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Short Communication

Mortality Attributable to Carbapenem-Resistant Nosocomial *Acinetobacter baumannii* Infections in a Turkish University Hospital

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SUMMARY: This study was performed to compare the mortality associated with carbapenem-resistant *Acinetobacter baumannii* (CRAB) and carbapenem-sensitive *A. baumannii* (CSAB) infections, to identify potential risk factors for CRAB infections, and to investigate the effects of potential risk factors on mortality in CRAB and CSAB patients. This retrospective case-control study was conducted in a university hospital between January 1, 2005 and December 30, 2006. One hundred and ten patients with CRAB and 55 patients with CSAB infection were identified during the study period. The mortality rate was 61.8% and 52.7% in CRAB and CSAB cases, respectively ($P = 0.341$). In CRAB cases, the risk factors for mortality were identified as intubation (odds ratio [OR], 3.3; 95% confidence interval [CI], 1.0–10.1; $P = 0.042$) and high APACHE II score (OR, 1.2; 95% CI, 1.1–1.3; $P = 0.000$), by multivariate analysis. Previous use of carbapenem (OR, 6.1; 95% CI, 2.2–17.1; $P = 0.001$) or aminopenicillin (OR, 2.5; 95% CI, 1.2–5.1; $P = 0.013$) were independently associated with carbapenem resistance. Although the mortality rate was higher among patients with CRAB infections, this difference was not found to be statistically significant. Previous use of carbapenem and aminopenicillin were found to be independent risk factors for infections with CRAB.

Acinetobacter baumannii has become an increasingly prevalent cause of nosocomial infections in intensive care units (ICUs) during the past 40 years. It has intrinsic resistance to certain antimicrobial agents and has acquired resistance to many others. As a consequence of this, treatment of infections attributed to *A. baumannii* is problematic (1). Although several investigators have provided evidence that *A. baumannii* infections are associated with high mortality, some suggest that morbidity and mortality can be influenced by many variables (2–8). However, a recently published commentary suggests that mortality associated with this microorganism is no longer a controversial issue (9). Another problem associated with management of infections caused by *A. baumannii* is the resistance of the pathogen to carbapenems (10–14). Carbapenem-resistant *A. baumannii* (CRAB) is frequently isolated in ICUs of Turkish hospitals (15). For infections with resistant *Acinetobacter* strains, antibiotic choice differs from infections with susceptible strains, and treatment with appropriate antibiotics according to the resistance pattern can influence the final outcomes. In this study, we aimed to evaluate risk factors for infection with CRAB in order to enable early detection and isolation of infected patients, and treatment with appropriate empirical antibiotics. We also investigated if there is a difference in mortality rates between CRAB and carbapenem-susceptible *A. baumannii* (CSAB) infections, and the mortality risk factors for CSAB and CRAB infections.

This retrospective case-control study was conducted in Zonguldak Karaelmas University Hospital, a 350-bed referral and tertiary care hospital. Patients admitted to the wards or ICUs of this hospital between January 1, 2005 and December 30, 2006 with either CSAB or CRAB infection were included in the study. Centers for Disease Control and Prevention (CDC) criteria were used to define nosocomial infections (16,17). In cases where there was an absence of clinical and laboratory indicators of infection, patients with positive cultures for the pathogens were considered as being colonized.

Patients colonized with *A. baumannii* or those younger than 16 years old were excluded from the study. *A. baumannii* infection was considered to have been acquired nosocomially if isolates were obtained from cultures taken ≥ 48 h following hospital admission or ≤ 10 days following discharge. Microorganism detection dates relate to days when cultures were taken. Only the first isolate of a patient diagnosed with CSAB or CRAB infection was included. Since no carbapenem resistance was detected in subsequent isolates of patients with CSAB infections, these subsequent isolates were excluded. Data were collected for all patients, including demographic, clinical, and microbiological data.

Prior exposure to antimicrobial agents was defined as treatment for at least 24 h within 14 days prior to *A. baumannii* isolation. Antimicrobial therapy for each patient was classified as appropriate or inappropriate according to rational antimicrobial rules. Since, colistin and tobramycin were not available in Turkey during the

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study period, patients infected with *A. baumannii* that was resistant to all antimicrobials, other than colistin and tobramycin, could not be treated with any antimicrobial agent. Antimicrobial therapy for these patients was recorded as being inappropriate. Patients with *A. baumannii* infections were categorized either as the case group (if *A. baumannii* isolates were resistant to imipenem or meropenem) or as the control group (if *A. baumannii* isolates were susceptible to imipenem and meropenem). There was no clustering of resistant isolates at any particular time or in any particular wards to suggest that outbreaks had occurred during the study period. Samples from potential infection sites were cultured from patients with suspected infection. *A. baumannii* clinical isolates were identified by conventional techniques (18), and were also confirmed using API 20 NE, a semiautomated system (bioMérieux, Marcy l'Etoile, France). Susceptibility to antibiotics was tested using the agar disk diffusion method and data were interpreted as recommended by the Clinical Laboratory Standards Institute (CLSI) (19). Resistance to imipenem and meropenem was verified by determination of minimal inhibitory concentrations with E-tests (AB Biodisk, Solna, Sweden) (19).

Data were analyzed using the SPSS version 15 statistical package (SPSS, Chicago, Ill., USA). Mortality attributable to carbapenem resistance was defined as the crude mortality rate of control patients subtracted from that of the infected cases (20). Potential risk factors were analyzed by univariate analysis. When approparite, chi-square tests or Fisher's exact tests were used to compare proportions. Quantitative variable differences between cases and controls were compared by Mann-Whitney U tests, as appropriate. A P-value of <0.05 was considered to be statistically significant. Odds ratios (OR) were also calculated. A multiple-regression logistic model was developed to identify the potential independent factors associated with mortality in CRAB and CSAB infections. Statistically significant and clinically relevant variables were entered into the multivariate logistic regression model, with 95% confidence intervals (CIs) calculated as estimators. Stratified analysis was carried out to determine mortality for CRAB and CSAB patients with pneumonia, or infections other than pneumonia. The stepwise Cox's proportional hazard model, with time to in-hospital death as the dependent variable, was employed for multivariate analysis to identify mortality risk factors in all patients with *A. baumannii* infection. Statistically significant and clinically relevant variables, including the variable of carbapenem resistance, were entered into the Cox's proportional hazard model. Adjusted associations were measured in terms of hazard ratios (HR) and the corresponding 95% CIs.

During the study period, 110 patients with CRAB infections (case group) and 55 patients with CSAB infections (control group) were identified. The mean age was 64 ± 16.2 and 59 ± 19.2 years old for case and control groups, respectively. Fifty-one percent and 60% of patients were male in the case and control groups, respectively. No statistically significant differences were found between the two groups in terms of age or gender ($P > 0.05$). The most frequent type of infection in both groups was pneumonia (70% in the case group and 72.7% in the control group). The mortality of CRAB patients with pneumonia was higher than that of CSAB patients with pneumonia (OR, 1.6). The mortality of patients with infections other than pneumonia was also higher in CRAB than in CSAB patients (OR, 2.4). However, these differences were not statistically significant ($P = 0.648$). The crude mortality rate among case patients was 61.8%, whereas it was 52.7% among control patients. Thus, the mortality rate attributable to CRAB cases was 9.1%. Although the mortality rate was higher in the case group, this difference was not statistically significant ($P = 0.341$).

Cox's proportional hazard model was used to identify risk factors for mortality in patients with *A. baumannii* infection. Carbapenem resistance was entered into the model as a variable. No statistically significant relationship was found between carbapenem resistance and mortality in patients with *A. baumannii* infection. However, treatment with inappropriate antimicrobial agents (HR, 2.0; 95% CI, 1.3–3.1; $P = 0.001$) and high APACHE II score (HR, 1.1; 95% CI, 1.0–1.1; $P = 0.000$) were associated with increased mortality in these patients.

Using univariate analysis, it was found that among the administrated antibiotics, only carbapenems were defined as being a statistically significant variable associated with CRAB infection ($P = 0.002$). No statistically significant relationships were found between the other variables and the incidence of CRAB infections (Table 1).

Using multivariate analysis, aminopenicillin (OR, 2.5; 95% CI, 1.2–5.1; $P = 0.013$) or carbapenem (OR, 6.1; 95% CI, 2.2–17.1; $P = 0.001$) use prior to *A. baumannii* isolation was identified as being an independent risk factor for infection with CRAB.

Intubation ($P = 0.001$) and urinary catheter use ($P = 0.029$) were found to be statistically significant risk factors for mortality in the case group. Furthermore, patients treated with inappropriate antimicrobial agents had higher mortality rates than the patients who were treated with appropriate antimicrobial agents ($P = 0.016$) (Table 2).

In the control group, chronic renal failure, cerebrovascular disease, central venous catheterization, intubation, and coexistence of laboratory proven MRSA infection were all found to be risk factors for mortality (Table 3).

Using multivariate analysis, intubation (OR, 3.3; 95% CI, 1.0–10.1; $P = 0.042$) and high APACHE II score (OR, 1.2; 95% CI, 1.1–1.3; $P = 0.000$) were defined as statistically significant risk factors for mortality in the case group, whereas cerebrovascular disease (OR, 38.4; 95% CI, 1.7–879.8; $P = 0.022$), intubation (OR, 28.2; 95% CI, 2.5–314.9; $P = 0.007$), and high APACHE II score (OR, 1.2; 95% CI, 1.0–1.4; $P = 0.021$) were independent risk factors for mortality in the control group.

In surviving CRAB patients, the hospital stay after *A. baumannii* isolation was longer than that of surviving CSAB patients, but not significantly ($P = 0.061$). In the case group, APACHE II scores were significantly higher than in the controls ($P = 0.022$). APACHE II scores were also significantly higher in nonsurvivors of the CRAB group ($P = 0.000$) (Table 4).

Table 1. Univariate analysis of risk factors for infection with carbapenem-resistant *A. baumannii*

Variable	CRAB $n = 110$ no. (%)	CSAB $n = 55$ no. (%)	*P*	OR[3)]
Diabetes mellitus	52 (47.3)	22 (40)	0.472[1)]	1.345
Chronic obstructive pulmonary disease	32 (29.1)	14 (25.5)	0.759[1)]	1.201
Chronic renal failure	14 (12.7)	10 (18.2)	0.482[1)]	0.656
Essential hypertension	34 (30.9)	14 (25.5)	0.585[1)]	1.310
Congestive heart failure	17 (15.5)	6 (10.9)	0.578[1)]	1.493
Solid tumor	14 (12.7)	10 (18.2)	0.482[1)]	0.656
Hematological malignancy	1 (0.9)	1 (1.8)	1[2)]	0.495
Cerebrovascular disease	10 (9.1)	10 (18.2)	0.152[1)]	0.45
Hepatic cirrhosis	3 (2.7)	1 (1.8)	1[2)]	1.514
Chemotherapy	6 (5.5)	0 (0)	0.180	—
Steroid therapy	5 (4.5)	0 (0)	0.170	—
Usage of H_2 receptor antagonists	8 (7.3)	10 (18.2)	0.064[1)]	0.353
Coronary arterial disease	7 (6.4)	0 (0)	0.097[2)]	1.068
Central venous catheter usage	78 (70.9)	36 (65.5)	0.592[1)]	1.286
Peripheral catheter usage	76 (69.1)	40 (72.7)	0.763[1)]	0.838
Intubation	83 (75.5)	38 (69.1)	0.494[1)]	1.375
Tracheostomy	14 (12.7)	5 (9.1)	0.666[1)]	1.458
Nasogastric tube	59 (53.6)	34 (61.8)	0.405[1)]	0.715
Urinary catheter usage	104 (94.5)	52 (94.5)	1[2)]	1
Throcic, abdominal, pelvic drain	24 (21.8)	9 (16.4)	0.536[1)]	1.426
Total parenteral nutrition	22 (20)	8 (14.5)	0.521[1)]	1.469
Another infection site	53 (48.2)	20 (36.4)	0.202[1)]	1.627
Previous aminopenicillin usage	50 (45.5)	17 (30.9)	0.110[1)]	1.858
Previous cephalosporin usage	43 (39.1)	25 (45.5)	0.502[1)]	0.753
Previous fluoroquinolones usage	30 (27.3)	16 (29.1)	0.922[1)]	0.901
Previous carbapenem usage	36 (32.7)	5 (9.1)	0.002[1)]	4.868
Previous metronidazole usage	13 (11.8)	10 (18.2)	0.368[1)]	0.595
Previous glycopeptitis usage	29 (26.4)	8 (14.5)	0.135[1)]	2.091
Previous aminoglycosides usage	6 (5.5)	6 (10.9)	0.214[2)]	0.465

[1)]: Chi-square test.
[2)]: Fisher's exact test.
[3)]: Odds ratio.
CRAB, carbapenem-resistant *A. baumannii*; CSAB, carbapenem-sensitive *A. baumannii*.

A. baumannii has been reported to be one of the main causes of nosocomial infections, particularly nosocomial pneumonia and bacteremia (21–24). In this study, similar to previous studies, the most frequent type of infection in both groups was with pneumonia (15,25).

Morbidity and mortality associated with *A. baumannii* infections has been a topic of continuing controversy. Since *A. baumannii* was previously recognized as a low-virulence pathogen, it was believed that the microorganism was not be a cause of mortality (6,26,27). Reported results from the Surveillance and Control of Pathogens of Epidemiologic Importance (SCOPE) study showed that mortality in patients with bloodstream infections of *A. baumannii* was not significantly different from that of patients with bloodstream infections of other pathogens (28). However, in two recent systematic reviews of the literature, it was reported that *A. baumannii* was associated with increased mortality (9,20). The studies included in these reviews showed that the mortality of patients with *A. baumannii* infections was significantly higher than that of patients without such infections (29,30). In our study, the mortality rates of CRAB and CSAB patients were compared, and in both groups the mortality rates were found to be very high. In some previous studies, mortality rates were also found to be as high as in the present study, while in others they were not (25,31–33). The influence of carbapenem resistance on mortality is still not clear. There are few studies in the literature that compare the mortality rates of CRAB and CSAB patients (33–37). Similar to the present study, most previous studies found no significant differences between mortality rates (24,33,37). In one similar published study, although the mortality rate of the CRAB patients was significantly higher than that of CSAB patients, the authors suggested that this might not be attributable to carbapenem resistance, but rather might be associated with more severe illness, inappropriate antimicrobial therapy, or primary source of infection. They analyzed these confounding factors on the mortality rates of patients with CRAB or CSAB infections, and by controlling these variables they reported that there was no statistically significant difference in mortality rates between the two groups (35). Similar to the results of this previous study, we found statistically significant relationships between the variables of inappropriate antimicrobial treatment and high APACHE II score and mortality in our patients. However, carbapen-

Table 2. Univariate analysis of mortality risk factors in patients with carbapenem-resistant *A. baumannii* infections

Variable	CRAB		*P*	OR[3)]
	Nonsurvivor *n* = 68 no. (%)	Survivor *n* = 42 no. (%)		
Diabetes mellitus	33 (48.5)	19 (45.2)	0.889[1)]	1.141
Chronic obstructive pulmonary disease	17 (25)	15 (35.7)	0.324[1)]	0.606
Chronic renal failure	10 (14.7)	4 (9.5)	0.619[1)]	1.638
Essential hypertension	26 (38.2)	8 (19.4)	0.057[1)]	2.631
Congestive heart failure	11 (16.1)	6 (14.3)	1[1)]	1.158
Solid tumor	7 (10.3)	7 (16.7)	0.497[1)]	0.574
Hematological malignancy	1 (1.5)	0 (0)	1[2)]	—
Cerebrovascular disease	8 (11.8)	2 (4.8)	0.312[2)]	2.667
Hepatic cirrhosis	1 (1.5)	2 (4.8)	0.557[2)]	0.967
Chemotherapy	4 (5.9)	2 (4.8)	1[2)]	1.251
Steroid therapy	4 (5.9)	1 (2.4)	0.647[2)]	2.563
Use of H_2 receptor antagonists	7 (10.3)	1 (2.4)	0.151[2)]	4.705
Coronary arterial disease	6 (8.8)	1 (2.4)	0.248[2)]	3.968
Central venous catheter usage	49 (72)	29 (69)	0.903[2)]	1.156
Peripheral catheter usage	47 (69)	29 (69)	1[1)]	1.003
Intubation	60 (88.2)	23 (54.8)	0.001[1)]	6.961
Tracheostomy	7 (10.3)	7 (16.7)	0.497[1)]	1
Nasogastric tube	40 (58.8)	19 (45.2)	0.234[1)]	1.729
Urinary catheter usage	67 (98.5)	37 (88)	0.029[2)]	—
Thoracic, abdominal, pelvic drain	15 (22)	9 (21.4)	1[1)]	1.038
Total parenteral nutrition	17 (25)	5 (11.9)	0.155[1)]	2.467
Another infection site	33 (48.5)	20 (47.6)	1[1)]	1.037
Polymicrobial specimen	12 (17.6)	10 (23.8)	0.589[1)]	0.685
MRSA infection	12 (17.6)	4 (9.5)	0.370[1)]	2.035
Inappropriate antibiotic therapy	35 (51.5)	11 (26.2)	0.016[1)]	2.9

Footnotes are in Table 1.

Table 3. Univariate analysis of mortality risk factors in patients with carbapenem-sensitive *A. baumannii* infections

Variable	CSAB		*P*	OR[3)]
	Nonsurvivor *n* = 29 no. (%)	Survivor *n* = 26 no. (%)		
Diabetes mellitus	12 (41.4)	10 (38.5)	1[1)]	1.129
Chronic obstructive pulmonary disease	5 (17.2)	9 (34.6)	0.243[1)]	0.394
Chronic renal failure	9 (31)	1 (3.8)	0.013[2)]	11.250
Essential hypertension	9 (31)	5 (19.2)	0.488[1)]	1.891
Congestive heart failure	3 (10.3)	3 (11.5)	1[2)]	0.885
Solid tumour	7 (24.1)	3 (11.5)	0.303[2)]	2.439
Hematological malignancy	1 (3.4)	0 (0)	1[2)]	—
Cerebrovascular diseae	9 (31)	1 (3.8)	0.013[2)]	11.250
Hepatic cirrhosis	0 (0)	1 (3.8)	0.473[2)]	—
Use of H_2 receptor antagonists	5 (17.2)	5 (19.2)	1[2)]	0.875
Central venous catheter usage	23 (79.3)	13 (50)	0.046[1)]	3.833
Peripheral catheter usage	21 (72.4)	19 (73)	1[1)]	0.967
Intubation	26 (89.7)	12 (46.1)	0.001[1)]	10.111
Tracheostomy	3 (10.3)	2 (7.7)	1[2)]	1.385
Nasogastric tube	20 (69)	14 (53.8)	0.382[1)]	1.905
Urinary catheter usage	29 (100)	23 (88.5)	0.099[2)]	—
Thoracic, abdominal, pelvic drain	4 (13.8)	5 (19.2)	0.721[2)]	1
Another infection site	14 (48.3)	6 (23)	0.097[1)]	3.110
Total parenteral nutrition	4 (13.8)	4 (15.4)	1[2)]	1
Polymicrobial specimen	6 (20.7)	4 (15.4)	0.733[2)]	1.435
MRSA infection	8 (27.6)	1 (3.8)	0.027[2)]	9.523
Inappropriate antibiotic therapy	5 (17.2)	1 (3.8)	0.197[2)]	0.192

Footnotes are in Table 1.

Table 4. Quantitative variable differences between patients with carbapenem-resistant *A. baumannii* and carbapenem-sensitive *A. baumannii* infections

	No.	Mean	SD	*P*
Duration of hospital stay prior to *A. baumannii* isolation (days)				
CRAB	110	18.1	14.0	
CSAB	55	15.7	12.3	0.219
Duration of hospital stay after *A. baumannii* isolation (days)				
CRAB	110	22.4	29.1	
CSAB	55	16.5	17.1	0.671
Duration of hospital stay after *A. baumannii* isolation (days)				
CRAB (survivor)	42	32.8	31.3	
CSAB (survivor)	26	20.2	17.8	0.061
Duration of ICU stay prior to *A. baumannii* isolation (days)				
CRAB	101	11.8	11.6	
CSAB	54	10.3	9.9	0.333
APACHE II score				
CRAB	110	21.0	7.7	
CSAB	55	18.6	6.7	0.022
CRAB (nonsurvivor)	68	24.1	6.3	
CRAB (survivor)	42	16.0	7.2	0.000

SD, standard deviation.

em resistance was not associated with mortality. In a recently published study, significantly higher mortality rates were found in patients with CRAB infections (36). While intubation and high APACHE II score were independent risk factors for mortality in patients with CRAB infections, cerebrovascular disease, intubation, and high APACHE II score were independent risk factors for mortality in patients with CSAB infections.

The spread of multiresistant *A. baumannii* infections is a major threat to hospitalized patients. Recent studies have identified many risk factors for CRAB infection, including previous ICU stay, prior exposure to third-generation cephalosporins, carbapenems and aminoglycosides, intravenous and intraarterial catheters, mechanical ventilation, surgical treatment, female gender, administration of total parenteral nutrition, urinary catheters, and use of nasogastric tubes (15,24,38–40). In the present study, previous use of carbapenem and aminopenicillin were found to be independent risk factors for CRAB infection. Although one previous study did not find carbapenem to be a risk factor, our study is in agreement with many others that found it to be so (15,24,33,38–40).

In conclusion, our study demonstrates that although patients with CRAB infections have higher mortality rates than those with CSAB infections, this difference is not statistically significant. However, it should be noted that the sample size of the present study was small and further case-control studies, with increased patient numbers, are needed to more fully address this issue. Similar to previous studies, we found prior use of carbapenem to be one of the most common risk factors for infection with CRAB.

Conflict of interest None to declare.

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