CLINICAL AND EPIDEMIOLOGICAL STUDY

Trauma is associated with a better prognosis in intensive care patients with *Acinetobacter* infections

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Abstract

Purpose Acinetobacter baumannii has emerged as a common cause of infection in war-related trauma, civilian trauma and other surgical emergencies. The aim of this study was to determine prognostic factors especially trauma, in critically ill surgical patients with *Acinetobacter* spp. infection in a reference emergency ICU.

Methods A retrospective review of medical records was conducted for all patients admitted to the ICU who developed *Acinetobacter* spp. infection from January 2007 to December 2009. Bivariate and multivariate analyses were made for 36 patients. The end-point analyzed was the in-hospital mortality.

Results The initial analysis revealed a majority of young (43.6 years \pm 17.1) men (92 %), trauma victims (78 %) and an in-hospital mortality of 30 %. Patients who had not suffered trauma presented with other surgical conditions and were on average older than trauma patients (57 \pm 12 versus 40 \pm 16 years). The overall APACHE II score average was 15.3. The ventilator-associated pneumonia was the main *Acinetobacter* infection diagnosed. In

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Surgical Emergency Intensive Care Unit, Hospital das Clínicas, University of São Paulo, São Paulo, Brazil bivariate analysis lower Glasgow coma scale (p = 0.01) was associated with increased chance of death and being victim of trauma was a protecting factor (OR: 0.16; 95 % CI: 0.03–0.89). Receiving adequate treatment made no difference to outcome (OR: 0.55; 95 % CI: 0.05–3.15). Multivariate analysis showed that only the presence of trauma was independently associated with prognosis and was a protecting factor.

Conclusion Trauma was a marker of good prognosis in emergency ICU patients with *Acinetobacter* spp. infection.

Keywords Acinetobacter \cdot Trauma \cdot ICU \cdot Mortality

Introduction

Mortality for *Acinetobacter baumannii* infections in critically ill patients is a continuing controversy [1]. Some investigators found high mortality rates in intensive care unit (ICU) patients with *Acinetobacter* infection: 58 % in Spain [2], 53.8 % in France [3], 42 % in Belgium [4] and 52 % in the United States [5]. On the other hand, lower death rates have been reported: 26.2 % in critically ill surgical patients in Florida [6] and 26 % in *Acinetobacter* bacteremia in an ICU in Taiwan [7].

In the emergency setting, *A. baumannii* has emerged as a common cause of infection associated with war-related trauma, affecting mainly skin and soft tissue and bone [8]. Recently *Acinetobacter* infections have also been described as frequent in patients with trauma unrelated to war [6, 9–11]. The aim of this study was to determine prognostic factors, with a special attention to trauma, in critically ill patients with *Acinetobacter* spp. infection in an Emergency Department ICU.

Methods

This study was performed in the Emergency Department ICU (ED-ICU) of Hospital das Clínicas, University of São Paulo, Brazil, a 2200-bed tertiary-care hospital. It is a 15-bed surgical ICU that admits trauma patients in this hospital, besides patients with other emergency surgical conditions. Other ICUs were not included in this study because the ED-ICU is the only unit that admits trauma patients in our hospital and it is the ICU in which *Acine*-tobacter infections are more frequent.

A retrospective review of medical records was conducted for all patients admitted to the ED-ICU who developed *Acinetobacter* spp. infection from January 2007 to December 2009. The inclusion of the patients was based on notifications of infection made by the hospital infection control team according to CDC/NHSN criteria [12]. Only the first *Acinetobacter* infection for each patient was included. Urinary tract infections were excluded from this analysis because it is difficult to differentiate retrospectively real UTI from the asymptomatic bacteriuria, especially in ICU patients, and because UTI are expected to have a low impact on mortality.

The identification of *Acinetobacter* species in this study was made by the clinical microbiology laboratory that released the results as *A. baumannii-calcoaceticus* complex using an automatic identification method (Vitek; bio-Merieux, Hazelwood, USA). This complex includes other pathogenic species besides *A. baumannii*, such as *A. calcoaceticus*, *A. tjernbergiae* (sp. 3), *A. ursingii* (sp.13). As the isolates were not available for further identification, we chose to refer to the microorganism as *Acinetobacter* spp.

We evaluated the prognostic factors associated with the endpoint "in-hospital mortality". The following variables were evaluated: age, sex, APACHE II score [13] and Glasgow [14] coma scale on admission, presence of trauma including body sites and types (blunt, penetrating, presence of fracture, skin excoriation), use of invasive devices, vasoactive drugs, blood products, hemodialysis and antimicrobials, Acinetobacter infection site and treatment, time elapsed from admission to diagnosis of infection. Treatment was considered adequate [15, 16] if started within 2 days of diagnosis of infection (culture collection), maintained for at least 5 days and if the drug was active in vitro against the isolate. Other hospital-acquired infections were also recorded. The patients underlying diseases were divided into two variables for analysis: (i) "health risk factors", defined as conditions not associated with an known end-organ dysfunction, such as smoking (without obstructive pulmonary disease), alcohol abuse (without cirrhosis or documented hepatic insufficiency), treated epilepsy, use of illicit drugs and isolated obesity, and (ii) "active co-morbid conditions", defined as actual end-organ dysfunction (uncontrolled or hard to control diabetes, history of myocardial infarction or coronary insufficiency symptoms, cardiac insufficiency, previous stroke, active cancer, chronic renal disease, obstructive pulmonary disease).

The ED-ICU did not use any routine prophylactic antibiotic protocol for trauma patients. However, in exposed fractures, aminoglycosides and clindamycin were initiated on admission to the emergency room.

Analysis of data

A database was made using the software in EpiData3.0 (EpiData Association, Odense, Denmark) and the analysis was performed using the software in EpiInfo 3.5.1 (CDC, Atlanta, GA).

A descriptive analysis of the patients was performed. An analysis was performed comparing trauma and non-trauma patients. A bivariate analysis was done evaluating factors associated with the endpoint (in-hospital mortality). For dichotomous variables, an odds ratio with 95 % confidence interval was determined and a two-sided Fisher's exact test was also done. For continuous variables, the Mann–Whitney test (a non-parametric median test) was used. A *p* value <0.05 was considered significant.

Multivariate analysis was performed for the study endpoint: "in-hospital mortality", using logistic regression including variables with a p value <0.20 in the bivariate analysis and one variable considered to be potentially biologically plausible. The variables intrinsically correlated with trauma were excluded from the multivariate analysis: number of fractures, thorax fracture, being submitted to neurosurgery and blunt trauma. The following variables were included in the multivariate analysis: trauma, Glasgow coma scale on admission, the presence of health risk factor, the presence of active co-morbid condition (biologically plausible) and age, divided into the following strata: 20–35, 36–50, 51–65 and >65 years. Male sex (100 % of trauma patients) was considered to be correlated with trauma thus was excluded from the analysis.

Results

Forty-four patients presented with *Acinetobacter* infection during the 3-year study period. Five were excluded because their records were not available and three were excluded due to age <18 years. Thus 36 patients were evaluated.

The characteristics of the population can be seen in Table 1. Most of the patients were men, young and with few or no underlying diseases. Before the *Acinetobacter*

 Table 1
 General characteristics of the entire cohort of patients with Acinetobacter infection, and in the groups of patients with and without trauma admitted to the Emergency Department Intensive Care Unit, Hospital das Clínicas, University of São Paulo (January 2007–December 2009)

	All patients	Trauma patients	Non-trauma patients	p value
Number of patients	36	28 (78 %)	8 (22 %)	
Age, mean \pm SD	43.6 ± 17.1	39.7 ± 16.5	57.12 ± 12.0	0.01
Median (IQR)	43.5 (26–55)	38.5 (24-52.5)	55 (52.5-61.5)	
Overall range	20-80	20–79	39-80	
Male sex, n (%)	33 (92 %)	28 (100 %)	5 (62 %)	0.01
Health risk factor, n (%)	10 (28 %)	9 (32 %)	1 (12 %)	0.27
Active co-morbid condition, n (%)	11 (31 %)	5 (8 %)	6 (75 %)	< 0.01
APACHE score, mean \pm SD	15.3 ± 7.4	14.4 ± 6.2	18.6 ± 11.2	0.59
Median (IQR)	14 (10-20)	14 (9.5–19.5)	12 (10–31)	
Overall range	05–36	05–27	08–36	
Glasgow score, mean \pm SD	10.5 ± 4.2	9.6 ± 4.2	13.6 ± 2.5	< 0.01
Median (IQR)	11.5 (7–14.5)	9.5 (6-14)	15 (13–15)	
Overall range	3–15	3–15	8–15	
Number of surgical operations per patient, mean \pm SD	2.8 ± 2.8	2.3 ± 1.6	4.4 ± 5.0	0.57
Median (IQR)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	2.5 (1.0-6.5)	
Overall range	0-15.0	0–7.0	0-15.0	
Patients submitted to surgery, n (%)	34 (94 %)	27 (96 %)	7 (87 %)	0.40
Types of surgery, n (%)				
Abdominal	15 (42 %)	8 (29 %)	7 (87 %)	< 0.01
Orthopedic	10 (29 %)	10 (37 %)	0	0.04
Thoracic	13 (36 %)	11 (39 %)	2 (25 %)	0.38
Neurosurgery	7 (19 %)	7 (25 %)	0	0.14
Number of fractures, mean \pm SD	2.0 ± 2.1	2.5 ± 2.1	0	< 0.01
Median (IQR)	2.0 (0-3.0)	2.0 (0.5-4.0)		
Overall range	0–7.0	0–7.0		
Occurrence of blunt trauma, n (%)	23 (70 %)	23 (92 %)	0	
Previous infection, n (%)	8 (22 %)	6 (21 %)	2 (25 %)	0.58
ICU length of stay previous to Acinetobacter infection (in days), mean \pm SD	13.4 ± 10.9	13.3 ± 7.8	13.9 ± 19.0	0.06
Median (IQR)	10 (7.5–14)	11 (9–14)	7 (5.5–13.5)	
Overall range	0–59	5–39	0–59	
Acinetobacter infections, n (%)				0.01
Ventilation associated pneumonia	20 (56 %)	17 (61 %)	3 (37 %)	
Surgical site infection				
Organ space	5 (14 %)	1 (4 %)	4 (50 %)	
Deep incisional	5 (14 %)	5 (18 %)	0	
Superficial incisional	1 (3 %)	1 (4 %)	0	
Blood stream infection	3 (8 %)	3 (11 %)	0	
Skin and soft tissues infection	1 (3 %)	1 (4 %)	0	
Lower respiratory tract infection	1 (3 %)	0	1 (12 %)	
Time from culture collection to antibiotic start (days), mean \pm SD	4.8 ± 4.7	4.1 ± 2.77	8.25 ± 9.97	0.72
Median (IQR)	4.5 (2–5)	4.5 (2-5.5)	4.5 (2.5–14)	
Overall range	0–23	0–12	1–23	
Adequate treatment, n (%)	8 (22 %)	7 (25 %)	1 (12.5 %)	0.41
Polimicrobial Acinetobacter infection, n (%)	27 (75 %)	22 (79 %)	5 (62 %)	0.31

SD standard deviation, IQR interquartile range

infection all patients had used invasive devices: urinary tract catheter in 100 %, central venous catheter in 95 %, mechanical ventilation in 92 % and arterial line for blood pressure measurement in 61 %. In this period, the use of vasoactive drugs was necessary in 72 % of the patients and the average duration of antimicrobial use was 11 days. The main antimicrobials used were third and fourth generation cephalosporins (89 %), vancomycin (64 %), clindamycin (50 %), piperacillin-tazobactam (19 %) and carbapenems (17 %). Infections previous to the *Acinetobacter* infection occurred in 22 % of the patients.

Among the infections considered to be inadequately treated, 59 % had initiated treatment more than 48 h after the date of the positive culture and 41 % had used antimicrobials to which *Acinetobacter* was resistant in vitro.

Other bacterial agents were isolated in the same sample as Acinetobacter in 27 patients (75 %) and the most frequent were P. aeruginosa (10 patients), Enterobacter spp. (five patients) and S. aureus (three patients). Other associated agents were: E. coli, K. pneumoniae, E. faecalis, Citrobacter koseri, Proteus mirabilis, Bacillus sp. and Providentia stuartii.

The in-hospital mortality was 30 %. For the in-hospital mortality, bivariate analysis (Table 2) showed that a lower Glasgow scale was significantly associated with an increase in mortality. Male sex, presence of trauma and increasing number of fractures were significantly associated with a better prognosis.

Logistic regression analysis (Table 3) showed that the presence of trauma was the only variable statistically associated with mortality and was a protecting factor.

Discussion

Our study was conducted to evaluate prognostic factors, especially trauma, in patients with *Acinetobacter* infections acquired in an ED-ICU. We concluded that patients who had suffered trauma presented a significantly better prognosis. If we consider only the patients with trauma, mortality was 21 % and was 62 % among patients without trauma. Surprisingly, other variables such as severity of patients' condition (APACHE II score), adequate treatment, infection site and use of vasoactive drugs were not significant prognostic factors.

Trauma patients were younger than non-trauma patients and presented with more health risk factors, especially alcohol abuse, and less active co-morbid conditions. In the bivariate analysis, the older age and the presence of health risk factors (HRF) tended to be associated with a greater risk of death. However, in the multivariate analysis, age and HRF were not statistically associated with death. A lower Glasgow coma scale on admission was associated in the bivariate analysis with an increased chance of death but was not confirmed as an independent factor in the multivariate analysis. Even though trauma patients had lower Glasgow scale values, trauma was a marker of good prognosis. This may be explained by the younger age and the low prevalence of active co-morbid conditions in trauma patients.

It was difficult to evaluate the independent impact of the variable male sex on mortality. It appeared to be correlated with trauma, as 100 % of the trauma patients were men.

The relationship between trauma and mortality in Acinetobacter infections has not been evaluated in comparative analytical studies. Troittier et al. [6] evaluated 271 Acinetobacter-infected patients from three ICUs. Mortality was 19.3 % in the trauma ICU versus 46.3 % in the surgical ICU and 60 % in the cardiac surgery ICU. The objective of their study was only to describe clinical cure rates, resistance and mortality of Acinetobacter infections; thus they did not provide a comparative analysis. Kang et al. [10] evaluated retrospectively the first episode of bacteremia in hospitalized trauma patients over a 5-year period. They found 93 patients with A. baumannii bacteremia, of which 86 % presented multidrug resistance. Only two died (from massive pulmonary embolization). This study included both ward and ICU patients and was descriptive; thus it did not make comparisons between groups. In an animal model, infected mice that received morphine had higher counts of Acinetobacter in various organs than those that did not receive the drug, and trauma without morphine did not lead to high Acinetobacter burdens. The authors concluded that morphine and not trauma sensitizes mice to Acinetobacter infection [17]. To our knowledge ours is the first comparative study to evaluate trauma as a prognostic factor in Acinetobacter infections.

Another aspect in our study is that the great majority of the patients (78 %) were considered to have been inadequately treated; however most (70 %) of these patients survived, suggesting that the Acinetobacter infection may not have had a decisive role in prognosis. Another finding that suggests this is that the infection site was not associated with prognosis although we would have expected infection sites such as ventilator-associated pneumonia to be more severe. This aspect may deserve further studies as ours was not adequate to evaluate this. Virulence factors and genotypes of Acinetobacter may have an important role in differences in mortality. The true pathogenic potential and virulence of Acinetobacter species are not well known. Many membrane proteins have been identified in recent years and mutations and changes in density of expression can lead to differences in the pathogenicity and virulence of this pathogen. An outer membrane protein, OmpA, was identified as an important pathogenic element for adhesion to epithelial cells and to trigger events that

 Table 2
 Bivariate analysis of the factors potentially associated with death during the entire period of hospitalization of patients with Acine-tobacter infection—Emergency Department Intensive Care Unit, Hospital das Clínicas, University of São Paulo (January 2007–December 2009)

	Death	Survival	OR (95 % CI)	p value
Number of patients	11 (30 %)	25 (70 %)		
Age (years), mean \pm SD	51.9 ± 14.0	40.0 ± 17.3		0.06
Median (IQR)	52 (42–56)	37 (24–55)		
Overall range	26-80	20-79		
Male sex, n (%)	8 (72 %)	25 (100 %)	*	0.02
Health risk factor, n (%)	5 (45 %)	5 (20 %)	3.33 (0.71–15.5)	0.12
Active co-morbid condition, n (%)	4 (36 %)	7 (28 %)	1.46 (0.32-6.63)	0.45
Trauma, <i>n</i> (%)	6 (54 %)	22 (88 %)	0.16 (0.03-0.89)	0.04
APACHE score, mean \pm SD	18.3 ± 9.7	13.9 ± 5.9		0.26
Median (IQR)	15 (11-27)	14 (9–19)		
Overall range	6–36	5-24		
Glasgow score, mean \pm SD	9.57 ± 4.2	13.6 ± 2.5		0.01
Median (IQR)	9.5 (6–14)	15 (8–15)		
Overall range	3-15	8-15		
Number of surgical operations per patient, mean \pm SD	2.1 ± 1.2	3.1 ± 3.2		0.49
Median (IQR)	2 (1-3)	2 (1-3)		
Overall range	1–5	0–15		
Patients submitted to surgery	11 (100 %)	23 (92 %)	*	0.47
Type of surgery				
Abdominal, n (%)	6 (54 %)	9 (36 %)	2.13 (0.50-9.01)	0.25
Orthopedic, n (%)	2 (18 %)	8 (33 %)	0.44 (0.07-2.56)	0.30
Thoracic, <i>n</i> (%)	3 (27 %)	10 (40 %)	0.56 (0.11-2.64)	0.36
Neurosurgery, n (%)	4 (36 %)	3 (12 %)	4.19 (0.75–23.44)	0.10
Number of fractures, mean \pm SD	0.54 ± 1.3	2.6 ± 2.16	,	0.001
Median (IQR)	0 (0–0)	2 (1-4)		
Overall range	0-4	0–7		
Fracture site, n (%)				
Skull	1 (9 %)	7 (28 %)	0.25 (0.03-2.4)	0.21
Face	0	4 (16 %)	*	0.21
Thorax	0	11(39 %)	*	< 0.01
Pelvis	0	2 (8 %)	*	0.47
Spine	0	3 (12)	*	0.32
Occurrence of blunt trauma, n (%)	6 (54 %)	17 (77 %)	0.35 (0.07-1.66)	0.17
Previous infection, n (%)	1 (9 %)	7 (28 %)	0.25 (0.03–2.4)	0.21
ICU length of stay previous to <i>Acinetobacter</i> infection (days), mean \pm SD	10.9 ± 5.1	14.6 ± 12.6	0.25 (0.05 2.1)	0.44
Median (IQR)	9 (7–17)	11 (8–13)		0.77
Overall range	9 (7–17) 0–59	5–19		
Acinetobacter infections, n (%)	0-57	5-17		0.31
Ventilation associated pneumonia	5 (45 %)	15 (60 %)		0.31
Surgical site infection	5 (45 %)	15 (00 %)		
Organ space	2 (18 %)	3 (12 %)		
Deep incisional	2 (18 %) 3 (27 %)			
•		2 (8 %)		
Superficial incisional	0	1 (4 %) 2 (12 %)		
Blood stream infection	0	3 (12 %)		
Skin and soft tissues infection	0	1 (4 %)		
Lower respiratory tract infection	1 (9 %)	0		0.22
Time from culture collection to antibiotic start, mean \pm SD	7.12 ± 7.33	3.62 ± 1.99		0.32
Median (IQR)	5 (2–9.5)	4 (2–5)		

Table 2 continued

	Death	Survival	OR (95 % CI)	p value
Overall range	1–23	0–6		
Adequate treatment, n (%)	2 (18 %)	6 (24 %)	0.7 (0.11-4.2)	0.53
Susceptibility to antimicrobials, n (%)				
Susceptibility to ampicillin-sulbactam	7 (63 %)	20 (80 %)	0.43 (0.09-2.1)	0.26
Susceptibility to carbapenems	5 (45 %)	11 (44 %)	1.06 (0.25-4.41)	0.60
Susceptibility to cefepime	3 (27 %)	5 (20 %)	1.5 (0.29–7.8)	0.46
Susceptibility to aminoglycosides	10 (91 %)	14 (56 %)	7.8 (0.86-71.06)	0.04
Polimicrobial Acinetobacter infection, n (%)	9 (82 %)	18 (72 %)	1.75 (0.3-10.2)	0.42

SD standard deviation, IQR interquartile range, CI confidence interval, OR odds ratio

* It was not possible to calculate OR

Table 3 Multivariate analysis of factors potentially associated within-hospital mortality in patients with Acinetobacter infection—Emergency Department Intensive Care Unit, Hospital das Clínicas,University of São Paulo (January 2007–December 2009)

	OR	95 % CI	p value
Trauma	0.03	0.001-0.75	0.03
Health risk factors	10.65	83.21-136.65	0.07
Glasgow	0.81	0.61-1.09	0.16
Active co-morbid condition	0.23	0.01-6.33	0.37
Age	2.83	0.71-11.33	0.14

CI confidence interval, OR odds ratio

will lead to cell apoptosis. As the most abundant protein on the cell surface, OmpA is also important for resistance to complement and biofilm formation. Other key proteins are the phospholipases C and D that are important for resistance to human serum, epithelial cell evasion and enhancing the toxicity to host epithelial cells [18]. The O-glycosylation system is also essential to maintain the virulence of the pathogen and formation of biofilm [19]. Different (identified by restriction analysis of 16S–23S ribosomal RNA) and intergenic spacer sequences can be associated with distinct clinical outcomes [20]. In our retrospective study we could not identify all these important factors but the evaluation of species and virulence factors in future epidemiological and clinical studies of *Acinetobacter* infections may be important.

The limitations of our study are that it involved a relatively small number of patients, was conducted in only one hospital and included only the surgical ICU and not other ICUs that take care of *Acinetobacter* infected patients. These factors may limit the generalization of our results and conclusions. Also, due to the retrospective nature of this study it was not possible to collect data that would have allowed the use of specific anatomical and severity trauma scores.

In conclusion, trauma was a marker of good prognosis in patients with infections caused by *Acinetobacter* spp.

Prospective studies enrolling more patients should be developed to confirm our findings.

Conflict of interest None of the above authors have any conflict of interest.

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