**Early Antibiotic Treatment for BAL-Confirmed Ventilator-Associated Pneumonia**

**A Role for Routine Endotracheal Aspirate Cultures**

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**Study objectives:** To test whether routine quantitative cultures of endotracheal aspirates obtained before the onset of ventilator-associated pneumonia (VAP) could help to predict the causative microorganisms and to select early appropriate antimicrobial therapy before obtaining BAL culture results.

**Design:** Prospective observational study.

**Setting:** French medical ICU.

**Patients:** A total of 299 patients received mechanical ventilation for at least 48 h.

**Interventions:** Endotracheal aspiration (EA) was performed twice weekly in all mechanically ventilated patients. A diagnosis of VAP was made by BAL culture. Only the EA performed just before the suspicion of VAP (EA-pre) were evaluated. This strategy (ie, the EA-pre-based strategy) was compared with an antibiotic therapy that would have been prescribed if the recommendations of both the American Thoracic Society (ATS) and Trouillet et al (Am J Respir Crit Care Med 1998; 157:531–539) had been applied.

**Measurements and results:** VAP was diagnosed (by BAL culture) in 41 of the 75 patients in whom BAL was performed. Among the 41 BAL specimens that were positive for VAP, EA-pre had identified the same microorganisms (with the same antibiotic resistance patterns) in 34 cases (83%). In one case, EA-pre was not available at the time BAL was performed (a case of early-onset VAP), but the empiric antibiotic therapy was adequate. While EA-pre did not give the same results as the BAL culture, the antibiotic therapy based on the results of the EA-pre was adequate in four other cases. Finally, antibiotic therapy was delayed in only two cases. Antibiotic treatment was therefore adequate in 38 of the 40 assessable cases (95%). If the Trouillet-based strategy had been used, the antibiotic treatment would have been adequate in 34 of the 41 cases (83%; \( p = 0.15 \) [vs EA-pre strategy]). Based on the ATS classification, the antibiotic treatment would have been adequately prescribed in only 28 of the 41 cases (68%; \( p = 0.005 \) [vs EA-pre strategy]).

**Conclusions:** Routine EA performed twice a week makes it possible to prescribe adequate antibiotic therapy (while waiting for BAL culture results) in 95% of the patients in whom a VAP is ultimately diagnosed by BAL culture.

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**Key words:** ARDS; BAL; empiric antibiotic therapy; endotracheal aspirate; mechanical ventilation; pneumonia

**Abbreviations:** ATS = American Thoracic Society; CI = confidence interval; CPIS = clinical pulmonary infection score; EA = endotracheal aspiration; EA-pre = endotracheal aspiration performed just prior to the suspicion of ventilator-associated pneumonia; Fio2 = fraction of inspired oxygen; IQR = interquartile range; OR = odds ratio; SAPS = simplified acute physiology score; SOFA = sequential organ failure assessment score; VAP = ventilator-associated pneumonia

Ventilator-associated pneumonia (VAP) is the most frequent ICU-acquired infection among patients receiving mechanical ventilation. The incidence varies from 9 to 20%. Although the attributable mortality rate for VAP is still debated, it has been shown that these infections prolong both the
duration of ventilation\(^5\)–\(^7\) and the duration of ICU stay.\(^8\)–\(^9\) Approximately 50\% of all antibiotics prescribed in an ICU are administered for respiratory tract infections.\(^10\) The absence of adequate antimicrobial therapy in patients with pneumonia, peritonitis, bacteremia, or meningitis is associated with an increased mortality rate.\(^11\)–\(^19\) Bronchoscopically directed sampling of lower respiratory tract secretions provides accurate microbiological data. However, it may do so too late in the course of VAP to improve survival. Indeed, Luna et al.\(^12\) showed that adequate antibiotic therapy can improve survival in patients with VAP only if administered early in the course of the illness, at a time when the microbiological data obtained by BAL are not available. Moreover, they also demonstrated that in case of inadequate initial empiric antibiotic therapy, the subsequent change in the antibiotic administered when BAL culture results are known did not decrease the mortality rate.\(^12\)

It can be argued that the outcome in VAP patients can be improved only if the initial antibiotic therapy is accurate and timely. The major drawback of a strategy based on bronchoscopically directed sampling of lower respiratory tract secretions (ie, a BAL-based strategy) is the necessary time to identify the etiologic agent of VAP leading physicians to prescribe broad-spectrum antibiotics during the 24 to 48 h period preceding the obtaining of the BAL culture results. The initial empiric antibiotic treatment often requires modification when quantitative culture results become available.\(^13\)–\(^23\) When using a BAL-based strategy, the choice of antibacterial agents must be broad enough to ensure that adequate coverage of all likely bacterial pathogens is provided during the 24 to 48 h period preceding the obtaining of BAL culture results. Initial treatment covering Gram-negative and Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus*, should then be provided unless infection to these organisms is excluded.\(^11\) The American Thoracic Society (ATS) guidelines for hospital-acquired pneumonia\(^24\) and the classification of Trouillet et al.\(^25\) can help to select an adequate initial antibiotic therapy. However, the extensive use of antibiotics, especially broad-spectrum antibiotics, is associated with the emergence of resistant pathogens and exposes patients to adverse effects.

Routine surveillance for bacterial colonization by endotracheal aspirates is used in a number of ICUs. However, to our knowledge, its appropriateness for the choice of initial antimicrobial treatment of suspected VAP, subsequently confirmed (or not) by BAL culture, has not been established. In the present study, we tested the hypothesis that the results of routine (ie, twice-a-week) quantitative cultures of endotracheal aspirates obtained before the onset of VAP can predict the causative microorganisms and thus make it possible to select appropriate early antimicrobial therapy before obtaining BAL culture results. In order to do this, we prospectively studied a series of consecutive adult patients who were suspected of having VAP in whom the causative bacteria were determined by BAL culture.

**Materials and Methods**

This prospective study was performed in the medical ICU of Sainte-Marguerite University Hospital in Marseille, France, over a 21-month period (ie, May 1, 2000, to January 31, 2002). In accordance with French law, no informed consent was mandatory, given that this epidemiologic study did not modify current diagnostic or therapeutic strategies.

**Patients**

Patients (\(\geq 18\) years of age) who had received mechanical ventilation for \(> 48\) h were prospectively included if VAP was suspected. Severely neutropenic patients (\(< 0.5 \times 10^9\) neutrophils per liter) and AIDS patients were excluded.

**Endotracheal Aspirates**

Routine surveillance included a microbiological analysis of endotracheal aspirates twice weekly in all patients until the tracheostomy cannula or endotracheal tube was removed. Endotracheal aspiration (EA) was performed using a sterile catheter with a specimen trap kit (model 534–16; Vygon; Ecouen, France), as previously described.\(^26\)–\(^27\) The suction tube was blindly introduced through the intubation or tracheotomy tube and was wedged into the tracheobronchial tree before suction. Bacterial identification and antibiotic susceptibility tests using standard methods were performed only for microorganisms that were present at a concentration \(\geq 10^9\) cfu/mL. The results of EA were not taken into account in the suspicion or diagnosis of VAP. Only the EAs that were performed just before the suspicion of VAP (EA-pre) were taken into account (Fig 1) for the evaluation of the strategy in question.

**Diagnosis of VAP**

One of the investigators made daily rounds in the ICU to identify eligible patients, to determine the onset of VAP based on...
diagnosis of VAP was established when the BAL quantitative susceptibility tests were performed using standard methods. A aliquots were pooled. Bacterial identification and antibiotic susceptibility was performed in each patient who was suspected of having VAP within 24 h after the development of a new infiltrate or the progression of a prior stable infiltrate. BAL was performed on ICU admission, and gas exchange degradation. A fiberoptic bronchoscopy examination was performed in each patient who was suspected of having VAP within 24 h after the development of a new infiltrate or the progression of a prior stable infiltrate. BAL was performed on ICU admission and gas exchange degradation. A fiberoptic bronchoscopy examination was performed in each patient who was suspected of having VAP within 24 h after the development of a new infiltrate or the progression of a prior stable infiltrate. BAL was performed on ICU admission and gas exchange degradation. A fiberoptic bronchoscopy examination was performed in each patient who was suspected of having VAP within 24 h after the development of a new infiltrate or the progression of a prior stable infiltrate. BAL was performed on ICU admission and gas exchange degradation. A fiberoptic bronchoscopy examination was performed in each patient who was suspected of having VAP within 24 h after the development of a new infiltrate or the progression of a prior stable infiltrate. BAL was performed on ICU admission and gas exchange degradation. A fiberoptic bronchoscopy examination was performed in each patient who was suspected of having VAP within 24 h after the development of a new infiltrate or the progression of a prior stable infiltrate. BAL was performed on ICU admission and gas exchange degradation. A fiberoptic bronchoscopy examination was performed in each patient who was suspected of having VAP within 24 h after the development of a new infiltrate or the progression of a prior stable infiltrate. BAL was performed on ICU admission and gas exchange degradation. A fiberoptic bronchoscopy examination was performed in each patient who was suspected of having VAP within 24 h after the development of a new infiltrate or the progression of a prior stable infiltrate.

Data Collection
The following information was recorded prospectively:

- On ICU admission: age; sex; cause of ICU admission; location prior to ICU admission; comorbidities; diagnosis; simplified acute physiology score (SAPS) II score; and sequential organ failure assessment (SOFA) score;
- At the time of BAL: SOFA score; Weinberg radiologic score; temperature; WBC count; PaO₂/FIO₂ ratio; clinical pulmonary infection score (CPIS); PaCO₂; results of quantitative cultures from specimens obtained by EA-pre; adjustment of ventilator parameters with implementation of FIO₂, positive end-expiratory pressure, or minute ventilation during the previous 24-h period; and the presence of antibiotics; and
- After BAL: results of the BAL bacteriologic culture; modification of antimicrobial treatment; length of mechanical ventilation; length of stay in the ICU; and outcome.

Criteria Evaluated
We first studied the ability of EA-pre to predict the organisms found by BAL. The results were considered to be exact only if all microorganisms that were present in the BAL fluid at a concentration of $\geq 10^4$ cfu/mL were also identified by EA-pre and had the same antibiotic susceptibility patterns, and if there were no other bacteria identified by the EA-pre. The selection of antibiotic therapy was left to the discretion of the attending physician who was in charge of the patient. Causative organisms were classified into the following two groups: organisms with a high risk of multidrug resistance included Pseudomonas species, Acinetobacter species, Stenotrophomonas species, and methicillin-resistant S. aureus; and organisms with a low risk of multidrug resistance included all other bacteria. We compared the antibiotic therapy that had been based on the results of EA (ie, the EA-pre-based strategy) with an antibiotic therapy that would have been prescribed if the recommendations of both the ATS (ie, the ATS-based strategy) and Trouillet et al (ie, the Trouillet classification-based strategy) had been applied. The classification by Trouillet et al is based on the prior duration of mechanical ventilation (ie, $< 7$ days or $\geq 7$ days) and on the presence or absence of antibiotic therapy during the 15 days preceding the episode. We were especially interested in the prescription of the following antibiotics: imipenem; anti-pseudomonal cephalosporin; and anti-pseudomonal penicillin with a β-lactamase inhibitor. We evaluated the duration of mechanical ventilation, the duration of ICU stay, and the ICU mortality rate in patients presenting with a VAP or not presenting with a VAP. We calculated the number of ventilator-free days and alive at day 60.

Statistical Analysis
The data are expressed as the mean ± SD for normally distributed data and median with interquartile range (IQR) for nonnormally distributed data. Continuous variables were compared using the Student t test for normally distributed variables and the Wilcoxon rank-sum test for nonnormally distributed variables. The χ² test or the Fisher exact test was used to compare categoric variables. A stratified analysis was performed in order to study the possible influence on mortality of the SAPS II score on ICU admission.

Results

Patient Characteristics
Over a period of 21 months, 299 patients received mechanical ventilation for at least 48 h. A total of 1,211 EA procedures were performed during the study period. Seventy-five BAL procedures were performed for suspicion of VAP on the basis of the criteria previously defined. Two episodes of VAP were suspected in eight patients, three episodes were suspected in one patient, and four episodes were suspected in one patient. The characteristics of the patients suspected of having VAP are provided in Table 1. VAP was diagnosed (by BAL culture) in 41 of the 75 patients (55%) in whom BAL was performed. The incidence of VAP was therefore 13.7% (95% confidence interval [CI], 9.8 to 17.6%) of the patients who had received mechanical ventilation for at least 48 h (10.4 patients per 1,000 ventilator-days). VAP was diagnosed in 12 of 41 patients (29%) between the third and the fifth day (ie, early-onset
VAP) and after the fifth day of mechanical ventilation (ie, late-onset VAP) in the remaining 29 patients (71%).

Concordance Between BAL and EA-Pre Cultures

Among the 41 positive BAL cultures, EA-pre had identified the same microorganisms (with the same antibiotic resistance patterns) in 34 cases (83%; 95% CI, 70 to 96%). Regarding only late-onset VAP, EA-pre had identified the microorganisms found by the BAL culture in 25 of the 29 cases (86%) [Table 2].

The discrepancies between a BAL culture with \(10^4\) cfu/mL and the EA-pre are shown in Table 3. In one case, EA-pre was not available at the time of the BAL procedure (a case of early-onset VAP), but the empiric antibiotic therapy was adequate. While it did not provide the same results as the BAL culture, the antibiotic therapy based on the results of the EA-pre was adequate in four other cases. Finally, antibiotic therapy was delayed in only two cases.

Twelve patients (29%) had microorganisms by the EA-pre and received antibiotics while waiting for BAL culture results, which were negative. No antibiotic was prescribed in the other 22 suspected patients with VAP who had a negative EA-pre finding and finally a negative BAL finding.

Adequacy of Antibiotic Therapy According to the Strategy Used

Antibiotic treatment was adequate in 38 of the 40 assessable cases (95%; 95% CI, 88 to 100%) when a strategy based on the results of EA-pre was used. The false-negative rate was therefore 5% (95% CI, 0 to 12%) when an EA-pre strategy was used. If the Trouillet-based strategy had been used, the antibiotic treatment would have been adequate in 34 of the 41 cases (83%; 95% CI, 72 to 94%; \(p = 0.15\) [vs EA-pre strategy]). Based on the ATS classification, antibiotic treatment would have been adequately prescribed in only 28 of the 41 cases (68%; 95% CI, 54 to 82%; \(p = 0.005\) [vs EA-pre strategy]). The EA-pre strategy led to the prescription of antibiotics in only 12 of the 34 patients (35%; 95% CI, 19 to 51%) in whom BAL culture results remained negative. In contrast, all of these 34 patients would have received antibiotics (prior to receiving BAL culture results) if the Trouillet-based strategy or the ATS-based strategy had been used (\(p = 0.001\) for both [vs EA-pre strategy]).

Microbiological Results

Pseudomonas aeruginosa was the most frequently isolated bacteria (24%) [Table 4]. Of the 12 cases, ticarcillin resistance was present in 7, all of which were late-onset VAP. Only 1 of the 12 cases of VAP that were related to S aureus was due to a methicillin-resistant strain of S aureus. Cases of late-onset VAP were due to bacteria that were classified as having a “high risk of multidrug resistance bacteria” in 11 of 29 cases (38%). Three of the 12 cases (25%) of early-onset VAP were due to bacteria that were classified as having a “high risk of multidrug resistance bacteria” (difference not significant [vs late-onset VAP]).

Antibiotic Therapy Spectrum

If it had been used, the Trouillet-based strategy would have led to a broader antibiotic therapy than the antibiotic therapy that we prescribed according
Table 3—Causes of Discrepancies Between EA-Pre and Positive BAL Culture*

<table>
<thead>
<tr>
<th>Microorganisms Identified by EA</th>
<th>Antibiotics Given Prior to BAL</th>
<th>BAL Culture Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>No result at the time of BAL</td>
<td>Amoxicillin + clavulanic acid</td>
<td>MSSA</td>
</tr>
<tr>
<td>Cefotaxime-R Serratia marcescens</td>
<td>Imipenem + aminoglycoside</td>
<td>Cefotaxime-S. marcescens + MSSA</td>
</tr>
<tr>
<td>Ticarcillin-S P aeruginosa + ampicillin-R Echerichia coli</td>
<td>Cefotaxime + aminoglycoside</td>
<td>Ticarcillin-S. P aeruginosa</td>
</tr>
<tr>
<td>No growth</td>
<td>No antibiotic</td>
<td>H influenzae</td>
</tr>
<tr>
<td>No growth</td>
<td>No antibiotic</td>
<td>Providencia stuartii</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>Amoxicillin + clavulanic acid</td>
<td>Streptococcus pneumoniae + ampicillin-R Proteus mirabilis</td>
</tr>
<tr>
<td>MSSA</td>
<td>Amoxicillin + clavulanic acid</td>
<td>MSSA + S pneumoniae + cefotaxime-S Klebsiella sp</td>
</tr>
</tbody>
</table>

*MSSA = methicillin-susceptible S. aureus.

to our EA-pre-based strategy in 23 cases. The antibiotic therapy based on EA-pre results was more accurate from an ecologic point of view (ie, a broader spectrum) than the ATS-based strategy in 18 cases. Moreover, the EA-pre strategy allowed prescription of an adequate dose of antibiotics in seven cases, while the antibiotic therapy chosen according to the Trouillet-based strategy would have been inadequate. In 13 cases, antibiotic therapy guided by EA results was adequate, while that administered according to the ATS-based strategy would have been inadequate. In eight cases and seven cases, respectively, the same antibiotic regimen was administered and was based on EA-pre results that were the same as those that would have been used according to the Trouillet-based strategy or the ATS-based strategy. Finally, compared with a treatment prescribed according to the Trouillet-based strategy or the ATS-based strategy, the EA-pre strategy was more adequate or made it possible to narrow the antibiotic spectrum in 30 cases and 31 cases, respectively, of the 41 cases. Conversely, these classifications were more accurate than the EA-pre-based strategy in only 2 of the 41 cases and never made it possible to narrow the antibiotic spectrum (p < 0.001 [ATS-based or Trouillet-based strategies vs EA-pre-based strategy]).

Use of Imipenem, Antipseudomonal Cephalosporin, or Antipseudomonal Penicillin With a β-Lactamase Inhibitor According to the Strategy

Based on EA-pre results, the use of these β-lactam antibiotics was restricted to 18 patients (45%; 95% CI, 30 to 60%), while they would have been used in 31 patients (76%; 95% CI, 63 to 89%) if the classification of Trouillet et al25 had been used (p = 0.01 [vs EA-pre strategy]) and in 33 patients (80%; 95% CI, 68 to 92%) if the ATS recommendations had been used (p = 0.002 [vs EA-pre-based strategy]) [Table 5]. Antibiotics were prescribed (based on the EA-pre results) in excess in eight patients in whom VAP was not confirmed by BAL culture results. If the Trouillet-based strategy or the ATS-based strategy had been used, one of these antibiotics would have been proposed in 31 of the 34 patients (91%; 95% CI, 81 to 100%) prior to obtaining the BAL culture results.

Comparison of Data According to BAL Results

As shown in Table 6, no criteria other than CPIS was associated with BAL results. The usual clinical criteria were not different whether the BAL culture was positive or not. The parameters noted on ICU admission were also comparable. The length of ICU stay (data not shown) and the mean length of mechanical ventilation...
(35 ± 23 vs 25 ± 13 days; p = 0.062) were not different between patients who developed at least one VAP and those with only a suspicion of VAP but who always had a negative BAL culture result. However, the number of ventilator-free days at day 60 was lower (p = 0.01) in patients who developed at least one VAP (median, 0 days; IQR, 0 and 19 days) when compared with patients with always negative BAL (median, 23 days; IQR, 2 and 43 days). The ICU survival rate was lower for patients who developed at least one VAP when compared with patients who did not develop VAP (38.5% vs 73.9%, respectively; p < 0.05). A stratified analysis showed that, after stratification in three categories, this difference in mortality rate remained for SAPS II scores on ICU admission from 36 to 50 (29% vs 80%, respectively; p = 0.03). However, there was no difference in mortality rate when the SAPS II score on ICU admission was < 36 (20% vs 30%, respectively) or > 50 (33% vs 57%, respectively).

Cost Evaluation

The total cost of the antibiotics administered while waiting for BAL culture results (based on the EA-pre culture results) and a routine EA specimen culture performed twice a week for all patients who received mechanical ventilation for > 48 h during the study period was €11,718. In comparison, the cost of empirical treatment with imipenem, amikacin, and vancomycin for 48 h (while waiting for the BAL culture result) for all patients who were suspected of having VAP during the study period would have been €7,773.

<table>
<thead>
<tr>
<th>Table 6—Clinical Findings at the Time of BAL*</th>
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<table>
<thead>
<tr>
<th>Finding</th>
<th>≥ 10⁴ cfu/mL (n = 41)</th>
<th>&lt; 10⁴ cfu/mL (n = 34)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature, °C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
<td>38.3 ± 0.9</td>
<td>38.5 ± 0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Minimum</td>
<td>37.0 ± 0.8</td>
<td>37.0 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>WBC count, ×10⁴ cells/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOFA score</td>
<td>8.2 ± 3.8</td>
<td>7.4 ± 3.6</td>
<td>NS</td>
</tr>
<tr>
<td>Weinberg score</td>
<td>6.7 ± 2.6</td>
<td>6.1 ± 2.3</td>
<td>NS</td>
</tr>
<tr>
<td>PaO₂/FIO₂ ratio</td>
<td>180 (139–248)</td>
<td>163 (137–234)</td>
<td>NS</td>
</tr>
<tr>
<td>PacO₂, mm Hg</td>
<td>39 (33–46)</td>
<td>40 (34–44)</td>
<td>NS</td>
</tr>
<tr>
<td>CPIS</td>
<td>6.6 ± 2.2</td>
<td>5.0 ± 1.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Ventilator adjustment (PEEP, FIO₂, minute ventilation) during the 24 h prior to BAL†</td>
<td>20 (49)</td>
<td>14 (41)</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of mechanical ventilation before VAP onset, d</td>
<td>11 (5–22)</td>
<td>11.5 (7–24)</td>
<td>NS</td>
</tr>
<tr>
<td>On antibiotics‡</td>
<td>15 (37)</td>
<td>14 (41)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Values given as mean ± SD, median (IQR), or No. (%), unless otherwise indicated. NS = not significant; PEEP = positive end-expiratory pressure.
†Positive end-expiratory pressure, FIO₂, or minute ventilation adjustment.
‡Unchanged during the last 72 h.

Table 5—Antibiotics Received by the 41 Patients With a VAP and Antibiotics That Would Have Been Prescribed According to the Classifications of Trouillet et al²⁵ and the ATS²⁴*
sults. Hayon et al32 studied the results of all cultures with prior EA specimen culture results 24 to 48 h later) was suspected. This method was useful for the diagnosis of VAP. However, the interval between prior specimen cultures and the onset of VAP was frequently long enough (mean duration, 8 ± 9 days) to permit the development of lung infection caused by microorganisms other than those previously isolated. Hayon and coworkers32 also have shown that when respiratory specimens were obtained < 72 h before distal sampling, all of the VAP-causative bacteria were isolated in 17 of 33 episodes (52%). Furthermore, for Hayon et al32 specificity reached 85% and 84%, respectively, for P aeruginosa and methicillin-resistant S aureus. Studying 27 patients, Dennesen et al33 performed routine surveillance including microbiological analysis of semiquantitative cultures of endotracheal aspirates on ICU admission and subsequently twice weekly. They reported that initial antimicrobial therapy based on the results of a semiquantitative EA culture was appropriate in all cases. These results and those presented here are in agreement with those of Delcaux and coworkers34 who showed that repeated quantitative cultures using specimens from a plugged telescopic catheter that were taken blindly via the endotracheal tube every 48 to 72 h in patients with ARDS identified VAP-causative bacteria in 67% of the VAP episodes. It has been clearly demonstrated12,13,35,36 that inadequate antibiotic treatment of VAP reduces the survival rate. A strong association between the initial administration of inadequate antimicrobial therapy for VAP and mortality has also been found.11–14 The initial administration of inadequate antibiotic therapy may partially explain the excess patient mortality associated with VAP, especially when it is attributed to antibiotic-resistant bacteria.9,31 Celis et al37 also found that inappropriate antibiotic therapy was associated with a relative odds ratio (OR) for death of 6.81. Rello et al14 noted that the attributable mortality rate for patients with VAP was 37% when patients received an inadequate initial treatment, while an attributable mortality rate of 15.4% was found in patients receiving adequate antibiotic therapy. Kollef and Ward11 found that the risk of hospital mortality was more than three times as great among patients with inadequate antibiotic therapy compared with patients who received adequate antibiotic therapy to treat the pathogens recovered from their mini-BAL cultures. Iregui et al39 reported that patients receiving antibiotic treatment that was delayed for ≥ 24 h after initially meeting the criteria for VAP had a significantly greater hospital mortality rate compared with the remaining patients with VAP. The choice of an adequate antimicrobial therapy also reduced hospital stay.40 However, the appropriateness of the empiric antibiotic therapy is difficult to predict. Rello and coworkers41 found a significant variation in the etiology of microorganisms that were isolated in three different ICUs. They found that both the ATS classification24 and the Trouillet et al25 classification failed to predict the presence of highly resistant pathogens in some patients who were considered to be in low-risk groups.

An inadequate antibiotic treatment prescription can occur in > 30% of cases. Kollef and Ward11 showed that the hospital mortality rate of patients who have their antibiotic therapy changed or whose therapy started following a mini-BAL culture was 61%, while the mortality rate of patients with no change in their antibiotic management was 33%. Thus, changing or modifying initially inadequate antibiotic treatment did not improve outcome, prob-
ably because the change occurred too late in the course of the illness to have a beneficial effect.

Clinicians have to wait 24 to 48 h before BAL culture results and bacterial antimicrobial sensitivity profiles become available. Therefore, if no routine surveillance of endotracheal aspirates is performed, it is necessary to treat patients with broad-spectrum antibiotics when VAP is suspected.\(^{24}\) Such an attitude is not safe because it increases the risk of bacterial selection of multiresistant bacteria. Indeed, the association of the prior administration of antibiotics and the occurrence of VAP due to antibiotic-resistant bacteria has been demonstrated.\(^{9,31}\) Trouillet et al\(^{25}\) identified prior antibiotic use (OR, 13.5), including the prior use of broad-spectrum antibiotics (OR, 4.1), as being independently associated with infection due to antibiotic-resistant bacteria. In the present study, the EA-pre strategy allowed a significant reduction in the prescription of antibiotics in patients who finally had negative BAL culture findings. It could be useful to take into account the time that elapsed between the onset of mechanical ventilation and the suspicion of VAP. Unlike cases of late-onset VAP, cases of early-onset VAP are usually related to low-resistance bacteria. However, multiresistant bacteria can be responsible for early-onset pneumonia. In the present study, 17% of early-onset VAP cases were due to multiresistant bacteria. Such attitudes can therefore lead to inadequate antibiotic treatment for some patients who have VAP. Finally, broad-spectrum antibiotics are expensive and increase the costs of a stay in the hospital.

Some authors have proposed different strategies to reduce the time between the suspicion of VAP and the prescription of adequate antibiotics. The direct examination of samples has been studied, but the opinions of authors are conflicting.\(^{42,43}\) If the specificity seems acceptable, the sensitivity of the test is surely not sufficient. This has been confirmed by the recent work by Sirvent et al,\(^{44}\) who evaluated the direct examination yield of mini-BAL samples. Much more importantly, if Gram staining and/or counts of infected cells can confirm the presence of pneumonia, they cannot evaluate antibiotic sensibility patterns, whereas routine EA (performed during the days preceding BAL) can provide this information.

Some limitations of the present study must be noted. For example, no genotypic analyses of the different strains that were isolated were performed. Moreover, nonbacteriologic pneumonia was excluded from the analysis. As demonstrated by Rello et al,\(^{41}\) the epidemiology of the pathogens causing VAP is likely to have geographic variations. The fact that the Trouillet classification is from Paris could explain in part its better performance in the present study compared to the ATS guideline.

Concerning the cost of routinely performed EA, the evaluation presented here showed that the difference vis-à-vis the potential advantages was minor between this strategy and systematic broad-spectrum antimicrobial treatment. Simplifying therapy is of interest in economic terms, obviously, but also because administering unnecessary antibiotics may lead to superinfection with more resistant strains and also to the emergence of multiresistant pathogens in the hospital.\(^{31}\) Such an approach to antibiotic therapy for VAP can be viewed as a strategy to balance the need to provide appropriate initial antibiotic treatment that is prescribed early to high-risk patients while avoiding unnecessary treatment with broad-spectrum antibiotics, which can further promote the antibiotic resistance of potentially pathogenic bacteria.

To conclude, routine EA would appear to be useful in the choice of adequate initial antibiotic therapy for the treatment of bacterial VAP. However, prospective comparative studies are required to evaluate the ability of this strategy to improve the outcome, to reduce hospitalization costs, and, finally, to control the bacterial ecology.

**REFERENCES**
