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Risk factors for 30-day mortality in patients with carbapenem-resistant *Acinetobacter baumannii* during an outbreak in an intensive care unit

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SUMMARY

This study assessed risk factors for 30-day mortality in 66 patients with carbapenem-resistant *Acinetobacter baumannii* (CRAB) infection or colonization during an outbreak in an intensive-care unit. Clinical and demographic characteristics were evaluated. The overall 30-day mortality was 47·0%. In the multivariate Cox regression model, septic shock [adjusted hazard ratio (aHR) 5·01, 95% confidence interval (CI) 2·32–10·01] and APACHE II score at onset of infection (aHR 1·11, 95% CI 1·04–1·18) were significantly associated with 30-day mortality. Administration of appropriate therapy was a protective factor, but it was not statistically significant (aHR 0·48, 95% CI 0·21–1·12). A sample of isolates tested ($n=27$) carried the $bla_{\text{OXA-23}}$ gene. Severity of baseline condition and severity of infection presentation were major risk factors for mortality during the outbreak. Patients who received appropriate therapy tended to have lower mortality rates, although therapy was started late and dosage was suboptimal in most cases.

Key words: *Acinetobacter baumannii*, carbapenems, mortality, multidrug resistance, outbreak, polymyxin B, treatment.

INTRODUCTION

Over the past three decades, *Acinetobacter baumannii* has emerged as one of the most important pathogens for healthcare institutions around the world [1–3]. This organism is particularly associated with ventilator-associated pneumonia, bacteraemia and urinary tract infection, especially in intensive-care units (ICUs) [1–3]. The ability of *A. baumannii* to survive under a wide range of environmental conditions and to persist on surfaces for extended periods of time make it a frequent cause of nosocomial outbreaks [1, 2], and many such incidents have been reported in recent years [4]. Additionally, the isolates responsible for these outbreaks are commonly resistant to multiple antimicrobials, including carbapenems.

The increasing rates of carbapenem-resistant *A. baumannii* (CRAB) isolates represents a major

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clinical and public-health concern since these drugs are the most potent therapy available against these organisms [5]. Polymyxins B and E (colistin) are frequently the only therapeutic option for these isolates [6, 7]. Multidrug-resistant (MDR) *A. baumannii*, including CRAB, colonization or infection tends to occur in patients with serious underlying diseases who are exposed to antimicrobial agents, have prolonged stay in an ICU, and are under mechanical ventilation [1–4]. Given the severity of illness in these patients crude mortality rates for MDR *A. baumannii* are usually high [3] and the attributable mortality of these infections regardless of the severity of underlying illness has proved very difficult to determine [3].

Several studies have described CRAB outbreaks worldwide and some have investigated factors associated with mortality due to CRAB [1–5]. However, none have focused on identifying specific risk factors for mortality in the context of an outbreak. Thus, the aim of the current study was to assess risk factors for 30-day mortality in patients with CRAB infection or colonization during an outbreak in an ICU from a tertiary-care hospital.

METHODS

Study design

A cohort study was performed at a general 22-bed ICU of the Ernesto Dornelles Hospital, a 300-bed tertiary-care hospital in Porto Alegre, Southern Brazil. The study period was from March 2006 (recovery of the index case) to December 2008. Patients with positive culture for CRAB were included in the study if the isolate was recovered during the ICU admission or within 72 h of discharge from the ICU. They were excluded if the CRAB was recovered <48 h after ICU admission. Only the first isolate of each patient was considered. All patients were followed up to death or to 30 days after onset of infection.

Data were collected from patients' medical charts and hospital epidemiology and infection control service records. The study was approved by the ethics committee of the Federal University of Rio Grande do Sul. Written informed consent was not required as the study was retrospective.

Variables and definitions

The primary outcome was 30-day mortality. Potential risk factors assessed were: age; sex; baseline diseases (malignancy; AIDS; neurological, pulmonary, digestive tract, renal or cardiac diseases; and diabetes), APACHE II score [8] at admission to the ICU and at onset of infection (defined as the day of culture collection that resulted in the growth of CRAB); arterial oxygen pressure/inspired oxygen fraction (PaO_2/FiO_2) at onset of infection; previous surgery; presence of mechanical ventilation at onset of infection; haemodialysis; polymicrobial infection (defined as the recovery of another organism at the same time from the same site of CRAB); presence of concomitant infection on the day of CRAB recovery (defined as the presence of an infection by another organism at a site distinct from that affected by CRAB); length of ICU stay before CRAB recovery; classification of the CRAB isolate as infecting or colonizing according to Centers for Disease and Control (CDC) criteria [9]; presentation with septic shock (systolic blood pressure <90 mmHg or a reduction by $\geqslant 40$ mmHg from baseline in the absence of other causes for hypotension persisting despite adequate fluid resuscitation, or need for vasopressor agents to maintain normal blood pressure levels) [10]; administration of appropriate therapy, defined as the use of an antimicrobial to which the isolate exhibited *in-vitro* susceptibility (polymyxin B and tigecycline were not tested for all isolates, but were considered appropriate therapy since all isolates tested were susceptible); time to initiate the therapy; and antimicrobial association (treatment with more than one antimicrobial agent).

Microbiology and molecular typing

Isolates were identified by the Vitek system (bioMérieux, France). Susceptibility was determined by the disk diffusion method and the results were interpreted according to Clinical and Laboratory Standards Institute (CLSI) criteria [11]. A sample of 27 isolates were tested for susceptibility to polymyxin B by agar dilution method and for tigecycline by E-test® (Slowna, Sweden). Minimum inhibitory concentrations (MICs) of imipenem and meropenem were also determined by E-test. The 27 isolates were also tested by multiplex PCR for $bla_{\text{OXA-23}}$, $bla_{\text{OXA-24}}$, $bla_{\text{OXA-58}}$ and $bla_{\text{OXA-51}}$ genes as described previously [12].

Twenty-four of these selected isolates were genotyped by pulsed-field gel electrophoresis (PFGE) using the restriction endonuclease *Apa*I. Analysis of PFGE patterns was performed by visual inspection using the criteria of Tenover *et al.* [13].

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Statistical analysis

All statistical analyses were performed using SPSS for Windows, version 13.0 (SPSS Inc., USA). Bivariate analyses were performed separately for each of the variables. *P* values were calculated using χ^2 or Fisher's exact tests for categorical variables and Student's *t* test for continuous variables. Variables for which the *P* value was in the bivariate analysis were included one by one in a Cox regression model according to their *P* value. Risk factors were checked for confounding and collinearity. A *P* value of $\leqslant 0{\cdot}10$ was set as the limit for acceptance or removal of the new terms in the model. Proportional hazards assumption was graphically checked inspecting the log[–log(*S*)] plot. All tests were two-tailed and $P \leqslant 0{\cdot}05$ was considered significant.

RESULTS

During the study period, 2918 patients were admitted to the ICU (annual mean 973 admissions), resulting in a total of 19042 patient-days (annual mean 6347 patient-days). Of the 2918 patients, 72 (2·5%) yielded at least one positive culture for CRAB. Six of these patients were excluded because the isolate was recovered within 48 h of ICU admission, resulting in 66 patients being included in the study. The isolates recovered from these 66 patients represented 60·0% of all *Acinetobacter* spp. isolates recovered during the study period ($n = 110$). The proportion of carbapenem resistance in *Acinetobacter* spp. from the ICU increased from 29·4% (10/34) in 2006, to 68·6% (24/35) in 2007 to 78·0% (32/41) in 2008. The overall incidence rate of CRAB was 3·78/1000 patient-days (1·49 in 2006, 4·32 in 2007, 5·45 in 2008).

The overall in-hospital mortality of patients with CRAB was 69·7% (46/66) and the 30-day mortality was 47·0% (31/66). The main characteristics of the patients are summarized in Table 1. The bivariate analyses of risk factors for 30-day mortality in the 66 patients are shown in Table 2. Considering the results of bivariate analysis, the following variables were included one by one in the Cox multivariate model: septic shock, APACHE II score at onset of infection, mechanical ventilation, bacteraemia, appropriate therapy, time to initiate appropriate therapy, and APACHE II score at admission. All variables remaining in the final multivariate model are shown in Table 3. Mortality rates of the 24 patients who received appropriate therapy compared to the 42 who did not receive appropriate therapy are shown in Figure 1.

Patients who received appropriate therapy were more frequently treated with polymyxin B (70·8%, 17/24), followed by ampicillin-sulbactam (16·7%, 4/24) and tigecycline (12·5%, 3/24). Of these patients, 30-day mortality was 35·3% (6/17) for those treated with polymyxin B, 25·0% (1/4) for those treated with ampicillin-sulbactam and 33·3% (1/3) for those treated with tigecycline ($P = 0{\cdot}86$). The 24 patients started therapy after a mean of 4·4 days (range 1–9 days) from CRAB recovery. All patients treated with polymyxin B received 50 mg/day by continuous intravenous infusion, except one who received 100 mg/day.

All 27 CRAB isolates proved to be OXA-23 producers, and all of them were also positive for $bla_{\text{OXA-51}}$. The MIC_{50} and MIC_{90} of imipenem and meropenem were both >32 mg/l. All tested isolates were susceptible to polymyxin B (both MIC_{50} and $MIC_{90} = 0{\cdot}5$ mg/l, range $<0{\cdot}25$–$0{\cdot}5$ mg/l) and tigecycline (both MIC_{50} and $MIC_{90} = 1{\cdot}5$ mg/l, range 0·125–2·0 mg/l). The amplified product of one $bla_{\text{OXA-23}}$-positive isolate was sequenced and confirmed as OXA-23 by a BLAST homology search.

Of the 24 isolates submitted to molecular typing, 13 (54·2%) represented a major clone (A) of which 11 had identical profiles and two were closely related. Nine further isolates represented a second clone (B), and the remaining two isolates were distinct.

DISCUSSION

This study was undertaken to evaluate risk factors for mortality in patients infected or colonized with CRAB. Our findings showed high overall in-hospital mortality (69·7%) and 30-day mortality (47·0%). The presence of septic shock and the APACHE II score at onset of infection were both independently associated with 30-day mortality in a multivariate Cox regression model. Administration of appropriate therapy was not statistically significant in the final model, but a clear trend to lower 30-day mortality rates in such patients was observed.

Our findings allow some conclusions. First, severity of infection presentation represented by septic shock at onset of infection, and severity of baseline condition represented by APACHE II score at onset of infection, are both the main predictors of 30-day mortality in ICU patients with CRAB, which is in accord with other studies assessing mortality by infections due to *A. baumannii* [14–17]. Second, we could not

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Table 1. *Characteristics of 66 patients with carbapenem-resistant* Acinetobacter baumannii (*CRAB*)

Variables	$n=66$ (%)
Age, years	70·1 ± 14·1
Sex, male	32 (46·5)
APACHE II score at admission	17·7 ± 4·8
Comorbidities	
Neurological	15 (22·7)
Cardiac	42 (63·6)
Pulmonary	24 (36·4)
Malignancy	6 (9·1)
Diabetes	17 (25·8)
Renal	19 (29·2)
Digestive tract	7 (10·3)
AIDS	1 (1·5)
Previous antimicrobial (30 days before CRAB recovery)	65 (98·5)
Aztreonam	2 (3·0)
Ceftriaxone	6 (9·1)
Ceftazidime	1 (1·5)
Cefepime	19 (28·8)
Piperacillin-tazobactam	17 (25·8)
Imipenem	11 (16·7)
Meropenem	37 (56·1)
Fluorquinolones (ciprofloxacin or levofloxacin)	12 (18·2)
Tigecycline	1 (1·5)
Anaerobicidal (metronidazole or clindamycin)	13 (19·7)
Vancomycin	47 (71·2)
Mechanical ventilation at onset of infection	40 (60·6)
Other infections	23 (34·8)
Previous surgery	38 (57·6)
Length of ICU stay before CRAB recovery, days	18·1 ± 14·1
APACHE II score at onset of infection	19·3 ± 7·0
Presentation with septic shock	22 (33·3)
Site of infection	
Pneumonia	19 (28·8)
Ventilator-associated pneumonia	22 (33·3)
Urinary tract	9 (13·6)
Primary bloodstream	7 (10·6)
Central venous catheter (CVC)	4 (6·0)
Bloodstream associated with CVC	1 (1·5)
Intra-abdominal	3 (4·5)
Central nervous system	1 (1·5)
Infected	56 (84·8)
Polymicrobial infection	3 (4·5)
CRAB bacteraemia	14 (21·2)
PaO_2/FiO_2 at onset of infection	224·3 ± 145·2
Appropriate therapy	24 (36·4)
Time to start appropriate therapy, days ($n=24$)	4·33 ± 2·00
Antibiotic association	1 (1·5)

PaO_2/FiO_2, arterial oxygen pressure/inspired oxygen fraction.
All variables are *n* (%) or median ± standard deviation.

unequivocally show the effect of appropriate therapy on 30-day mortality in ICU patients. Although 30-day mortality rates were decreased in those who received appropriate therapy, this variable was not statistically significant in the final multivariate model (adjusted hazard ratio 0·48, $P=0·09$). Even though

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Table 2. *Bivariate analysis of risk factors for 30-day mortality in the 66 patients with carbapenem-resistant* Acinetobacter baumannii (*CRAB*)

Variables	30-day mortality			
	Non-survivors ($n=31$)	Survivors ($n=35$)	Relative risk (95% CI)	*P*
Age, years	71·8 ± 12·7	68·6 ± 15·2	n.a.	0·36
Sex, male	12 (48·4)	17 (48·6)	1·00 (0·60–1·66)	0·87
APACHE II score at admission	19·1 ± 4·9	16·5 ± 4·4	n.a.	0·03
Comorbidities				
Neurological	6 (19·4)	9 (25·7)	0·82 (0·41–1·61)	0·79
Cardiac	19 (61·3)	23 (65·9)	0·91 (0·54–1·52)	0·90
Pulmonary	12 (38·7)	12 (34·3)	1·11 (0·66–1·86)	0·91
Malignancy	3 (9·7)	3 (8·6)	1·07 (0·46–2·49)	0·60
Diabetes	6 (19·4)	11 (31·4)	0·69 (0·34–1·39)	0·40
Renal	11 (36·7)	8 (22·9)	1·40 (0·84–2·35)	0·34
Digestive tract	5 (16·1)	2 (5·7)	1·62 (0·93–2·81)	0·33
AIDS	1 (3·2)	0 (0)	2·17 (0·67–2·81)	0·47
Mechanical ventilation at onset of infection	25 (80·6)	15 (42·9)	2·71 (1·29–5·69)	0·004
Other infections	14 (45·2)	9 (25·1)	1·54 (0·94–2·52)	0·16
Previous surgery	21 (67·7)	17 (48·6)	1·55 (0·87–2·75)	0·19
Length of ICU stay before CRAB recovery, days	16·9 ± 14·3	19·1 ± 14·1	n.a.	0·54
APACHE II score at onset of infection	22·7 ± 5·9	16·0 ± 6·2	n.a.	⩽0·001
Septic shock	20 (64·5)	2 (5·7)	3·64 (2·14–6·17)	⩽0·001
Site of infection			n.a.	0·35
Pneumonia	11 (35·5)	8 (22·9)		
Ventilator-associated pneumonia	10 (32·3)	12 (34·3)		
Urinary tract	2 (6·5)	7 (20·0)		
Primary bloodstream	5 (16·1)	2 (5·7)		
Central venous catheter (CVC)	1 (3·2)	3 (8·6)		
Bloodstream associated with CVC	1 (3·2)	0 (0)		
Intra-abdominal	1 (3·2)	2 (5·7)		
Central nervous system	0 (0)	1 (2·9)		
Infected	28 (90·3)	28 (80·0)	1·67 (0·62–4·45)	0·41
Polymicrobial infection	1 (3·2)	2 (5·7)	0·70 (0·14–3·54)	0·55
CRAB bacteraemia	11 (35·5)	3 (8·6)	2·04 (1·32–3·17)	0·008
PaO_2/FiO_2 at onset of infection	216·7 ± 168·0	236·8 ± 101·9	n.a.	0·69
Appropriate therapy	8 (25·8)	16 (45·7)	0·61 (0·32–0·94)	0·02
Time to start appropriate therapy, days ($n=24$)	3·12 ± 2·0	5·00 ± 1·9	n.a.	0·03
Antibiotic association ($n=21$)	0 (0)	1 (6·3)	1·46 (0·49–4·33)	0·76

CI, Confidence interval; n.a., not applicable; PaO_2/FiO_2, arterial oxygen pressure/inspired oxygen fraction.
All variables are *n* (%) or median ± standard deviation.

we attempted to control for disease severity using the APACHE II score, residual confounding may explain this non-significant result. Additionally, we believe that the magnitude of the effect of therapy on outcome was probably affected by the delay in administration of the first dose after the onset of infection and by the administration of polymyxin B (most patients were treated with this drug) in dosages lower than those currently recommended [5, 6]. Importantly, the high mortality rates found in our study, which may be partially explained by the severity of the patients' infection, are possibly related to this low proportion of patients (36·4%) who received appropriate therapy. This latter finding as well as the delay in starting therapy may have occurred owing to a potential underestimation of the pathogenic role of CRAB.

Interestingly, time to initiate therapy in the 24 patients who received appropriate therapy was significantly lower in patients who died within 30 days in bivariate analysis, which is in contrast to many findings demonstrating that the earlier appropriate therapy is employed the lower the mortality

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Table 3. *Multivariate analysis of factors associated with 30-day mortality*

Variables	aHR (95% CI)	*P*
Septic shock	5·01 (2·32–10·01)	<0·001
APACHE II score at onset of infection	1·11 (1·04–1·18)	0·002
Appropriate therapy	0·48 (0·21–1·12)	0·09

aHR, Adjusted hazard ratio; CI, confidence interval.

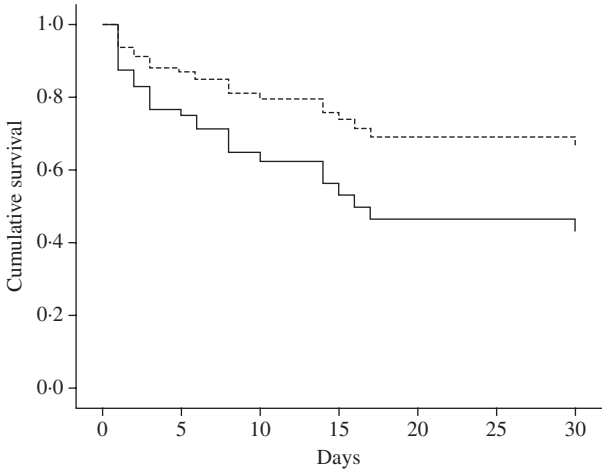

Fig. 1. Adjusted survival curves of patients according to administration of appropriate therapy (*P* value for this variable = 0·09). Mortality rates of the 24 patients who received appropriate therapy (- - -) = 76/1000 patient-days. Mortality rates of the 42 patients who did not receive appropriate therapy (——) = 255/1000 patient-days. Survival curves adjusted for APACHE II score at onset of infection and presentation with septic shock.

[15, 16, 18–20]. Nevertheless, this variable was not significantly associated with outcome in the multivariate model and this may be easily explained by the fact that patients who presented with septic shock at onset of infection received appropriate treatment significantly earlier than those who had no such a presentation (3·0 ± 1·6 days *vs.* 4·9 ± 2·0 days, respectively; $P = 0·03$).

Interestingly, our study did not show a significant difference in 30-day mortality between patients classified as colonized by CRAB, according to CDC criteria, and those infected by those organisms. Although it might be due to lack of statistical power, it is possible that some patients could have been misclassified using these criteria, since we do not believe that a real colonization would have the same impact as active infections in the patients' outcomes.

Of patients who received appropriate therapy, there was no significant difference in 30-day mortality according to the antimicrobial used. Most patients were treated with polymyxin B, and 16/17 patients treated with this drug had CRAB pneumonia or ventilator-associated pneumonia (data not shown). It has been shown when using the currently recommended dosages of polymyxin B that peak free-plasma concentration are around 2 mg/l or even lower [21]. The low MICs for polymyxin B found in the tested isolates of our study could partially explain the relatively good responses observed for patients treated with this drug, considering the low dose regimens administered.

Although not all isolates could be recovered for molecular evaluation, all tested isolates proved to be OXA-23 producers which is a major resistance mechanism to carbapenems in *A. baumannii* isolates [5, 22, 23] and has been associated with many CRAB outbreaks worldwide, including in Brazil [24–26]. Additionally, all isolates had the *OXA-51* gene, which has been shown to be intrinsic to *A. baumannii* [27].

Our study has some limitations that should be noted. First, there are the limitations that are characteristic of studies using a retrospective design. However, most of our variables were objective and not affected by subjective evaluation. A possible single exception, classification as infected or colonized, was assessed prospectively by the infection control team of this hospital for surveillance purposes. Additionally, not all isolates were tested for polymyxin B and tigecycline, and all were considered susceptible to these agents. Nonetheless, isolates from distinct clones were tested, most were from patients who had received these drugs (data not shown) and all presented MICs within the susceptible range for polymyxin B and all had MICs $\leqslant 2$ mg/l for tigecycline. It should also be noted that E-test for tigecycline, used in our study, may overestimate the MIC of *A. baumannii* isolates [28].

Another limitation of our study, which did not affect our main findings, is that not all isolates had their genetic basis of resistance determined and not all were submitted to molecular typing. The outbreak in the institution of this study occurred in parallel with a large city-wide outbreak after a long period of stable carbapenem susceptibility rates [26, 29], and although the great majority of the isolates recovered from distinct institutions of our city were also OXA-23 producers, in a few isolates no carbapenemase was detected [26]. Thus, it is possible that another resistance mechanism might be responsible for the

carbapenem-resistant phenotype of the remaining isolates, considering the characteristic of the isolates recovered from other institutions in our city. The same consideration can be applied to species-level identification as not all isolates were tested for $bla_{\text{OXA-51}}$, therefore it is possible that some isolates belonged to other species of the *A. calcoaceticus–A. baumannii* complex.

In summary, our study showed that severity of baseline condition and severity of infection presentation were major risk factors for mortality in patients with CRAB infections at an ICU during an outbreak caused by these organisms. Patients who received appropriate treatment tended to have lower mortality rates, despite delay in administration and low-dosage regimens. Appropriate therapy may be the only modifiable variable able to improve outcome of these patients.

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DECLARATION OF INTEREST

None.

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