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International Journal of Infectious Diseases 17 (2013) e1225–e1228

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Acinetobacter baumannii ventilator-associated pneumonia: epidemiology, clinical characteristics, and prognosis factors

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ARTICLE INFO

Article history:
Received 3 May 2013
Received in revised form 27 June 2013
Accepted 19 July 2013

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Acinetobacter baumannii
Ventilator-associated pneumonia
Epidemiology
Prognosis

SUMMARY

Objective: The aim of this study was to describe the epidemiological characteristics of *Acinetobacter baumannii* ventilator-associated pneumonia (VAP) and to identify factors predictive of a poor outcome.
Methods: A retrospective study was conducted over 16 months in a Tunisian intensive care unit (ICU). All adult patients with *A. baumannii* VAP were included.
Results: Ninety-two patients were included in they study; 41 (44.6%) were admitted because of multiple trauma. The mean age of the patients was 44.5 ± 19.5 years. All patients needed mechanical ventilation on admission. The mean SAPS II score was 39 ± 15. The mean delay before VAP onset was 8.1 ± 4.7 days. On VAP onset, 57 patients (62%) developed septic shock. Only 14.2% of isolated strains were susceptible to imipenem; none were resistant to colistin. The mean duration of mechanical ventilation was 20 ± 11 days. The mean duration of ICU stay was 24.3 ± 18.7 days. ICU mortality was 60.9%. In the multivariate analysis, factors predictive of a poor outcome were previously known hypertension (odds ratio 5.8, 95% confidence interval 1.4–24.9; $p = 0.018$) and VAP-related septic shock (odds ratio 8.5, 95% confidence interval 3–23.7; $p < 0.001$).
Conclusion: A. baumannii VAP is associated with a high mortality. Hemodynamic impairment is predictive of a poor outcome.
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1. Introduction

Ventilator-associated pneumonia (VAP) is a frequent nosocomial infection in critically ill patients, with a high mortality rate, reaching up to 33–50%.[1,2] During recent decades, *Acinetobacter baumannii*, a microorganism characterized by rapid development of resistance to the majority of antimicrobials, has emerged as a pathogen frequently incriminated in lower respiratory tract infections in critically ill patients.[3,4] Data available in the literature reveal an important disparity in bacterial ecology between countries. *A. baumannii* is known to be endemic in countries of North Africa and the Middle East.[5,6] However, several outbreaks have also been reported in European countries.[7,8] Recently, we reported that *A. baumannii* was responsible for 29.4% of VAP in our intensive care unit (ICU), coming in second to *Pseudomonas aeruginosa*.[9] Even though the hallmark of *A. baumannii* VAP is its multidrug resistance, the prognostic impact of this complication remains controversial and results have been conflicting.[3,10] Moreover, factors predictive of a poor outcome have rarely been investigated.[11] Thus, the aim of this study was to describe the epidemiological and clinical characteristics of *A. baumannii* VAP and to identify factors predictive of a poor outcome in critically ill patients who develop this nosocomial complication.

2. Patients and methods

2.1. Study design

This retrospective observational study was conducted from August 1, 2010 to November 30, 2011 in our medical surgical ICU (Habib Bourguiba Hospital, Sfax, Tunisia). The study was approved by the local ethics board.

2.2. Patients

All medical files of patients older than 15 years admitted to the ICU were reviewed retrospectively. We included in our study all patients with confirmed *A. baumannii* VAP. VAP was defined as pneumonia that occurred within 48 h after commencing mechanical ventilation.[2] Pneumonia was defined according to the criteria of the US Centers for Disease Control and Prevention. The diagnosis required two or more of the following criteria to be met: (1) fever

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http://dx.doi.org/10.1016/j.ijid.2013.07.014

increase of ≥1 °C or body temperature >38.3 °C; (2) leukocytosis (25% increase and $\geq 10 \times 10^9$/l) or leukopenia (25% decrease and $\leq 5 \times 10^9$/l); and (3) purulent tracheal secretion (>25% neutrophils per high-power field). It also required one of the following criteria to be met: (1) new or persistent infiltration on chest radiography; (2) some microorganisms isolated from pleural effusion and tracheal secretion; (3) radiographic cavitation or histological evidence of pneumonia pathogens; or (4) positive sputum culture from a quantitative bacterial bronchoalveolar lavage (BAL) culture of 10^5 colony-forming units (CFU)/ml.[11] In our study, the diagnosis needed to be confirmed with a lower respiratory tract sample using a quantitative culture with a predefined positive threshold of 10^4 CFU/ml for BAL. Patients with a positive culture lower than the predefined threshold, those with no clinical symptoms, and/or those without radiological evidence of an alveolar infiltrate were considered to have *A. baumannii* colonization and were excluded from the study.

2.3. Data collection

Demographic, clinical, and biological findings on admission were obtained from the patients' medical charts and reviewed retrospectively. Clinical severity was assessed using the Simplified Acute Physiology Score (SAPS II), The Glasgow Coma Scale (GCS) and the Sequential Organ Failure Assessment (SOFA) score.[12,13] In trauma patients, the severity of injury was assessed by the Injury Severity Score (ISS).[14] We also recorded the delay in onset of *A. baumannii* VAP and the susceptibility of isolated strains to antimicrobial agents. Antibiotics received before VAP onset were mentioned for each patient included. Clinical severity at VAP onset was evaluated using the SOFA score.[13] For each patient, we noted the delay in appropriate antimicrobial therapy as well as the duration of this therapy. Antimicrobial treatment was considered as appropriate if at least one agent was active against the isolated strain of *A. baumannii*. After culture results were known, the antimicrobial regimen was maintained or adapted on the basis of sensitivity testing.

2.4. Follow-up and outcome

All patients were followed up until death or ICU discharge. For each patient, we recorded further nosocomial events, the duration of mechanical ventilation, and the length of ICU stay (LOS).

2.5. Statistical analysis

Qualitative variables were expressed as percentages, whereas quantitative variables were expressed as means ± standard deviations or medians. Univariate analysis comparing survivors and non-survivors was performed in order to identify factors significantly correlated with mortality. Qualitative variables were compared using the Chi-square test or Fisher's exact test, whereas all quantitative variables were compared by *t*-test or Mann–Whitney test, as appropriate. The normal distribution of quantitative variables was checked using the Kolmogorov–Smirnov test. All tests were two-sided. The level of significance was set at $p < 0.05$. Variables were then subjected to a multivariate analysis with a logistic regression procedure and forward stepwise selection of $p < 0.10$, in order to identify independent factors predicting death in critically ill patients suffering *A. baumannii* VAP. Odds ratios (OR) were calculated with 95% confidence intervals (95% CI). SPSS version 18 was used for the statistical analyses (SPSS Inc., Chicago, IL, USA).

3. Results

Between September 1, 2009 and November 30, 2011, 2197 adult patients were admitted to our ICU. *A baumannii* was isolated in the BAL in 111 (5%) cases, but the diagnostic criteria for VAP were fulfilled in only 92 patients (4.2%); these patients were included in our study.

3.1. Baseline characteristics and therapeutic management on admission

The mean age of the patients was 44.5 ± 19.5 years (ranging from 18 to 91 years). The male to female sex ratio was 2.1. Forty-one patients (44.6%) were admitted because of multiple trauma, 24 (26.1%) were admitted because of acute respiratory failure, and seven patients (7.6%) were admitted for postoperative care. Other causes leading to ICU admission were coma for 13 patients (14.1%) and severe hypotension for seven patients (7.6%). Fourteen patients (15.2%) had a previous history of chronic obstructive pulmonary disease (COPD), and diabetes mellitus and/or hypertension were known in 36 patients (39.1%). The mean SAPS II was 39 ± 15 and the mean SOFA score was 8 ± 5, and the mean ISS was 48 ± 24 in trauma patients. On admission, 57 patients (62%) were hypotensive and needed vasopressor support. The mean Glasgow Coma Scale (GCS) score was 10 ± 4. Mechanical ventilation was instituted within the first 24 h in all cases. Eighty-eight patients (95.7%) received curative or prophylactic postoperative antimicrobial therapy. Amoxicillin–clavulanic acid was given to 45 patients (48.9%).

Biological findings on admission are summarized in Table 1.

3.2. A. baumannii *VAP characteristics*

The mean delay to VAP onset regarding mechanical ventilation was 8.1 ± 4.7 days (ranging from 3 to 32 days). Before VAP, 26 patients (28.3%) were re-intubated and 27 patients (29.3%) required a surgical tracheotomy. Moreover, at onset of VAP, 81 patients (88%) were receiving antimicrobial agents and 16 patients (17.4%) developed this nosocomial event while receiving imipenem. At onset of VAP, 19 patients were receiving cefotaxime (20.7%), 32 were

Table 1
Biological findings on admission

Parameters	*n*	Median	Mean	SD	Minimum	Maximum
pH	92	7.37	7.35	0.12	6.96	7.61
$PaCO_2$ (mmHg)	92	35	36	9.8	18	90.6
PaO_2 (mmHg)	92	125	131	51	52	269
$[HCO_3^-]$ (mmol/l)	92	20	20	5.2	6.7	40
SaO_2 (%)	92	98.3	97	3.7	82	100
PaO_2/FiO_2 (mmHg)	92	234	245	109	81	500
Leukocytes ($\times 10^9$/l)	92	13.750	14.270	6.134	1.800	28.000
Hb (g/dl)	92	10.7	10.8	2.7	4.9	16.2
Platelet count ($\times 10^9$/l)	92	164.5	179.7	92	27	472
BUN (mmol/l)	92	8	11.7	10.3	2.5	46.8
Creatinine (μmol/l)	92	102	162	138	30	624

Hb, hemoglobin; BUN, blood urea nitrogen.

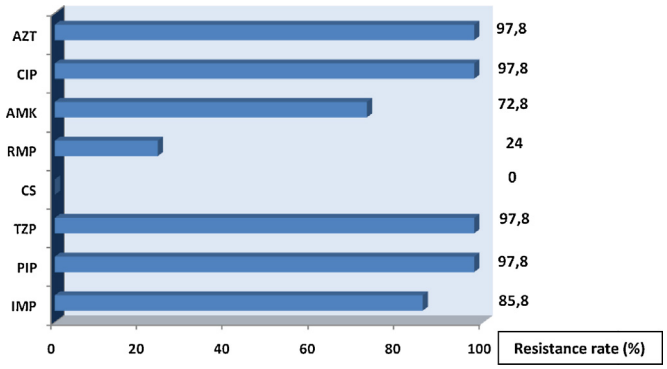

Figure 1. Antimicrobial susceptibility of isolated strains. The number of strains tested for antimicrobial susceptibility was 92. AZT, aztreonam; CIP, ciprofloxacin; AMK, amikacin; RMP, rifampin; CS, colistin; TZP, piperacillin–tazobactam; PIP, piperacillin; IMP, imipenem.

receiving amoxicillin–clavulanic acid (34.8%), 18 were receiving fluoroquinolones (19.6%), and only two patients were receiving amikacin (2.1%). Microbiological findings showed that 85.8% of isolated strains were resistant to imipenem, whereas no resistance to colistin was recorded (Figure 1).

On clinical examination, mean temperature was 38.3 ± 1.6 °C. Fifty-seven patients (62%) experienced septic shock requiring vasopressor support. The alveolar infiltrate was unilateral in 58 cases (63%). Associated pleural effusion was found in 10 patients (10.9%), and six patients (6.9%) developed a pulmonary abscess. Appropriate antimicrobial therapy was instituted within 1.8 ± 1.6 days regarding VAP onset (range 0–5 days). Colistin was the agent most used as the empirical antibiotic, as it was given to 86 patients (93.5%). When microbiological results were obtained, colistin was introduced or continued in combination with rifampin in six cases (6.5%) and with imipenem in 96 (93.5%) cases. The mean duration of antimicrobial treatment was 10.6 ± 6.6 days. Only nine patients (9.8%) had an associated *A. baumannii* bloodstream infection. Further relapse of *A. baumannii* VAP was recorded in three patients (3.3%).

3.3. Prognosis factors

The mean duration of mechanical ventilation was 20 ± 11 days (ranging from 6 to 55 days). The mean duration of ICU LOS was 24.3 ± 18.7 days. Fifty-six deaths were recorded in the ICU (60.9%). ICU mortality was significantly lower in trauma patients (19/41 vs. 37/51; $p = 0.01$). GCS was significantly lower in survivors (9 ± 4 vs. 11 ± 4; $p = 0.011$). Patients with known hypertension had a significantly higher mortality compared with the other patients (17/20 and 39/72, respectively; $p = 0.018$). No significant difference was found between survivors and non-survivors regarding the remaining clinical and biological baseline characteristics (Table 2).

The mean delay to onset of VAP was similar in the two groups studied: 7.9 ± 4 days in survivors and 8.2 ± 5.2 days in non-survivors ($p = 0.778$). However, mortality was significantly higher in patients with VAP complicated by septic shock needing vasopressors (44/57 (77.2%) vs. 12/35 (34.3%); $p < 0.001$). Similarly, the SOFA score at VAP onset was significantly higher in those who died compared to the survivors (8.4 ± 2.8 vs. 6.5 ± 3.1; $p = 0.004$). Biological findings at VAP onset showed that patients with a poor outcome had lower PaO_2/FiO_2 ratios (209 ± 104 vs. 265 ± 122 mmHg; $p = 0.021$), higher blood urea nitrogen levels (16.7 ± 12.1 vs. 10.6 ± 7.8 mmol/l; $p = 0.004$), and higher serum creatinine levels (156 ± 114 vs. 112 ± 94 μmol/l; $p = 0.049$). However, leukocyte and platelet counts were similar in the two groups studied. Moreover, *A. baumannii* susceptibility to imipenem had no impact on ICU mortality. In fact, mortality was 61.5% in patients with sensitive strains and 60.8% in patients with resistant strains ($p = 0.733$). Moreover, when analyzing the antimicrobial agents that our patients were receiving at VAP onset, we found that ICU mortality was significantly lower in patients who were receiving amoxicillin–clavulanic acid (46.9% vs. 70.2%; $p = 0.03$), whereas no correlation was found for the other agents. Appropriate antimicrobial treatment was also instituted with a similar delay regarding VAP onset: 1.8 ± 1.7 days in survivors and 1.8 ± 1.6 days in non-survivors ($p = 0.979$). In the multivariate analysis, independent factors predicting a poor outcome were previously known hypertension (OR 5.8, 95% CI 1.4–24.9; $p = 0.018$) and VAP-related septic shock (OR 8.5, 95% CI 3–23.7; $p < 0.001$) (Table 3).

Table 2
Comparison of baseline characteristics between patients who survived and patients who died

	Survived ($n = 36$)	Died ($n = 56$)	p-Value
Age, years, mean ± SD	40.3 ± 16.8	47.2 ± 20.8	0.095
Previous diabetes mellitus, *n*/%	3/8.3	13/23.2	0.092
Previous hypertension, *n* /%	3/8.3	17/30.4	0.018
SAPS II, mean ± SD	39 ± 17	40 ± 14	0.764
SOFA score, mean ± SD	8.5 ± 7	8 ± 3.5	0.569
Shock, *n* /%	21/38.2	34/61.8	0.82
GCS, mean ± SD	9 ± 4	11 ± 4	0.011
pH, mean ± SD	7.34 ± 0.13	7.35 ± 0.11	0.53
$PaCO_2$, mmHg, mean ± SD	35.9 ± 8	36.2 ± 10.9	0.885
PaO_2, mmHg, mean ± SD	146 ± 54	132 ± 47	0.125
Bicarbonates, mmol/l, mean ± SD	19.2 ± 4.7	20.3 ± 5.5	0.352
SaO_2, %, mean ± SD	97.6 ± 2.8	96 ± 4.2	0.14
PaO_2/FiO_2, mmHg, mean ± SD	264 ± 118	231 ± 101	0.156
Leukocytes, $\times 10^9$/l, mean ± SD	14.350 ± 6.458	14.217 ± 5.975	0.92
Platelets, $\times 10^9$/l, mean ± SD	177.8 ± 87	181 ± 96	0.869

SD, standard deviation; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; GCS, Glasgow Coma Scale.

Table 3
Multivariate analysis of factors predicting ICU mortality

Factors	p-Value	OR	95% CI	
			Minimum	Maximum
Previously known hypertension	0.018	5.8	1.4	24.9
Trauma	0.767	0.84	0.03	4.7
SOFA score >7 at VAP onset	0.58	1.47	0.37	5.9
VAP-related septic shock	< 0.001	8.5	3	23.7
PaO_2/FiO_2 <250 mmHg at VAP onset	0.164	2.3	0.7	7.2
Creatinine >150 μmol/l at VAP onset	0.874	1.2	0.23	3.5
Delay of appropriate antimicrobial treatment >2 days	0.979	1.01	0.33	3.1

ICU, intensive care unit; OR, odds ratio; CI, confidence interval; SOFA, Sequential Organ Failure Assessment; VAP, ventilator-associated pneumonia.

4. Discussion

Multidrug-resistant organisms are a growing concern in the ICU. Critically ill patients who develop VAP experience increased morbidity and mortality.[15] In 1993, Fagon et al. reported that for pneumonia caused by *Pseudomonas aeruginosa* or *Acinetobacter spp*, the attributable mortality was as high as 42.8%, with a relative risk of death of 2.5.[10] Available data in the literature suggest that mortality related to this nosocomial event varies from 26% to 68%.[10,16,17] Even though the reported mortality is high, only a few studies have been conducted to identify factors predictive of a poor outcome in patients developing this nosocomial event. Our results show septic shock and previous hypertension to be independent factors predicting a poor outcome. Whether or not these findings are specific to *A. baumannii* VAP cannot be formally established. In fact, Lisboa et al., in a prospective observational study including 441 VAP episodes, reported that septic shock was an independent factor predicting ICU mortality (OR 4.4, 95% CI 2.71–7.15). Unlike in

our study, Lisboa et al. included VAP episodes due to heterogeneous microorganisms and *A. baumannii* represented only 10.9% of all isolates.[18] Thus, the identification of previous hypertension as an independent factor associated with a poor outcome may be explained by a worse tolerance of hemodynamic impairment with more organ dysfunction compared with other patients.

Studies aimed at identifying predictive factors in ICU patients with *A. baumannii* VAP remain scarce. Chang et al. reported the following to be independent factors predicting 30-day in-hospital mortality in ICU patients with *A. baumannii* VAP: creatinine >1.6 mg/dl, inadequacy of initial antimicrobial therapy, CURB score ≥3, and C-reactive protein ≥120 mg/l.[11] Garnacho-Montero et al., in a prospective study including 81 episodes of VAP in critically ill patients, reported that the SOFA score on the day of VAP diagnosis was the only predictor of in-hospital mortality. Among all these episodes, 41 were due to *A. baumannii*. Interestingly, the authors reported that there was no significant difference in mortality related to the causative microorganisms (58.5% in patients with *A. baumannii* VAP vs. 65.9% in patients with VAP caused by other pathogens; $p = 0.3$).[3]

Inadequate empirical therapy of VAP is an independent predictor of mortality in heterogeneous populations of ICU patients.[3,19] This rule is also true in critically ill patients developing *A. baumannii* VAP.[19] In our study, the mean delay to the institution of appropriate antibiotic therapy was similar between survivors and non-survivors. This may be explained by the fact that in almost all cases, empirical antimicrobial therapy included colistin. This drug was chosen as a first-line antibiotic regimen in accordance with our local microbiological ecology.[20] In our study, colistin was given in combination with imipenem or with rifampin, as such associations have been reported to be synergic and prevent the development of colistin-resistant mutants.[21]

Even though factors predictive of a poor outcome related to *A. baumannii* VAP in critically ill patients have rarely been investigated, several limitations of our work should be mentioned. First, the retrospective nature of our study did not allow us to estimate the mortality attributable to this nosocomial event and only ICU mortality was recorded. Second, we included a heterogeneous population with different causes leading to ICU admission. Studies focusing on particular subgroups, such as trauma patients, may identify other predictive factors of a poor outcome more accurately. In fact, antimicrobial therapy was not standardized according to the susceptibility of the isolated strains.

In conclusion, hemodynamic impairment is particularly associated with a poor outcome in critically ill patients with *A. baumannii* VAP. In ICUs where this pathogen is endemic, empirical antibiotic therapy should include drugs that are effective according to the microbiological ecology. In Tunisian ICUs, colistin appears to be an appropriate first-line antimicrobial drug in critically ill patients developing late-onset VAP.

Funding source: None.

Conflict of interest: No conflict of interest to declare.

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