Mortality of Nosocomial Pneumonia in Ventilated Patients: Influence of Diagnostic Tools

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The overmortality induced by nosocomial infections, especially pneumonia in ventilated patients (VNP), is still a matter of controversy because it is difficult to know precisely the respective effects of VNP per se and both the underlying illness and the severity of the disease that indicates ICU stay. During a 3-yr period, for each patient mechanically ventilated for more than 48 h we recorded underlying illness, reason for mechanical ventilation, clinical and therapeutic data collected during the first 48 h of ventilation, and death in the ICU. Patients with suspicion of VNP (S-VNP) according to clinical, radiologic, and biologic criteria underwent bronchoscopy with protected specimen brush (PSB) and bronchoalveolar lavage culture (BAL-C). VNP was confirmed (C-VNP) if PSB $\geq 10^3$ cfu/ml and/or BAL-C $\geq 10^4$ cfu/ml. Prognostic multivariate analysis was performed introducing S-VNP and C-VNP as time-dependent covariates. Of the 387 studied patients, 112 S-VNP and 56 C-VNP were observed with overall mortality of 43% (168 patients). MacCabe, APACHE II score, shock, use of sedatives and absence of enteral nutrition were additively associated with an increased mortality as well as C-VNP (relative risk [RR]: 1.8, p = 0.007). Nevertheless, when S-VNP and C-VNP were simultaneously introduced in the Cox model, only S-VNP remained associated with increased mortality. In patients suspected of VNP, confirmation of VNP using PSB and/or BAL-C adds no prognostic information. Whether this could be explained by the lack of sensitivity of protected distal samples or the severity of underlying conditions of S-VNP patients is still an open issue. A multivariate analysis based on follow-up data during the ICU course of ventilated patients will be initiated in the near future. Timsit J-F, Chevret S, Valcke J, Misset B, Renaud B, Goldstein FW, Vaury P, Carlet J. Mortality of nosocomial pneumonia in ventilated patients: influence of diagnostic tools. AM J RESPIR CRIT CARE MED 1996;154:116–23.

The overmortality induced by nosocomial pneumonia in ventilated patients (VNP) remains a controversial issue in literature. Previous studies have reached conflicting conclusions regarding whether the severity of the underlying illness or the development of nosocomial pneumonia was the most highly predictive factor of a poor prognosis and of prolonged hospitalization (1–3). One of the most confusing results is the effect of selective digestive decontamination (SDD) upon ventilator-associated pneumonia. Whereas SDD strongly decreases the rate of nosocomial pneumonia in ventilated patients, SDD reduces intensive care unit (ICU) mortality only marginally. Most studies used weak clinical definition for nosocomial pneumonia (1, 2, 4, 5). The clinical criteria commonly used for diagnosing lower respiratory tract infections appear nonspecific and it is therefore possible that more than 50% of patients included in previous series did not actually have pneumonia (6). On the contrary, criteria that lead to suspicion of nosocomial pneumonia might select a subset of severe patients with a worse evolution during ICU stay and consequently with a more severe prognosis; therefore, these criteria could have introduced a bias in measuring attributable mortality of nosocomial pneumonia (2).

The purpose of this prospective study was to evaluate prognostic factors in ICU patients mechanically ventilated for more than 48 h and particularly the association between VNP and mortality, by distinguishing two time-dependent events: suspicion of VNP and confirmation of VNP during the ICU stay.

METHODS

Criteria for Eligibility

This case study was carried out between August 1990 and April 1993, and included all consecutive patients admitted to the surgical and medical ICU of the Hôpital Saint Joseph (Paris, France). These patients constituted the inception cohort for the prognostic study, provided that they were mechanically ventilated for more than 48 h.

Data Collection and Baseline Data

All included patients were prospectively followed daily until ICU discharge. For each patient, standardized forms were completed recording diagnosis, orgin (from other ICU or home), main clinical features and laboratory findings at ICU admission, treatment modalities, in particular with regard to respiratory support and antimicrobial treatment, nosocomial pneumonia, and outcome. Diagnosis of nosocomial pneumonia in VNP was reported together with the results of microbiologic tests from the protected distal samples. Causes of death were recorded.

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Pneumonia

Nosocomial pneumonia was suspected in mechanically ventilated patients (S-VNP) by the staff physicians according to the appearance under ventilation of persistent pulmonary infiltrates on the chest X-ray and at least one of the following clinical or biologic findings (7): (*1*) purulent tracheal secretions, (*2*) body temperature > 38.5° C or < 36.5° C, (*3*) white blood cell count > 10×10^9/L or < 4×10^9/L. When VNP was suspected, fiberoptic bronchoscopy with protected specimen brush and bronchoalveolar lavage were performed for each patient within 12 h according to previously described protocol (8, 9). Confirmed VNP (C-VNP) was defined, according to the recommendations of the First International Consensus Conference on the Clinical Investigation of Ventilator Associated Pneumonia (10), by a positive protected specimen brush ($\geq 10^3$ cfu/ml) and/or by a positive culture of bronchoalveolar lavage fluid ($\geq 10^4$ cfu/ml). No patient received new antimicrobials before bronchoscopy.

Risk Factors

From the data collected within the first 48 h of ICU admission, the simplified acute physiologic score (SAPS) (11) and the acute physiology and chronic health evaluation (APACHE II) (12) were computed. Chronic health status was assessed using the Knauss score (12). History of chronic obstructive pulmonary disease (COPD) (13) and MacCabe score (14) were recorded. At admission, occurrence of shock (15) and coma (defined by a score ≤ 10 by the Glasgow coma scale [16]) was noted.

When VNP was suspected, organ system failure (OSF) (17) and SAPS were measured prospectively, as were use of prior antimicrobial therapy, duration of mechanical ventilation, temperature, change in temperature in the prior 2 d, blood leukocyte count, blood polymorphonuclear cells and lymphocytes counts, Pa_{O_2}/FI_{O_2} ratio, bilirubin, and platelets.

Finally, when VNP was diagnosed, the isolated microorganism was reported, with special mention of "high-risk" strains (18) (*Pseudomonas aeruginosa* and *Acinetobacter baumannii, Staphylococcus aureus*, and polymicrobial episodes of pneumonia).

Follow-up Guidelines

Therapeutic decisions were left to the discretion of the attending physicians and discussed daily with the medical staff. We routinely followed patients' tracheal and rectal colonization and if decided, antibiotic treatment was chosen on the basis of Gram-stain examination of BAL fluid and results of previous colonization samples. All patients were monitored until their discharge from the hospital and changes in the clinical and therapeutic course were recorded. Postmortem histopathologic investigations were performed as often as possible, especially when cause of death remained uncertain.

Statistical Analysis

The main endpoint was the overall survival from the date of inclusion (48 h after ICU admission). Patients who were discharged alive from ICU were censored at the time of their discharge. Kaplan-Meier estimate of survival was computed.

We first studied the prognostic value for death of several baseline characteristics, assessed within the first 48 h of ICU admission, including demographic characteristics (age, sex, chronic underlying disease, associated neoplasm, MacCabe), cause of ICU admission and diagnosis, severity of the patients (SAPS, APACHE II, Glasgow coma scale, shock, infection), use of mechanical ventilation (onset and cause for mechanical ventilation), and other therapeutic modalities (antimicrobial, H2 antagonists, sedatives, paralytic agents). Search for prognostic factors was based on the log-rank rest, which compares the distribution of survival times in several subsets. Variables found to be associated with the outcome by the log-rank test at a 5% level, that is, influencing the survival time, were then entered into a Cox model. Continuous variables were categorized according to the median value observed on the entire sample. A step-down procedure allowed us to sequentially select the variables that were significantly related to the outcome, as tested by the likelihood ratio test. Thus, variables that did not add predictive information to the remainders were not kept in the model.

As a second step, to summarize prognostic information, a multivariate analysis was carried out. The dependence of the risk of death (i.e., the probability that an individual i dies at time t, conditional on he (she) having survived to that time) on p explanatory covariates, Zi(t), was expressed through the Cox model as follows:

$$\alpha_i(t;Z_i) = \alpha 0(t)\exp(\beta_1 Zi_1[t] + \beta_2 Zi_2[t] + \ldots + \beta_p Zi_p[t])$$

where the p covariates appearing in the model with a corresponding β_p coefficient, were either assessed at baseline [Zi(t) = Zi] such as APACHE II, MacCabe score, shock, mechanical ventilation, use of sedatives and parenteral feeding, or time-dependent, as the occurrence of suspected VIP or bacteriologically confirmed VNP.

The covariates were incorporated under their native coding into the Cox model, all discrete but APACHE II, assuming that the relationship between the latter and the risk of death was loglinear.

Finally, in order to further study the differences between C-VNP patients and S-VNP patients, similar prognostic analysis was performed on the subset of suspected VNP patients, using reported measures of prognostic covariates at the time of suspicion. Consequently, the endpoint was computed from the date of suspicion of VNP. During the study period, the patients were included in the study only for their first ICU admission. The first episode of suspected VNP was the sole considered for statistical analysis.

Levels of significance were represented by p values derived from two-sided tests. A p value ≤ 0.05 was considered significant. Statistical analysis was performed using BMDP (Biomedical Computer Programs, University of California, Los Angeles, CA) and SAS (Statistical Analysis Systems, Inc., Carey, NC) software packages.

The protocol was approved by the hospital ethics committee. No informed consent was mandatory according to French legislation, given that this epidemiologic study does not modify either current diagnostic or therapeutic strategy.

RESULTS

Population

Between August 1990 and April 1993, 690 patients were admitted to the unit. Twenty patients were admitted twice. Among the 670 first ICU admissions, 387 patients (58%) were mechanically ventilated for more than 48 h and were included in the study. Patients' baseline characteristics are displayed in Table 1. Mean duration (± SD) of ICU stay of the patients included was 19 ± 19 d (median 13; range: 2 to 112 d).

Pneumonia

VNP was suspected in 112 patients and confirmed by protected specimen brush (PSB) and/or bronchoalveolar lavage culture (BAL-C) in 56 patients (38 positive PSB and 36 positive BAL-C) with an estimated incidence of VNP at 14.5% (95% CI: 11 to 18%). Bronchoalveolar lavage was not performed in 25 patients because of unstable hemodynamic condition or Pa_{O_2}/FI_{O_2} ratio less than 150 mm Hg, while PSB was not performed in two cases for technical reasons. Characteristics at admission and in the 24 h preceding suspicion of VNP did not differ between patients suspected of VNP without further confirmation and patients with diagnosed VNP except in the existence of underlying chronic illness (Table 2). At the time of suspicion of pneumonia, 44 of the 112 patients (39%) were on antibiotics (22 of 56 in each group). The duration of prior antibiotic therapy was 6.6 ± 3.4 d (range: 3 to 17 d) and 7.9 ± 4.9 d (range: 3 to 19 d) in S-VNP and C-VNP respectively (NS). The most commonly prescribed antibiotics for the 112 patients were penicillin or amoxicillin (n = 4), oxacillin (n = 4), amoxicillin clavulanate (n = 10), ureidopenicillin (n = 5), fluoroquinolones (n = 8), aminoglycosides (n = 4), glycopeptides (n = 8), and cotrimoxazole (n = 3), equally distributed in S-VNP and C-VNP groups. Five of the 56 S-VNP and nine of the 56 C-VNP received SDD (p = 0.84, log-rank test) during the first 48 h of mechanical ventilation. At the time of the suspicion of pneumonia, only three patients in the S-VNP group and seven patients in the C-VNP group were still receiving SDD. Sixty-nine organisms were recovered from episodes of nosocomial pneu-

TABLE 1

PATIENTS' CHARACTERISTICS AT ADMISSION (n = 387)

	Number (%) or Mean (*SD*)*
Age, yr	65 (16)
Diagnosis	
COPD	50 (13)
Other pulmonary	34 (9)
Cardiology	35 (9)
Neurology	40 (10)
Other medicine	29 (8)
Digestive surgery	88 (23)
Vascular surgery	68 (17)
Cardiac surgery	22 (6)
Other surgery	21 (5)
Reason for ventilation	
Scheduled surgery	30 (9)
Unscheduled surgery	70 (18)
Cardiac failure	47 (12)
Neurologic failure	75 (19)
ARDS	93 (24)
COPD	59 (15)
Other pulmonary	13 (3)
SAPS	14.5 (5)
APACHE II	19.7 (6)
MacCabe	
1	100 (26)
2	240 (62)
3	47 (22)
Chronic illness	186 (49)
Previous history of COPD	104 (27)
Glasgow coma score < 10	85 (22)
Shock	128 (33)
Creatinine, μmol/L	162 (40)
Infection	166 (43)
Pneumonia at admission	53 (13)
Admission from other units	268 (69)

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; ARDS = acute respiratory distress syndrome; SAPS = simplified acute physiologic score; APACHE = acute physiology and chronic health evaluation.

* Results are expressed as number of cases (percent) for qualitative variables and as mean (standard deviation) for quantitative variables.

monia in significant concentrations (Table 3). The microorganisms recovered were always highly resistant to previous antibiotherapy.

The percentage of patients free from confirmed pneumonia was 98.5% (SD: 0.6%) at Day 2 (4 d of mechanical ventilation), 97.6% (SD: 0.8%) at Day 5 (1 wk of mechanical ventilation), 87.6% (SD: 0.8%) at Day 12 (2 wk of mechanical ventilation).

The results of PSB and BAL-C in the 56 patients suspected to have pneumonia without further confirmation were PSB < 10^2 cfu/ml and BAL-C < 10^3 cfu/ml in 46 cases, PSB < 10^2 cfu/ml and BAL-C < 10^4 cfu/ml in four cases, PSB < 10^3 cfu/ml and BAL-C < 10^3 cfu/ml in four cases, PSB < 10^3 cfu/ml and BAL-C < 10^4 cfu/ml in two cases. In the confirmed VNP group, all but four patients were considered as true positive of PSB and BAL and treated by the medical staff. There were two deaths autopsy-proven to be unrelated to nosocomial pneumonia among the four untreated patients. Eleven patients received adapted antibiotics after bronchoscopy in the nonconfirmed VNP group (other septic focus with the same microorganism: four cases; treatment adapted to Gram-stain examination and stopped after negative culture results: four cases; patients considered by the medical staff as false-negative results of PSB and BAL-C: three cases).

Eleven patients were suspected to have nosocomial pneumonia more than one time. Only one patient developed C-VNP after a first episode of suspected nonbacteriologically confirmed pneumonia.

The overall mortality of the patients (i.e., after 2 d of mechanical ventilation) was 43% (168 deaths). Overall mortality was 58%

TABLE 2

CHARACTERISTICS OF SUSPECTED VNP PATIENTS (n = 112)

	Not Confirmed VNP (*n* = 56)	Confirmed VNP (*n* = 56)
At Admission		
Diagnositc		
COPD	7 (12)	10 (18)
Other pulmonary	3 (5)	5 (9)
Cardiology	3 (4)	5 (9)
Neurology	7 (14)	4 (7)
Other medicine	4 (7)	5 (9)
Digestive surgery	16 (29)	14 (25)
Vascular surgery	10 (18)	9 (16)
Cardiac surgery	5 (9)	3 (5)
Other surgery	1 (2)	1 (2)
Reason for ventilation		
Scheduled surgery	3 (5)	3 (5)
Emergency surgery	10 (18)	6 (12)
Cardiac failure	5 (9)	8 (14)
Neurologic failure	11 (20)	8 (14)
ARDS	17 (29)	17 (30)
COPD	9 (17)	11 (20)
Other pulmonary	1 (2)	3 (5)
Age, yr	68 (4)	65 (4)
SAPS	14.5 (1.1)	14.4 (1.3)
APACHE II	19.8 (1.3)	19.7 (1.6)
MacCabe		
1	16 (29)	14 (25)
2	34 (61)	39 (70)
3	6 (10)	3 (5)
Chronic illness	24 (43)	29 (52)†
Previous history of COPD	17 (30)	16 (29)
Glasgow coma scale < 10	19 (34)	17 (30)
Shock	27 (48)	21 (38)
Creatinine, μmol/L	142 (25)	157 (32)
Infection	26 (46)	21 (38)
Pneumonia at admission	10 (18)	8 (14)
Admission from other units	41 (73)	36 (64)
24 h before suspicion of VNP		
Ventilation before suspicion, days	11 (2.6)	14 (3.4)
SAPS	13.9 (1.5)	13.6 (1.3)
OSF	1.7 (0.2)	1.6 (0.2)
Pa_{O_2}/FI_{O_2} ratio, mm Hg	234 (30)	232 (27)
Temperature, °C	38 (0.3)	38.4 (0.3)
WBCs, 10^9/L	17.6 (2.6)	17.3 (2.5)
Lymphocyte count, 10^9/L	1.4 (0.3)	1.2 (0.2)
Platelet count, 10^9/L	220 (27)	210 (30)
Bilirubin, μmol/L	44 (16)	47 (23)
Deaths	32 (57)	34 (61)

Definition of abbreviations: VNP = nosocomial pneumonia in ventilated patients; COPD = chronic obstructive pulmonary disease; SAPS = simplified acute physiologic score; OSF = number of organ system failures; ARDS = acute respiratory distress syndrome; APACHE = acute physiology and chronic health evaluation.

* Results are expressed as number (percent) of cases for qualitative variables and as mean (standard deviation) for quantitative variables.

† p = 0.03 (log-rank test). The other variables are not significantly different between groups.

TABLE 3

MICROORGANISMS RECOVERED AT SIGNIFICANT CONCENTRATION* FROM EPISODES OF PNEUMONIA

Staphylococcus aureus	18
Staphylococcus eipdermidis	3
Streptococcus pneumoniae	3
Streptococcus species	7
Other gram-positive	3
Haemophilus species	9
Pseudomonas aeruginosa	11
Acinetobacter baumannii	8
Other *Enterobacteriaceae*	7
Total (n microorganisms/n episodes)	69/56

* Growth of microorganisms greater than or equal to 10^3 cfu/ml for protected specimen brush and/or greater than or equal to 10^4 cfu/ml for bronchoalveolar lavage culture.

TABLE 4
Part I

PROGNOSTIC FACTORS OF MECHANICALLY VENTILATED PATIENTS (UNIVARIATE ANALYSIS)

	Number of Patients	Number of Deaths	p (Log-rank Test)
Age, yr			
< 70	204	80	0.25
> 70	183	88	
SAPS			
< 14	173	55	0.0001
> 14	214	113	
APACHE II			
< 20	187	51	0.0001
> 20	199	116	
Chronic illness			
Yes	201	80	0.09
No	186	88	
MacCabe			
Not fatal	100	26	0.0001
Ultimately fatal < 5 yr	240	110	
Ultimately fatal < 1 yr	47	32	
Nosocomial patients			
Yes	119	45	0.04
No	268	123	
Cause of admission			
Medicine	188	73	0.07
Surgery	199	95	
COPD			
Yes	104	42	0.17
No	283	126	
Cancer			
Yes	70	35	0.14
No	317	133	
Pneumonia at admission			
Yes	53	29	0.11
No	334	139	
Shock at admission			
Yes	128	76	0.0001
No	257	91	
GCS at admission			
< 10	85	44	0.13
> 10	302	124	
Infection at admission			
Yes	166	76	0.58
No	221	92	
Temperature < 38.4° C and > 36° C (at admission)			
Yes	199	74	0.055
No	188	94	
BUN at admission			
< 10, mmol/L	179	66	0.08
> 10, mmol/L	187	94	
Creatinine at admission			
< 100, μmol/L	166	59	0.02
> 100, μmol/L	188	97	

Definition of abbreviations: GCS = Glasgow coma scale; BUN = blood urea nitrogen; SAPS = simplified acute physiologic score; APACHE = acute physiology and chronic health evaluation.

(65 of 112) in S-VNP and 57% (33 of 56) in C-VNP patients. The survival rate was 97% (SD = 0.8%) at Day 1 (third day of mechanical ventilation), 89% (SD = 1.6%) at Day 3, 81% (SD = 2%) at Day 6, and 70% at Day 12 (SD = 2.6%).

Prognostic Analysis

Table 4 summarizes the results of the univariate prognostic analysis. Thirteen variables were selected as prognostic by the log-rank test, namely SAPS, APACHE II, MacCabe, prior infection, shock, creatinine level, diagnosis, cause of ventilation, use of antimicrobials, sedatives, paralytic agents, parenteral nutrition, and gastric aspiration. Of the previous 13, five variables remained associated with a poor outcome when introduced simultaneously into a Cox model: APACHE II > 20, high MacCabe score, shock, all three variables assessed on ICU admission, and the use within the first 48 h of mechanical ventilation of both sedatives and parenteral feeding.

Otherwise, suspected VNP and confirmed VNP were both associated with an increased risk of death, with estimated relative risk at 2.1 and 1.7 respectively (Table 5). Such increased relative risks remained after adjusting for the previous five selected baseline prognostic variables, with estimated relative risk of death after S-VNP at 2 ($p = 0.01$ by the likelihood ratio test) and after C-VNP at 1.8 ($p = 0.007$) (Table 6). However, when the two events, S-VNP and C-VNP, were simultaneously introduced into a Cox model, the bacteriologic confirmation of VNP was not associated with any additional overmortality as compared with suspected patients (relative risk [RR] = 1.0, $p = 0.96$), even after adjust-

TABLE 4
Part II

PROGNOSTIC FACTORS OF MECHANICALLY VENTILATED PATIENTS (UNIVARIATE ANALYSIS)

	Number of Patients (*n* = 387)	Number of Deaths (*n* = 168)	p (Log-rank Test)
Diagnostic			
COPD	50	16	
Other pulmonary	34	21	
Cardiology	35	14	
Neurology	40	13	0.0002
Other medicine	29	9	
Digestive surgery	88	47	
Vascular surgery	68	30	
Cardiac surgery	22	15	
Other surgery	21	3	
Cause of ventilation			
Scheduled surgery	30	7	
Emergency surgery	70	26	
Cardiac failure	47	23	
Neurologic failure	75	22	0.0002
ARDS	93	66	
COPD	59	20	
Other pulmonary	13	4	
Use during the first 2 d of mechanical ventilation of:			
Antimicrobials	223	110	0.03
H2 blockers	45	17	0.21
Sedatives	300	145	0.03
Paralytic agents	51	34	0.003
Selective digestive decontamination	59	24	0.82
Enteral nutrition	54	15	0.02
Gastric aspiration	298	142	0.02

Definition of abbreviations: COPD = chronic obsructive pulmonary disease; ARDS = acute respiratory distress syndrome.

ing for variables previously selected as prognostic (adjusted RR = 1.2) The relative risk of death of confirmed VNP as compared with nonsuspected patients was similarly estimated at 2.

Prognostic analyses secondly dealt with the subset of the 112 patients who were suspected of VNP. The factors associated with an increased risk of mortality 24 h before suspicion of pneumonia were SAPS ($p = 0.0001$), bilirubin level ($p = 0.004$), platelet level ($p = 0.0001$), temperature ($p = 0.004$), number of organ system failures ($p = 0.0001$), and lymphocyte count ($p = 0.01$). Only three variables were additively associated with poor outcome: SAPS ($p = 10^{-4}$), body temperature ($p = 0.028$), and lymphocyte count ($p = 0.021$). Survival after suspicion of VNP was not different whether or not VNP was confirmed by PSB and/or BAL-C (RR = 1.01, $p = 0.95$) (Figure 1) even adjusted over the three selected prognostic variables (RR = 1.15, $p = 0.59$). In the same way, when taking into account variables at admission and variables at the time of suspicion of nosocomial pneumonia upon the 112 patients suspected to have pneumonia, SAPS at admission, APACHE II, shock at admission, admission from hospital ward, cause of mechanical ventilation, diagnosis at admission, SAPS, and OSF 24 h before suspected pneumonia, as well as temperature, lymphocyte count, platelet count, and bilirubin level were univariately associated with prognosis. Using multivariate analysis, admission from the hospital ward, SAPS and APACHE II at admission, as well as SAPS 24 h before sus-

TABLE 5

OVERMORTALITY INDUCED BY NOSOCOMIAL PNEUMONIA (UNIVARIATE ANALYSIS USING COX MODEL)*

	β Coefficient	Relative Risk	p Value
Tested independently			
Suspicion of VNP	0.73	2.1	0.0001
Diagnosed VNP	0.54	1.7	0.01
Tested simultaneously			
Suspicion of VNP	0.72	2.0	0.0014
Diagnosed VNP	0.01	1.0	0.96

Definition of abbreviation: VNP = nosocomial pneumonia in ventilated patients.

* Statistical analysis was done introducing suspected VNP and diagnosed VNP as time-dependent covariates independently and then simultaneously into a Cox model. (If we take into account in the prediction of death the suspicion of VNP, its diagnosis by distal samples does not help in predicting mortality).

TABLE 6

PROGNOSTIC FACTORS OF MECHANICALLY VENTILATED PATIENTS (MULTIVARIATE ANALYSIS)*

	p Value at the Last Step	Relative Risks (*confidence interval*)
Diagnostic	0.17	
Cause of ventilation	0.10	
SAPS	0.87	
APACHE II	$< 10^{-4}$	
Nosocomial	0.39	
MacCabe	$< 10^{-4}$	
Shock on admission	10^{-4}	
Coma at admission	0.7	
Creatinine	0.74	
H2 blockers	0.11	
Sedatives	0.02	
Paralytic agents	0.09	
Enteral nutrition	0.04	
Gastric aspirates	0.79	
Diagnosed VNP	0.007	1.8

Definition of abbreviations: VNP = nosocomial pneumonia in ventilated patients; SAPS = simplified acute physiologic score; APACHE = acute physiology and chronic health evaluation.

* A stepwise backward procedure was used to retain or to exclude variables at each step, using likehood ratio tests. Variables associataed with prognosis were then introduced into a Cox model using "diagnosed VNP" as a time-dependent covariate.

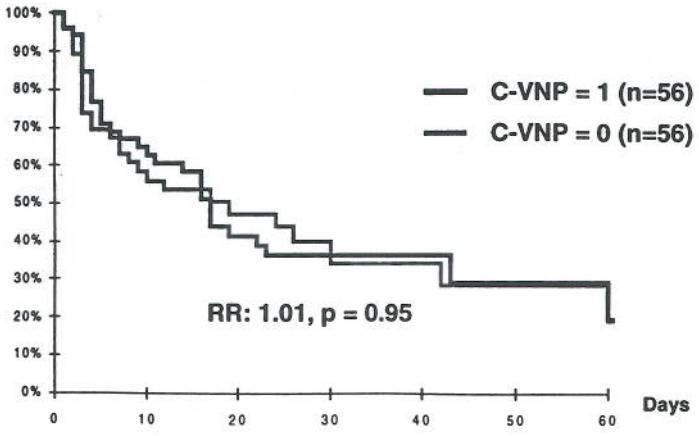

Figure 1. Kaplan-Meier estimates of survival after suspected nosocomial pneumonia. The overall mortality was not different whether the nosocomial pneumonia was confirmed (C-VNP = 1) or not (C-VNP = 0) by protected specimen brush and/or culture of the bronchoalveolar lavage fluid.

picion of pneumonia were associated with prognosis. Prognosis, even adjusted with these four preselected parameters, remained not different between S-VNP and C-VNP groups (adjusted OR = 1.15, p = 0.94).

None of the high-risk microorganisms (i.e., multimicrobial pneumonia, *Staphylococcus aureus, Pseudomonas aeruginosa,* and *Acinetobacter baumannii*) increased the risk of death using log-rank analysis. But, when using chi-square analysis *P. aeruginosa* and *A. baumannii* pneumonia were associated with an increased risk of death (16 of 19 versus 18 of 37, p = 0.01).

DISCUSSION

While most clinicians believe that nosocomial pneumonia is responsible for a high mortality, considerable controversy remains in the literature regarding both the incidence and the weight upon prognosis of nosocomial pneumonia in the ICU setting. Some investigators deny any causal link of mortality to nosocomial pneumonia (3, 4, 19) whereas others, using appropriate case control studies matched by demographic factors and underlying disease (2, 5) or multivariate cohort studies (20), either in the entire hospital or in the ICU, demonstrate that mortality is increased by 1.5- to 3.9-fold.

The problem becomes even more complex with the results of the numerous trials and meta-analyses regarding the effect of SDD of the digestive tract. Although SDD decreases by more than twofold the rate of nosocomial pneumonia, its effect on ICU mortality is very marginal (odds ratio [OR] > 0.8) and reaches a statistical significance in only one (21) out of three (22, 23) well-conducted meta-analyses using several thousand patient cohorts even if decreased mortality is probably difficult to ascertain considering the ratio between reduction in occurrence of pneumonia and reduction in mortality.

Different explanations might be proposed to understand these conflicting results. A couple of methodological problems could be important to take into account. First, inclusion criteria differ between studies that focus on nosocomal pneumonia acquired in hospital (1, 5), in ICU (2, 20), or in patients receiving mechanical ventilation (3, 4, 19, 24, 25). Moreover, criteria used to define pneumonia are not standardized, which could account for a large degree of variability in reported estimates of pneumonia mortality and increased length of hospital stay. It is why we selected ICU patients mechanically ventilated for more than 48 h to obtain a homogeneous population presumably without pneumonia in incubation at admission. Second, nosocomial pneumonia is usually introduced in studies regarding mortality as a binary variable (yes or no). So, if one patient dies after 50 d of mechanical ventilation, the "weight" on the mortality of a VNP occurring 2 d after inclusion is considered to be the same as those of a VNP occurring 2 d before death. In our statistical design, introducing suspected VNP and confirmed VNP as time-dependent events allows a better estimation of the effect of each observed event.

Some points about methodology and results of our study must be discussed. The incidence of pneumonia in our study is less than in many other studies but similar to those from Fagon and coworkers (6). The rate of nosocomial pneumonia observed in this study (14.5%) appears to be lower than reported in other studies. It is probably due in part to the greater specificity of the criteria used for diagnosis in our study. We should note that the incidence of suspected bacterial pneumonia in our series (29%) is similar to the incidence of episodes of pneumonia reported in studies using clinical criteria for case definition. The mean time of pneumonia (14 d) is also longer than some other series. This finding is probably due to the low rates of polytrauma and head injury patients and the low rate of drug poisoning which probably decrease the incidence of gastric aspiration and of early-onset pneumonias.

Two patients suspected of pneumonia without bacteriologic confirmation had borderline results of PSB and BAL-C and should be considered as misdiagnosed pneumonia. However, borderline results of protected specimen brush (i.e. $\geq 10^2$ cfu/ml) have been reported to be associated with pneumonia in only 35% of cases (26). In the same way, the four C-VNP not treated and the three S-VNP considered as pneumonia by the medical staff might have introduced a bias in the analysis. However, data from autopsy and follow-up of surviving patients made this hypothesis unlikely.

A main concern is to know if ICU patients die from or with nosocomial pneumonia. The role of the underlying condition of the patients is of considerable importance and numerous studies have demonstrated that sever underlying illness predisposes to the development of nosocomial infection, especially pneumonia (4, 24). These items must be carefully assessed in the studies, whether they used a case control or a multivariate methodology, and adjustments must be made according to these risk factors. Other very important risk factors must also be taken into account. In a recent, well-conducted case control study, Fagon and coworkers (25) demonstrated that confirmed VNP (diagnosed by clinical criteria plus protected specimen brush and/or percentage cells containing bacteria in bronchoalveolar lavage) increased the risk of mortality (RR: 2) when compared with control patients. Patients were carefully matched on age, simplified acute physiologic score (11) on admission (SAPS), indication for ventilatory support, date of admission, and duration of exposure to risk. Our data regarding the prognostic impact of confirmed pneumonia fully support these data. The occurrence of nosocomial pneumonia was shown to achieve a 1.8-fold increase in the risk of death. However, in our study, the main result is that suspicion of VNP does increase the risk of death to the same extent (RR: 2.0). Numerous events occurring during the ICU stay could modify the risk of developing pneumonia, including the persistence of very high severity scores, or the development of multiple organ system failure including acute respiratory distress syndrome (ARDS). In these severe patients, the overmortality induced by nosocomial VNP might become marginal and difficult to ascertain (3). In our study, bacteriologic confirmation of VNP based on protected specimen brush and/or bronchoalveo-

lar lavage culture (> 10^4 cfu/ml) did not add any prognostic information as compared with that obtained through the suspicion of VNP (RR: 1.0). Nevertheless, the occurrence of VNP, either suspected clinically or confirmed, increased by twofold the risk of death compared with that of nonsuspected patients. Another explanation could be that the patients suspected of having nosocomial pneumonia, but without further confirmation using protected distal samples, must be considered as misdiagnosed pneumonia because of the poor negative predictive value of these tests. This hypothesis is strongly defended by several researchers (27). However, a large number of studies (7–10, 28–33) regarding the diagnostic yield of various distal samples as well as the recommendations of a recent international consensus about ventilator-associated pneumonia (34) suggest that about two-thirds of the episodes of suspected pneumonia in ventilated patients are not confirmed to be real pneumonia but should be defined as a "pneumonia-like syndrome" related to various pathologic processes that mimic pneumonia but that do not require specific antibiotic therapy. These processes might be associated with severe processes with a similar ICU mortality. However, no current data permit one to definitely support this conclusion. Moreover, most of the false-negative results mentioned with distal samples are due to the presence of some kind of effective antibiotic therapy which is known to decrease the diagnostic yield of those techniques (35). None of our patients were treated with antibiotics active against the strains detected or recently introduced, making this explanation unlikely.

To conclude, our data demonstrate, in our unit, that the patients in whom a pneumonia is suspected but not confirmed experienced a similar mortality to patients with definite pneumonia. These findings do not demonstrate that nosocomial pneumonia in severe ICU patients does not have any prognostic implication but underline the fact that further studies targeting the issue of mortality must follow appropriate designs. Adjustments using only initial prognostic factors are probably not accurate because they do not take into account the evolution of the risk during ICU stay. Other dynamic risk factors must be assessed, especially daily assessment of severity using either general severity indexes or organ dysfunction scoring systems and occurrence of iatrogenic events, drug reactions, and other nosocomial infections.

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