bacteraemia was detected in 13 of the cases. Carbapenems and amikacin resistance rates are shown in Figure 1 and Figure 2. The ratio of the resistance to amikacin in our institute was found stable over the years. We detected tigecyline resistance in 2 cases and colistin in one case.

The overall mortality rate was 64.4%. Mortality rates by year are shown in Figure 3. The highest mortality rate (92%) was found in 2012. General features of the cases according to mortality are shown in Table 1. Gender, comorbid diseases, carbapenem/amikacin resistance have found no significant effect on mortality (Table 1).

The mean age of the survivors (60.1 ± 13.5/years) was significantly lower than that of non-survivors (70.8 ± 9.8/years) (p= 0,001) and the mortality rate of patients over 65 years old was higher (70.9%) than others (45.2%) (p= 0.018).

Laboratory analysis of all cases is shown in Table 2.

There was no difference between the groups according to the laboratory assessments (Table 3). Anemia (hemoglobin< 8 g/dL) hypernatremia (Na> 145 mmol/L), hyponatremia (Na< 135 mmol/L), uremia (BUN> 30 mg/dL), hipoalbuminemia (albumin< 3.5 g/dL), and bacteremia have found no significant effect on mortality.

DISCUSSION

In this study which we evaluated cases with nosocomial LRTI caused by *A. baumannii* as expected the mean age of patients who died was higher than the survivors. Unexpectedly carbapenem resistance, invasive procedures performed in ICU and laboratory analysis had no effect on mortality.

A. baumannii has become an important pathogen in recent years, and *A. baumannii* infections cause high morbidity and mortality in ICU patients.[15,16] In our cases the overall mortality rate was 64.4% and the highest mortality rate was 92%

in 2012. The effects of this microorganism are aggravated due to increased resistance to broad-spectrum antibiotics, including carbapenems.[12-14] Several studies have been published in Turkey on *A. baumannii* resistance to broad-spectrum antibiotics. Gulhan et al. reported the resistance of *A. baumannii* in 2004-2006 as 7-25% for meropenem, 59-59% for amikacin, 80-88% for ceftazidime, 54-82% for ciprofloxacin, 83-87% for cefepime, and 78-87% for gentamicin.[23] We found higher resist-
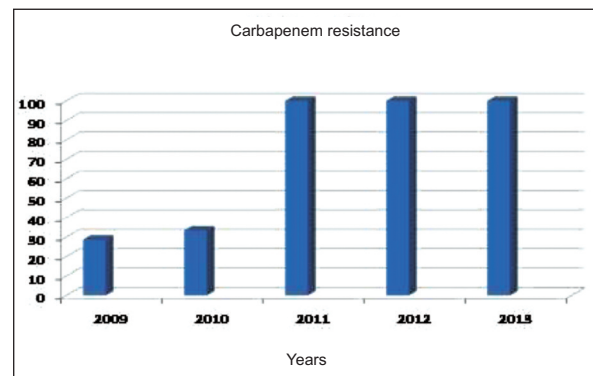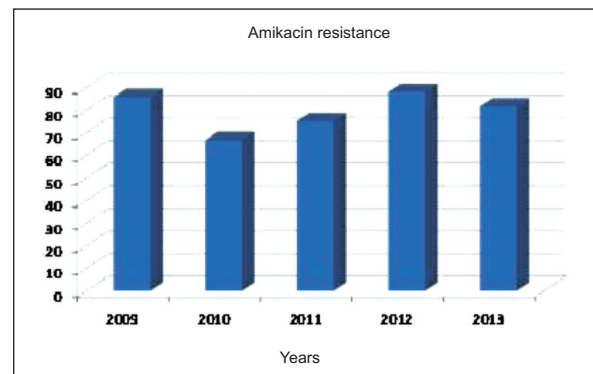

FIGURE 1: Carbapenem resistance over the years.

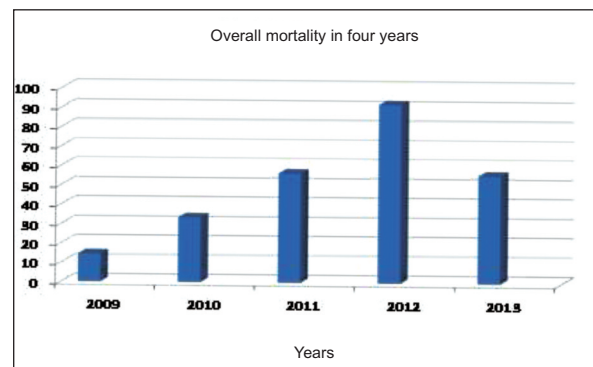**FIGURE 2:** Amikacin resistance over the years.

FIGURE 3: Overall mortality in four years.

TABLE 1: General features of the cases.			
	All cases n (%)	**Nonsurvivors n (%)**	**Survivors n (%)**	**P**
Advanced age (age > 65/ years)	53 (61.6)	39 (70.9)	14 (45.2)	0.018
Gender				0.701
Male	56 (65.1)	35 (63.6)	21 (67.7)	
Female	30 (34.9)	20 (36.4)	10 (32.3)	
Chronic cardiopulmonary disease^a	36 (41.9)	26 (47.3)	10 (32.3)	0.175
Intubation	68 (79.1)	43 (78.2)	25 (80.6)	0.787
Reintubation	23 (26.7)	15 (27.3)	8 (25.8)	0.883
Urgent intubation	25 (29.8)	17 (31.5)	8 (26.7)	0.644
Parenteral nutrition	32 (37.2)	21 (38.2)	11 (35.5)	0.804
Enteral nutrition	53 (61.6)	32 (58.2)	21 (67.7)	0.381
Oral/nasal gastric feeding tube	65 (75.6)	38 (69.3)	27 (87.1)	0.062
Central venous catheterization	35 (40.7)	23 (41.8)	12 (38.7)	0.778
Cardiopulmonary resuscitation	27 (31.8)	18 (33.3)	9 (29.0)	0.682
Carbapenem resistance*	74 (85.1)	51 (91.1)	23 (74.2)	0.057
Amikacin resistance	70 (80.5)	44 (78.6)	26 (83.9)	0.550

^aCongestive heart failure and/or chronic obstructive lung disease.

*Fisher exact chi square test (chi-square test was used for the other parameters).

TABLE 2: Laboratory analyses of the cases.			
Laboratory Analysis	**All cases (Mean ± SD)**	**Nonsurvivors (Mean ± SD)**	**Survivors (Mean ± SD)**	**p**
BUN (mg/dL) (n= 85)	37.9 ± 24.0	41.3 ± 3.2	32.0 ± 4.4	0.086
Creatinine (mg/dL) (n= 85)	1.6 ± 1.6	1.7 ± 1.7	1.3 ± 1.3	0.210
Na (mmol/L)*(n= 85)	140.4 ± 8.2	142.4 ± 8.9	138.7 ± 6.7	-
Albumin (g/dL) (n= 77)	2.6 ± 0.5	2.6 ± 0.6	2.7 ± 0.5	0.644
Hemoglobin (g/dL) (n= 85)	10.1 ± 1.7	10.2 ± 1.7	9.8 ± 1.6	0.263
WBC (n= 85)	14.3 ± 10.8	15.4 ± 12.4	12.9 ± 5.2	0.236
CRP (mg/L) (n= 84)	125.7 ± 62.2	130.4 ± 63.8	117.1 ± 59.5	0.352
PCT (ng/mL) (n= 81)	7.616 ± 17.498	7.626 ± 2.698	7.600 ± 14.294	0.995

*Mann Whitney U test was used. Chi-square test was used for the other parameters.

ance rates for both meropenem and amikacin. According to the results of MYSTIC study, in Turkey the most effective antibiotics against *Acinetobacter spp.* are carbapenems.[24] In HITIT study, higher and various resistance to broad-spectrum antibiotics were reported (ceftriaxone; 88.5-96.7%; ceftazidime; 53.9-96.7%; cefepime; 53.8-86.7%; cefoperazone sulbactam; 34.6%-46.6%; piperacillin tazobactam; 33.3-93.3% and imipenem; 38.5-60%).[25] Kuscu et al. reported carbapenem resistance at 80%.[26] In our study, *A. baumannii* resistance to broad-spectrum antibiotics was concordant with

the literature. All of the *A. baumannii* isolates were resistant to gentamicin, third- and fourth generation cephalosporins, and quinolones. In our study, an increasing resistance to carbapenems was observed over the years. Carbapenem resistance was 28.6% and 33.3% in 2009 and 2010, respectively. Also, all of the *A. baumannii* isolates since 2011 were resistant to carbapenems. Increasing carbapenem resistance is being observed worldwide. In ICUs in Greece, carbapenem resistance among *A. baumannii* rose from approximately 75% in 2005 to 95% in 2010.[27,28] Our results are also concordant with this literature.

TABLE 3: Mainly laboratory parameters of the cases according to mortality.				
Lab. parameters	All cases n (%)	Nonsurvivors n (%)	Survivors n (%)	p
Uremia (BUN> 30 mg/dl)	46 (54.8)	33 (62.3)	13 (41.9)	0.710
Hypernatremia (Na> 145 mmol/L)	32 (38.1)	23 (43.4)	9 (29.0)	0.191
Hypoalbuminemia (albumin< 2.5 g/dL)	31 (40.8)	19 (40.4)	12 (41.4)	0.934
Anemia (hemoglobin< 8 g/dL)	12 (14.1)	6 (50.0)	6 (50.0)	0.314
Bacteraemia	13 (19.4)	9 (20.5)	4 (17.4)	1.000

MDR *A. baumannii* is an important cause of hospital-acquired infection and it is associated with an increased length of hospital stay and high mortality.[9,10] MDR *A. baumannii* is defined as resistance to more than three classes of antibiotics. Dent et al. reported that MDR *Acinetobacter* is associated with significant mortality compared with sensitive strains.[29] We did not found any effect of carbapenem or amikacin resistance on the mortality rate. Aydemir et al. reported mortality rates of 61.8% and 52.7% for the carbapenem-resistant and sensitive *A. baumannii* cases, respectively. We found a higher mortality rate in both groups and our study demonstrates that patients with carbapenem-resistant *A. baumannii* (CRAB) infections have higher mortality than carbapenem-sensitive *A. baumannii* (CSAB) infections, but the difference we found was not as statistically significant as that in the study by Aydemir et al. Although Lemos et al. reported a significant difference in the mortality rate between patients with MDR isolates and those with multidrug-susceptible isolates.[17,30] Patients with CRAB pneumonia have a higher mortality rate than that from CSAB pneumonia in Zheng et al. study.[31] But we found no statistical difference between the two groups.

We did not find any effect on mortality of parenteral/enteral feeding, oral/nasal gastric feeding tubes, mechanical ventilation, cardiopulmonary resuscitation, central venous catheterization, or intubation. In several studies, parenteral nutrition, intubation and mechanical ventilation were reported as risk factors for mortality.[18,19,31,32] Although bacteraemia was identified as an independent risk factor for mortality, we were unable to find any effect on mortality.[33] Zheng et al. described chronic respiratory diseases and cerebrovascular diseases as risk factors for mortality but in our cases we did not find similar results.[31]

Several studies evaluating the effects of various laboratory tests on mortality have been published. Tasbakan et al. reported lower albumin and higher CRP levels in nonsurvival cases.[34] Zilberberg et al. reported that hyponatremia was associated with increased mortality.[35] We did not find any significant effect of laboratory parameters (Na, BUN, albumin, creatinine, hemoglobin, WBC and CRP) on mortality.

Only tigecycline and colistin are fully effective antibiotics against *A. baumannii* strains isolated in 2011 from patients with mechanical ventilation-associated pneumonia.[36] We detected tigecyline resistance in 2 cases and colistin in one case. These results were very favourable.

In conclusion; *A. baumannii* is an important pathogen in ICUs. This agent is resistant to most broad-spectrum antibiotics. Over the years, carbapenem resistance has been increasing worldwide. The mortality rate in cases with *A. baumannii* infection is very high. Invasive procedures have no apparent effect on mortality. As expected, our results showed that advanced age have increased mortality but there was no effect of comorbid diseases. Currently, tigecycline and colistin are effective agents against MDR *A. baumannii* infections in our adult ICU.

We need prospective studies with more patients for detecting antibiotic resistance in ICUs. In this study the absence of radiological findings which may be effective on mortality of the cases is a deficiency.

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