Research

Impact of nosocomial pneumonia on the outcome of mechanically-ventilated patients

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Background: Nosocomial pneumonia (NP) is a common complication in mechanically-ventilated patients and is considered to be one of the most common causes of morbidity and mortality. However, assessment of the associated mortality is not staightforward as it shares several risk factors with NP that confound the relationship. The aim of this study was to evaluate the impact of NP on the mortality rate in an intensive care unit. During the study period (January-December 1995) all patients under mechanical ventilation for a period > 48 h ($n = 314$) were prospectively evaluated, and the prognostic factors of NP, which have been identified in previous studies, were recorded.
Results: Pneumonia was diagnosed in 82 patients. The overall mortality rate was 34% for patients with NP compared to 17% in those without NP. Multivariate analysis selected the following three prognostic factors as being significantly associated with a higher risk of death: the presence of multiple organ failure [odds ratio (OR) 6.71, 95% CI, $P < 0.001$]; the presence of adult respiratory distress syndrome (ARDS) (OR 3.03, 95% CI, $P < 0.01$), and simplified acute physiology score (SAPS)> 9(OR 2.89, 95% CI, $P < 0.05$).
Conclusions: In mechanically-ventilated patients NP does not represent an independent risk factor for mortality. Markers of severity of illness were the strongest predictors for mortality.

Keywords: mechanical ventilation, mortality, nosocomial pneumonia

Introduction

Nosocomial pneumonia (NP) is a common complication in mechanically-ventilated patients, and despite some advances in antibiotic therapy it remains one of the most common causes of morbidity and mortality [1–3]. However, the assessment of mortality is not straightforward as it shares several risk factors with NP, confounding the relationship. Although several studies have been undertaken in order to clarify this relationship [4–13], definite conclusions have not been reached. Moreover, recent studies have shown that appropriate antibiotic therapy can have a favorable impact on the outcome of NP [14]. The purpose of this study was to evaluate the prognostic factors in patients with ventilator-associated pneumonia, and determine whether attributable mortality would be absent in the setting of adequate empiric therapy.

Methods

Patients

From January to December 1995, all mechanically-ventilated patients admitted to our ICU were prospectively entered into the study. At the time of entry, age, sex, admitting service, smoking history, serum albumin level, history of chronic obstructive pulmonary disease (COPD), severity of illness according to the method of McCabe and Jackson [15], indication for ventilatory support, altered level of consciousness (Glasgow Coma Score < 8), the acute physiology and chronic health evaluation (APACHE II) score [16], and simplified acute physiology score [17] (SAPS) were recorded for each patient. Temperature, blood leukocytosis/mm^3 and PaO_2/FiO_2 were recorded daily. Chest radiographs were also obtained on a daily basis.

A fiberoptic bronchoscopy (FB) was performed within the first 24 h after the clinical diagnosis of pneumonia was suspected when the patients showed at least three of the following criteria: fever ≥ 38.5°C; purulent tracheobronchial secretions; leukocytosis (≥ 12,000/mm^3) or leukopenia (< 4000/mm^3), and new, progressive or persistent (> 24 h) infiltrate on the chest radiograph, this latter criterium being always present. Protected specimen brush (PSB) and bronchoalveolar lavage (BAL) samples were also obtained.

Specimen collection

The procedure was performed while patients were ventilated with 100% oxygen, without positive end-expiratory pressure, and with continous finger pulse oximetry (Ohmeda Biox, 3740 Louisville, CO, USA) and electrocardiographic monitoring.

The fiberoptic bronchoscope (Olympus BF P20D, Olympus Optical Corp of America, New Hyde Park, NY, USA) was introduced into the trachea through a ≥ 8 mm diameter endotracheal tube via a sterile connector (Bodai Suction Safe, Y: Sontek Medical, Lexington, MA). It was then advanced next to the orifice of the sampling area in order to visualize the entrance to the radiographically abnormal bronchial sub-segment.

The technique of PSB sampling in intubated patients has been described previously [18]. No suction was applied before taking the specimens and no local anesthetic agents were used. The sequence of sampling was always PSB followed by BAL and both procedures were performed in the same bronchial sub-segment except in those cases in which PSB caused significant bleeding. In these patients PSB was followed by BAL in the adjacent subsegment of the same bronchus. Bronchoalveolar lavage was carried out with 150 ml sterile saline solution in 50 ml aliquots, each of them being hand aspirated to permit sufficient suction without collapsing the airway. The first aliquot, intended to be a bronchial wash, was discarded and the subsequent ones were pooled and submitted for cytological and bacteriological analysis.

Processing of specimens

Specimens were immediately delivered to the laboratory and quantitatively processed for bacterial and fungal cultures using standard methods, as have been described previously [18].

Data analysis

Bacterial counts ≥ 10^3 cfu/ml for PSB and ≥ 10^4 cfu/ml for BAL samples were used as the cutoff point to establish a positive result. Recovery of > 1% of squamous epithelial cells in the BAL specimen was considered an accurate predictor of heavy oropharyngeal contamination, ie an unsatisfactory specimen.

Outcome and diagnostic categories

Subsequent changes in clinical outcome and radiographic findings were recorded and alternative explanations for the findings, such as atelectasis or pulmonary edema, were always excluded. Atelectasis was diagnosed when complete resolution of the infiltrates occurred during the first 48 h after its appearance. Cardiogenic and non-cardiogenic pulmonary edema was diagnosed by pulmonary arterial catheterization and response to appropriate therapy. Multiple organ failure (MOF) was defined according to the criteria of Bell *et al*[19]. The time without antibiotics and the type of treatment received before and after the procedure were recorded. Antibiotic therapy was started immediately after bronchoscopy, and the decision to modify it, according to the culture results, was left to the attending physician.

The diagnosis of pneumonia was based on:

1. consolidated foci and polymorphonuclear leukocyte accumulation in the bronchi and adjacent alveoli, shown by a necropsy study performed within 5 days after sampling procedures;

2. positive blood and/or pleural fluid cultures;

3. rapid cavitation of the lung infiltrate, and

4. clinical outcome consistent with bacterial pneumonia while receiving appropriate antibiotic therapy for the organisms cultured in PSB and/or BAL in significant growth.

Pneumonia was considered excluded if one or more of the following criteria was fulfilled:

1. full recovery without appropriate antimicrobial therapy or without changes in the antibiotic therapy initiated at least 72 h before the appearance of infiltrates, and

2. no signs of bacterial pneumonia at autopsy when available within 5 days after sampling procedures.

The presence or absence of each of the following potential risk factors were recorded: prior antimicrobial therapy; presence of bacteremia; development of pneumoniarelated complications; radiographic spread of the infiltrates; APACHE II and SAPS at the time when pneumonia was diagnosed, and days of mechanical ventilation until ICU discharge or death. Patient outcome (dead/alive) was determined at discharge.

No regimen for NP prophylaxis or selective decontamination of the digestive tract was employed.

The study protocol was approved by the Clinical Research Committee of the hospital.

Statistical analysis

Data are expressed as mean ± standard deviation. Univariate analysis was performed using the Chi-square test for categorical variables, Student's *t* test for normally distributed variables and the MannWhitney U test for non-normally distributed variables. Multivariate analysis was performed using the logistic regression technique. All variables were entered using two categories (0 = absent, 1 = present). For those variables with more than two categories, a cutoff point was selected according to the results of univariate analysis. $P < 0.05$ was considered significant.

Results

The study population consisted of 314 patients, 214 men and 100 women with a mean age of 55.65 ± 16.94 years (range 14-94). Patients had been admitted to the ICU because of respiratory failure ($n = 74$), heart failure ($n = 53$), impaired consciousness or loss of muscular strength as a result of neurological disorders ($n = 49$), multiple trauma ($n = 30$), postoperative respiratory insufficiency ($n = 28$), COPD ($n = 23$), and miscellaneous conditions ($n = 57$). Pneumonia was the final diagnosis in 82 (26%) of the 314 patients. Diagnosis was obtained by means of PSB (25 cases), BAL (45 cases), blood cultures (21 cases), pleural fluid culture (six cases), cavitation (two cases) and autopsy (15 cases). *Staphylococcus aureus* ($n = 26$), *Pseudomonas aeruginosa* ($n = 25$) and *Haemophilus influenzae* ($n = 16$) were the most frequent etiologies. Pneumonia was polymicrobial in 16 cases (19%). Twenty-eight high-risk microorganisms were isolated, with an associated mortality of 32%, which is the same rate observed in the remaining cases. The specific mortality of these microorganisms was as follows: *P aeruginosa* 32% (8/25); *S maltophilia* 0% (0/1); *Acinetobacter baumanii* 100% (1/1), and methicilin-resistant *S aureus* 0% (0/1).

At the time of suspicion of pneumonia 33 of the 82 patients (40%) were on antibiotics. The duration of prior antibiotic therapy (within 10 days before the diagnosis of pneumonia) was 12.1 ± 11 days. There were nine patients in whom FB was performed after beginning new antibiotics. Five of these patients (55%) subsequently died.

Twenty-eight patients (34%) developed early-onset pneumonia (< 5 days after hospitalization). *Staphylococcus aureus* ($n = 13$), *H Influenzae* ($n = 11$) and *S pneumoniae* ($n = 4$) alone or in combination accounted for 60.7% of the cases of early-onset pneumonia, whereas Gram-negative bacilli were present in only 11 of the episodes. The associated mortality in early-onset pneumonia was 41%. Gram-negative bacilli were shown in 34 of 54 (66.9 %) episodes of late-onset pneumonia (≥ 5 days after hospitalization). The mortality of late-onset pneumonia was 30%. The most commonly prescribed antibiotics for patients with pneumonia were the association of third generation cephalosporines and vancomycin, or aminoglycosides.

Table 1 shows the clinical characteristics of the patients. There were 17 patients clinically suspected of having pneumonia in whom this condition was not subsequently confirmed. Three of these patients (18%) died compared with 28 out of the 82 confirmed cases.

The overall mortality rate in patients with pneumonia was 34% (28/82) compared with 17% (39/232) in patients without pneumonia. Seventythree of the 82 patients with pneumonia were initially treated with adequate antibiotics according to the microbiological results. Twenty-three of these patients died compared with five of the nine patients who did not receive adequate therapy initially. Univariate analysis (Table 2) shows that nine variables (nonurgent postoperative patients, SAPS > 9 on admission, ARDS, APACHE II > 20 on admission, MOF, bacteremia, coma, shock and NP) were significantly associated with mortality. However, the stepwise logistic regression analysis identified only three of these (MOF, SAPS > 9 and ARDS) as significant predictors of outcome (Table 3). Within the group of patients with NP, the stepwise logistic regression analysis identified the presence of shock, ARDS, and APACHE II > 22 at the time of diagnosis of pneumonia as independent prognosis factors (Table 4). Days of mechanical ventilation and days in the ICU were significantly higher in patients with NP compared to those without NP (20.76 ± 18.1 *vs* 11.3 ± 10.3, and 20 ± 18.8 *vs* 14.5 ± 11.1, respectively; $P < 0.05$).

Discussion

The real impact of NP in ventilated patients is difficult to ascertain because risk factors for pneumonia such as underlying disease or the severity of illness also predispose patients to a greater mortality, and therefore these are potentially confounding variables.

In this study we performed a multivariate analysis, controlling variables known to be associated with mortality in order to evaluate how it is influenced by NP. However, we have been unable to demonstrate an independent contribution of NP to patients' mortality. Our results, however, provide evidence of a strong relationship between factors that are markers of severity of illness and risk of death. In fact, SAPS> 9, the presence of ARDS and MOF were the most important determinants of outcome. These results are comparable to those found by other authors using either case control studies [4,8,12] or multivariate cohort analysis [6,7,9,10]. However, other investigators have reported a consistent relationship between NP and mortality [15,11,13], particularly when pneumonia was caused by

Table 1
Characteristics of the 314 patients studied

	Number of non-NP patients ($n = 232$)	Number of NP patients ($n = 82$)
Age	57.38 ± 16.24	50.77 ± 18.38
Sex (male/female)	144/88	70/12
Diagnostic category (%)		
Medical	132 (57)	28 (34.14)
Trauma	17 (7.3)	25 (30.48)
Surgical	83 (35.7)	29 (35.36)
APACHE II		
On admission	15.3 ± 6.7	17.96 ± 6.96
On diagnosis of NP	N/A	19.63 ± 7.10
SAPS		
On admission	11.38 ± 5	13.46 ± 5.85
On diagnosis of NP	N/A	14.91 ± 3.46
PO_2/FiO_2		
On admission	311.2 ± 152.6	261.47 ± 140.49
On diagnosis of NP	N/A	146.55 ± 61.29
McCabe score (%)		
Non-fatal	137 (59.02)	55 (67.07)
Ultimately fatal	93 (40.9)	26 (31.70)
Fatal	2 (0.08)	1 (0.012)
COPD	16 (7)	7 (13.46)
Corticosteroids therapy	34 (14.65)	14 (17.07)
Coma	33 (14.2)	16 (19.51)
Length of ICU stay	14.5 ± 11.1	20.07 ± 18.17
Length of MV	11.03 ± 10.3	20.76 ± 18.80

COPD = chronic obstructive pulmonary disease; MV = mechanical ventilation; NP = nosocomial pneumonia; SAPS = simplified acute physiology score.

Table 2
Variables significantly associated with mortality (univariate analysis)

Factor	Survivors ($n = 247$)	Non-survivors ($n = 67$)	*P*	OR (95% CI)
Non-urgent postoperative patients	43	4	0.01	2.97 (1.10-7.93)
SAPS > 9	165	60	0.001	3.68 (1.68-8.06)
ARDS	36	34	0.001	6.03 (3.33-10.95)
APACHE II > 20 on admission	41	28	0.001	3.50 (1.94-6.30)
MOF	45	48	0.001	10.72 (5.80-19.80)
Bacteremia	36	22	0.001	2.86 (1.54-5.32)
Coma	32	17	0.01	2.23 (1.148-4.32)
Shock	36	17	0.05	1.99 (1.03-3.83)
NP	54	28	0.001	2.48 (1.40-4.39)

ARDS = adult respiratory distress syndrome; CI = confidence interval; MOF = multiple organ failure; NP = nosocomial pneumonia; OR = odds ratio.

antibiotic-resistant microorganisms [20–22]. Timsit *et al*[13] recently found that confirmation of ventilator-associated pneumonia using PSB and/or BAL added no prognostic information. In our work there were 17 patients clinically suspected of having pneumonia without further confirmation. Three of these patients died, a very similar mortality rate to those without pneumonia. In our study, none of the high-risk microorganisms (*S aureus, P aeruginosa* and *Acinetobacter spp*) were associated with an increased risk of death, whereas most of the work done on this subject has demonstrated that NP is associated with mortality in ICU

Table 3
Variables independently associated with mortality (multivariate analysis)

	OR	95% CI	*P*
MOF	6.71	(3.28-13.71)	0.001
SAPS > 9	2.89	(1.10-7.86)	0.05
ARDS	3.03	(1.48-6.21)	0.01

ARDS = adult respiratory distress syndrome; CI = confidence interval; MOF = multiple organ failure; OR = odds ratio; SAPS = simplified acute physiology score.

Table 4
Factors independently associated with mortality in patients with nosocomial pneumonia (multivariate analysis)

	OR	95% CI	*P*
Shock	12.50	3.5-44.0	0.01
ARDS	12.00	1.0-33.6	0.01
APACHE II > 22*	1.27	0.99-1.3	0.05

ARDS = adult respiratory distress syndrome; CI = confidence interval; MOF = multiple organ failure; OR = odds ratio. *At the time of diagnosis of pneumonia.

patients. Our results do not concur with these findings, probably reflecting the fact that our study is of a lower power.

Different explanations might be proposed to explain these conflicting results. The inclusion criteria differ between studies; some authors did not match patients according to the presence/absence of mechanical ventilation [5,8], the confounding factors were not always controlled [5], and strict criteria to define NP were used in only a few cases [11–13]. This may account in part for a large degree of variability in the rates of mortality. In our study, we selected patients under mechanical ventilation for > 48 h to obtain a homogeneous population, and we used specific criteria to define NP in order to exclude patients without pneumonia. Definitions for pneumonia are probably somewhat arbitrary and most episodes should be classified as `probable' pneumonia according to the American College of Chest Physicians Guidelines [23], but in our opinion restricting the assessment to `definite' episodes alone represents an important bias.

Another way of analyzing attributable mortality is to take the SAP score at the time pneumonia was diagnosed and look at the predicted mortality compared to the actual observed mortality. According to this, the overall mortality among ICU patients with SAPS of 14 was 30% [17], which is close to the 34% mortality observed among our patients with pneumonia.

Another important aspect in our study is that these patients received antibiotic treatment promptly after PSB or BAL, without waiting for microbiological results. In our study, 73 out of the 82 patients (89%) with pneumonia were initially treated with adequate antibiotics according to the microbiological results. Twenty-three out of these patients (28%) died in comparison with five out of nine patients (55%) who did not receive adequate therapy initially. Recent data by Luna *et al*[14] have shown that the accuracy of initial empirical therapy has a great impact on survival. Early and appropriate therapy could explain the discrepancy between our findings and those of other investigators.

In conclusion, our results suggest that after controlling for the other determinants of outcome, NP is not a major cause of mortality in mechanically ventilated patients.

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