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Acinetobacter etiology respiratory tract infections associated with mechanical ventilation: what impacts on the prognosis? A retrospective cohort study

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ABSTRACT

Introduction: Acinetobacter species treatment often represents a challenge. The main objective of this study is identify predictors of ICU mortality in patients submitted to mechanical ventilation (MV).
Materials and methods: Retrospective cohort study. Patients with MV > 48 h who developed a respiratory tract positive culture for *Acinetobacter* were included, and distinguished among colonized, ventilator-associated pneumonia (VAP) or ventilator-associated tracheobronchitis (VAT) patients. Primary outcome was ICU mortality.
Results: 153 patients were in MV and presented positive culture for *Acinetobacter calcoaceticus-baumanii complex*, 70 of them with VAP, 59 with VAT and 24 patients were colonized. The factors related to ICU mortality were VAP (OR 2.2, 95% CI 1.1–4.5) and shock at the time of diagnosis (OR 4.8, 95% CI 1.8–2.3). In multivariate analysis, only SOFA score at the time of diagnosis (OR 1.06, 95% CI 1.03–1.09) was related with ICU mortality. A paired-matched analysis was performed to assess effect of dual therapy on outcomes, and no effect was found in terms of clinical cure, ICU or hospital mortality or duration of antimicrobial therapy.
Conclusions: Previous comorbidities and degree of associated organic injury seem to be more important factors in the prognosis than double antibiotic therapy in patients with *Acinetobacter*-related respiratory infection.

1. Introduction

Acinetobacter species have emerged as one of the most troublesome classes of pathogens in health care institutions globally due to their remarkable ability to acquire resistance. *Acinetobacter* species have great persistence in the environment, making them one of the organisms that threatens the current antibiotic era [1] [2]. These bacteria are a common cause of late-onset ventilator associated pneumonia (VAP), which occurs >5–7 days after admission to the hospital, and are associated with an increased prevalence of multidrug-resistant organisms in recent years, especially in the intensive care unit (ICU) setting [3] [4].

Adequate empirical therapy of severe infections caused by *Acinetobacter* is crucial in terms of survival [5]. Due to the increasing antimicrobial resistance and the lack of well-designed studies, treatment for *Acinetobacter* infections often represents a challenge [6]. There are open questions in this scenario, especially regarding mono- or double therapy in carbapenem-resistant *Acinetobacter* infections, with conflicting results reported in the literature [7] [8] [9]. Treatment duration for infections caused by *Acinetobacter* has been assessed in observational studies including predominantly VAP and bloodstream infections, with a duration of treatment ranging from 10 to 22 days [6]. There was a strong trend to reduced relapse rates in long-course treatment [10], to a great extent due to a study that reported lower relapses of nonfermenting gram-negative bacilli (primarily *Pseudomonas* and *Acinetobacter*), but with a low number of patients included with *Acinetobacter* infection [11]. The optimal time course of intravenous antibiotic for symptomatic ventilator-associated tracheobronchitis (VAT), especially in multidrug-resistant pathogens, is also an open question.

The main objective of this study was to identify predictors of ICU mortality and clinical cure in patients subjected to mechanical ventilation (MV) with respiratory infection due to *Acinetobacter* identified in tracheal specimens, especially with regard to short- versus long-course of treatment and mono- versus double antibiotic therapy.

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2. Materials and methods

A retrospective cohort study was conducted in the adult ICU of the Hospital Nossa Senhora da Conceição, an 800-bed tertiary hospital located in Porto Alegre, Brazil, from January 2011 to September 2014. The ICU has 59 beds and covers all medical and surgical cases. The study was approved by the local ethics committee (institutional review board number 60248716.3.0000.5530) and was reported according to STROBE recommendations [12].

2.1. Study population

Informed consent was waived because of the observational nature of the study. The study cohort included all patients who were mechanically ventilated for >48 h and who developed culture-positive *Acinetobacter* in endotracheal aspirates (ETA) or bronchoalveolar lavage (BAL). Patients with polymicrobial VAP and patients with other previous or concurrent infections were excluded in the study. Eligible patients were identified by review of clinical culture results as part of the hospital's surveillance program to identify multidrug-resistant isolates.

2.2. Clinical and microbiological diagnostics methods and definitions

A diagnosis of ventilator-associated lower respiratory tract infection was based on the presence of at least two of the following criteria: body temperature of >38.5 °C or <36.5 °C, leucocyte count >12,000 cells per μL or <4000 cells per μL, and purulent ETA or BAL. All episodes of infection had to have a positive *Acinetobacter* isolation from the ETA of at least 10^5 colony-forming units (CFU) or from BAL of at least 10^4 CFU per mL. VAT was defined as meeting the aforementioned criteria with no radiographical signs of new pneumonia; VAP was defined by the presence of new or progressive infiltrates on chest radiograph [13]. Patients with no clinical symptoms or radiological evidence of an infiltrate were considered to have colonization. The diagnosis of VAP, VAT or colonization was performed by reviewing images and electronic medical records of each patient by one of two researchers (F·S or W.L.N), both with clinical experience in the management of similar patients as well as in the definition of VAP cases by epidemiological criteria. Doubtful cases were reviewed by both researchers and were settled by consensus. We defined clinical cure if the patient had resolution of symptoms and signs at the end of therapy. Species identification and antibiotic susceptibility testing were performed using a VITEK® system (BioMérieux SA, Marcy-l'Étoile, France) in accordance with Clinical and Laboratory Standards Institute (CLSI) standards. Clinical and treatment data were obtained retrospectively from the patient's medical charts and electronic records. Demographic records, underlying diseases, Sequential Organ Failure Assessment (SOFA) score at the time of *Acinetobacter* culture, duration of stay in an ICU, administration of individual antimicrobials, mono- or dual antimicrobial therapy and time of antimicrobial treatment were recorded. Antimicrobial therapy was primarily based on the clinical judgment of primary care physicians, according to local guidelines. The antibiotics and dosages for normal renal function prescribed were: polymyxin B (25,000 UI per kg as a loading dose followed by 15,000 UI per kg every 12 h), ampicillin-sulbactam (3 g every 4 h), meropenem (2 g every 8 h over 3 h), amikacin (20 mg per kg once a day), ceftazidime (2 g every 8 h) and tigecycline (100 mg as a loading dose followed by 50 mg every 12 h). Appropriate antimicrobial therapy was defined as administration of at least one antimicrobial agent to which the causative pathogen was susceptible. Antimicrobial therapy that did not meet this definition was considered inappropriate.

2.3. Clinical outcomes

The primary outcome measure was ICU mortality, and secondary outcomes were clinical cure of infection, hospital mortality and *Acinetobacter* reinfection. Chronic critical illness was defined according to ProVent 14 criteria [14].

2.4. Statistical analysis

Continuous variables were reported as the means with standard deviation (SD) when distributed normally or as medians with interquartile range when skewed. Differences between mean values were tested via Student's *t*-test, and differences between medians were assessed using the Mann-Whitney *U* test. Categorical data were summarized as proportions, and chi-square test or Fisher's exact test was used to examine differences between groups. We developed a multivariate analysis using Cox regression. Variables were selected using a backward stepwise procedure, *P* values < 0.2 were used as the cutoff for including them in the models. Covariates in the model included demographics, comorbidities, SOFA score, antibiotic therapy and time of antibiotic therapy. We also developed a propensity score considering factors associated with dual therapy. Subsequently, we matched patients according to the probability of receiving dual or monotherapy and evaluate outcomes. All tests were two-tailed, and a p value < 0.05 was deemed a priori to represent statistical significance. Analysis were performed in SPSS 19.0 software (IBM SPSS, Armonk-NY, USA) and matching was performed in R (3.4.3), using "*matchit*" package.

3. Results

One hundred fifty-three patients underwent MV and presented with positive cultures for *Acinetobacter calcoaceticus-baumannii complex* (93% carbapenem-resistant). Seventy patients (45%) presented diagnostic criteria for VAP, 59 (38.6%) for VAT and 24 patients (15.6%) were defined as colonized patients. The most common antibiotics used in monotherapy were polymyxin B ($n = 32$) and ampicillin-sulbactam ($n = 15$). Amikacin, ceftazidime, piperacillin-tazobactam and meropenem were used alone in one patient each. The most commonly dual therapies used in this population were polymyxin B plus meropenem ($n = 25$) and polymyxin B plus ceftazidime ($n = 20$). Polymyxin B plus ampicillin-sulbactam ($n = 13$), polymyxin plus amikacin ($n = 13$), ampicillin-sulbactam ($n = 3$), polymyxin B plus tigecycline ($n = 2$) and ceftazidime plus amikacin ($n = 2$) were also used. The time of ICU stay prior to the culture of *Acinetobacter* was 20 days, and 45 patients (29.4%) had septic shock at the time of diagnosis. Clinical characteristics are presented in Table 1. ICU mortality was 66% (101 patients) and hospital mortality was 72% (111 patients). Seventy-seven patients had clinical cure of VAP or VAT and showed no difference in their treatment times.

The factors related to ICU mortality were VAP and shock at the time of diagnosis (Table 2). Although bacteremia was not associated with ICU mortality, this variable was positive when hospital mortality was assessed ($p = 0.037$). Its OR could not be calculated, since 100% of the 12 patients who had bacteremia (7.8% of the total patients) also died in hospital.

A multivariate analysis exploring ICU mortality was performed with the 129 patients who received treatment for VAP or VAT. The statistical model included SOFA, number of days of antibiotic treatment, adequate empirical therapy, VAP, bacteremia on diagnosis and monotherapy. Shock at the time of diagnosis and hemodialysis were excluded from the model by collinearity with the SOFA criteria. In this analysis, the only variable that was identified as related to the increase in ICU mortality was SOFA score at the time of diagnosis (Table 3).

A total of 109 patients received treatment for VAP or VAT for more than seven days, and 38 of them received a long course (>14 days). There was no difference in the mortality rate of this population when compared to the rate of those who received antimicrobial therapy for a period of between 7 and 14 days (63% versus 59%, respectively, OR 1.1; CI 95% 0.5–2.6, $p = 0.83$). When the treatment time (between 7 and 14 days or >14 days) was included in the multivariate analysis

Table 1
Main clinical characteristics.

Clinical chart	n or mean (% or SD)
Male sex	97 (63.4%)
Age (years)	58.8 (14.8)
SOFA at diagnosis	7.6 (3.7)
Hospital stay (days)	20.6 (18.6)
VAP	70 (45.8%)
VAT	59 (38.6%)
Acinetobacter colonization	24 (15.6%)
HIV infection	21 (13.7%)
Solid neoplasy	27 (17.6%)
Hematological neoplasy	11 (7.2%)
Heart failure	26 (17%)
COPD	22 (14.4%)
Previous stroke	34 (22.2%)
Hemodialysis	60 (39.2%)
Shock at time of diagnosis	45 (29.4%)
Carbapenem-resistant Acinetobacter	143 (93.5%)
Polymixin B treatment	105 (68.6%)
Tigecycline treatment	3 (2%)
Carbapenem treatment	31 (20.3%)
Aminoglycoside treatment	20 (13.1%)
Ampicillin-sulbactam treatment	27 (17.6%)
Cephalosporine treatment	21 (13.7%)
Double treatment	78 (51%)
Time of treatment (days)	10 (4.4)
Time for adequate antibiotic therapy (days)	2 (2.2)
Bacteremia at diagnosis	12 (7.8%)
ARDS at diagnosis	8 (5.2%)

Legend: ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency syndrome; SOFA, sequential organ failure assessment; VAP, ventilator-associated pneumonia; VAT, ventilator-associated tracheobronchitis.

model (replaced the continuous variable treatment time), there was also no statistical significance regarding the change in ICU mortality (OR 1.08; 95% CI 0.80–1.47; $p = 0.5$).

A propensity score to predict receiving dual or monotherapy was calculated in the whole sample, adjusting for presence of chronic critical illness, presence of shock and use of carbapenem and polymyxin B. Then, a paired-matched analysis was performed to assess effect of dual therapy on outcomes, and no effect was found in terms of clinical cure, ICU or hospital mortality or therapy duration (ESM 1).

4. Discussion

In this retrospective cohort study, respiratory tract infection secondary to *Acinetobacter* was associated with high mortality in critically ill patients. Carbapenem-resistant *Acinetobacter* colonization was strongly associated with patient severity [15] and may be a sign of poor prognosis, especially in patients with prolonged ICU stay. In our cohort, only SOFA score on the day of *Acinetobacter* respiratory tract-associated infection was independently associated with ICU mortality, reinforcing findings previously described in the literature [15] [16] [17] in which patient severity was an important factor in establishing prognosis after infection. It is well established that the severity of VAP is an important prognostic variable to highlight the degree of injury (bacteremia in the diagnosis) and the presence of hypotension at the time of diagnosis. Therefore, intrinsic variables such as comorbidities, the degree of organic injury induced by the infection as well as bacterial pathogenicity may have a more significant impact on the outcome than will the time to adequate therapy, time of treatment, use of dual therapy or even the use of one class of antimicrobial over another.

We did not find an association between VAP and ICU mortality; however, the low sample size may have made it impossible to establish an association between the variable and the outcome. We can consider that there is the possibility of a spectrum of evolution of severity in lung injury, from the evolution of colonization by *Acinetobacter* to a clinically significant infection without radiological repercussion (TAV) or from progression to injury with radiological repercussion (VAP) [18] [19]. It is not possible rule out the fact that a spectrum of greater pulmonary involvement may be associated with a worse prognosis [20] [13].

Combined therapy was not associated with better prognosis in respiratory tract *Acinetobacter* infections in various clinical settings and susceptibility profiles [16] [8], and in this study, we also did not find an association between dual therapy and ICU mortality, even in a population mostly composed of carbapenem-resistant species. Combination antibiotic therapy was associated with appropriate initial treatment, with controversial beneficial results when definitive therapy was instituted [21] [22]. Our records were consistent with current guidelines in which polymyxin-based therapy is advocated in cases of ampicillin-sulbactam or carbapenem resistance [23] and despite doubts regarding the pharmacokinetic and pharmacodynamic efficacies with the use of polymyxin monotherapy [24]. Our results showed no differences

Table 2
Variables associated with ICU mortality – univariate analysis.

Variable	ICU non-survivors n or mean (% or SD)	ICU survivors n or mean (% or SD)	Univariate analysis: OR (95% CI)	p
Male sex	64 (63.4%)	33 (63.5%)	0,9 (0.49–1.90)	1.0
VAP	53 (52.5%)	17 (32.7%)	2,2 (1.12–4.58)	0.026
VAT	33 (32.7%)	26 (50%)	0,4 (0.24–0.96)	0.053
Acinetobacter colonization	15 (14.9%)	9 (17.3%)	0,8 (0.39–2.04)	0.810
HIV infection	16 (15.8%)	5 (9.6%)	1,7 (0.6–5.10)	0.331
Solid neoplasy	20 (19.8%)	7 (13.5%)	1,5 (0.66–4.00)	0.378
Hematological neoplasy	9 (8.9%)	2 (3.8%)	2,4 (0.53–11.72)	0.331
Heart failure	18 (17.8%)	8 (15.4%)	1,1 (0.42–2.92)	0.820
COPD	18 (17.8%)	4 (7.7%)	2,6 (0.84–8.15)	0.142
Previous stroke	22 (21.8%)	12 (23.1%)	0,9 (0.40–2.09)	0.842
Hemodialysis	44 (43.6%)	16 (30.8%)	1,7 (0.85–3.58)	0.162
Shock at diagnosis	39 (38.6%)	6 (11.5%)	4,8 (1.88–12.34)	<0.001
Polymyxin treatment	71 (70.3%)	34 (65.4%)	1.2 (0.67–2.55)	0.580
Carbapenem treatment	23 (22.8%)	8 (15.4%)	1.6 (0.63–3.93)	0.398
Aminoglycoside treatment	14 (13.9%)	6 (11.5%)	1.2 (0.44–3.42)	0.806
Ampicillin-sulbactam treatment	17 (16.8%)	10 (19.2%)	0.85 (0.37–2.03)	0.828
Cephalosporin treatment	14 (13.9%)	7 (13.5%)	1.0 (0.34–2.75)	1.000
Dual antibiotic treatment	54 (53.5%)	24 (46.2%)	1.3 (0.63–2.64)	0.403
Monotherapy treatment	31 (30.7%)	19 (36.5%)	0.7 (0.38–1.55)	0.470
Bacteremia at diagnosis	11 (10.9%)	1 (1.9%)	6.2 (0.78–49.65)	0.064
Adequate empirical therapy	29/86 (33.7%)	7/43 (16.3%)	2.6 (1.03–6.59)	0.042
SOFA score at diagnosis	8.6 (3.7)	5.7 (2.6)		<0.001
Time of treatment	9.5 (5.1)	11.1 (2.1)		0.529

Legends: COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency syndrome; SOFA, sequential organ failure assessment; VAP, ventilator-associated pneumonia; VAT, ventilator-associated tracheobronchitis.

Table 3
Variables associated with ICU mortality – multivariate analysis.

Variable	ICU non-survivors	ICU survivors	Multivariate analysis: OR (95% CI)	P
VAP	53 (52.5%)	17 (32.7%)	0.9 (0.91–1.55)	0.151
Monotherapy treatment	31 (30.7%)	19 (36.5%)	0.97 (0.74–1.23)	0.824
Bacteremia at diagnosis	11 (10.9%)	1 (1.9%)	1.0 (0.71–1.37)	0.836
Adequate empirical therapy	29/86 (33.7%)	7/43 (16.3%)	1.0 (0.80–1.32)	0.468
SOFA score at diagnosis	8.6 (3.7)	5.7 (2.6)	1.06 (1.03–1.09)	0.001
Time of treatment			0.98 (0.96–1.01)	0.160

Legends: SOFA, sequential organ failure assessment; VAP, ventilator-associated pneumonia.

among different antimicrobial regimens. Adjunctive inhaled therapy, especially based on colistin or aminoglycosides, was not employed in our patients. Inhaled therapy is a promising antimicrobial strategy in this setting, with a possible improvement in clinical cure but with uncertain effects on mortality or other harmful effects [23].

All of our patients who developed bacteremia died in the ICU, and a high mortality in this scenario has been previously described in general VAP patients [25] [26] and specifically in the *Acinetobacter* population, where it was associated with a carbapenem-resistance profile and previous exposure to broad-spectrum antibiotic therapy, primarily for treatment of VAP [27]. Age and increased length of ICU stay are known risk factors for this complication [26], and delay in detection of *Acinetobacter* bacteremia and consequent effective antimicrobial treatment may explain the results found in our study.

Despite the fact that colistin-based combination therapy for MDR *Acinetobacter* including the addition of rifampin, carbapenems, sulbactam and tetracyclines may improve microbiologic eradication rates and possibly better cure and survival rates [4] [29] [7] [30], our data did not support an increased benefit of dual over monotherapy in our *Acinetobacter* cohort. Studies comparing the effectiveness of dual over monotherapy in MDR *Acinetobacter* infections are scarce and conflicting. Similar results to ours were described in the literature despite a colistin susceptibility profile [31]. Differences among various studies may have resulted from microbiological properties, infection types and antibiotic dosing schemes, but may also have arisen because of small sample sizes and a high potential for confounding and selection bias [31]. We did not find any effect of dual therapy even after matching a sample according to propensity score to receive two or more drugs. Outcomes in our sample seemed not to be affected by combination of drugs to treat *Acinetobacter*, even after adjustment, despite a small difference in time to adequate treatment. The importance of prompt treatment in nosocomial infection has been challenged recently [32], and our finding is in accordance with this concept.

We did not find differences among distinct antimicrobial classes in terms of ICU mortality rate, despite complete sensitivity to polymyxin in the samples of our cohort. This result was in accordance with the literature, where various antimicrobial combinations in a colistin-based therapy did not achieve better outcomes [33] [34]. The low number of patients treated with antimicrobials other than polymyxin, as well as the great heterogeneity in the combination therapies in use, does not allow us to provide any conclusions regarding the superiority of one antimicrobial class over another. However, such data reinforce the recommendation for individualized therapy, considering the resistance profile of *Acinetobacter*, the site of primary infection, the complications developed by the patient and the pharmacokinetic-pharmacodynamic profile of the antibiotics in use.

There are limitations in this study that should be acknowledged. First, the fact that this was a single-center study may limit the generalizability of the results to different settings. Second, the retrospective design of the study did not allow us to completely exclude confounding biases among established correlations, and some data such as appropriate administration of antibiotics were incomplete. Third, as a retrospective study, time of antibiotic treatment was quite heterogeneous, depending on the decisions of the clinical team during the management and the clinical response of the patients. Therefore, it was not possible to establish precisely whether or not prolonged antimicrobial therapy was associated with changes in prognosis. Despite the fact that there were no apparent differences in outcomes, the number of patients did not allow us to present definitive conclusions regarding the use of one class of antimicrobial agents over another. Our sample size was also insufficient to demonstrate an increase in mortality in patients with VAP compared to that in patients with VAT. We also found an extremely high rate of patients with inadequate empiric antimicrobial therapy, and although we found no difference in ICU mortality in these patients, the impact of delayed effective antimicrobial therapy (approximately 2 days) on the various analyzed variables could not be better characterized. Finally, we did not perform additional microbiological analyses (matrix associated laser desorption-ionization – time of flight or polymerase chain reaction).

5. Conclusion

Respiratory tract infections associated with MV caused by *Acinetobacter* were associated with a high mortality in ICU, occurring mainly in patients with prolonged hospitalization. The patient's previous comorbidities and the degree of organ dysfunction caused by the infection were significantly associated with the outcomes, more so than the use of appropriate empirical therapy, the duration of antibiotic therapy or the use of dual antimicrobial therapy.

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Conflict of interest statement

The authors confirm that they have no conflicts of interest in the elaboration of this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2018.10.034.

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