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Excess ICU mortality attributable to ventilator-associated pneumonia: The role of early vs late onset

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Abstract *Objective:* To determine the impact of ventilator-associated pneumonia (VAP) on ICU mortality, and whether it is related to time of onset of pneumonia. *Design:* Prospective cohort study. *Setting:* 16-bed medical-surgical ICU at a university-affiliated hospital. *Patients and measurements:* From 2002 to 2003, we recorded patients receiving mechanical ventilation for > 72 h. Patients developing an infection other than VAP were excluded. Patients definitively diagnosed with VAP ($n = 40$) were cases and patients free of any infection acquired during ICU stay ($n = 61$) were controls. The VAP-attributed mortality was defined as the difference between observed mortality and predicted mortality (SAPS II) on admission. *Results:* Mechanical ventilation was longer in VAP patients (25 ± 20 vs 11 ± 9 days; $p < 0.001$), as was ICU stay (33 ± 23 vs 14 ± 12 days; $p < 0.001$). In the non-VAP group, no difference was found between observed and predicted mortality (27.9 vs 27.4%; $p > 0.2$). In the VAP group, observed mortality was 45% and predicted mortality 26.5% ($p < 0.001$), with attributable mortality 18.5%, and relative risk (RR) 1.7 (95% CI 1.12–23.17). No difference was observed between observed and predicted mortality in early-onset VAP (27.3 vs 25.8%; $p > 0.20$); in late-onset VAP, observed mortality was higher (51.7 vs 26.7%; $p < 0.01$) with attributable mortality of 25% and an RR 1.9 (95% CI 1.26–2.63). Empiric antibiotic treatment was appropriate in 77.5% of episodes. No differences in mortality were related to treatment appropriateness. *Conclusions:* In mechanically ventilated patients, VAP is associated with excess mortality, mostly restricted to late-onset VAP and despite appropriate antibiotic treatment.

Keywords Ventilator-associated pneumonia · Attributable mortality · Morbidity · Late-onset pneumonia

Introduction

Nosocomial pneumonia is the most frequent infection acquired in the Intensive Care Unit (ICU), accounting for as much as 25% of the nosocomial infection burden. Pneumonia in patients under mechanical ventilation, known as ventilator-associated pneumonia (VAP), remains an important issue due to its related morbidity and mortality, despite advances in antibiotic therapy and organ-function supportive treatments. The incidence of VAP is variable, ranging from 9 to 27%, and length of mechanical ventilation (MV) is one of the most significant factors [1, 2].

The ICU mortality in patients with VAP is high, ranging from 30 to 70%. It is related mostly to the underlying disease and the severity of the acute illness. Some case-control studies suggest that the mortality attributable to VAP ranges from 33 to 50% [1, 3–18]. Factors commonly related to this increased mortality are inappropriateness of

the empiric antibiotic treatment, the existence of bacteraemia and the virulence of the microorganisms. Nevertheless, similar studies have failed to prove any excess mortality attributable to VAP, suggesting that outcome may be related mainly to the severity of the underlying critical illness [9, 15]. This apparent contradiction may be due to differences in severity, early or late onset of VAP, the microorganisms involved, the appropriateness of the empiric antibiotic treatment or the presence or absence of other infectious diseases during ICU stay.

Our hypothesis was that VAP has a significant attributable mortality, but that this is due mainly to late-onset VAP. The objective of this study was to determine whether VAP has any attributable mortality and the relative role of early vs. late onset. To this end, we compared MV patients with VAP with those without VAP in the absence of any other infectious disease.

This study was presented in part as an abstract at the 17th Annual Congress of the ESICM [19].

Material and methods

This prospective observational study was performed in a 16-bed medical-surgical ICU at a university-affiliated hospital over a 2-year period (2002–2003). All patients submitted to MV for more than 72 h were recorded and prospectively followed during ICU stay. Exclusion criteria were the presence of any infection other than VAP acquired during ICU stay. Clinical variables recorded on admission were: age; gender; diagnostic category; severity of illness by SAPS II; and mortality risk predicted by SAPS II. Variables recorded during ICU stay were: length of MV; length of ICU stay; and outcome. Informed consent was not required by the ethics committee since confidentiality was guaranteed and no interventions were performed. Patients who developed VAP were compared with those who did not. The VAP was clinically diagnosed based on: the appearance of a new and persistent infiltrate on chest X-ray with fever (T° > 38.3 °C), purulent bronchial secretions, leucocytosis (> 10,000/mm^3) or leucopaenia (< 4000/mm^3) and hypoxaemia defined as PaO2/FiO2 < 250 mmHg. The clinical diagnosis was always confirmed by microbiological tests (protected catheter brush, bronchoalveolar lavage, or quantitative tracheal aspirate) carried out prior to the introduction of the initial empiric antibiotic. The VAP was defined as early onset when it developed in the first 4 days of MV, and as late onset when it appeared after the fourth day [3].

Appropriate empiric antibiotic treatment was defined when at least one of the drugs administered was effective against the pathogens obtained on the antibiogram and administered immediately after the microbiological diagnostic test was carried out. The only exception was the case of *Pseudomonas aeruginosa*, in which two effective drugs were required.

Attributable mortality was defined as the difference between observed mortality and mortality predicted by SAPS II on admission.

Statistical analysis

A descriptive analysis was performed. Continuous variables were expressed as means ± SD. Associations between categorical variables were assessed with the chi-square test or the Fisher's exact test. Student's *t*-test was used to compare groups on continuous variables. To control for potential confounding factors, a multivariate logistical regression analysis evaluating the possible covariates of inadequate antibiotic treatment, early-onset VAP and late-onset VAP on the prediction of ICU mortality was performed. Logistical regression was used for the estimation of coefficients. The odds ratios (OR) and 95% confidence intervals (CI) were calculated according to standard methods. The Hosmer-Lemeshow test was used to assess goodness-of-fit [20]. Statistical significance was defined as $p < 0.05$.

Results

A total of 101 patients met the inclusion criteria. Forty patients developed VAP during ICU stay. No differences between patients with VAP and those without were observed in terms of age, gender, diagnosis, and SAPS II on admission (Table 1). The most common diagnoses on admission were neurological diseases, respiratory failure and trauma (Table 1). The length of MV in non-VAP patients was similar to that of VAP patients at the time the condition was diagnosed.

The VAP group comprised 11 (27.5%) episodes of early-onset VAP and 29 (72.5%) episodes of late-onset VAP. The characteristics of patients with early and late episodes are shown in Table 2. The microorganisms involved in early-onset VAP were: Gram-negative bacilli ($n = 4$; 36%); *H. influenzae* ($n = 3$; 27%); *S. pneumoniae* ($n = 2$) (18%); *S. aureus* ($n = 1$; 9%); and polymicrobial ($n = 1$; 9%). In the late-onset VAP they were: *P. aeruginosa* ($n = 15$; 52%); methicillin-sensitive *S. aureus* ($n = 8$; 28%); *Enterobacteriaceae* ($n = 5$; 17%); and *S. pneumoniae* ($n = 1$; 3%).

The ICU mortality in the non-VAP group was 27.9%, closely matching SAPS-II-predicted mortality 27.4% ($p > 0.20$). In contrast, mortality in the VAP group was higher than predicted (45 vs. 26.5%; $p < 0.01$), yielding an attributable mortality of 18.5% (95% CI 3.1–34.8), or a relative risk of 1.7 (95% CI 1.1–23.2; Fig. 1).

Further analysis revealed that the excess mortality related to VAP was restricted mainly to patients with late-onset VAP. In early-onset VAP, mortality was similar to predicted mortality (27.3 vs. 25.8%; $p > 0.20$), whereas

Table 1 Clinical characteristics on ICU admission

Characteristics	VAP ($n=40$)	Non-VAP ($n=61$)
Age (years)	60 ± 20	63 ± 17
Female (%)	33	28
SAPS II (points)	38 ± 15	35 ± 16
SAPS II mortality risk (%)	26 ± 22	27 ± 20
Diagnosis (%)		
Respiratory failure	28	31
Neurological	30	26
Trauma	20	15
Cardiovascular	10	15
Cardiac arrest	7	8
Other	5	5
Length of mechanical ventilation before VAP or length of MV in non-VAP group (days)	13.3 ± 8.5	11.5 ± 9

All results were non-significant

Table 2 Clinical characteristics of patients with early and late episodes of VAP

Characteristics	Early VAP ($n=11$)	Late VAP ($n=29$)	Significance (p)
Age (years)	54 ± 19	62 ± 20	n.s.
Female (%)	19	31	n.s.
SAPS II (points)	38 ± 12	38 ± 16	n.s.
SAPS II mortality risk (%)	26 ± 16	27 ± 25	n.s.
Diagnosis (%)			
Respiratory failure	9	34	n.s.
Neurological	36	27	n.s.
Trauma	27	17	n.s.
Cardiovascular	9	10	n.s.
Cardiac arrest	18	3	n.s.
Other	–	7	n.s.
Length of MV before VAP (days)	4 ± 3	13 ± 9	0.001

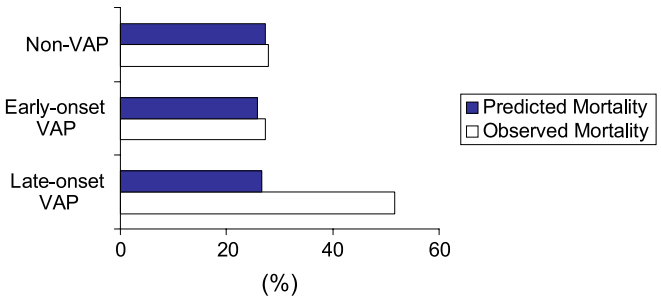

Fig. 1 Predicted and observed mortality in patients without VAP, with early-onset VAP and with late-onset VAP

late-onset VAP showed a significantly higher ICU mortality than predicted (51.7 vs. 26.7%; $p < 0.01$), with an estimated attributable mortality of 25% (95% CI 6.2–43.4%) or a relative risk of death of 1.9 (95% CI 1.2–2.69).

The empiric antibiotic treatment was appropriate in 31 patients (77.5%), with a non-significant trend towards greater appropriateness in early-onset than in late-onset VAP (91 vs. 72%; $p > 0.2$). In terms of outcome, attributable mortality in appropriately treated VAP was slightly lower than in inappropriately treated VAP (17.7 vs. 21.7%; $p > 0.4$), with a non-significant reduction in RR (1.6 vs. 1.95; $p > 0.49$).

Multivariate analysis, adjusted for appropriateness of empiric antibiotic treatment, showed late-onset VAP to be the only independent factor associated with ICU mortality, OR = 3.60 (95% CI 1.23–10.46; Table 3).

Total length of mechanical ventilation in non-VAP patients was shorter than in VAP patients (11 ± 9 25 ± 20 days; $p < 0.001$), as was ICU length of stay (14 ± 12 vs. 33 ± 23 days; $p < 0.001$).

Table 3 Independent variables selected by multivariate analysis as associated with ICU mortality, expressed as odds ratio (OR) with 95% confidence interval (CI)

Variable	OR (95% CI)	Significance (p)
Early-onset VAP	1.38 (0.27–6.85)	0.69
Late-onset VAP	3.60 (1.23–10.46)	0.01
Appropriateness of antibiotic treatment	1.70 (0.61–4.75)	0.30

Hosmer-Lemeshow test ($p = 0.72$)

Discussion

The results of this study show that patients that develop VAP have a higher risk of death than predicted by ordinary risk-assessment tools. This excess mortality is restricted mainly to patients with late-onset VAP, and is only marginally reduced with appropriate empirical antibiotic treatment.

Mortality in patients with VAP is a controversial subject because the target population is severely ill and the level of associated mortality is high. Several studies have attempted to clarify the issue [7–13, 15, 17, 18, 21, 22]. Bueno-Cavanillas et al. [23] found that critically ill patients with a nosocomial infection, mainly bacteraemia and pneumonia, have a higher mortality. Moreover, using multivariate analysis Fagon [24] found that VAP was the nosocomial infection associated with the highest risk of death, as a direct consequence of the infection. Whereas some authors using case-control designs have suggested that the attributable mortality of VAP may range from 25 to 76% [8, 12, 17, 18, 21], others have failed to demonstrate any excess mortality attributable to VAP [7, 9–11, 13, 15].

Our study has two main strengths: firstly, the majority of confounding factors, i. e. age, gender, diagnosis categories, severity of illness on admission and length of MV before VAP, were similar in patients that developed VAP and in those that did not. Secondly, patients with any other infection were excluded from the analysis; thus, a major confounding factor was eliminated.

An important finding of this study is the impact of the time of onset of VAP on attributable mortality. The better prognosis for early-onset VAP may be related to the lower virulence of the microorganisms involved and to the fact that empiric treatment was more frequently appropriate. In the multivariate analysis evaluating the possible covariates of inadequate antibiotic treatment, early-onset VAP and late-onset VAP on prediction of ICU mortality, late-onset VAP was the only independent factor associated with ICU mortality. These results confirm that early-onset VAP does not increase mortality when caused by non-multi-resistant bacteria and an appropriate antibiotic regime is administered, as some authors have suggested [25–29].

In terms of the applicability of our results to other scenarios, some details deserve mention: the microorganisms involved, the proportion of early- vs. late-onset VAP and the appropriateness of treatment. In our study, *P. aeruginosa* and *S. aureus* were the most common causes of VAP. Some studies [30–32] found *S. aureus* predominantly in early-onset VAP, whereas in our patients it was most common in late-onset VAP. Two factors account for this difference: firstly, our definition of early onset, restricted to the first 4 days of MV, and, secondly, our universal use of continuous aspiration of subglottic secretions, which is recognized to be a reducing and delaying factor for VAP [33]. This preventive technique appears to be the only factor that explains our lower rate of early-onset VAP.

Inappropriateness and delay in antibiotic treatment has been associated in some studies with worse outcome in VAP [34–38], although others have failed to prove this association [39, 40]. The most interesting issue is that the association is commonly found in studies with a high rate of inappropriateness (up to 50%) but not in studies with low rates of inappropriateness (around 20%). Our study, in which inappropriateness was recorded in 23% of cases, supports this hypothesis by showing a slight, non-significant trend toward lower attributable mortality when treatment was appropriate. On the other hand, in a recent multicentre study about the mortality associated with late-onset pneumonia in the ICU, Moine et al. [34] also found that late-onset pneumonia independently contributed to ICU patient mortality, but only when empirical antibiotic treatment was not appropriate. In this study the initial empiric antibiotic therapy was considered immediately effective in 38% of cases and the overall ICU mortality was 47% among patients with late-onset pneumonia and 22% among patients without episodes of late-onset pneumonia, with standard mortality ratio (SMR) calculated with SAPS II of 1.55 for patients with pneumonia and 0.84 for patients without episodes of late-onset pneumonia. In our study, the SMR in late-onset episodes of pneumonia was 1.9, with an overall ICU mortality of 51.7% vs. a predicted mortality of 26.7%. This higher mortality was attributed in part to a high incidence of *P. aeruginosa* among our late-onset pneumonia episodes (52%) compared with 31.4% among episodes in the study by Moine et al. [34], despite the higher incidence of appropriate empirical antibiotic therapy in our study.

In accordance with previous studies [26, 27], our data demonstrate a longer duration of MV and ICU stay in patients with VAP than in patients without VAP.

Our study has some potential limitations. The sample size is large enough to demonstrate differences in VAP attributable mortality, but not large enough to explore the subgroup of appropriate treatment or the differential effect of microorganisms with different levels of virulence. The single-centre design is sensitive to effects caused by centre-specific approaches, such as sedation, paralysis or weaning, that clearly have a strong influence on the major risk factor, i. e. length of MV. Our approach for estimation of attributable mortality is also debatable. One of the methods of calculating attributable mortality is a case-control study of patients with and without VAP after matching for the most recognized variables that influence mortality, i. e. age, severity of illness and diagnosis on admission. Nevertheless, we prefer the definition of attributable mortality as the difference between observed mortality and the mortality rate predicted by commonly used severity scores [41]. Comparison of predicted and observed death rates may provide an assessment of the overall quality of care in a given ICU. When applied to specific groups of patients, comparison of predicted and observed death rates may indicate an excess mortality associated with a com-

plication, or a lower mortality due to a new therapeutic intervention. It is still unclear which score is the best score. Older scores, such as APACHE II, have lower calibration but are widely accepted among clinicians [42]. SAPS III, a very new score, has very good calibration, but it has not yet been fully evaluated in all clinical conditions. We therefore used second-generation scores (APACHE II and SAPS II) for these comparisons in order to estimate attributable mortality. We chose SAPS II simply for financial reasons. Additionally, SAPS II calculated at the same time as VAP diagnosis has proved useful in two previous studies [6, 39]. Both SAPS II and APACHE II scores have been used to measure performance in the ICU setting; however, neither of them can be relied on to provide prognostic information for individual patients. On the other hand, the predicted mortality measured by SAPS II or APACHE II is not uniform in all types of patients and ICUs, and an expanded SAPS II has recently been recommended for calculating the standardized mortality rate or to measure the performance of ICUs [43, 44]; however, SAPS II has proved to predict outcome accurately in our medical-surgical ICU, and similar predicted and observed death rates (27.9 vs. 27.4%) were also found within the overall control group in the present study.

Conclusion

In conclusion, in this study, VAP was associated with a significant attributable mortality. Further analysis revealed that the significant attributable mortality only applied to patients with late-onset episodes of VAP. The choice of appropriate antibiotic treatment only slightly reduces this excess mortality.

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