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Mortality associated with late-onset pneumonia in the intensive care unit: results of a multi-center cohort study

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Abstract *Objective*: To evaluate the attributable mortality associated with late-onset nosocomial pneumonia (LOP) while taking into account the severity at admission, the evolution of the patients during the first 4 days after admission to the ICU and the appropriateness of initial empiric antibiotic treatment. *Design*: Multicenter cohort study with prospective standardization of diagnostic interventions when nosocomial pneumonia develops. *Setting*: Medical and surgical ICUs of four university-affiliated teaching hospitals. *Patients*: Seven hundred sixty-four consecutive patients requiring ICU hospitalization for at least 4 days. *Main outcome measures*: The clinical and biological data as well as the therapeutic data and the outcome were prospectively recorded from the day of admission to ICU discharge. Simplified Acute Physiologic Score (SAPS II) and Logistic Organ Dysfunction (LOD) score were collected and computed within the first 4 calendar days of ICU admission. Variables associated with the outcome were selected using a stepwise Cox model. The time to acquisition of the first LOP was then introduced in the final model as a time-dependent covariate. The analysis was stratified by ICU center. Finally, as initial antibiotic therapy could have an impact on the increased risk of death induced by LOP, the Cox model was applied again introducing LOP immediately adequately treated and LOP not immediately adequately treated as two different time-dependent covariates. *Results*: Late-onset pneumonia developed in 89 patients (12%). A McCabe score of more than 1, SAPS II score and increases in SAPS between days 1 and 2, days 2 and 3, and days 3 and 4 were significantly associated with an increased risk of death. When the time to acquisition of the first episode of LOP was introduced into the Cox model, the LOP occurrence was associated with increased mortality, even adjusted over the selected prognostic parameters and after stratification by center (hazard ratio (HR)=1.53, 95% CI 1.02–2.3, p=0.04). When LOP immediately adequately treated and LOP not immediately adequately treated were separately introduced into the Cox model, inappropriately treated LOP remained significantly associated with an increased risk of mortality (HR=1.69, 95% CI 1.08–2.65, p=0.022), whereas appropriately treated LOP did not (HR=1.44, 95% CI 0.75–2.76, p=0.27). *Conclusion*: These data suggest that, in addition to severity scores, the underlying medical conditions and the evolution of severity within the first 4 days in ICU, late-onset pneumonia independently contribute to ICU patient mortality when empirical antibiotic treatment is not immediately appropriate.

Keywords Multicenter · Attributable mortality · Late-onset pneumonia · Nosocomial pneumonia · Adequate or inadequate antibiotic treatment

Introduction

The extra mortality induced by nosocomial pneumonia in ventilated patients remains a controversial issue in the 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 outcome and of prolonged hospitalization [1, 2, 3]. Variables that may influence the extent to which nosocomial pneumonia increases morbidity or mortality include the patient population affected, timing of the onset of pneumonia, diagnostic strategy, causative organism and adequacy of initial therapy. For example, several studies have suggested that specific microorganisms responsible for ventilator-associated pneumonia (e.g., *Pseudomonas aeruginosa* or *Acinetobacter* species) were important determinants of patient outcome [4, 5, 6].

It has also been demonstrated that in pneumonia occurring more than 96 h after ICU admission, namely late-onset pneumonia (LOP), there was an increased likelihood of infection with resistant gram-negative organisms including *Pseudomonas aeruginosa* and *Acinetobacter* species [7, 8]. Then LOP may carry a high risk of mortality and morbidity, probably because cases are often caused by resistant organisms which are difficult to treat, and may result in delayed or ineffective antibiotic therapy. However, LOP occurred in patients staying in the ICU for days, often with persistent very high severity of illness and this could be a very important confounding factor. We therefore performed a prospective study to evaluate risk factors for death in patients admitted to an ICU for more than 96 h, and particularly the association between LOP and mortality. Our particular concern was to take into account illness severity on admission, but also daily variation of illness severity within the first 4 days on the ICU and appropriateness of initial empiric antibiotic treatment, in evaluating the specific attributable mortality associated with pneumonia.

Methods

Criteria for eligibility

This study was conducted during an 18-month period within the medical and surgical ICUs of four university-affiliated teaching hospitals: one medical ICU in Hôpital Louis Mourier (Colombes, France), two medical-surgical ICUs in Hôpital Saint Joseph (Paris, France) and in Hôpital Avicenne (Bobigny, France), and one surgical ICU in Hôpital Antoine Béclère (Clamart, France). Consecutive patients older than 16 years and hospitalized in the ICU for at least 5 calendar days were eligible for the study.

Data collection and baseline data

During the study period (January, 1997 to July, 1998), all the patients hospitalized for more than 48 h in ICU were followed for the appearance of nosocomial infections. In those patients, we recorded prospectively the clinical and biological data as well as the therapeutic data from the day of admission to ICU discharge. The investigators were particularly involved in the data base creation. All codes and definitions were created prior to the study start. Senior physicians completed report forms. Another investigator reviewed all the report forms before they were keyed. For each patient, standardized forms were completed at ICU admission and daily until ICU discharge or death. The following data were recorded: diagnosis, main clinical features and laboratory findings, treatment modalities, especially respiratory support, antimicrobial treatments, nosocomial pneumonia and outcome. From the data collected within the first 4 calendar days (Ds) of ICU admission, the Simplified Acute Physiologic Score (SAPS II) [9] and the Logistic Organ Dysfunction (LOD) score [10] were computed. Chronic health status was assessed using the Knaus classification [11]. McCabe score [12] was also recorded. Diagnosis of nosocomial pneumonia was reported together with the results of microbiological tests from the protected distal samples. All changes in the clinical and therapeutic course were recorded. Only those patients hospitalized in a ICU for at least 5 calendar days were entered in this study.

Late-onset pneumonia

At the beginning of the study investigators decided to use the same following definitions of nosocomial pneumonia: LOP (occurring more than 96 h after admission) [6, 7, 13] was suspected by the staff physicians according to the appearance of persistent pulmonary infiltrates on the chest X-ray and at least one of the following clinical or biological findings [14]: (1) purulent tracheal secretions, (2) body temperature higher than 38.5°C or lower than 36.5°C, (3) white blood cell count more than 10×10^9/l or less than 4×10^9/l. When pneumonia was suspected, fiberoptic bronchoscopy with protected specimen brush and/or bronchoalveolar lavage or single-sheeted blind plugged telescopic catheter were performed for each patient [15, 16, 17, 18]. Confirmed LOP was defined, according to the recommendations of the First International Consensus Conference on the Clinical Investigation of Ventilator Associated Pneumonia [19], by a positive protected specimen brush ($\geq10^3$ cfu/ml), by a positive plugged telescopic catheter ($\geq10^3$ cfu/ml) or by a positive culture of bronchoalveolar lavage fluid ($\geq10^4$ cfu/ml). None of the patients received any new antimicrobials before respiratory bacteriological procedures. Previous antibiotic use was defined as antibiotic administration for more than 48 h prior to the suspicion of pneumonia.

Therapeutic decisions were left to the discretion of the attending physicians and discussed daily with the medical staff in each center. No common therapeutic regimens were recommended in any case. When infection was strongly suspected because of clinical signs of severe sepsis and/or septic shock, the patient's physician prescribed empiric antimicrobial therapy without delay. Treatment was further adapted or ordered according to the results of bacterial pulmonary cultures, susceptibility testing of antimicrobials and/or clinical response. An "uncovered" microorganism was considered when an isolated microorganism was not susceptible to any of the antibiotics administered. Inappropriate initial antibiotic treatment was defined by the isolation of at least one pathogen with a significant threshold in the bacteriological samples resistant or intermediate to the antibiotics prescribed. All patients were monitored until their discharge from the hospital and changes in the clinical and therapeutic course were recorded.

Statistical analysis

Patients with and without LOP were compared using Mann Whitney or Fischer exact test, as appropriate. A stepwise logistic regression was computed to select independent risk factors for LOP.

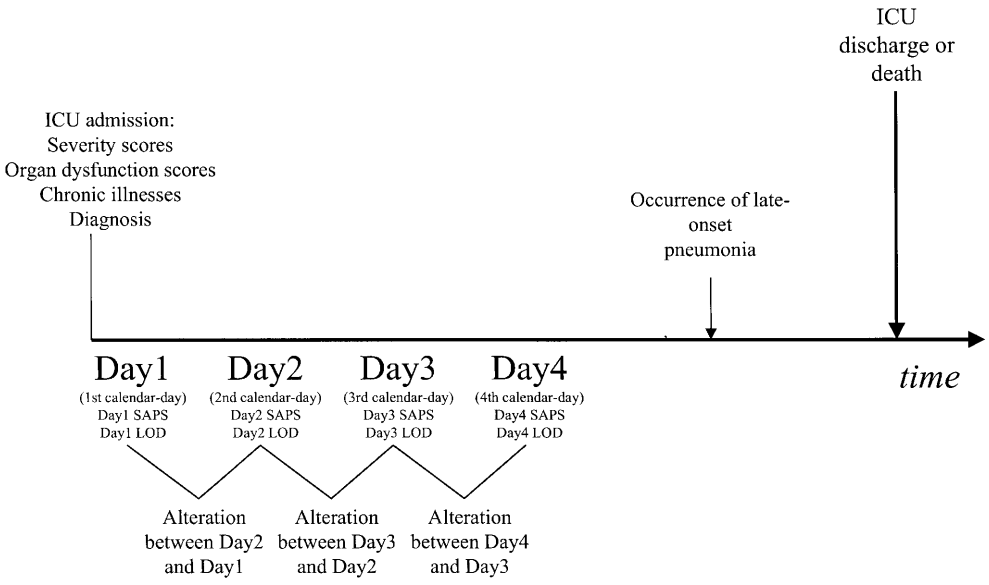

Fig. 1 Study design: the occurrence of ICU discharge or death defined the end point. Prognostic covariates were measured at admission. Severity scores were computed during the first 4 calendar days. Alteration of scores between consecutive calendar days: when a score increased, it was given the value of 1, otherwise the value was 0. Finally, the time to acquisition of late-onset pneumonia was introduced as a time-dependent covariate in the model

The main end point was the overall survival from the date of inclusion (the 5th calendar day after ICU admission). Patients who were discharged alive from the ICU were no further evaluated after their discharge. The Kaplan-Meier estimate of survival was computed. We first studied the prognostic value for death of several baseline characteristics, assessed within the first 5 days of ICU admission, including demographic characteristics (age, sex, chronic underlying disease, history of COPD, associated neoplasm, associated immunosuppression and McCabe score), cause of ICU admission and diagnosis severity of the patients on admission (SAPS II, LOD score, Glasgow coma scale), severity of the patients' conditions within the first 4 calendar days (SAPS II and LOD score were computed daily), and severity alterations (SAPS II and LOD score alterations between days 1 (D1) and 2 (D2), days 2 and 3 (D3), and days 3 and 4 (D4)) (Fig. 1). All variables were introduced as dummy variables except SAPS II (after checking for log-linearity assumption).

Score alterations rather than daily scores were introduced into the model at the first step to avoid over-fitting. Only the directions of changes were included on the basis of the non-parametric modeling using generalized additive proportional hazard (PH) models [20]. According to the plot of the estimated functions for each score alteration using smoothing splines, the direction of change was the most important predictor to delineate two groups of interest (low- and high-risk groups). Alteration of severity scores took the value "1" when scores increased and the value "0" otherwise. Search for prognostic factors was based on the log-rank test, which compares the distribution of survival times in several subsets. Variables found to be associated with the outcome by the log-rank test at the 5% level, i.e., influencing the survival time, were then entered into a Cox model. Severity score alteration instead of days 1–4 severity scores were used to avoid over-fitting. A backward procedure allowed for sequentially selecting the variables that were significantly related to the outcome, as tested by the likelihood ratio test at the 5% level. Thus, variables that did not add predictive information to the remainders were not kept in the model. Hazard ratios were computed (with 95% confidence interval) and were used to measure relative risk.

As a second step, the time to acquisition of the first LOP was introduced in the final model as a time-dependent covariate. The analysis was stratified by center, as ICU mortality and LOP incidence were different among the centers. The Gail and Simon test was used to evaluate the interaction between HR of mortality associated with nosocomial pneumonia and center [21]. Finally, as initial antibiotic therapy could have an impact on the extra risk of death induced by LOP, the Cox model was applied again while LOP immediately adequately treated and LOP not immediately adequately treated were introduced simultaneously as two time-dependent covariates. Levels of significance were represented by p values derived from two-sided tests. A p value of 0.05 or less

Table 1 Patients' characteristics at admission and within the first 24 h after admission (n=764) (*COPD* chronic obstructive pulmonary disease)

	Number (%) or mean (SD)
Age (years; mean ± SD)	63±17
Sex M/F, *n* (%)	460 (60)/ 304 (40)
Diagnosis, *n* (%)	
COPD	68 (9)
Other pulmonary	275 (36)
Cardiology	166 (22)
Neurology	100 (13)
Other medical specialty	134 (18)
Digestive surgery	201 (26)
Other surgery	79 (10)
Trauma	26 (3)
Diagnostic category, *n* (%)	
Scheduled surgery	72 (9)
Emergency surgery	159 (21)
Medical	533 (70)
SAPS II, mean ± SD	42±10
MacCabe score, *n* (%)	
≥5 years	388 (51)
<5 years	287 (37)
<1 year	89 (12)
Chronic illness, *n* (%)	375 (49)
Previous history of COPD, *n* (%)	68 (9)
Immunosuppression, *n* (%)	107 (14)
Septic shock/other shock at admission, *n* (%)	66 (9)/ 79 (10)
Pneumonia at admission, *n* (%)	148 (19)
Acute renal failure at admission, *n* (%)	48 (6)
Glasgow coma score <8 at admission, *n* (%)	94 (12)
Admission from other units, *n* (%)	398 (52)

Table 2 Characteristics of the patients with late-onset nosocomial pneumonia[a] (*LOD* logistic organ dysfunction, *D* day)

	Patients with late-onset pneumonia *n*=89	Patients without late-onset pneumonia *n*=675	*p* values
Age (year)	66±14	62±18	0.05
Sex M/F	66(74)/23(26)	394(58)/281(42)	0.5
Admission diagnosis			
Medicine	60 (67)	473 (70)	0.2
Scheduled surgery	5 (6)	67 (10)	
Emergency surgery	24 (27)	135 (20)	
SAPS II score	45±13	41±18	0.02
SAPS D1	40±14	37±16	0.1
SAPS D2	39±12	33±16	<0.0001
Increase in SAPS between D1 and D2[b]	42 (47)	204 (30)	0.002
SAPS D3	37±12	32±16	<0.0001
Increase in SAPS between D2 and D3[b]	27 (30)	215 (32)	0.8
SAPS D4	36±12	31±17	<0.0001
Increase in SAPS between D3 and D4[b]	30 (34)	222 (33)	0.9
SAPS D5	36±11	32±18	<0.0001
LOD score D1	4.5±2.8	3.7±2.8	0.005
LOD score D2	4.2±2.2	3.3±2.5	<0.0001
Increase in LOD score between D1 and D2[c]	29 (33)	164 (24)	0.09
LOD score D3	4.1±2.5	3.0±2.5	<0.0001
Increase in LOD score between D2 and D3[c]	23 (26)	164 (24)	0.8
LOD score D4	4.1±2.4	3.0±2.6	<0.0001
Increase in LOD score between D3 and D4[c]	22 (25)	168 (25)	0.9
LOD score D5	3.9±2.1	3.2±3.0	0.0003
MacCabe score >1	50 (56)	326 (48)	0.2
Chronic illness	47 (56)	328 (48)	0.5
Previous history of COPD	20 (22)	48 (7)	0.001
Immunosuppression	12 (13.5)	95 (14)	0.6
At admission			
Septic shock	11(12)	65 (10)	0.5
Other shock	9(10)	91 (13)	0.4
Pneumonia	35 (39)	126 (19)	0.00012
Coma	14 (15)	77 (11)	0.5
Admission from other units	51 (57)	320 (47)	0.09
Days in ICU when pneumonia developed	12±10	NA	–
Duration of mechanical ventilation	27.5±20	7.3±11	<0.0001
Length of ICU stay	33±24	12±13	<0.0001
Total length of hospital stay	52±34	30±28	<0.0001
Expected probability of death according to SAPS II	36±24	33±28	0.8
ICU deaths	42 (47)	146 (22)	<0.0001
Hospital deaths	50 (56)	189 (28)	<0.0001

[a] Values are reported as means ± SD and *n* (%) for quantitative and qualitative variables, respectively. Comparison was performed using Mann-Whitney or Fisher exact test as appropriate

[b] Number of patients who had an increase in SAPS II within the first 4 days post-admission in ICU – i.e. between D1 and D2, D2 and D3, and D3 and D4

[c] Number of patients who had an increase in LOD score within the first 4 days post-admission in ICU – i.e. between D1 and D2, D2 and D3 and D3 and D4

was considered to indicate statistical significance. Statistical analysis was performed using SAS (Statistical Analysis System, Carey, N.C.) software package.

Results

Population

A total of 764 patients requiring ICU hospitalization for at least 5 calendar days were consecutively admitted to the four different ICUs. Patients' baseline characteristics are shown in Table 1. Eighty percent of these patients required mechanical ventilation within the first 24 h after admission. The median duration of ICU stay and hospital stay was 9 days (range 5–126) and 24 days (range 5–249), respectively.

Late-onset pneumonia

Late-onset pneumonia developed in 89 patients (12%). In 69 (77.5%) cases, it occurred 7 days or more post-admission. The general characteristics of this population

Table 3 Microorganisms recovered from first episodes of late-onset pneumonia

Gram-positive	36
Staphylococcus aureus (SA)	19
Oxacillin-sensitive SA	5
Oxacillin-resistant SA	14
Coagulase negative *Staphylococcus*	8
Streptococcus pneumoniae	1
Streptococcus species	6
Other Gram-positive	2
Gram-negative bacteria (GNB)	71
Haemophilus species	8
Pseudomonas aeruginosa/species	27/1
Acinetobacter baumannii	1
Escherichia coli	9
Enterobacter cloacae	7
Klebsiella species	5
Other *Enterobacteriaceae* / GNB	6/7
Anaerobes	1
Candida/yeast	**2**
Total (microorganisms/episodes)	110/89

and the selected risk factors for the occurrence of LOP in univariable analysis are shown in Table 2. Of the variables selected, two remained significantly associated with the occurrence of LOP in the multivariable analysis: pneumonia at admission (odds ratio (OR)=2.79, 95% CI 1.42–3.65; p=0.0006) and a median LOD score at D2 greater than 4 (OR=2.58, 95% CI 1.65–4.05; $p<10^{-4}$).

At the time of the LOP suspicion, 50 of the 89 patients had already received antimicrobials (amoxicillin: 10; amoxicillin/clavulanate: 10; third generation cephalosporins: 9; ureidopenicillin: 4; imipenem: 2; aminoglycosides: 4; fluoroquinolones: 10; glycopeptides: 7; macrolides: 6; metronidazole: 5; fluconazole: 7; other: 6).

One hundred ten organisms were recovered from the protected distal samples of patients with LOP (Table 3). The initial antibiotic treatment was with one antibiotic in 11 cases, with two in 34 cases and consisted of three or more antibiotics in other cases. The initial empiric antibiotic therapy instituted was considered immediately effective or appropriate in 34/89 cases (38%). It was effective in 60/89 (68%) cases in the first 24 h.

The overall ICU mortality of the total population (i.e., requiring ICU hospitalization for at least 5 calendar days) was 25% (188 deaths). Overall ICU mortality was 47% among LOP patients and 22% among patients without episodes of LOP. The standard mortality ratio was 1.55 for LOP patients and 0.84 for patients without episodes of LOP.

Prognostic analyses

Table 4 summarizes the results of the univariable prognostic analyses. Other covariates, (particularly previous history of COPD and pneumonia at admission) were not associated with ICU death. Of the variables selected as prognostic by the log-rank test, five remained significantly associated with a poor outcome in the final Cox model: McCabe score more than 1, SAPS II and increases in SAPS between D1 and D2, D2 and D3, and D3 and D4 (Table 5). When the occurrence of the first episode of LOP was introduced into the Cox model as a time-dependent binary covariate, it was associated with an increased risk of mortality, even adjusted over the selected prognostic parameters and after stratification by center (HR=1.53, 95% CI 1.02–2.3, p=0.04). When LOP immediately adequately treated and LOP not immediately adequately treated were separately introduced into the Cox

Table 4 Prognostic factors of patients hospitalized in ICU for more than 96 h (univariate analysis)[a]

	Number of deaths n=188	Number of patients alive n=576	p (log-rank test)
Age (years)	68±15	61±18	$<10^{-4}$
MacCabe score >1	128 (68)	248 (43)	$<10^{-4}$
Chronic illness	119 (63)	256 (44)	$<10^{-4}$
Immunosuppression	37 (20)	70 (12)	0.02
SAPS II score	52±18	25±16	$<10^{-4}$
SAPS D1	43±17	29±13	$<10^{-4}$
SAPS D2	44±20	27±13	$<10^{-4}$
SAPS D3	44±20	26±14	$<10^{-4}$
Increase in SAPS between D1 and D2[b]	88 (47)	166 (29)	0.0006
Increase in SAPS between D2 and D3[b]	73 (39)	169 (29)	0.02
Increase in SAPS between D3 and D4[b]	80 (43)	172 (30)	0.0017
LOD score D1	4.7±2.9	2.5±2.0	$<10^{-4}$
LOD score D2	5.1±3.5	2.2±2.0	$<10^{-4}$
LOD score D3	5.1±3.3	2.2±2.0	$<10^{-4}$
Increase in LOD score between D1 and D2[c]	61 (32)	129 (22)	0.0017
Increase in LOD score between D2 and D3[c]	66 (35)	121 (21)	0.0019
Increase in LOD score between D3 and D4[c]	64 (34)	126 (22)	0.0018
Admission from other units	100 (53)	271 (47)	0.002

[a] Values are reported as means ± SD and n (%) for quantitative and qualitative variables, respectively
[b] Number of patients who had an increase in SAPS II within the first 4 days post-admission in ICU – i.e. between D1 and D2, D2 and D3 and D3 and D4
[c] Number of patients who had an increase in LOD score within the first 4 days post-admission in ICU – i.e. between D1 and D2, D2 and D3 and D3 and D4

Table 5 Prognostic factors of patients hospitalized in ICU more than at least 5 calendar days (multivariable analysis)[a] (*HR* hazard ratio, *CI* confidence interval)

	First model[b]		Second model[c]	
	p value	HR (95% CI)	*p* value	HR (95% CI)
MacCabe score >1	$<10^{-4}$	2.43 (1.72–3.44)	$<10^{-4}$	2.12 (1.51–2.99)
SAPS II score	$<10^{-4}$	1.03 (1.02–1.04)	$<10^{-4}$	1.03 (1.02–1.04)
Increase in SAPS between D1 and D2[d]	0.004	1.56 (1.16–2.11)	$<10^{-4}$	2.01 (1.48–2.74)
Increase in SAPS between D2 and D3[d]	$<10^{-4}$	1.84 (1.40–2.50)	$<10^{-4}$	1.97 (1.44–2.69)
Increase in SAPS between D3 and D4[d]	$<10^{-4}$	1.80 (1.33–2.44)	0.004	1.56 (1.16–2.11)
Late-onset pneumonia occurrence[b]	0.04	1.54 (1.10–2.30)	–	–
Late-onset pneumonia appropriately treated[c]	–	–	0.27	1.44 (0.75–2.76)
Late-onset pneumonia inappropriately treated[c]	–	–	0.022	1.69 (1.08–2.65)

[a] All variables significant in the univariate analysis were introduced into a Cox model. To avoid over-fitting, score alterations rather than daily scores were introduced in the multivariate model at the first step. Analysis was stratified by center

[b] The acquisition of the first nosocomial pneumonia was introduced in the first final model as a time-dependent covariate simultaneously with the five previously selected covariates

[c] As initial antibiotic therapy could have an impact on the increased risk of death induced by LOP, the Cox model was applied again while introducing LOP immediately adequately treated and LOP not immediately adequately treated as two different time-dependent covariates (second model)

[d] Number of patients who had an increase in SAPS II within the first 4 calendar days in ICU – i.e. between D1 and D2, D2 and D3 and D3 and D4

Table 6 Baseline characteristics and crude outcomes of the four ICU populations

ICUs, centers	I *n*=235	II *n*=245	III *n*=93	IV *n*=191	*p*
Age (years; mean ± SD)	66±16	64±17	59±23	60±16	0.003
Diagnosis, *n* (%)					$<10^{-4}$
MOF/shock	65 (28)	48 (20)	29 (31)	32 (16)	
Acute respiratory failure	82 (35)	93 (38)	11 (12)	81 (42)	
COPD exacerbation	28 (12)	35 (14)	1 (1)	4 (2)	
Acute renal failure	11 (5)	15 (6)	11 (12)	11 (6)	
Coma	31 (13)	34 (14)	6 (6)	22 (12)	
Trauma	1 (0.4)	1 (0.4)	9 (10)	3 (2)	
Other	17 (7)	19 (8)	26 (28)	38 (20)	
Diagnostic category, *n* (%)					$<10^{-4}$
Medical	153 (65)	210 (86)	33 (35)	137 (72)	
Scheduled surgery	32 (14)	4 (2)	11 (12)	25 (13)	
Emergency surgery	50 (21)	31 (13)	49 (53)	29 (15)	
SAPS II (mean ± SD)	41.3±15	44±16	33±16	46±9	$<10^{-4}$
MacCabe score, *n* (%)					$<10^{-4}$
≥5 years	72 (30)	129 (53)	72 (77)	115 (60)	
<5 years	144 (61)	83 (34)	13 (14)	47 (25)	
<1 year	19 (9)	33 (13)	8 (9)	29 (15)	
Chronic illness[a], *n* (%)					$<10^{-4}$
None	113 (48)	108 (44)	64 (69)	104 (54)	
Respiratory	54 (23)	68 (28)	7 (8)	31 (16)	
Cardiac	42 (18)	39 (16)	2 (2)	9 (5)	
Hepatic	12 (5)	19 (8)	15 (16)	12 (6)	
Immunosuppression	27 (11)	32 (13)	8 (9)	40 (21)	
Pneumonia at admission, *n* (%)	53 (22.5)	64 (26.1)	6 (6.4)	38 (19.8)	10^{-4}
Admission from other units, *n* (%)	135 (58)	100 (41)	57 (61)	74 (39)	10^{-4}
Duration of mechanical ventilation (days)	13±14	10±16	6±13	7±11	$<10^{-4}$
Length of stay in ICU (days)	16±17	14 ±16	14.±20	12±12	0.6
Total length of stay in hospital (days)	36±31	33±34	33±30	28±21	0.3
ICU/hospital mortality rates (%)	28/38	17/25	25/33	30/34	0.004/0.01
Predicted hospital mortality % (SAPS II)	32±32	36±28	21±20	39±18	$<10^{-4}$

[a] According to Knaus definitions

Table 7 Late-onset pneumonia in the four different ICU populations

ICUs, centers	I	II	III	IV	*p*
Late-onset pneumonia, *n* (%)	45 (19)	22 (9)	11 (12)	11 (6)	0.0003
Days in ICU when pneumonia developed (mean ± SD)	13±10	9±2	12±17	14±9	0.5
High-risk germs[a], *n* (%)	22 (49)	11 (50)	3 (27)	7 (64)	0.1
Initial appropriate antibiotic coverage[b]	19 (42)	9 (41)	4 (36)	2 (18)	0.26
24 h appropriate antibiotic coverage[b]	30 (67)	17 (77)	6 (55)	7 (64)	0.9
Late-onset pneumonia occurrence					0.08[c]
Hazard ratio[d]	2.95	1.07	1.86	0.149	
95% Confidence interval	1.7–5.2	0.39–2.9	0.65–5.3	0.02–1.2	
p value	2.10^{-4}	0.89	0.24	0.07	

[a] Oxacillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa* or *Acinetobacter* species

[b] Appropriate antibiotic treatment was considered when at least one effective drug was included in the antibiotic treatment. Values are reported as *n* (%)

[c] The Gail and Simon test was used to evaluate the interaction between hazard ratio of mortality associated with nosocomial pneumonia and center

[d] Adjusted for the pre-selected covariates (see Table 6)

model, LOP not immediately adequately treated remained significantly associated with an increased risk of mortality (HR=1.69, 95% CI 1.08–2.65, p=0.022), whereas LOP immediately adequately treated did not (HR=1.44, 95% CI 0.75–2.76, p=0.27].

Late-onset pneumonia according to intensive care unit

Differences in baseline characteristics and crude outcomes between the four ICU populations are shown in Table 6. Incidence of LOP (p=0.0003) and mortality rate (p=0.003) among the different ICU populations were statistically different (Tables 6 and 7). The adequacy of the initial empiric antibiotic therapy was not different among centers. Among the different centers, antibiotic therapy was appropriate in 55–77% of the episodes in the first 24 h. The LOP occurrence was not always associated with increased mortality among the different ICUs. The HRs, even adjusted over the selected prognostic parameters, were different among the ICUs, ranging from 0.149 (95% CI 0.02–1.2) to 2.95 (95% CI 1.7–5.2) (Table 7). However, the center effect did not reach statistical significance (p=0.08, Gail and Simon test).

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 effect upon prognosis of nosocomial pneumonia in the ICU setting. Our large prospective multicenter study was designed to evaluate attributable mortality associated with LOP after careful adjustment for the severity at admission, the evolution of severity during the first 4 days of ICU stay and the appropriateness of initial empiric antibiotic treatment. We found that pneumonia on ICU admission and a median LOD score greater than 4 at D2 post-ICU admission were associated with an increased risk of the occurrence of late-onset nosocomial pneumonia. Moreover, the severity assessed by SAPS II at admission, as well as the evolution of severity within the first 4 calendar days in ICU, were associated with an increased risk of death in the ICU. After adjustment for these selected prognostic parameters – i.e. McCabe score more than 1, SAPS II and increases in SAPS II within the first 4 calendar days post-admission in ICU – LOP occurrence was associated with a 1.58-fold increased risk of death in patients hospitalized in ICUs. Nevertheless, when appropriateness of initial empiric antibiotic treatment was introduced into the Cox model, inappropriately treated LOP remained significantly associated with an increased risk of death in patients hospitalized in ICUs, whereas appropriately treated LOP did not.

In previous studies targeting the issue of mortality [2, 4, 22, 23, 24, 25, 26, 27], confounders and secondary exposures as factors influencing the outcome of ICU patients with or without nosocomial pneumonia – i.e. daily assessment of severity, length of stay before infection and other nosocomial infections – were not totally excluded. Since severity of illness assessed by SAPS II or APACHE II is considered to be one of the main prognostic factors in ICU patients, most of those studies have only used severity of illness at admission to the ICU to adjust and pair controls to cases. Very few studies have looked at trends in severity in the first few days in the ICU as a prognostic factor and tried to adjust for this very important confounding factor. In a recent study, Soufir et al. [28] showed, in a case control study, that adjusting for severity at 3 or 7 days before the onset of a nosocomial bacteremia dramatically decreased the attributable mortality of this event when compared to the one found when adjusting only for admission severity. In our study, we made particular efforts to adjust the estimation for the initial prognostic factors but also for the evolution of the risk during ICU stay. Dynamic risk factors

were assessed, especially daily assessment of severity, using either general severity indices or organ dysfunction scoring systems, within the first 4 calendar days in ICU. We found that severity indices measured on admission, such as SAPS II, and daily increase of this illness severity score within the first 4 days post-admission were associated with an increased risk of death in ICUs. Furthermore, even after adjustment for these selected prognostic parameters, LOP was associated with an increased risk of death.

The reality of an attributable mortality due to nosocomial pneumonia is still debated [2, 4, 22, 23, 24, 25, 26, 27]. The occurrence of nosocomial pneumonia was shown to achieve a 1.8- to 4-fold increase in the risk of death [2, 4, 22, 24]. However, these results differ from those of Papazian and co-workers [25], Bregeon and colleagues [27] and Baker and colleagues [26]. In these three studies, survival was similar among patients with pneumonia and controls. Differences across these different studies may be partly explained by differences in patients, methods and diagnostic strategies. Criteria used to define pneumonia were not standardized and this could account for a large degree of variability in the reported estimates of pneumonia incidence, mortality and increased length of hospital stay in the literature.

In our study, the manner of diagnosing nosocomial pneumonia was prospectively standardized among the centers. This study used stringent objective diagnostic criteria for the diagnosis of pneumonia. However, the incidence rates of LOP were higher in centers with increased mortality induced by LOP (centers I and III in Table 5). These results could be explained by differences among the various teams in their manner of suspecting pneumonia. One might conclude that LOP was under-diagnosed in some centers, leading to an underestimation of the risk of death associated with LOP. The accuracy of chest X-ray in diagnosing new pulmonary infiltrate is known to be low [29, 30]. Similarly, clinical findings do not improve the low diagnostic accuracy [30]. However, we carefully designed this study to standardize our routine practice. We discussed the results with all the investigators to find any differences in the manner of diagnosing pneumonia and this hypothesis seems unlikely. Unfortunately, audits were not performed in the ICUs to confirm this hypothesis.

The diagnostic accuracy of the bacteriological sample procedures might have influenced the results. Centers I and II preferentially used fibroscopically directed samples and centers III and IV preferentially used blind plugged telescoping catheters. In all centers, a specimen that yielded 10^3 cfu/ml or more was required to make the diagnosis. However, the difference in the diagnostic accuracy of these techniques appeared too smooth to explain the difference observed [31, 32, 33]. Moreover, centers using the same quantitative culture techniques have totally different incidence rates and risks of mortality induced by LOP.

In our study, the increase in mortality associated with LOP varies among centers. The HRs of LOP for inducing death, even adjusted over the selected prognostic parameters, were between 0.149 and 2.95. However, this observable center effect did not reach statistical significance. These discrepant results could not clearly be explained by various baseline characteristics being significantly different among the centers (Table 6). For example, Heyland et al. have recently shown that the attributable increase in mortality was largely seen in medical patients, with essentially no effect seen in surgical patients [23]. The two centers in our study that showed the highest HRs of death (2.95 in center I and 1.86 in center III) enrolled 65% and 35% surgical patients, respectively, compared to 14% and 28% surgical patients enrolled in the centers with either no effect (center II: HR: 1.07) or even 'protective effect' (center IV, HR: 0.15) of LOP on mortality. Furthermore, neither the high-risk germ – i.e. *Pseudomonas aeruginosa*, *Acinetobacter* species and *Staphylococcus aureus* – incidence [4, 5, 6, 34] nor an initial inappropriate empiric antibiotic treatment [23, 35, 36, 37] could explain these differences among the centers. The discrepancies of the results among centers strongly argue for the stratification of the statistical analyses in further multicenter studies in this field.

The main finding of our study is the major effect of an inappropriate initial empiric antibiotic treatment on LOP mortality. After adjustment for the selected prognostic parameters – i.e. McCabe score more than 1, SAPS II and increases in SAPS II within the first 4 calendar days post-admission to ICU – LOP occurrence was significantly and independently associated with an increased risk of death in patients hospitalized in ICUs. Nevertheless, when the initial empiric antibiotic treatment was appropriate, the occurrence of LOP was no longer significantly associated with an increased risk of death, whereas inappropriately treated LOP was. These results are in accordance with previous reports [35, 38, 39]. In studies specially devoted to attributable nosocomial pneumonia mortality [2, 4, 22, 23, 24, 25, 26, 27], the appropriateness of initial antimicrobial therapy as such was rarely mentioned. In other studies providing this information, the percentage of patients who received inappropriate initial antibiotic therapy varies greatly, from 10% to 73% [23, 28, 35, 37, 38, 39, 39, 40, 41]. These differences in initial antibiotic therapy appropriateness could partly explain the controversy concerning the reality of an attributable mortality due to nosocomial pneumonia [2, 4, 22, 23, 24, 25, 26, 27].

Finally, many studies looking at the outcome of nosocomial pneumonia or, more specifically, at the attributable mortality of this disease have been performed. Nevertheless, the increased mortality induced by nosocomial pneumonia in ventilated patients remains a controversial

issue in the literature. In our multicenter study, the main interesting finding is that the mortality attributable to LOP, after adjusting for baseline factors – i.e. initial prognostic factors, but also severity of illness in the first 4 days of ICU stay – is dependent on the appropriateness of the initial empiric antibiotic treatment. These results might justify clinicians considering the early use of broad-spectrum antibiotic therapy in their patients with suspected LOP.

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