RESEARCH ARTICLE

Risk factors and attributable mortality of carbapenem-resistant acinetobacter baumannii infections.

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Abstract

Background: The incidence density, the risk factors and the attributable mortality of carbapenem-resistant Acinetobacter baumannii (CR-AB) infections are rarely investigated. Aim: The aim of the present study was to determine the risk factors for CR-AB infection and to investigate whether CR-AB infection significantly increases the 28-day ICU mortality rate.

Methods: A matched case-control study was conducted at the Medical/Surgical intensive care unit (ICU) of "SOTIRIA" general hospital in Athens, Greece from January 2009 to March 2010. Out of 156 ICU-admitted patients, 50 case-control pairs were selected. Cases were patients who acquired microbiologically documented CR-AB infection, while control patients without A. baumannii infection and were matched to the cases on APACHE II score, age, and length of ICU stay. Results: The incidence density of CR-AB infections was 16.8 /1000 ICU days. Multivariate conditional logistic regression analysis showed that the previous exposure to more than three different antibiotic classes was the only independent risk factor for the development of CR-AB (OR=34.0, 95% CI=2.22-522, P=0.01). The 28-day ICU mortality rates for cases and controls were 54% and 52%, respectively. Thus, the crude attributable mortality for CR-AB infections was 0.02 (95% CI=-0.18-0.22, P=0.84). Multivariate logistic regression analysis showed that CR-AB infection was not an independent predictor for 28-day ICU mortality rate (OR=1.40, 95% CI=0.46-4.22,P=0.55).

Conclusions: Previous exposure to more than three different antibiotic classes was independently and significantly associated with the development of CR-AB. CR-AB infection was not associated with 28-day ICU mortality.

Keywords: Acinetobacter baumannii, carbapenem resistance, nosocomial infection, mortality, ICU

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Introduction

Carbapenem resistance in Acinetobacter spp has emerged as a significant health problem over the last decade, leaving limited option for antimicrobial therapy.[1] Surveillance studies indicate that the percentage of carbapenem-resistant isolates gradually increased over the last years in Europe, North America and Latin America.[1] The proportion of imipenem-resistant A. baumannii isolates at tertiary-care hospitals in Greece was 84,5% for intensive care units (ICU), 84,1% for surgical wards and 75,1% for medical wards between January and June 2010 (Greek system for Surveillance of Antimicrobial Resistance, GSSAR.

CR-AB infections can extend ICU stay and hospital stay 15 and 30 days, respectively and have an attributable hospital mortality of 20% and ICU mortality of 4%.[2]

Hospital CR-AB outbreaks have been described previously.[3,4] Few case-control studies have been performed to determine risk factors of CR-AB infection. [2,3,5,6] Identified risk factors include blood transfusion, colonization density,[2] severity of disease, high TISS-28 score,[3] prolonged hospital stay, previous ICU stay, prior antibiotic exposure including exposure to aminoglycosides, carbapenems[5] and third - generation cephalosporins.[6]

In addition, controversy exists regarding the mortality attributable to CR-AB.[2,5] More data regarding the risk factors for CR-AB infection are needed in order to prevent CR-AB infection and to optimize therapy.

The aim of our study was to determine the risk factors for CR-AB infection and to investigate whether CR-AB infection significantly increases the 28-day ICU mortality rate.

Methods

Study Population

This study was conducted from January 2009 to March 2010 at the eight-bed Medical-Surgical ICU of "SOTIRIA" general hospital in Athens, Greece. During this period, all adults patients admitted to ICU and ventilated for at least 48 hours were included in the study. Comparisons were made between patients with CR-AB infections and patients without A. baumannii (AB) infections. All patients who acquired microbiologically documented CR-AB infection ≥48 hours after ICU admission were defined as case patients. Patients without microbiologically documented AB infection were defined as control patients. The controls were randomly chosen from the list of all ICU patients without AB infections during the study period. One control was individually matched to each case based on APACHE (Acute Physiology And Chronic Health Evaluation) II score (±5 points), age (±5years), and length of ICU stay (±2days) before onset of CR-AB infection (for cases) or before ICU discharge (for controls). During the study period, 53 of 156 patients met the case definition. Three of the cases were excluded from the study because it was not possible to find appropriate controls for them. Another five patients with carbapenem sensitive Acinetobacter baumannii (CS-AB) infection were excluded from the study. A total of 50 case-control pairs were the analysis population.

Data Collection

Surveillance of CR-AB infections included daily clinical examination of the patients, daily reviewing of the patient's medical record, Kardex data, and all microbiological data of a positive blood culture result. Data were recorded on individual forms for each patient. The form included age, gender, cigarette smoking, alcohol intake, obesity, disease severity determined by the Acute Physiology and Chronic Health Evaluation (APACHE) II score at admission, co-morbidity determined by the weighted Charlson co-morbidity index at the time of admission diagnosis, transfer from another hospital or ward to the ICU, indwelling devices, culture and antimicrobial susceptibility test results, length of ICU stay and time between admission and isolation of the first positive A. baumannii culture. Prior exposures to antibiotics and other drugs were also recorded. All data were recorded by a well trained research nurse and reviewed by an infectious disease specialist. The study protocol was approved by the ethical committee of the hospital, in which the study was conducted.

Definitions

Health care-associated infections were defined according to the criteria of the Centers for Disease Control and Prevention.[7] Infection was confirmed in each patient by the physician in charge of his or

her care. Until the microbiological documentation of micro-organisms, all patients received empirical antibiotic treatment based on the most common isolated pathogens in our ICU (A. baumannii and Pseudomonas aeruginosa). Attributable 28-day ICU mortality was calculated by subtracting the mortality of the controls from that of the cases. The 28-day ICU mortality ratio was defined as the ratio of the mortality of cases to that of the controls. Prior exposure to antibiotics was defined as the receipt of a systemic antimicrobial agent for at least 48-hour during the 14-day period prior to isolation of A. baumannii. CR-AB was defined if an A. baumannii isolate was resistant to both imipenem and meropenem.

Microbiological Analysis

Antimicrobial susceptibilities were determined by disk diffusion method and an automated method (bioMerieux, Vitek II, France). Isolates resistant to imipenem and meropenem (minimum inhibitory concentration>8mg/L) were considered carbapenem-resistant regardless of their susceptibility to other antibiotics. Intermediately susceptible strains were accepted as resistant.

Statistical analysis

Potential risk factors for CR-AB infections were tested using univariate and multivariate conditional logistic regression analysis in 50 cases with CR-AB infection and 50 controls without AB infection. Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables were expressed as a percentage of the total number of patients analyzed. Variables with a P-value less than 0.2 in the univariate analysis were entered into the multivariate analysis. The association between CRAB infection and death at the ICU was tested using univariate and multivariate logistic regression models after controlling for several confounders and checking for co linearity. All tests were two-tailed and a p-value below 0.05 was considered significant. Odds ratios (OR) and 95% confidence intervals (95% CI) were computed. All statistical analyses were performed using SPSS version 16.

Results

During the study period, a total of 156 patients with 3.151 patient days were hospitalized in the ICU. The incidence of CR-AB infection was 33.9% and the incidence density was 16.8 cases/1000 ICU days. The most frequent types of infections were ventilator-associated pneumonia (70%), blood stream infections (24%), and catheter associated urinary tract infections (6%).

All isolates were susceptible to colistin. The resistance rates to tigecycline, amikacin/gentamycin and ampicillin-sulbactam were 62%, 72%, and 64% respectively.

Out of the total of 156 hospitalized patients, 50 case-control pairs were studied. The mean age of patients with CR-AB and without AB infection was 67.5±13.8 and 68.7 ±14,5 years respectively. The mean APACHE II score at admission of patients with CR-AB and without AB infection was 16.6±5.2 and 16.3±4.5 respectively. The mean length of ICU stay for the cases before onset of CR-AB infection was 13.9±7.6 days and the mean length of ICU stay after onset of CR-AB infection was 17.6±16.0 days. The overall mean length of ICU stay of patients with CR-AB and without AB infection was 29.7±18.7 and 14.9±10.1 days, respectively.

Tables 1 and 2 show the univariate conditional logistic regression analysis of the potential risk factors for CR-AB infection related to clinical characteristics, invasive procedures and prior therapy. Tobacco smoking (p=0.19), Charlson co-morbidity index larger than two points (p=0.04), diabetes mellitus (p=0.14), intra-abdominal surgery (P=0.07) and cardiovascular disease as a reason for ICU admission (p=0.18), use of gastric ulcer prophylaxis medications (p=0.15) and previous administration of more than three antibiotic classes (p=0.01) were risk factors for CR-AB infection at the 0.20 p-value level. Receipt of carbapenem was not a risk factor for CR-AB

infection (p=0.53).

When all these variables were inserted into a multivariate conditional logistic regression model, only previous administration of more than three antibiotic classes (OR=34.0, 95% CI 2.22-522, P=0.01) was an independent risk factor for CR-AB infection (data not shown).

The overall mortality was 42% on day 14, and 54% on day 28. A total of 27 of 50 patients (54%) with CR-AB infection died within 28-ICU days, and 26 of 50 (52%) without CR-AB died. The crude 28-day ICU attributable mortality was 0.02, (95% CI=-0.18, 0.22, P=0.84).

Tables 3 and 4 show the univariate logistic regression analysis of risk factors for 28-day ICU mortality related to clinical characteristics, invasive procedures and prior therapy. Only APACHE II score at admission (p=0.002), haemodialysis (p=0.01), tracheostomy (P=0.005), and use of gastric ulcer prophylaxis medications (p=0.03) were significantly associated with 28-day ICU mortality.

The crude 28-day ICU mortality ratio for CR-AB vs. no AB infection was 1.08 (95% CI 0.49-2.38, P=0.84). When we adjusted this association for all the variables that were associated at the p-value level of 0.20 either with CR-AB infection or with mortality, CR-AB infection was still not associated with death at the ICU (OR=1.40, 95% CI 0.46-4.22, P=0.55). However, in that same model, APACHE II score at admission (OR=1.13, 95% CI 1.00-1.28, P=0.05), presence of tracheostomy (OR=0.04, 95% CI 0.004-0.35 P=0.004), and use of gastric ulcer prophylaxis drugs (OR=6.65, 95% CI 1.10-40.0, P=0.04) were significantly associated with 28-day ICU mortality (data not shown).

Discussion

In 2001, the International Network for the Study and Prevention of Emerging Antimicrobial Resistance (INSPEAR) defined the emergence of carbapenem resistance in Acinetobacter species as a sentinel event, warranting prompt epidemiological and microbiological interventions.[8] Carbapenem resistance has also become a great concern for the treatment of serious Acinetobacter infections due to concomitant resistance against multiple antimicrobial agents.

Few data exist on the incidence and incidence density of CR-AB infection. In the present study, the incidence (33.9%) and incidence density of CR-AB infection (16.8 /1000 patient-days) were quite high. In contrast, low incidence rates of CR-AB infection (4.6%) were found in other studies.[2] This difference likely reflects variation in the characteristics of the cases, diagnostic strategies or infection definitions, and highlights the development and implementation of a multidisciplinary approach and a comprehensive infection control program ('bundle'), the importance of which has been demonstrated in many studies.[4]

Few case-control studies have been performed to determine the risk factors specific for CR-AB infections. Risk factors of CR-AB infection include not only prior exposure to antibiotics, but also variable related to host defenses.[2,3,5,6] In our study, the previous exposure to more than three different antibiotic classes was the only independent risk factor for CR-AB infection. The risk for CR-AB infections was 34 times higher for patients who received more than three different antibiotic classes. The identification of previous antibiotic selection pressure: exposure to more than three different antibiotic classes as a risk factor is not unexpected. It has also been observed by Playford and colleagues for the acquisition of CR-AB[2] and by Depuydt and colleagues in patients with multidrug resistance ventilator-associated pneumonia.[9] These findings emphasize the importance of continued surveillance of microorganisms and antimicrobial agents to provide clinicians with information for choosing empirical therapy and revision of

antimicrobial prescribing policies.

Furthermore, the lack of association between CR-AB infection and specific antibiotic classes, including carbapenemes is consistent with previous studies[2,10,11] and may reflect the high prevalence of the carbapenem resistant strains in our ICU, or the large diversity of antibiotic usage. Treatment with a large number of broad-spectrum antibiotics is a surrogate marker of disease severity[12-14] and could ablate a patient's pre-existing microflora.[2]

The influence of carbapenem resistance on the mortality of patients infected with A. baumannii is still subject to debate because of methodological heterogeneity among studies. Some studies have reported that CR-AB infection is associated with significantly increased mortality rate.[5,15-17] However, other studies have found no significant difference in mortality between patients with ventilator-associated pneumonia (VAP) and bacteremia caused by CR-AB compared to patients with VAP and bacteremia due to CS-AB isolates.[18-20] Similarly, Daniels and colleagues in a retrospective, propensity score matched study have reported that the 28-day mortality of patients with MDR A. baumannii HCAI was not significantly different from that of patients with non–MDR A. baumannii HCAI (4.8%).[21] Sunenshine and colleagues[22] conducted also a retrospective cohort study to examine outcome of patients with MDR Acinetobacter infection compared with patients with susceptible Acinetobacter infections and patients without Acinetobacter infections. They demonstrated that patients infected with MDR strains of Acinetocter have longer lengths of stay in both the hospital and ICU than patients infected with drug-susceptible Acinetobacter and patients without Acinetobacter infection when they controlled for severity of disease. They also found a trend toward increased mortality rates among patients with MDR Acinetobacter infection. However, the difference was not statistically significant when they controlled for severity of disease. Our matched case-control study examined the 28-day ICU mortality rate of patients with CR-AB infections compared with patients without AB infections and demonstrated that CR-AB infections are not independently associated with increased 28-day ICU mortality. These results should be interpreted with caution because of the small patient number and highlight the need for multicentre studies involving a larger number of patients to advance our understanding of the mortality associated with CR-AB infection. Additionally, the non significant attributable mortality for CR-AB infection could reflect the administration of appropriate antibiotic therapy, the importance of which has been demonstrated in many studies.[23-25]

An important finding in the present study was that the high crude 28-day ICU mortality rate (54%) of patients with CR-AB infection, which could be attributed to the underlying disease severity, as the 28-day ICU mortality in the control group was also high (52%).[26] These findings justify the effort to reduce the nosocomial transmission of CR-AB. In addition to the decreased mortality and the economic benefits that would result from reducing CR-AB infections, such efforts may also provide benefits in reducing the risk of transmission of other multiresistant organisms and the use of broad-spectrum antibiotics.

Finally, in consistence with other studies,[27,28] it was found that CR-AB infection was not associated with 28-day ICU mortality. However, APACHE II score at admission, use of gastric ulcer prophylaxis drugs were significantly associated with 28-day ICU mortality in a multivariate model. These factors related to disease severity and are largely unmodifiable. The protective relationship between tracheotomy and ICU mortality highlights the benefits of tracheotomy and such invasive procedures should be encouraged in order to decrease the high 28-day ICU mortality of studied population.

The strengths of our study were the sound selection of controls matched to the cases on

APACHE score, age and length of ICU stay that limit the possibility of selection bias, and the study of multiple risk factors for CR-AB infection. We had also several potential limitations. The sample was relatively small and this led to several large confidence intervals, although this is a common problem in studies assessing risk factors for infections because of multidrug-resistant microorganisms. Moreover, the study was performed at one ICU, and the results may not be generalized to other settings. Our findings highlight the need for a multicentre study involving a larger number of patients.

Conclusion

In conclusion, this matched case-control study verified a large incidence, incidence density and 28-day ICU mortality due to CR-AB infection, which justify the continued study of this common infectious disease problem. Previous exposure to more than three different antibiotic classes was the only independent risk factor for the development of CR-AB infection. CR-AB infection was not associated with 28-day ICU mortality before or after adjustment for several other risk factors. Special attention should be paid to infection control practices and prudent antibiotic use in ICUs, where CR-AB infections are endemic. Large multicentre studies of CR-AB infection are further warranted.

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ANNEX

Table1. Univariate conditional logistic regression analysis of risk factors for CR-AB infection related to clinical characteristics

Risk factors	Patients with CRAB infection, n (%)	Patients without AB infection, n (%)	OR	95% CI	P-value
Demographics					
Male	31 (62%)	32 (64%)	1.20	0.37-3.93	0.76
Alcohol	3 (6%)	7 (14%)	0.43	0.11-1.66	0.22
Tobacco	10 (20%)	16 (32%)	0.54	0.21-1.35	0.19
Obesity	3 (6%)	2 (4%)	1.50	0.25-8.98	0.66
Admission from medical ward	29 (58%)	22 (44%)	1.64	0.77-3.46	0.20
Underline diseases					
Charlson index>2 points	18 (36%)	9 (18%)	3.25	1.06-9.97	0.04
Diabetes mellitus	13 (26%)	7 (14%)	2.20	0.76-6.33	0.14
Malignancy	7 (14%)	4 (8%)	2.00	0.50-8.00	0.33
Arterial hypertension	15 (30%)	13 (26%)	1.22	0.51-2.95	0.66
Cause of ICU admission					
Respiratory failure	39 (78%)	40 (80%)	0.88	0.32-2.41	0.80
Intra-abdominal surgery	7 (14%)	1 (2%)	7.00	0.86-56.9	0.07
Cardiovascular disease	3 (6%)	7 (14%)	0.33	0.07-1.65	0.18
Multiple injury	1 (2%)	2 (4%)	0.50	0.05-5.51	0.57
Invasive procedures					
Bronchoscopy	11 (22%)	8 (16%)	1.60	0.52-4.89	0.41
Tube thoracostomy	6 (12%)	5 (10%)	1.20	0.37-3.93	0.76
Haemodialysis	11 (22%)	9 (18%)	1.25	0.49-3.17	0.64
Tracheostomy	8 (16%)	6 (12%)	1.40	0.44-4.41	0.57

OR=odds ratio; 95% CI=confidence interval;

Table2. Univariate conditional logistic regression analysis of risk factors for CR-AB infection related to prior therapy

Risk factors	**Patients with CR-AB infection, n (%)**	**Patients without AB infection, n (%)**	**OR**	**95% CI**	**P-value**
Previous special treatments					
Blood transfusion	17 (34%)	19 (38%)	0.83	0.36-1.93	0.67
Gastric ulcer prophylaxis	41 (82%)	46 (92%)	0.38	0.10-1.41	0.15
Previous antibiotic use					
> 3 antibiotics classes	47 (94%)	34 (68%)	14.0	1.84-107	0.01
Anti-Pseudomonas penicillins	30 (60%)	29 (58%)	1.27	0.58-2.80	0.55
Ampicillin-Sulbactam	8 (16%)	9 (18%)	0.88	0.32-2.41	0.80
3rd generation cephalosporins	11 (22%)	8 (16%)	1.50	0.53-4.21	0.44
Quinolones	18 (36%)	22 (44%)	0.75	0.35-1.59	0.45
Metronidazole	10 (20%)	6 (12%)	2.33	0.60-9.02	0.22
Clintamycin	7 (14%)	9 (18%)	0.75	0.26-2.16	0.59
Glycopeptides	13 (26%)	14 (28%)	0.91	0.39-2.14	0.83
Carbapenemes	24 (48%)	27 (52%)	0.77	0.34-1.75	0.53
Aminiglycosides	11 (22%)	12 (24%)	0.89	0.34-2.30	0.81

OR=odds ratio; 95% CI=confidence interval;

Table 3. Univariate logistic regression analysis of risk factors for 28-day ICU mortality related to clinical characteristics

Risk factors	**Non survivors N=53 (%)**	**Survivors N=47 (%)**	**OR**	**95% CI**	**P value**
Demographics					
Sex					
Male	36 (67.9%)	27 (57.4%)	0.63	0.28-1.43	0.28
Female	17 (32.1%)	20 (42.6%)			
Age (mean ±SD)	69.87±12.83	66.13±15.31	1.01	0.99-1.04	0.18
APACHE II score (mean ±SD)	17.92±4.66	14.74±4.56	1.16	1,06-1.29	0.002
Alcohol	7 (13.2%)	3 (6.4%)	2.23	0.54-9.18	0.26
Tobacco	17 (32.1%)	9 (19.1%)	1.99	0.78-5.04	0.14
Obesity	3 (5.7%)	2 (4.3%)	1.35	0.21-8.44	0.74
Admission from community	6 (11.3%)	10 (21.3%)	0.15	0.15-141	0.18
Underline diseases					
Charlson co morbidity index>2 points	14 (26.4%)	13 (27.7%)	0.93	0.38-2.27	0.88
Diabetes mellitus	12 (22.6%)	8 (17.1%)	1.42	0.52-3.86	0.48
Malignancy	6 (11.3%)	5 (10.6%)	1.07	0.30-3.37	0.91
Arterial hypertension	16 (30.2%)	12 (25,5%)	1.26	0.52-0.34	0.60
CR-AB infection	27 (50.9%)	23 (48.9%)	1.08	0.49-2.37	0.84
Cause of admission					
Respiratory failure	41 (77.4%)	38 (80.9%)	0.80	0.30-2.13	0.66
Intra-abdominal surgery	5 (9.4%)	3 (6.4%)	7.52	0.34-6.77	0.57
Cardiovascular disease	6 (11.3%)	4 (8.5)	0.39	0.09-161	0.64
Multiple injury	1 (1.9%)	2 (4.3%)	0.43	0.03-4.93	0.50
Invasive procedures					
Bronchoscopy	8 (15.1%)	11 (23.4%)	0.58	0.21-1.59	0.29
Tube thoracostomy	7 (13.2%)	4 (8.5%)	1.63	0.44-5.98	0.45
Haemodialysis	16 (30.2%)	4 (8.5%)	4.64	0.48-3.43	0.01
Tracheostomy	22 (4I.5%)	33 (70,2%)	0.30	0.13-0.69	<0.001

OR=odds ratio; 95% CI=confidence interval;

Table 4. Univariate logistic regression analysis of risk factors for 28-day ICU mortality related to prior therapy

Risk factors	**Non survivors N=53 (%)**	**Survivors N=47 (%)**	**OR**	**95% CI**	**P value**
Previous special treatments					
Blood transfusion	18 (34%)	18 (38.8%)	0.82	0.36-1.87	0.65
Gastric ulcer prophylaxis	50 (94.3%)	37 (78.7%)	4.50	1.15-17.52	0.03
Sedatives	43 (81.1%)	36 (76.6%)	1.31	0.50-3.44	0.57
Inotropic drugs	44 (83%)	32 (68.1%)	2.29	0.89-5.88	0.08
Corticosteroids	26 (49.1%)	20 (42.6%)	1.30	0.59-2.86	0.51
Prior antibiotic use					
No antibiotics classes>3	42 (79.2%)	39 (83%)	0.78	0.28-2.15	0.63
Anti-Pseudomonas penicillins	31 (58.5%)	26 (55.3%)	1.13	0.51-2.51	0.74
Ampicillin-Sulbactam	7 (13.2%)	10 (21.3%)	0.56	1.19-1.62	0.28
Third-generation cephalosporins	8 (15.1%)	11 (23.4%)	0.58	0.70-6.11	0.29
Quinolones	19 (35.8%)	21 (44.7%)	0.69	0.31-1.54	0.36
Metronidazole	9 (17%)	7 (14.9%)	1.16	0.39-3.43	0.77
Clintamycin	7 (13.2%)	9 (19.1%)	0.64	0.21-1.88	0.42
Glycopeptides	16 (30.2%)	11 (23.9%)	1.37	0.56-3.37	0.48
Carbapenemes	29 (54.7%)	22 (46.8%)	1.37	0.42-2.02	0.43
Aminoglycosides	10 (18.9%)	13 (27.7%)	0.60	0.23-1.55	0.29

OR=odds ratio; 95% CI=confidence interval;