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Impact of appropriateness of initial antibiotic therapy on the outcome of ventilator-associated pneumonia

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Abstract *Objectives*: To evaluate the impact of appropriate initial antibiotic therapy (AB) on the outcome of ventilator-associated pneumonia (VAP). *Design*: Retrospective study (1992–97). *Patients and methods*: Episodes of VAP diagnosed on both clinical and microbiological criteria after ≥48 h of mechanical ventilation (MV). Initial AB was considered appropriate when all significant organisms were susceptible to at least one of the antibiotics started after distal bronchial sampling. Antibiotic treatment was modified within 48 h when susceptibility testing was available. Outcome was recorded at the ICU and hospital discharge. *Results*: One hundred and eleven patients were included (SAPS II = 48 ± 18, age = 62 ± 14 years, mean duration of MV before VAP = 12 ± 9 days). Initial AB was appropriate in 55 patients (49.5 %). No difference between appropriate initial AB and inappropriate initial AB was found concerning severity indices at the time of VAP diagnosis. ICU length of stay was shorter with appropriate initial AB than with inappropriate initial AB for survivors (12 ± 11 days vs 20 ± 24 days, $P = 0.01$). Crude hospital mortality tended to be lower with appropriate initial AB than with inappropriate initial AB (47.3 % vs 60.7 %, odds ratio = 1.72, 95 % CI = 0.81–3.7). Relative crude mortality reduction with appropriate initial AB was 22 %, 95 % CI = –10 % to 45 %. *Conclusion*: Inappropriate initial AB of VAP during the first 48 h increased ICU length of stay after VAP diagnosis and tended to increase crude hospital mortality despite equal severity of illness at the time of VAP diagnosis, when compared to appropriate initial AB in a population of 111 ICU patients.

Key words Ventilator-associated pneumonia · Initial antibiotic therapy · Mortality

Introduction

Pneumonia represents the second cause of nosocomial infections (13–18 %), but is the first cause of mortality from nosocomial infections [1, 2]. Nosocomial pneumonia occurs in 8–20 % of ICU patients, with an increased frequency when they are mechanically ventilated, and its mortality ranges from 25 to 75 % according to studies [3]. The reality of an attributable mortality due to ventilator-associated pneumonia (VAP) is still debated, ranging from 1.2 % to 27.1 % [4, 5, 6].

"High-risk" pathogens, *Pseudomonas aeruginosa* especially, may increase mortality due to VAP when compared to other pathogens [4, 7]. Moreover, they are an independent factor of mortality due to VAP [8]. Previous use of antibiotic therapy (AB) before VAP diagnosis is a risk factor of mortality [9], of selection of resistant bacteria [10], especially *P. aeruginosa* [7]. The effect of inappropriate initial AB on mortality is much debated. Inappropriate initial AB increased mortality during post-operative peritonitis [11] and during septic shock in bacteremic patients [12]. Inadequate treatment of in-

fections among patients requiring ICU admission was an independent factor of hospital mortality [13]. During VAP, inappropriate initial AB was an independent factor of mortality in some studies [14, 15, 16]. Inappropriate initial AB increased attributable mortality due to VAP [17, 18], but not in all studies [5, 19]. However, in these studies, the severity of illness in patients was often low, not well-balanced between groups, and not evaluated at the onset of VAP diagnosis. The aim of our study was to evaluate the impact of inappropriate initial AB on outcome of VAP.

Materials and methods

Selection of patients

A retrospective study, including all patients with VAP diagnosed during a 5-year period (1992–1997), was carried out in a 12-bed medical-surgical intensive care unit (ICU). Patients had to be intubated for more than 48 h. No community-acquired pneumonias were included. Diagnosis of VAP was established with new pulmonary infiltrates and at least three of the following criteria: (a) purulent respiratory secretions; (b) body temperature > 38 °C or ≤36.5 °C; (c) white blood cell count≥10,000/mm^3 or ≤4,000/mm^3; (d) deterioration of PaO_2/FiO_2 ratio > 20 mmHg, in association with a positive distal bronchial sampling yielding at least one pathogen [20]. The sampling was blind or performed under fiberoptic examination with a telescopic plugged catheter (TPC, threshold 10^3 cfu/ml) [21], and was always performed under fiberoptic examination with a protected specimen brush (PSB, threshold 10^3 cfu/ml) [22], and bronchoalveolar lavage (BAL, threshold 10^4 cfu/ml) [23]. In our unit, the choice of sampling method depends on the physician in charge and the availability of the laboratory. Bronchial sampling is possible all around the clock in our ICU.

Antibiotic therapy

Our usual practice is to begin initial AB just after bronchial sampling, guided by direct microbiological examination when possible (TPC, BAL), or a known tracheal colonization. The physician in charge prescribes initial AB. There is no written protocol in our ICU for initial AB of VAP. Previous AB is changed or empiric AB begun after a debate among the ICU medical team. AB is always adapted as soon as susceptibility testing is available (48–72 h). Susceptibility testing was assessed with the disc-diffusion method, and breakpoints were defined by the Antibiogram Committee of the French Society for Microbiology [24]. First-line AB was defined for the following classes: (a) β-lactam: oxacillin, amoxicillin, amoxicillin plus clavulanic acid, piperacillin, cefotaxime or ceftriaxone; (b) fluoroquinolone: pefloxacin or ofloxacin; (c) aminoglycoside: gentamicin or netromycin. Second-line AB was defined as follows: (a) β-lactam: piperacillin plus tazobactam, cefepime or cefpirome, ceftazidime, and imipenem; (b) fluoroquinolone: ciprofloxacin; (c) aminoglycoside: amikacin or isepamycin. Vancomycin serum levels were routinely performed to achieve residual levels between 20 and 25 mg/l.

Data collection

Age, gender, diagnosis, and SAPS II [25] were recorded on admission. Reasons for mechanical ventilation (MV) were classified as follows [26]: (a) acute respiratory failure due to chronic obstructive pulmonary disease; (b) acute respiratory failure; (c) post-operative MV; (d) self-poisoning; (e) neurological; and (f) miscellaneous. Duration of MV before the diagnosis of VAP was collected. Previous AB was recorded (type, duration, and indication). Severity indices such as SAPS II [25], PaO_2/FiO_2 ratio, organ dysfunction and/or infection score ODIN [27], and x-ray score [28] were calculated during the 24 h previous to VAP diagnosis. Inappropriateness or appropriateness of initial AB and total duration of AB was noted. Length of stay in the ICU and duration of MV were recorded. Outcomes at discharge from the ICU and from hospital were noted.

Definitions

Inappropriate initial AB was defined by the isolation of at least one pathogen with a significant threshold in the distal bronchial sampling, resistant or intermediate to the AB prescribed. For *P. aeruginosa*: (a) an aminoglycoside alone was considered inappropriate; (b) a combination therapy was required unless *P. aeruginosa* was susceptible to only one AB. Mortality was considered to be attributable to VAP when it was the direct cause of death (ARDS, septic shock, and multiple organ failure) within 7 days after VAP diagnosis, or a contributing factor in patients with comorbidity [29]. When VAP occurred later than 5 days of MV, it was considered as a late-onset VAP [8]. An isolation of yeast alone was not considered as pneumonia, even with a significant threshold value.

Statistical analysis

Data are expressed as mean ± standard deviation or percentages. Patients with initial appropriate AB were compared to those with inappropriate AB. Mann–Whitney or Kruskal–Wallis tests were used for comparison of quantitative data. The chi-squared test, with Yates' correction when needed, was used for comparison of proportions. A stepwise logistic regression was performed to identify factors independently associated with an initial inappropriate AB during VAP. Quantitative data were classified according to the median value of the population. A forward Wald method was used, with 0.10 for entry into the model and 0.05 for removal. Odds ratios and 95 % confidence intervals (95 % CI) were calculated. (SPSS6.1, SPSS, Chicago, Ill., USA). The increase in mortality due to initial inappropriate AB was calculated as the ratio between the crude mortality (ICU, hospital) of both groups. The predicted mortality of the SAPS II score was compared with observed mortality in both groups. $P < 0.05$ was considered significant.

Results

During the study period, 3,618 patients were admitted to our ICU, with 763 patients mechanically ventilated for more than 48 h (21 %). In this subgroup, 111 patients developed pneumonia (14.5 %). Their mean age was 62 ± 14 years, and SAPS II was 48 ± 18. Causes of admission in the ICU are summarized in Table 1. Twenty-five patients had community acquired pneumonia. Med-

Table 1 Characteristics of the patients on admission, main causes of admission in ICU and reasons for mechanical ventilation. Values are mean ± SD or number and percentage (*AB* antibiotic therapy, *SAPS* Simplified Acute Physiologic Score, *COPD* chronic obstructive pulmonary disease, *ARF* acute respiratory failure, *ARDS* acute respiratory distress syndrome, *MV* mechanical ventilation)

	Appropriate AB ($n = 55$)	Inappropriate AB ($n = 56$)	P
Age (years)	59 ± 15	65 ± 13	0.06
SAPS II	49 ± 16	47 ± 19	0.45
Gender			
Men	38 (69 %)	36 (64 %)	0.73
Women	17 (31 %)	20 (36 %)	
Patient			
Medical	39 (76 %)	39 (70 %)	0.71
Scheduled surgery	8 (15 %)	11 (20 %)	
Emergency surgery	5 (9 %)	8 (10 %)	
Cause of ICU admission			
Respiratory failure	23 (42 %)	28 (50 %)	0.38
COPD	10	13	
Acute respiratory failure	7	9	
ARDS	6	6	
Neurological diseases	16 (29 %)	7 (12.5 %)	0.03
Coma	14	5	
Miscellaneous	2	2	
Cardiovascular diseases	11 (20 %)	11 (20 %)	0.96
Shock	6	8	
Cardiac arrest	4	1	
Miscellaneous	1	2	
Intraabdominal diseases	2 (4 %)	7 (12.5 %)	0.17
Peritonitis	1	3	
Other	1	4	
Miscellaneous	3 (5 %)	3 (5 %)	0.98
Acute renal failure	2	3	
Lactic acidosis	1	0	
Cause of MV			
ARF on COPD	11 (20 %)	13 (23 %)	0.11
ARF	17 (31 %)	25 (45 %)	
Post-operative	7 (13 %)	10 (18 %)	
Neurological	16 (29 %)	7 (12 %)	
Miscellaneous	4 (7 %)	1 (2 %)	

ical admission accounted for 73 % of patients. The main causes of MV are displayed in Table 1. VAP occurred 13 ± 8 days after admission and 12 ± 9 days after MV. Eighty-nine percent of patients had four or five diagnosis criteria for VAP. Forty-nine percent of patients ($n = 54$) received previous ongoing AB at the onset of VAP, essentially for community-acquired infections (pneumonia, intraabdominal infections, etc.). The mean duration of previous ongoing AB before VAP was 9 ± 5 days. Microbiological diagnosis of VAP was made with a TPC in 74 cases (67 %), a PSB in 27 cases (24 %), and BAL in ten cases (9 %).

Fifty-six patients received an inappropriate initial AB (50.5 %, 95 % CI = 40.8–60.0). This group did not differ from the group of patients with appropriate initial AB according to admission characteristics (Table 1), and severity indices at the time of VAP diagnosis (Table 2). At the onset of VAP diagnosis, previous AB ($P < 0.01$) and higher radiological score ($P < 0.05$) were significantly associated with inappropriate initial AB in univariate analysis (Table 2) and in multivariate analysis (Table 3). Thirty-eight out of fifty-four patients (70 %) with previous AB received inappropriate initial AB, and 18/57 patients (32 %) without previous AB received inappropriate AB ($P < 0.001$). The duration of previous AB in patients receiving AB did not differ between the two groups (8 ± 6 days with appropriate initial AB vs 9 ± 4 days with inappropriate initial AB, $P = 0.12$). All patients received AB after distal bronchial sampling. Fifty-seven patients without previous AB had empiric AB started. Twenty-eight patients with prior ongoing AB had AB changed, while 26 patients with prior AB had the same AB regimen pursued (53.6 % of inappropriate AB vs 88.5 %, $P = 0.005$). The regimens of empiric AB are summarized in Table 4.

The use of second-line β-lactam or vancomycin was significantly higher in the appropriate AB group than in the inappropriate one ($P = 0.003$ and $P = 0.04$, respectively). Among the 56 patients with inappropriate initial AB, 31 had unanticipated resistance (55.3 %) and 25 had an absence of consideration of one of the species involved in the VAP (44.7 %). All the 56 patients with inappropriate initial AB had this adapted, and 24 patients of the appropriate group (44 %) were

Table 2 Characteristics of the patients on VAP diagnosis. Values are mean ± SD or numbers and percentages (*VAP* ventilator-associated pneumonia, *AB* antibiotic therapy, *SAPS* Simplified Acute Physiologic Score, *ODIN* organ dysfunction, *MV* mechanical ventilation)

	Appropriate AB ($n = 55$)	Inappropriate AB ($n = 56$)	P
SAPS II	46 ± 20	47 ± 16	0.74
PaO_2/FiO_2	168 ± 66	175 ± 82	0.62
ODIN	3 ± 1	3 ± 1	0.92
X-ray score	5.7 ± 1.9	6.7 ± 1.9	0.01
Delay/admission (days)	13 ± 10	13 ± 9	0.96
Delay/MV (d)	12 ± 10	12 ± 9	0.95
Late-onset VAP	37 (67)	46 (82)	0.11
Previous ongoing AB	16 (29)	38 (68)	< 0.001
Monomicrobial VAP	32 (58)	36 (64)	0.64

Table 3 Predictive factors of inappropriateness of initial AB during VAP in multivariate analysis (*AB* antibiotic therapy, *VAP* ventilator-associated pneumonia, *CI* confidence interval)

Risk factor	Odds-ratio	95 % CI	P
Previous AB	5	3.3–7.6	0.0002
X-ray score ≥6	2.9	1.9–4.5	0.014

Table 4 Main empiric antimicrobial therapy used. Values are numbers and percentages (*AB* antibiotic therapy)

Empiric AB	Appropriate AB ($n = 55$)	Inappropriate AB ($n = 56$)	P
β-Lactam			
First line	20 (36)	31 (66)	0.003
Second line	35 (64)	16 (34)	
Aminoglycosides			
First line	7 (27)	4 (27)	0.98
Second line	19 (73)	11 (73)	
Fluoroquinolones			
First line	8 (31)	7 (41)	0.48
Second line	18 (69)	10 (59)	
Antistaphylococcal			
Vancomycin	26 (93)	15 (68)	0.04
Other	2 (7)	7 (32)	
Miscellaneous	5	12	

changed to the most simple appropriate AB. Pathogens yielded by distal bronchial sampling were mainly gram-negative bacilli (Table 5), without any statistical difference between the two groups ($P = 0.41$). Seventy-seven percent of the *S. aureus* isolated were oxacillin-resistant. The number of non-fermenting gram-negative bacilli *(A. baumanii, P. aeruginosa, S. maltophilia)* was higher in the inappropriate initial AB group but the difference did not reach statistical significance ($P = 0.11$). The number of non-fermenting gram-negative bacilli tended to be higher in the group of patients with previous AB (56 %) than in the group without previous AB (44 %, $P = 0.16$). The duration of previous AB was not higher in patients with VAP due to a non-fermenting gram-negative bacilli when compared to other patients (9 ± 6 days vs 8 ± 4 days, $P = 0.73$). None of the yeast isolated was considered to be responsible for VAP. Episodes with inappropriate initial AB are detailed in Table 6. The pathogens are listed with the type of inappropriate initial AB and the number of patients treated. A relationship with the outcome of these patients with inappropriate initial AB is presented too.

The evolution of patients after VAP diagnosis and AB is summarized in Table 7. For survivors, an increase in the length of stay in the ICU after VAP diagnosis (11.4 days, 95 % CI = 4.1 days–18.7 days) and a trend towards an increase in the duration of MV (8.3 days, 95 % CI = 1.3 days–15.3 days) were observed in the group with inappropriate initial AB. No statistically significant difference in hospital mortality was observed between the groups (47 % with appropriate initial AB vs 61 % with inappropriate initial AB). The relative benefit in crude ICU mortality with an appropriate initial AB was 0.79, 95 % CI = 0.51–1.22, and the relative benefit in crude hospital mortality with an appropriate initial AB was 0.78, 95 % CI = 0.55–1.10. The relative risk reduction in crude hospital mortality between inappropriate initial AB and appropriate initial AB was 22 %, 95 % CI = –10 % to 45 %. The predicted mortality of a SAPS II score of 49 in the appropriate AB group was 43.7 %. The observed mortality of 47 % did not differ (95 % CI = 33.8 %–60.2 %). However, the predicted mortality of the inappropriate AB group with a SAPS II score of 46, was 36.9 %. The observed mortality of 61 % did significantly differ from predicted mortality in this group (95 % CI = 48.2 %–73.8 %). The impact of inappropriate AB on mortality when considering the pathogens were the following: odds ratio = 4.6, 95 % CI = 0.5–45.6 with non-fermenting gram-negative bacilli, and odds ratio = 7.4, 95 % CI = 0.8–77.9 with oxacillin-resistant *S. aureus*.

Discussion

In this study, we were not able to find any statistically significant differences in mortality rates when comparing appropriate initial AB with inappropriate initial AB for VAP, but observed mortality was significantly higher than predicted mortality in the inappropriate ini-

Table 5 Pathogens identified in 111 cases of VAP. Values are numbers and percentages (*VAP* ventilator-associated pneumonia, *AB* antibiotic therapy, *GNB* gram-negative bacilli, *ORSA* oxacillin-resistant *Staphylococcus aureus*, *OSSA* oxacillin-sensitive *Staphylococcus aureus*)

	Appropriate AB (n = 79)	Inappropriate AB (n = 80)
Gram-negative bacilli	44 (56)	45 (56)
Enterobacteriaceae	17	12
E. coli	7	3
E. cloacae	4	3
S. marcescens	0	4
K. pneumoniae	3	2
P. mirabilis	2	0
C. freundii	1	0
Non-fermenting GNB	22	31
A. baumanii	3	9
P. aeruginosa	18	21
S. maltophilia	1	1
Other GNB	5	2
H. influenzae	5	2
Gram-positive cocci	35 (44)	31 (39)
S. aureus	23	24
ORSA	19	17
OSSA	4	7
Streptococcus spp.	10	6
S. pneumoniae	2	1
Miscellaneous	0	4 (5)
Yeasts	0	3
Anaerobes	0	1

Table 6 Episodes with inappropriate initial AB (*AB* antibiotic therapy, *S* survived, *D* crude mortality, *Da* mortality attributable to pneumonia, *ORSA* oxacillin-resistant *S. aureus*, *B* β-lactam, *A* aminoglycoside, *Q* quinolone, *G* glycopeptide, *E* erythromycin)

Pathogen	Patients *(n)*	Initial AB	Outcome *(n)*		
			S	D	Da
ORSA	5	B	2	3	2
ORSA	5	B+A	0	5	2
ORSA	7	B+Q	3	4	3
P. aeruginosa	5	B	2	3	0
P. aeruginosa	1	G	1	0	0
P. aeruginosa	1	E	1	0	0
P. aeruginosa	7	B+A	1	6	2
P. aeruginosa	3	B+G	1	2	0
P. aeruginosa	1	G+A	0	1	1
A. baumanii	1	B	1	0	0
A. baumanii	2	G	0	2	0
A. baumanii	2	B+G	1	1	0
A. baumanii	3	B+A+G	1	2	2
S. marcescens	2	B	1	1	1
S. marcescens	1	G	1	0	0
S. marcescens	1	B+Q	1	0	0
E. cloacae	2	B	0	2	1
E. cloacae	1	B+E	1	0	0
E. coli	1	B	0	1	0
E. coli	1	B+A	0	1	0
K. pneumoniae	1	B+A	1	0	0
H. influenzae	1	B	1	0	0
Prevotella sp.	1	B+A	1	0	0

tial AB group. Moreover, inappropriate initial AB was associated with survivors with an increase in the length of stay in the ICU and a trend towards an increase in the duration of MV. It should be emphasized that initial AB was modified within 48–72 h according to susceptibility testing. AB was then appropriate, at least secondarily, in all patients and for most of the duration of treatment. Only a dramatic effect on outcome of a short (less than 48–72 h) delay in active AB could have been detected.

Some of the characteristics of this study may have influenced the results. It was a retrospective study, but all the VAP during the study period were included, and no patient was excluded because of missing data. Otherwise, the retrospective feature could have been an advantage because the prescription of initial AB was not influenced by a prospective evaluation during which a large spectrum initial AB could have been chosen. Another feature of this study is the lack of power. The difference in mortality rate (appropriate initial AB vs inappropriate initial AB) is a variable in published studies (from 2.5% to 44%), when this difference does exist [15, 17, 18, 19, 29]. In this study, with 47% mortality in the appropriate initial AB group and 61% in the inappropriate initial AB group, 173 patients per group had to be included to find a statistical difference with a 5% bilateral alpha and a power of 80%. Statistical significance was not reached maybe because of the small number of patients. In addition, the definition of attributable mortality we chose was necessarily loose because it was not a case control study [4, 6]. Moreover, the main judgment criterion of the study was not only mortality but also other outcome variables.

Few studies are available in the literature about the impact of initial AB on outcome, apart from VAP. During post-operative peritonitis, inappropriate initial AB increased mortality to 24% when compared to the group with appropriate initial AB [11]. Moreover, inappropriate initial AB was an independent risk factor of mortality in the multivariate analysis. In another study evaluating 453 patients with a bacteremic septic shock, inappropriate initial AB increased mortality to 10% when compared to the group with appropriate initial AB [12]. Recently, it has been shown that inappropriate AB was independently associated with mortality in a large cohort of patients infected in the ICU [13]. During VAP, the increase in mortality induced by inappropriate initial AB was variously appreciated. The study with the largest population (490 patients) did not focus on VAP but on nosocomial pneumonia [17]. In this study, inappropriate initial AB did not increase the mortality rate (34.9% vs 32.4%), but increased the numbers of shocks

Table 7 Outcome after VAP diagnosis. Values are mean ± SD or numbers and percentages. ICU length of stay and duration of MV are expressed only for survivors. (*VAP* ventilator-associated pneumonia, *AB* antibiotic therapy, *OR* odds ratio, *CI* confidence intervals, *MV* mechanical ventilation, *ICU* intensive care unit, *LOS* length of stay, *Attr.* attributable)

	Appropriate AB ($n = 55$)	Inappropriate AB ($n = 56$)	OR	95 % CI	*P*
Duration of AB (days)	11 ± 6	12 ± 6	–	–	0.28
Total duration of MV (days)	12 ± 11	20 ± 24	–	–	0.06
ICU LOS (days)	17 ± 11	29 ± 25	–	–	0.01
Crude ICU mortality	21 (38 %)	27 (48 %)	1.5	(0.7–3.2)	0.38
Attr. ICU mortality	11 (23 %)	15 (31 %)	1.6	(0.6–3.5)	0.39
Crude hospital mortality	26 (47 %)	34 (61 %)	1.7	(0.8–3.6)	0.21
Attr. hospital mortality	12 (20 %)	16 (27 %)	1.4	(0.6–3.4)	0.41

and gastrointestinal bleeding episodes. Two recent studies addressed the question of mortality of VAP due to inappropriate initial AB: one found an association [29], one failed to conclude [19]. A recent case-controlled study evaluating attributable mortality of VAP failed to show any difference between appropriate and inappropriate initial AB [5]. The differences observed between groups in the mortality rate were the same as in our study, with a 15–20 % increase in mortality with inappropriate initial AB. In fact, three studies came to the conclusion that mortality due to VAP was increased with inappropriate initial AB [15, 18]. Luna et al., concluded that only appropriate initial AB, when started before bronchial sampling, was associated with a decreased mortality [18]. However, beginning AB before bronchial sampling might influence the threshold of BAL, as mentioned recently [30]. The study by Kollef et al. had an extremely high rate of inappropriate initial AB: 44/60 patients (73 %), which might not be representative of the population of VAP [15]. In the study by Rello et al., no adjustment on severity of illness at the time of VAP onset was performed [29]. Mortality rates of patients with VAP diagnosis and inappropriate initial AB ranges from 35 to 91 %. The studies that found that inappropriate initial AB was an independent risk factor of mortality were those with the highest mortality (91 %) [14], or the highest inappropriate initial AB rate (73 %) [15]. In the last study [16], the results of the multivariate analysis should be analyzed with caution because the number of variables entered in the model seems to be too high when compared to the number of cases [31]. Thus, the effect on inappropriate initial AB on the duration of MV and length of stay (LOS) are scarce in the literature.

The percentage of patients who received inappropriate initial AB is quite different depending on the studies, and varies from 10 % to 73 % [14, 15, 16, 17, 18, 19, 29]. In a large cohort of ICU patients, initial AB was considered inappropriate in 26 % of patients, but appropriate in 45.2 % of the patients receiving AB for a community-acquired infection [13]. The availability and the updating of a treatment protocol, the knowledge of the colonization of patients, the need to limit selection pressure and cost of AB regimens, and the sensitivity profile of pathogens may influence the frequency of inappropriateness of initial AB. Of note is the lower proportion of patients in the inappropriate initial AB group treated with second-line β-lactam and vancomycin. The concern about limiting costs and ecological pressure should be counterbalanced by the concern regarding the appropriateness of initial AB. The rate we observed is in the mean range and separated patients into two groups of comparable size, strengthening the study power. This rate might be due to the severity of the definitions of inappropriate AB we chose and the lack of unit protocol starting to use broad-spectrum initial AB for VAP at the time of the study. Severity indices are not always mentioned in studies about VAP [29]. When they are mentioned, the scores calculated are lower than those in our study [17]. Only one study in the literature tried to evaluate the severity indexes at the time of VAP diagnosis [32]. The authors showed that when pneumonia is diagnosed the severity of illness was the most important predictor of survival. Yet, although severity indices were well balanced between the two groups at the time of VAP diagnosis, no statistically significant difference in mortality was observed. Nevertheless, the significant increase in ICU LOS for survivors and the trend towards an increase in the duration of MV should be emphasized. Only one study reported an increased LOS and an increased duration of MV when initial AB was inappropriate in comparison with appropriate AB [13]. Nevertheless, this was true for all the nosocomial infections together, not just for VAP alone, and included the total ICU LOS and the total duration of MV, not only after infection diagnosis.

In the multivariate analysis, we found previous AB and a high radiological score independently associated with inappropriate initial AB during VAP. The impact of previous AB has been shown: an increase in mortality rate with selection of multi-drug-resistant pathogens [9], selection of *P. aeruginosa* and *Acinetobacter* spp. [28], but this was not found in other studies [33]. In our study, the duration of previous AB was not longer in the appropriate than in the inappropriate initial AB group. In our population of 111 patients, we could not demon-

strate a statistically significant association between previous AB and the isolation of non-fermenting gram-negative bacilli. Moreover, we did not modify the threshold of bronchial sampling when patients received previous AB, most often for community acquired infection, as has been suggested [30], and we considered bacteria growing at concentrations under the threshold as non-significant for treatment. A higher radiological score in the inappropriate initial AB group is more difficult to explain. A higher radiological score may lead the physician in charge of the patient to diagnose a pulmonary edema, and then to prescribe a narrower-spectrum initial AB while waiting for the susceptibility test.

In conclusion, this study showed that inappropriate initial AB was documented in half of the patients and was associated with a trend towards increased hospital mortality, especially when compared with the predicted mortality of SAPS II. Moreover, survivors who received wrong initial AB choices have a longer duration of MV and length of stay in the ICU. Observational prospective studies on this subject are not easy to conduct because awareness of the ongoing study might influence medical prescription. However, if our results, combined with the results of other studies, are confirmed, it might cautiously justify the prescription of an extended-spectrum initial AB, especially in the case of previous AB or a high radiological score, beginning after bronchial sampling and subsequently adapted within the 48 h of susceptibility testing becoming available. Such a strategy could improve the care of patients with VAP.

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