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Original Article

Risk factors for hospital infections caused by carbapanem-resistant *Acinetobacter baumannii*

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Abstract

Introduction: *Acinetobacter baumannii* is one of major causative agents of severe, life-threatening hospital infections (HIs), especially in intensive care units (ICUs). Our aim was to discover the risk factors associated with the emergence of HIs caused by carbapenem-resistant *Acinetobacter baumannii* (CRAB), as well as those associated with death in patients who suffer from such infections.

Methodology: A prospective cohort study was conducted over a five-year period in the medical-surgical ICU of the Clinical Centre in Kragujevac, Serbia. The study group comprised patients who had HIs caused by CRAB, while the control group comprised patients infected with carbapenem-sensitive *Acinetobacter baumannii*.

Results: In total, 137 patients developed HIs caused by *Acinetobacter baumannii.* The mean age of the patients was 59.65 ± 16.08 years, and 99 (72.26%) of them were males. In 95 patients (69.35%), the infection was caused by CRAB. There were six independent risk factors for CRAB infections: use of mechanical ventilation, previous stay in another department, stay in ICU for more than a month, and previous use of carbapenems, aminoglycosides, and metronidazole. Three independent risk factors were found for death in patients with HIs caused by CRAB: use of mechanical ventilation, previous stay in another department, and previous use of carbapenems.

Conclusions: The results of this study can be helpful when identifying patients with risk of HIs caused by CRAB and in planning preventive measures. Modification of known risk factors and appropriate institutional policy of antibiotic utilization are important measures that may decrease the incidence and mortality of such infections.

Key words: *Acinetobacter baumannii*; carbapenems; hospital infections; risk factors.

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Introduction

Modern medicine is facing growing problems related to hospital infections (HIs) caused by microorganisms resistant to available antibiotics. An important example of such a microorganism is *Acinetobacter baumannii (A. baumannii)*, which rapidly develops resistance to multiple antimicrobial drugs [1]. *A. baumannii* became a major causative agent of severe, life-threatening HIs such as pneumonia, wound infections, meningitis, urinary tract infections, central venous catheter-related infections, and bacteremia, especially in intensive care units (ICUs) [2-5].

Carbapenems are the antibiotics of choice for treatment of serious infections caused by *A. baumannii.* However, there are several studies that report a constant increase of carbapenem-resistant strains of *A. baumannii* (CRAB) causing HIs. An additional problem is the multidrug-resistant nature of such isolates, which further complicates treatment of HIs due to the limited choice of effective antibiotics.

Only a handful of studies have dealt with risk factors associated with HIs caused by CRAB. Previous studies have focused mainly on outbreaks of *A. baumannii* and did not discriminate between colonized and infected patients [6,7]. Additional knowledge is required about prevention of HIs caused by *A. baumannii* and the optimal choice of therapy.

The aim of our study was to discover the risk factors associated with the emergence of HIs caused by CRAB, as well as those associated with death in patients who suffer from such HIs.

Methodology

A prospective cohort study was conducted during the period 1 January 2011 to 31 December 2015 in the medical-surgical ICU of the Clinical Centre in Kragujevac, Serbia, which has 18 hospital beds and is attended annually by about 850 critically ill patients. During this period, all adult patients (over 18 years of age) admitted to the ICU who developed HIs caused by *A. baumannii* of any localization were included in the study. The criterion for exclusion was the isolation of pathogens within 48 hours after admission to an ICU. In addition, if microbiological tests were repeated on the samples from the same location, only the first isolate was analyzed.

The study group comprised patients who had HIs caused by CRAB, while the control group comprised patients infected with *A. baumannii* sensitive to carbapenems (CSAB).

Diagnosis of HIs caused by *A. baumannii* and their anatomical localization in each patient were assessed according to the criteria of the Centers for Disease Control (CDC) [8]. Surveillance of HIs included daily clinical examination of the patients and daily review of the patient's medical record and all microbiological and laboratory data. In order to exclude patients colonized with *A. baumannii*, each of the cases was analyzed by the study group, and more complex cases were evaluated by a special study group composed of three independent experts in infectious diseases. Each patient was followed to the final outcome (cure and discharge from hospital or death).

Data on potential risk factors were recorded on individual forms for each patient and included the following: (i.) intrinsic factors: gender, age, the existence of co-morbidities or conditions (diabetes mellitus, cancers of different localization, injury, hypertension); and (ii.) factors related to healthcare: previous hospitalization in another ward of the same hospital, urgent admission, dates of admission and discharge (both at hospital and ICU), diagnostic and therapeutic procedures performed on a patient (venous catheters, urinary catheter, mechanical ventialtion, surgery), date of the first isolation of positive *A. baumannii* culture, and data about administered antibiotics. Prior exposure to antibiotics was defined as administration of a systemic antimicrobial agent for at least 24 hours during the 14-day period before isolation of *A. baumannii.*

Isolation and identification of agents causing HIs was done using conventional biochemical methods in the microbiology laboratory of the Clinical Centre in Kragujevac [9]. Interpretation of the results was done according to the guidelines issued by the Clinical and Laboratory Standards Institute [10]. Sensitivity of the isolates was tested to the following antibiotics: amoxicillin+clavulanic acid (30 μg/mL), piperacillin-tazobactam (110 μg/mL), cefotaxime (30 μg/mL), ceftriaxone (30 μg/mL), ceftazidime (30 μg/mL), cefepime (30 μg/mL), imipenem (10 μg/mL), meropenem (10 μg/mL), gentamicin (10 μg/mL), amikacin (30 μg/mL), ciprofloxacin (5 μg/mL), trimethoprim-sulfamethoxazole (2.5 μg/mL), and tigecycline (15 μg/mL). CRAB was determined if the *A. baumannii* isolate was resistant to both imipenem and meropenem. In cases of discrepancy, imipenem resistance served as the reference. Multi-resistance was defined as acquired non-susceptibility to at least one agent from three or more different antibiotic groups, and pan-resistance as non-susceptibility to all antimicrobial categories [11].

An additional nested comparative study was done on patients who died from HIs. Mortality was defined as death documented to have occurred within 30 days following infection with *A. baumannii*. The patients who died after CRAB infection were compared to the patients who died after CSAB infection.

The study was approved by the ethics committee of the Clinical Centre, Kragujevac.

The data were analyzed by descriptive statistics, using measures of central tendency (mean), variability (standard deviation from the mean), and relative numbers. After testing for normality of the data distribution using the Kolmogorov-Smirnov test, significance of difference in values of continuous variables between the study groups was tested by student's t-test for independent samples. Significance of difference in categorical variables between the study groups was tested by the Chi-square test or Fisher's test (when values in some cells of contingency tables were lower than five, or zero). The differences were considered significant if probability of a null hypothesis was below 0.05. Associations between putative risk factors and the study outcomes were tested by univariate and multivariate logistic regressions, and expressed as crude or adjusted odds ratios. All calculations were done in SPSS for Windows software, version 18 (Chicago: SPSS Inc.).

Results

During the observed period, 137 patients admitted to the ICU developed HIs caused by *A. baumannii*, based on the pre-defined criteria. Themean age of the patients was 59.65 ± 16.08 years (range: 19–91 years),

and 99 (72.26 %) of them were males. In 95 patients (69.35%), the infection was caused by CRAB. The difference between study groups in relation to the sites of HIs was not statistically significant (p > 0.05). The most common types of infections in the group with CRAB and in the group with CSAB were pneumonia (56.8% versus 61.9%, respectively) and surgical site infection (17.9% versus 19.0%, respectively), followed by bloodstream infection (20.0% versus 11.9%, respectively), urinary tract infection (2.1% versus 4.8%, respectively), and other infections (3.2% versus 2.4%, respectively).

Results of the univariate analyses of putative risk factors for acquiring HIs caused by CRAB, including clinical characteristics, invasive procedures, and prior therapy, are shown in Table 1. The following risk factors were significantly associated with CRAB infections: comorbidity such as hypertension or cancer, concomitant HI, placement of central venous catheter or urinary catheter, use of mechanical ventilation, previous stay in another department, prolonged stay in hospital and ICU, hospitalization longer than one month, prolonged stay in hospital until infection, number of prescribed antibiotics and their prolonged

Table 1. Risk factors for hospital infections with carbapenem-resistant *Acinetobacter baumannii*.

Variable	Univariate analysis			Multivariate analysis*	
	CRAB n = 95 (%)	CSAB n = 42 (%)	p	aOR (95% CI)	p
Age	60.73 ± 15.86	57.21 ± 16.69	0.242		
Age > 65 years	42 (44.2)	18 (42.9)	0.883		
Male gender	70 (73.7)	29 (69.0)	0.576		
Comorbidities					
Hypertension	28 (29.5)	4 (9.5)	**0.011**		
Diabetes mellitus	16 (16.8)	5 (11.9)	0.460		
Cancer	14 (14.7)	1 (2.4)	**0.033**		
Injury	36 (37.9)	19 (45.2)	0.419		
Existence of other HIs	43 (45.3)	9 (21.4)	**0.008**		
Invasive procedures					
Central venous catheter	80 (84.2)	23 (54.8)	**< 0.001**		
Urinary catheter	95 (100.0)	38 (90.5)	**0.002**		
Mechanical ventilation	77 (81.1)	16 (38.1)	**< 0.001**	20.8(2.8–152.3)	**0.003**
Surgical intervention	79 (83.2)	29 (69.0)	0.062		
Hospitalization					
Emergency admission	90 (94.7)	39 (92.9)	0.665		
Previous stay in another department	73 (76.8)	20 (47.6)	**0.001**	8.2(1.1–62.6)	**0.042**
Hospitalization (days)	38.08 ± 19.06	22.91 ± 9.41	**< 0.001**		
Hospitalization > 1 month	57 (60.0)	7 (16.7)	**< 0.001**		
ICU (days)	27.62 ± 15.50	16.05 ± 8.19	**< 0.001**		
ICU > 1 month	39 (41.1)	2 (4.8)	**< 0.001**	22.2(1.2–420.4)	**0.039**
Length of stay before HIs (days)	15.00 ± 11.82	9.71 ± 6.70	**0.008**		
Antibiotics					
No antibiotics	3.97 ± 1.50	2.48 ± 0.97	**< 0.001**		
Antibiotics (days)	27.53 ± 11.45	17.36 ± 7.25	**< 0.001**		
Days of antibiotic therapy before HIs	12.25 ± 7.96	7.02 ± 4.16	**< 0.001**		
Antibiotics before HIs > 7 days	73 (76.8)	20 (48.6)	**< 0.001**		
Previous antibiotics use					
Piperacillin-tazobactam	7 (7.4)	1 (2.4)	0.251		
Carbapenems	52 (54.7)	4 (9.5)	**< 0.001**	54.8(2.6–1147.4)	**0.010**
Second-generation cephalosporin	18 (18.9)	4 (9.5)	0.166		
Third-generation cephalosporin	40 (42.1)	16 (38.1)	0.660		
Aminoglycosides	37 (38.9)	7 (16.7)	**0.010**	11.8(1.4–98.5)	**0.022**
Ciprofloxacin	17 (17.9)	2 (4.8)	**0.040**		
Vancomycin	31 (32.6)	1 (2.4)	**< 0.001**		
Metronidazole	37 (38.9)	7 (16.7)	**0.010**	32.9(2.5–428.7)	**0.008**
Trimethoprim-sulfametoxazole	3 (3.2)	2 (4.8)	0.644		

*Shown when significant; Results are presented as $\bar{x}$ ± SD or n (%); HIs: hospital infections; aOR: adjusted odds ratio; CI: confidence interval; CRAB:carbapenem-resistant *Acinetobacter baumannii*; CSAB:carbapenem-sensitive *Acinetobacter baumannii*; ICU: intensive care unit.

use, administration of antibiotics for more than seven days before HIs, and previous administration of carbapenems, aminoglycosides, ciprofloxacin, vancomycin, or metronidazole ($p < 0.05$).

The multivariate logistic regression identified six independent risk factors for CRAB infections: use of mechanical ventilation (aOR = 20.8; 95% CI = 2.8–152.3; p = 0.003), previous stay in another department (aOR = 8.2; 95% CI = 1.1–62.6; p = 0.042), stay in ICU for more than a month (aOR = 22.1; 95% CI = 1.2–420.4; p = 0.039), and previous use of carbapenems (aOR = 54.8; 95% CI = 2.7–1147.4; p = 0.010), aminoglycosides (aOR = 11.8; 95% CI = 1.4–98.5; p = 0.022), and metronidazole (aOR = 32.9; 95% CI = 2.5–428.7; p = 0.008) (Table 1). The Hosmer-Lemeshow goodness-of-fit test for this logistic regression model was $\chi^2 = 3.378$;p = 0.908.

Lethal outcome occurred in 67 (49.91%) patients. There were 48 (71.64%) patients who died with CRAB and 19 (28.36%) patients who died with CSAB infections, but the difference was not statistically significant (p = 0.568). The mean age of patients with a lethal outcome was 61.88 ± 14.68 years (range: 20–91 years), and 44 of them (65.67%) were men.

Results of the univariate analyses of the risk factors for death in patients with HIs caused by CRAB are shown in Table 2. The following risk factors were significantly associated with death in patients with

Table 2. Risk factor for death in patients with hospital infections caused by carbapenem-resistant *Acinetobacter baumannii*.

Variable	Univariate analysis			Multivariate analysis*	
	CRAB n = 48 (%)	CSAB n = 19 (%)	p	aOR (95% CI)	p
Age	62.29 ± 14.14	60.84 ± 16.70	0.721		
Age > 65 years	23 (47.9)	11 (57.9)	0.462		
Male gender	16 (33.3)	7 (36.8)	0.785		
Comorbidities					
Hypertension	16 (33.3)	2 (10.5)	0.058		
Diabetes mellitus	11 (22.9)	2 (10.5)	0.248		
Cancer	7 (14.6)	0 (0)	0.079		
Injury	15(31.3)	9 (47.4)	0.215		
Existence of other HIs	24 (50.0)	4 (21.1)	**0.030**		
Invasive procedures					
Central venous catheter	44 (91.7)	13 (68.4)	**0.016**		
Mechanical ventilation	46 (95.8)	13 (68.4)	**0.002**	504.3 (2.1–123,055.3)	**0.026**
Surgical intervention	40 (83.3)	12 (63.2)	0.074		
Hospitalization					
Emergency admission	46 (95.8)	17 (89.5)	0.322		
Previous stay in another department	38 (79.2)	6 (31.6)	**< 0.001**	60.5(3.3–1,121.9)	**0.006**
Hospitalization (days)	31.60 ± 17.04	21.32 ± 12.62	**0.020**		
Hospitalization > 1 month	21 (43.8)	4 (21.1)	0.083		
ICU (days)	24.56 ± 15.29	16.00 ± 8.47	**0.025**		
ICU > 1 month	15 (31.3)	2 (10.5)	0.079		
Length of stay before HIs (days)	13.96 ± 8.82	10.63 ± 8.79	0.168		
Antibiotics					
No antibiotics	3.88 ± 1.56	2.26 ± 1.24	**< 0.001**		
Antibiotics (days)	26.19 ± 11.98	17.05 ± 8.86	**0.004**		
Days of antibiotic therapy before HIs	11.81 ± 7.84	7.11 ± 4.81	**0.018**		
Antibiotics before HIs > 7 days	37 (77.1)	9 (47.4)	**0.018**		
Previous antibiotics use					
Piperacillin-tazobactam	4 (8.3)	1 (5.3)	0.666		
Carbapenems	27 (56.3)	2 (10.5)	**0.001**	120.5(1.1–13497.3)	**0.047**
Second-generation cephalosporin	9 (18.8)	2 (10.5)	0.413		
Third-generation cephalosporin	21 (43.8)	8 (42.1)	0.903		
Aminoglycosides	17 (35.4)	2 (10.5)	**0.042**		
Ciprofloxacin	12 (25.0)	1 (5.3)	0.066		
Vancomycin	13 (27.1)	1 (5.3)	**0.048**		
Metronidazole	15 (31.3)	0 (0)	**0.006**		

* Shown where significant; Results are presented as $\bar{x}$ ± SD or n (%); HIs: hospital infections; aOR: adjusted odds ratio; CI: confidence interval; CRAB:carbapenem-resistant *Acinetobacter baumannii*; CSAB:carbapenem-sensitive *Acinetobacter baumannii*; ICU: intensive care unit.

CRAB infections: concomitant HI, placement of central venous catheter, use of mechanical ventilation, previous stay in another department, prolonged stay in hospital and ICU, number of prescribed antibiotics and their prolonged use, having taken antibiotics for more than seven days before HIs, and previous administration of carbapenems, aminoglycosides, vancomycin, or metronidazole ($p < 0.05$).

The multivariate analysis identified three independent risk factors for death in patients with HIs caused by CRAB: use of mechanical ventilation (aOR= 504.3; 95% CI = 2.1–123,055.3; p = 0.026), previous stay in another department (aOR= 60.5; 95% CI = 3.3–1,121.9; p = 0.006), and previous use of carbapenems (aOR= 120.5; 95% CI = 1.1–13497.3; p = 0.047) (Table 2). The Hosmer-Lemeshow goodness-of-fit test for this logistic regression model was $\chi^2 = 1.561$;p = 0.992.

The tested *A. baumannii* isolates showed high rates of resistance (70%–100%) to the majority of antibiotics except tigecycline (Table 3). However, a statistically significant difference in resistance rate between CRAB and CSAB isolates was only observed concerning cefepime (74.4% versus 90.2%, respectively; p = 0.042). During the study period, outbreaks of hospital infections caused by *A. baumannii*were not registered.

Discussion

During the last decade, *A. baumannii* came into the focus of healthcare systems because the incidence of HIs caused by this bacterium is constantly rising; it successfully survives in hospital environments and acquires resistance to a wide spectrum of antibiotics [12].

The fact that mechanical ventilation was the only invasive medical procedure associated with HIs caused by CRAB in our study is not surprising, because other researchers reported the same findings [13,14]. This procedure is frequently used in patients with respiratory failure, poor gas exchange, or increased difficulty breathing. It is related to lung injury and adverse neurological outcomes, and it also opens the door for infectious agents. Microorganisms from the environment adhere to ventilator tubes and make a biofilm, which is out of reach of antibiotics and neutrophils. Additionally, these usually critically ill patients demand frequent and intensive contact with medical staff during care (introduction of venous catheters, endotracheal intubation, placement of urinary catheter, administration of drugs, etc.), which may disrupt protective barriers. This is why some authors have suggested that significant reduction in the frequency of HIs can be achieved by using noninvasive ventilation instead, such as nasal continuous positive pressure ventilation or nasal synchronized intermittent mandatory ventilation.

Previous stays in another department (in the same or in another hospital) increased the risk of CRAB infection 8.2 times (95% CI = 1.1–62.6; p = 0.042), and also increased the risk of death, which can be explained by increased exposure to microorganisms in the hospital environment, extension of hospitalization, or the use of antibiotics that leads to development of resistance [13,14]. Rosa *et al.* [15] reported that patients exposed to a contaminated hospital environment were at 2.77 times greater risk of acquiring CRAB than were unexposed patients (95% CI = 1.5–5.1; p = 0.002).

Our study showed an association between HIs caused by CRAB and stays in the ICU for longer than a month (OR = 22.2; 95% CI = 1.2–420.4; p = 0.039), which was expected because previous studies reported the same finding. Baran *et al.* [16] showed that risk of this infection was three times higher for patients in an ICU (95% CI = 1.4–6.9; p = 0.005). Playford *et al*. [17], in a retrospective case/control study, found that prolonged ICU stay (median length of stay: 15 days; 95% CI = 9–21 days) and prolonged hospital stay (30

Table 3. Comparison of antimicrobial resistance of *Acinetobacter baumannii* to selected antibiotics.

Antimicrobial agent	CRAB n/N (%)	CSAB n/N (%)	p
Amoxicillin+clavulanic acid	19/21 (90.5)	11/13 (84.6)	0.606
Piperacillin-tazobactam	71/83 (85.5)	26/35 (74.3)	0.144
Cefotaxime	73/73 (100.0)	26/26 (100.0)	-
Ceftriaxone	82/82 (100.0)	35/35 (100.0)	-
Ceftazidime	82/83 (98.8)	38/38 (100.0)	0.497
Cefepime	65/87 (74.7)	37/41 (90.2)	**0.042**
Gentamicin	53/62 (85.5)	18/22 (81.8)	0.683
Amikacin	81/85 (95.3)	32/36 (88.9)	0.195
Ciprofloxacin	84/87 (96.6)	35/38 (92.1)	0.285
Trimethoprim-sulfamethoxazole	67/83 (91.8)	25/30 (83.3)	0.207
Tigecycline	5/59 (8.5)	5/24 (20.8)	0.117

n: number of resistant isolates; N: number of isolates with available results; CRAB: carbapenem-resistant *Acinetobacterbaumanii*; CSAB: carbapenem-sensitive *Acinetobacterbaumanii.*

days, range: 11–38 days) were independently associated with CRAB infection. In patients with prolonged stays in the ICU, normal microbiological flora becomes replaced with bacterial strains from the hospital environment; it is well known that ICUs are populated with endemic multi-resistant microorganisms, and one of them is *A. baumannii*. Colonization of patients with such bacterial clones usually precedes infection, which is a consequence of drop in mechanisms of defense against microorganisms or utilization of invasive medical procedures. An additional factor that promotes colonization and infection by drug-resistant pathogens in ICU patients is exposure to antimicrobial therapy. In many ICUs, broad-spectrum antibiotics are predominantly used, which select multi-resistant bacterial strains. Prolonged stay in ICU increases the chances of contact with patients who are already colonized or infected with multi-resistant pathogens. The patients in ICUs are frequently elderly and have comorbidities, which further weakens their immunity and defense against infection. Furthermore, in countries with limited resources such as Serbia, ICUs are usually understaffed and overpopulated with patients, a situation that creates opportunity for neglect of aseptic techniques and basic hygiene, leading to emergence of HIs and further spread of resistant microbes from patient to patient [18].

Earlier studies also showed that previous exposure to antibiotics is maybe the most important risk factor for HIs caused by multi-resistant pathogens. In our study, previous exposure to antibiotics was defined as at least 24 hours of therapy with antibiotics within 14 days prior to isolation of *A. baumannii*. Many of our patents received several antibiotics before the microbiological analysis became positive. Previous exposure to carbapenems predisposed patients in our study to HIs caused by CRAB (OR = 54.8; 95% CI = 2.6–1147.4; p = 0.01); Sheng *et al*. [19] reported similar findings, though the strength of association was lower (OR = 2.6; 95% CI = 1.4–5.4; p = 0.02). These results underline the necessity for strict control of carbapenem prescription in order to preserve their efficacy in the future, since these antibiotics are still a mainstay in the treatment of serious infections due to *A. baumannii*. Hospitals that introduced control of carbapenem prescriptions succeeded in halting further increase of *A. baumannii* resistance to this group of antibiotics.

Aminoglycosides, especially amikacin, are widely used in empiric therapy of critically ill patients, so their association with HIs caused by CRAB has broad relevance. Risk of HIs caused by CRAB after previous use of aminoglycosides was 11.8 times higher (95% CI = 1.4–98.5; p = 0.022) in our study, which is in accordance with the results of some recent studies [20]. This should be taken into account when evaluating potential benefits and harms of administering an aminoglycoside to a patient in the ICU.

Metronidazole is also frequently used in critically ill patients in the ICU. Our study confirmed the results of other authors that linked previous use of metronidazole with the emergence of HIs caused by CRAB [21]. However, how metronidazole predisposes patients for HIs caused by CRAB is not clear; we could only speculate that decreased burden of anaerobic bacteria creates empty space ready to be invaded by multi-resistant hospital flora, including *A. baumannii.*

In our study, previous use of piperacillin-tazobactam, second- and third-generation cephalosporins, ciprofloxacin, or vancomycin were not associated with HIs caused by CRAB after adjustment for other variables, although ciprofloxacin and vancomycin showed significant influence when taken separately (p = 0.040 and p < 0.001, respectively). An explanation could be found in the lower utilization rate of these antibiotics in patients from our study. Broad-spectrum antibiotics, like the ones mentioned, help to select multi-resistant bacterial strains because they eradicate concurrent (yet sensitive) microorganisms.

A particularly worrying result of our study was the high resistance rate of CRAB isolates (> 75%) to other antibiotics. It is important to have this in mind when choosing the most appropriate antibiotic for empirical therapy. To date, *A. baumannii* has become resistant to almost all available antimicrobial agents [22].

A large multicenter study that included 266 medical centers showed regional variability of *A. baumannii* sensitivity to imipenem; it was marked from good in North America and Europe (≥ 74%) to poor or moderate in Latin America and Asia/Pacific Rim (60.6% and 69.2%, respectively) [23]. However, an increase in the incidence of *A. baumannii*-resistant strains was reported worldwide; America-wide surveillance data demonstrated that resistance to carbapenems increased nearly eightfold, from 5.2% in 1999 to 40.8% in 2010 [24]. European surveillance data from 2012 [25] showed that the *A. baumannii*from ICUs is resistant in 68.8% of cases, which is a similar rate to that found in our study. Multi- and pan-resistant strains makes treating patients very difficult because they cause prolonged hospitalization, increased treatment costs, and increased hospital mortality [26]. One of the most important elements of therapeutic approach nowadays is good knowledge of local *A. baumannii* resistance patterns [27].

Our study had certain limitations. First, it was a single-center study, which may introduce institutional bias concerning choice of participants or medical practice. Second, we were not able to conduct laboratory testing of mechanisms of *A. baumannii* resistance to antibiotics.

Conclusions

This study showed that mechanical ventilation, previous stay in another department, stay in an ICU for more than a month, and previous use of certain antibiotics (carbapenems, aminoglycosides, and metronidazole) are independent risk factors for the development of CRAB. Furthermore, risk factors for death in patients with HIs caused by CRAB are use of mechanical ventilation, previous stay in another department and previous use of carbapenems.

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References

1. Sopirala MM, Mangino JE, Gebreyes WA, Biller B, Bannerman T, Balada-Llasat JM, Pancholi P (2010) Synergy testing by Etest, microdilution checkerboard, and time-kill methods for pan-drug-resistant *Acinetobacter baumannii*. Antimicrob Agents Chemother 54: 4678-4683.
2. Jung JY, Park MS, Kim SE, Park BH, Son JY, Kim EY, Lim JE, Lee SK, Lee SH, Lee KJ, Kang YA, Kim SK, Chang J, Kim YS (2010) Risk factors for multi-drug resistant *Acinetobacter baumannii* bacteremia in patients with colonization in the intensive care unit. BMC Infect Dis 10: 228.
3. Chuang YC, Cheng CY, Sheng WH, Sun HY, Wang JT, Chen YC, Chang SC (2014) Effectiveness of tigecycline-based versus colistin- based therapy for treatment of pneumonia caused by multidrug-resistant *Acinetobacter baumannii* in a critical setting: A matched cohort analysis. BMC Infect Dis 14: 102.
4. Falagas ME, Karveli EA (2007) The changing global epidemiology of *Acinetobacter baumannii* infections: A development with major public health implications. Clin Microbiol Infect 13: 117-119.
5. Fournier PE, Richet H (2006) The epidemiology and control of *Acinetobacter baumannii* in health care facilities. Clin Infect Dis 42: 692-699.
6. Henig O, Weber G, Hoshen MB, Paul M, German L, Neuberger A, Gluzman I, Berlin A, Shapira C, Balicer RD (2015) Risk factors for and impact of carbapenem-resistant *Acinetobacterbaumannii* colonization and infection: matched case-control study. Eur J ClinMicrobiol Infect Dis 34: 2063-2068.
7. Thatrimontrichai A, Apisarnthanarak A, Chanvitan P, Janjindamai W, Dissaneevate S, Maneenil G (2013) Risk factors and outcomes of carbapenem-resistant *Acinetobacter baumannii* bacteremia in neonatal intensive care unit: a case-case-control study. Pediatr Infect Dis J 32: 140-145.
8. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM (1988) CDC definitions for nosocomial infections. Am J Infect Control 16: 128-140.
9. Kiska DL, Gilligan PH (1999) *Pseudomonas* and *Bulkholderia.* In: Murray PR, Baron EJ, Pfaller MA, Tenover FC, Yolken RH, editors. Manual of Clinical Microbiology, 7th edition. Washington, DC: American Society for Microbiology. 517-525.
10. Clinical and Laboratory Standard Institute (2010) Performance standards for antimicrobial susceptibility testing. Wayne, PA: CLSI.
11. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, HindlerJF, KahlmeterG, Olsson-Liljequist B, Paterson DL, Rice LB, Stelling J, Struelens JM, Vatopoulos A, Weber JT, Monnet DL (2012) Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. ClinMicrobiol Infect 18: 268-281.
12. Karageorgopoulos DE, Falagas ME (2008) Current control and treatment of multidrug-resistant *Acinetobacter baumannii* infections. Lancet Infect Dis 8: 751-762.
13. Dizbay M, Tunccan OG, Sezer BE, Hizel K (2010) Nosocomial imipenem-resistant *Acinetobacter baumannii* infections: epidemiology and risk factors. Scand J Infect Dis 42: 741-746.
14. Vaze ND, Emery CL, Hamilton RJ, Brooks AD, Josh SG (2013) Patient Demographics and Characteristics of Infection with Carbapenem-Resistant *Acinetobacter baumannii* in a Teaching Hospital from the United States. Adv Infect Dis 3: 10-16.
15. Rosa R, Arheart KL, Depascale D, Cleary T, Kett DH, Namias N, Pizano L, Fajardo-Aquino Y, Munoz-Price LS (2014) Environmental exposure to carbapenem-resistant *Acinetobacter baumannii* as a risk factor for patient acquisition of *A. baumannii*. Infect Control HospEpidemiol 35: 430-433.
16. Baran G, Erbay A, Bodur H, Ongürü P, Akinci E, Balaban N, Cevik MA (2008) Risk factors for nosocomial imipenem-resistant *Acinetobacter baumannii* infections. Int J Infect Dis 12: 16-21.
17. Playford EG, Craig JC, Iredell JR (2007) Carbapenem-resistant *Acinetobacterbaumannii* in intensive care unit patients: risk factors for acquisition, infection and their consequences. J Hosp Infect 65: 204-211.
18. Cristina ML, Spagnolo AM, Ottria G, Sartini M, Orlando P, Perdelli F; Galliera Hospital Group (2011) Spread of multidrug carbapenem-resistant *Acinetobacter baumannii* in different wards of an Italian hospital. Am J Infect Control 39: 790-794.
19. Sheng WH, Liao CH, Lauderdale TL, Ko WC, Chen YS, Liu JW, Lau YJ, Wang LH, Liu KS, Tsai TY, Lin SY, Hsu MS, Hsu LY, Chang SC (2010) A multicenter study of risk factors and outcome of hospitalized patients with infections due to carbapenem-resistant *Acinetobacter baumannii*. Int J Infect Dis 14: e764-e769.
20. Chen YH, Chiueh CC, Le YJ (2014) Risk factors of carbapenem-resistant *Acinetobacter baumannii* infection among hospitalized patients. J ExpClin Med 6: 143-146.
21. Gulen TA, Guner R, Celikbilek N, Keske S, Tasyaran M (2015) Clinical importance and cost of bacteremia caused by nosocomial multi drug resistant *Acinetobacter baumannii*. Int J Infect Dis 38: 32-35.

22. Falagas ME, Rafailidis PI, Matthaiou DK, Virtzili S, Nikita D, Michalopoulos A (2008) Pandrug-resistant *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* infections: characteristics and outcome in a series of 28 patients. Int J Antimicrob Agents 32: 450-454.
23. Reinert RR, Low DE, Rossi F, Zhang X, Wattal C, Dowzicky MJ (2007) Antimicrobial susceptibility among organisms from the Asia/Pacific Rim, Europe and Latin and North America collected as part of TEST and the in vitro activity of tigecycline. J Antimicrob Chemother 60: 1018-1029.
24. Adams-Haduch JM, Onuoha EO, Bogdanovich T, Tian GB, Marschall J, Urban CM, Spellberg BJ, Rhee D, Halstead DC, Pasculle AW, Doi Y (2011) Molecular epidemiology of carbapenem-non susceptible *Acinetobacter baumannii* in the United States. J ClinMicrobiol 49: 3849-3854.
25. European Centre for Disease Prevention and Control (2015) Annual Epidemiological Report 2014. Antimicrobial resistance and healthcare-associated infections. Stockholm: ECDC. 8 p.
26. Young LS, Sabel AL, Price CS (2007) Epidemiologic, clinical, and economic evaluation of an outbreak of clonal multidrug-resistant *Acinetobacter baumannii* infection in a surgical intensive care unit. Infect Control HospEpidemiol 28: 1247-1254.
27. Michalopoulos A, Falagas ME (2010) Treatment of *Acinetobacter* infections. Expert OpinPharmacother 11: 779-788.

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