Intensive Care Med (2004) 30:1327–1333
DOI 10.1007/s00134-004-2292-7

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# Efficacy of adequate early antibiotic therapy in ventilator-associated pneumonia: influence of disease severity

Received: 15 December 2003
Accepted: 25 March 2004
Published online: 9 June 2004


Outcomerea is supported by nonexclusive educational grants from Aventis Pharma, France, Wyeth-Lederle and Centre National de la Recherche Scientifique (C.N.R.S)

Electronic Supplementary Material
Supplementary material is available in the online version of this article at http://dx.doi.org/10.1007/s00134-004-2292-7

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**Abstract** *Objective:* To test the hypothesis that the outcome of patients with ventilator-associated pneumonia (VAP) depends on both their baseline severity at VAP onset and the adequacy of empirical antibiotic therapy. *Design and setting:* Prospective clinical study in six intensive care units in Paris, France. *Patients:* One hundred and forty-two patients with VAP after $\geq$ 48 h of mechanical ventilation. *Measurements and results:* Patients were compared according to whether adequate antibiotics were started when VAP was first suspected (D0). At day 0, the rate of adequate antibiotic therapy was 44.4% and rose to 92% at day 2. Outcomes were recorded at the ICU and hospital discharge. Overall, no significant mortality difference was found with and without adequate early antibiotics. When patients were also classified based on the initial Logistic Organ Dysfunction score (LOD), mortality was significantly higher with inadequate early antibiotic therapy in the groups with LOD $\leq$ 4 (ICU mortality: 37% vs 7%, $P$=0.006; hospital mortality: 44% vs 15%, $P$=0.01). A multivariate logistic regression confirmed that inadequate antibiotic therapy increased mortality in patients with LOD $\leq$ 4 after adjustment on other prognostic factors. *Conclusions:* Inadequate empirical treatment seemed to be associated with a poor prognosis only in patients with LOD $\leq$ 4. These results need to be confirmed by further studies before any reappraisal of current guidelines for empirical antibiotic therapy of VAP can be envisaged.

**Keywords** Ventilator-associated pneumonia · Initial antibiotic therapy · Baseline severity · LOD score · Prognosis · Mortality

## Introduction

Ventilator-associated pneumonia (VAP) occurs in roughly 25% of the patients requiring mechanical ventilation for more than 48 h. It is responsible for high mortality rates and an increased length of stay in intensive care units (ICUs) [1, 2].

An adequate early treatment is undoubtedly a major prognostic factor [3, 4]. Guidelines from the American Thoracic Society help physicians choose the most appropriate empirical antibiotic therapy according to specific risk factors and severity of pneumonia [5].

Nevertheless, these guidelines might lead in some cases to an inappropriate narrow-spectrum antibiotic therapy. Furthermore, they do not take into account the baseline severity of patients which is also an important prognostic factor and seems to be correlated, at least partly, to the microorganisms involved in VAP [6, 7].

Consequently, the baseline severity of patients is probably essential to consider when starting an antibiotic therapy for a suspicion of VAP. To test this hypothesis, we evaluated patients outcome focusing the analysis on both their baseline severity at VAP onset and the adequacy of initial antibiotic therapy.

## Material and methods

### Selection of patients

From January 1997 to February 2000, we prospectively screened all consecutive patients who were admitted to six medical or surgical ICUs and who required mechanical ventilation for at least 48 h. All patients who experienced one episode of VAP during their ICU stay were enrolled in the study. Only the first episode of VAP was considered for analysis.

The diagnosis of VAP was suspected in patients with purulent respiratory secretions, fever $\geq$ 38.5 °C or hypothermia $\leq$ 36 °C, leukocytosis >$12.10^9$/l or leukopenia <4. $10^9$/l and new or progressive infiltrates on chest radiograph. The diagnosis of VAP had to be confirmed by microbiological studies of specimens obtained by telescopic plugged catheter (TPC), protected specimen brush (PSB) or bronchoalveolar lavage (BAL). Collection of these specimens and processing for microbiological studies were performed as previously described [8, 9]. Bacteriologic sampling was performed in all patients on the day VAP was suspected (day 0), before instituting new antimicrobials. Patients in whom antimicrobials had been initiated or modified within 48 h before bronchoscopy were excluded [10].

### Data collection

For each patient, the following variables were recorded:

- at ICU admission: age, gender, admission for medical or surgical reasons, the Logistic Organ Dysfunction Score (LOD), SAPS II, MacCabe, chronic illnesses, and immunologic status.
- At day 0 (i.e., the day the VAP was suspected): the Logistic Organ Dysfunction score (LOD), SAPS II, presence of multiresistant bacteria and adequacy of empirical antibiotic therapy.
- At hospital discharge or death: lengths of ICU and hospital stays and mortality rates.

These data were entered in the OutcomeRéa database which includes clinical, laboratory test and epidemiological data routinely recorded for all patients admitted to the six ICUs that participated in the present study.

### Definitions

Thresholds of $\geq 10^3$ CFU/ml for TPC and PSB and of $\geq 10^4$ CFU/ml for BAL fluid were required for microbiological confirmation of VAP. Adequate antibiotic therapy was defined as administration of at least one antimicrobial agent effective on each microorganism retrieved from microbiological specimens in concentrations greater than the thresholds specified above. Adequate antibiotic therapy in case of *Pseudomonas aeruginosa* was defined as a combination of two effective drugs (betalactam and aminoglycoside or ciprofloxacin) [11, 12]. Early antibiotic therapy was defined as initiation of empirical antibiotics as soon as the diagnosis of VAP was suspected (day 0) and after bronchoscopy was performed.

### Early antibiotic therapy and evaluation

The choice of antimicrobials was decided by the medical staff according to the following risk factors: length of mechanical ventilation, background of previous known patients and unit colonization, previous antibiotic therapy, and results of direct examination of pulmonary secretions when available. Institution of antibiotic therapy as soon as VAP suspicion was not routinely considered except in patients with severe hypoxemia ($PaO_2/FiO_2$<200 mmHg) or hemodynamic failure requiring the use of catecholamines, and when alternative diagnoses were heavily suspected or confirmed (intra-alveolar hemorrhage, hypersensitivity pneumonitis, cardiogenic pulmonary edema). Regimens considered inadequate based on microbiological study results were changed.

The primary evaluation criteria were the ICU and hospital mortality rates, and the secondary evaluation criteria the lengths of ICU and hospital stays. Mortality rates were analysed according to presence or absence of adequate early antibiotic therapy and to disease severity at first suspicion of VAP, as assessed using the LOD score. The LOD score was chosen rather than the SAPS II or the APACHE scores because it is based on organ dysfunctions and can be calculated daily. The LOD score was transformed into a dummy variable according to its median value [13].

### Statistical analysis

Results were expressed as numerical values and percentages for categorical variables, and as medians and quartiles (Q1–Q3) for continuous variables. Comparisons were based on the Fisher exact test or chi-square test for categorical data and on Wilcoxon tests or Kruskal-Wallis tests for continuous data as appropriate.

The relationship between adequacy of antibiotic therapy and collected variables was computed using a logistic regression model where vital status at hospital discharge was the outcome variable of interest. The assumption that quantitative variables were linear in the logit was checked using cubic polynomials and graphical methods. Search for prognostic factors was assessed using a stepwise logistic regression. When this assumption was not verified, the variables were transformed into dummy variables based on their median value [14]. All variables that were clinically relevant or had a $P<.10$ by univariate analysis were entered into the logistic regression model.

A pooled test of all two-way interactions was performed on the final model. In case of significant interactions, odds ratio and confidence intervals were estimated while taking into account correlation between the two interaction variables using the covariance matrix.

## Results

### Patients

During the study period, 742 patients requiring mechanical ventilation for more than 48 h were admitted to the six ICUs and included in the OutcomeRéa database. One hundred and forty-two patients had confirmed VAP and were enrolled in the study. Patients who did and did not receive adequate early antibiotic therapy were comparable at ICU admission and at first suspicion of VAP (Table 1).

### Microbial investigations

TPC, PSB, and BAL cultures yielded 196 microorganisms, of which the most common were *P. aeruginosa* (54 episodes) and *Staphylococcus aureus* (38 episodes). All the microorganisms are listed in Table 2.

Among patients with a LOD score $\leq$ 4, the rate of multiresistant bacteria significantly differed between those who did and did not receive adequate early antibiotic therapy (0% vs 33%, $P<0.01$). Multiresistant bacteria identified were *P. aeruginosa* (*n*=6), methicillin-resistant *S. aureus* (*n*=5), *Stenotrophomonas maltophilia* (*n*=2) and *Acinetobacter baumanii* (*n*=1).

### Early antibiotic regimen

Sixty-three patients received adequate early antibiotic therapy and 79 did not. Among these 79 patients, 28 received inadequate antibiotic therapy on day 0: inadequate monotherapy in 9 cases, inadequate bitherapy in 11 cases and inadequate tritherapy in 8 cases. Not surprisingly, the main reasons for inadequacy was the presence of *P. aeruginosa* (*n*=15), *S. maltophilia* (*n*=1), meticillin-resistant *S. aureus* (*n*=3), *A. baumannii* (*n*=2), and extended spectrum beta-lactamase Enterobacteriaceae (*n*=2). In eight other cases the spectrum of the new antimicrobials was not adequate (yeast *n*=1, aztreonam and Streptococci *n*=3, vancomycin alone and Enterobacteriaceae *n*=3, coamoxyclav and *E. coli n*=1). For the remaining 51 patients, institution of antibiotic therapy was decided on day 1 on the basis of microbiological results. Overall, the rate of adequacy was 44.4% (63/142) on day 0, 81% (115/142) on day 1, 92% (130/142) on day 2, and 100% on day 3 or later. In every case, antibiotic therapy was modified according to microbiological results as soon as possible.

**Table 2** Microorganisms recovered from first episodes of pneumonia (*SA Staphylococcus aureus*)

| | Adequate | Inadequate |
|---|---|---|
| Gram-positive | | |
| *Staphylococcus aureus* | 19 | 19 |
| Oxacillin-sensitive SA | 6 | 8 |
| Oxacillin-resistant SA | 13 | 11 |
| Coagulase negative *Staphylococcus* | 3 | 2 |
| *Streptococcus pneumoniae* | 1 | 3 |
| *Streptococcus* species | 6 | 6 |
| Other Gram-positive | 2 | 0 |
| Gram-negative bacteria | | |
| *Haemophilus influenzae* | 10 | 8 |
| *Pseudomonas aeruginosa*/species | 18/0 | 36/3* |
| *Acinetobacter baumannii* | 0 | 4 |
| *Escherichia coli* | 5 | 12 |
| *Enterobacter cloacae* | 6 | 7 |
| *Klebsiella* species | 8 | 1 |
| Other *Enterobacteriaceae* | 5 | 7 |
| Anaerobes | 1 | 0 |
| *Candida*/yeast | 3 | 1 |
| Total (microorganisms/episodes) | 87/63 | 109/79 |

*$P<0.01$ between both groups

**Table 1** Main characteristics in patients who did and did not receive adequate early antibiotic therapy. Early antibiotic therapy is defined as antibiotics started as soon as VAP was suspected. Quantitative variables are expressed as mean ± standard deviation (median) and qualitative variables as number (%) (*AB* antibiotic therapy)

| | Adequate AB | Inadequate AB | *P* value |
|---|---|---|---|
| | *n*=63 | *n*=79 | |
| On admission | | | |
| Age | 66±14 (68) | 65±15 (67) | 0.53 |
| LOD score | 5.1±2.5 (5) | 5.6±2.6 (6) | 0.15 |
| SAPS II score | 46.7±16 (45) | 51±16 (50) | 0.1 |
| Transfer from ward | 38 | 47 | 0.9 |
| Medical patients | 44 | 58 | 0.63 |
| Scheduled surgical patients | 11 | 12 | 0.7 |
| At least one chronic illness | 34 | 37 | 0.5 |
| Immunosuppression | 10 | 10 | 0.6 |
| MacCabe | | | |
| 1 | 33 | 28 | 0.07 |
| 2 | 23 | 44 | |
| 3 | 7 | 7 | |
| At first suspicion of VAP | | | |
| LOD score | 5.4±2.9 (5) | 4.5±2.5 (4) | .07 |
| SAPS II score | 44.7±15.8 (42) | 40±12.6 (39) | .12 |
| Previous antimicrobials | 28 (44) | 35 (45) | .23 |
| Days since admission | 9.8±8.6 (7) | 10.1±8.8 | .47 |

**Table 3** Outcome of patients who did and did not receive adequate early antibiotic therapy. Early antibiotic therapy is defined as antibiotics started as soon as VAP was suspected and bacteriological exams performed. Quantitative variables are expressed as mean± standard deviation (median) and qualitative variables as number (%) (*AB* antibiotic therapy)

| | Adequate AB | Inadequate AB | *P* value |
|---|---|---|---|
| | *n*=63 | *n*=79 | |
| ICU death | 23 (36.5) | 36 (45.6) | 0.31 |
| Hospital death | 30 (47.6) | 41 (51.9) | 0.73 |
| Length of ICU stay (days) | 29.4±21 (24) | 30±20 (25) | 0.76 |
| Length of hospital stay (days) | 41±40 (34) | 48±42 (38) | 0.97 |

**Table 4** Influence of adequate early antibiotic therapy according to the disease severityat first suspicion of VAP. Early antibiotic therapy is defined as antibiotics started as soon as VAP was suspected. Quantitative variables are expressed as mean±standard deviation (median) and qualitative variables as number (%)

| | Adequate AB | Inadequate AB | *P* value |
|---|---|---|---|
| | *n*=63 | *n*=79 | |
| LOD >4 (*n*=72) | | | |
| Median LOD at first suspicion of VAP | 7 (5–9) | 6 (5–8.5) | 0.21 |
| Median SAPS II at first suspicion of VAP | 49 (44–74) | 46 (39–53) | 0.1 |
| ICU death | 21/36 (59%) | 20/36 (55.6%) | 0.81 |
| Hospital death | 26/36 (72%) | 22/36 (61%) | 0.31 |
| LOD ≤4 (*n*=70) | | | |
| Median LOD at first suspicion of VAP | 3 (2–4) | 3 (2–4) | 0.54 |
| Median SAPS II at first suspicion of VAP | 34 (28–37) | 35 (29–40) | 0.79 |
| ICU death | 2/27 (7%) | 16/43 (37%) | 0.006 |
| Hospital death | 4/27 (15%) | 19/43 (44%) | 0.01 |

Outcome

The overall ICU and hospital mortality rates were 41.5% (59 patients) and 50% (71 patients), respectively. Overall, mortality rates were similar in patients who did and did not receive adequate antibiotic therapy on D0 (Table 3).

Among patients with LOD scores ≤4 at first suspicion of VAP (D0), the risk of death was significantly lower in those who receive than in those who did not receive adequate early antibiotic therapy (ICU mortality: OR: 0.135, 95% CI, 0.03–0.647; hospital mortality: OR: 0.22, 95% CI, 0.07–0.745) despite a similar level of severity at admission (as assessed by SAPS II, and MacCabe scores) and at Day 0 ($PaO_2/FiO_2$ ratio: adequate: 278+163 vs inadequate 227+92 mmHg, *P*=0.07, use of inotropes: adequate 10(37%) vs inadequate 9(21%), *P*=0.14).

Interestingly, mortality dramatically increased with length of inadequate antibiotic therapy (7.4% when adequate antibiotic therapy was started on day 0, 25.8% when it was started on day 1 and 50% when it was started on day 2 or later, *P*=0.01).

On the other hand, among the patients with more severe disease (LOD score >4) at first suspicion of VAP, mortality rates were similar in the groups that did and did not receive adequate early antibiotic therapy (ICU mortality: OR: 1.12, 95% CI, 0.44–2.85; hospital mortality: OR: 1.66, 95% CI, 0.61–4.45) and mortality was not influenced by length of inadequate antibiotic therapy (Table 4). The stratified Mantel-Haenszel OR estimate was 1.82 (95% CI=.83–4.06, *P*=0.15) for ICU mortality and 1.45 (95% CI=.67–3.19, *P*=0.39) for hospital mortality. Lengths of ICU and hospital stays were similar (Table 4).

Variables associated with outcome in univariate analysis were: SAPS II at ICU admission, transfer from ward, non-fatal diseases according to MacCabe score, LOD the day of VAP, *P. aeruginosa*-related VAP and meticillin-resistant *S. aureus*-related VAP. When these variables were introduced into a stepwise logistic regression model, only LOD greater than 4 [odds ratio: 4.7 (95% CI: 2.2-10) *P*<0.0001] and non-fatal disease according to MacCabe score [OR=0.31 (95% CI : 0.14–0.74), *P*=0.003] remained associated with prognosis. As our goal was to test the hypothesis that inadequation of antibiotic therapy might play a differential role according to patients severity, we forced into the model the adequation of antibiotic therapy and the interaction term between LOD score and adequation of antibiotic therapy. As the interaction was highly significant, adjusted odds ratio were estimated using the covariance matrix (Table 5).

## Discussion

Our results indicate that the outcome of patients with VAP depends on both their severity at VAP onset and the adequacy of early empirical antibiotic therapy, thus confirming our initial hypothesis.

When all patients were combined, mortality rates were similar in patients who did and did not receive adequate early antibiotic therapy. However, when we stratified the patients according to disease severity at first suspicion of

**Table 5** Prognostic factors in VAP determined by a stepwise logistic regression: interaction between LOD score and adequacy of early antibiotic therapy. As there was a significant interaction between LOD and adequacy of treatment, estimation of adjusted odds ratio were calculated using the covariance matrix (*AB* antibiotic therapy)

| | OR | 95% CI |
|---|---|---|
| MacCabe | | |
| Non-fatal | 1 | |
| Fatal or ultimately fatal | 3.389 | (1.51–7.63) |
| LOD ≤4 and adequate AB | 1 | |
| LOD ≤4 and inadequate AB | 7.24 | (1.48–35.5) |
| LOD >4 and adequate AB | 24.9 | (4.79–129) |
| LOD >4 and inadequate AB | 16.5 | (2.48–110) |

VAP, we found that adequate early antibiotic therapy was associated with significantly lower mortality, and that mortality dramatically increased with length of inadequate antibiotic therapy, in the subgroup that had a median LOD score ≤4. Importantly, the reduction in mortality remained significant after ICU discharge. For the more severe patients, on the contrary, neither the adequacy of initial treatment nor the length of inadequate antibiotic therapy influenced the prognosis.

Thus, contrary to a widely held view where patients with higher severity are considered to be at high risk of poor outcome when empirical therapy is inadequate, the adequacy of empirical therapy might actually be even more important in patients with lesser disease severity. Any delay in starting adequate antibiotic therapy was associated with a poor prognosis in patients with a LOD score ≤ 4, who might therefore benefit from an early broad-spectrum antibiotic therapy, all the more as they are also likely to be infected by multiresistant bacteria. This hypothesis could have a major impact on the antibiotic management of VAP and needs thus to be confirmed by further investigations.

Available studies evaluating the impact of empirical antibiotic therapy in VAP have produced conflicting results: some found a positive correlation between adequate empirical antibiotics and survival whereas others did not [15, 16, 17, 18, 19]. Many reasons may explain these discrepancies.

First, the link between VAP and mortality is still controversial [15, 20, 21 ,22, 23, 24]. These contradictory results are probably ascribable to differences in patients since it has been reported that the risk of death varies with patients populations [15]. Moreover, adequate antibiotic therapy was defined in some studies as a favorable clinical response and in others as in vitro susceptibility of recovered organisms to first-line empirical antibiotics.

Second, in the studies that found higher mortality rates when antibiotic therapy was inadequate, the patients who received inadequate antibiotic therapy were those with VAP caused by the most difficult-to-treat microorganisms. This is a characteristic of adverse prognostic significance independently of the adequacy of first-line antibiotics.

Third, the diagnosis of VAP is difficult to make. The clinical, laboratory, and radiological signs commonly used to diagnose pneumonia are very common in ICU patients and can be related to infectious or non-infectious conditions. Because of this lack of specificity, they cannot be used to diagnose VAP and other methods are required. The best diagnostic strategy remains undefined. Recent data suggest that both invasive and noninvasive microbial investigations are effective in providing the diagnosis [9, 25]. Unfortunately, their sensitivity is limited. It was about 50–80% in the few studies that compared invasive microbiological studies to histology [26, 27, 28, 29, 30]. The relatively poor sensitivity of invasive and non-invasive diagnostic techniques is ascribable to the heterogeneity of bacterial load and pulmonary lesions in VAP [31, 32]. Specimens from two contiguous pulmonary segments often yield different quantitative results. Accordingly, negative cultures of pulmonary secretions do not exclude the diagnosis of VAP and positive cultures sometimes reflect simple colonization. These considerations must be kept in mind when analysing the impact of empirical antibiotic therapy.

Finally, the impact of patients baseline severity on the efficacy of empirical antibiotic therapy has never been clearly settled. The baseline severity of some patients is so high that no effect of adequate early antibiotic therapy on mortality of VAP can be documented. In contrast, patients with intermediate baseline severity may benefit the most from an adequate early antibiotic therapy [33]. It probably explains why, in our study, adequate early antibiotic therapy influence outcome only in the group of patients with a LOD score≤4, but not in the group of patients with a LOD score >4.

In conclusion, our data suggest that early broad-spectrum antibiotic therapy, rapidly followed by deescalation according to microbiological results, should be administered in all patients, even in the less severe ones, as soon as VAP is suspected. Yet, reappraisal of current guidelines for empirical antibiotic therapy of VAP cannot be recommended on the basis of a single study and further evaluation is needed, particularly regarding the risk of selection pressure and emergence of multiresistant bacteria.

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