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## Previous endotracheal aspirate allows guiding the initial treatment of ventilator-associated pneumonia

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**Abstract Objectives:** Any delay in adequate antibiotic treatment compromises the outcome of ventilator-associated pneumonia (VAP). However, the diagnosis and optimal treatment of VAP remain a challenge for intensivists. We assessed the potential impact of using results of routine weekly endotracheal aspirate (EA) cultures to guide initial antibiotic treatment for VAP. **Design and setting:** Retrospective analysis of prospectively collected data in a medical–surgical intensive care unit (ICU) of a university hospital. **Patients and methods:** We studied 113 VAP episodes and evaluated the concordance between the latest EA and the broncho-alveolar lavage (BAL). We stratified patients into three groups: concordant EA–BAL (concordant group), discordant EA–BAL (discordant group) and EA not performed group. We then compared the adequacy of the antibiotic prescribed initially and outcomes between the three groups. **Measurements and main results:** Ninety assessable EA–BAL samples were evaluated. When guided by EA, the initial antibiotic regimen was adequate in 85% of situations, a proportion significantly superior ( $P < 0.05$ ) to that resulting from application of the ATS guidelines (73%). When clinicians did not have a pre-VAP EA to guide their treatment (EA not performed group), only

61% of treatments were adequate. No significant difference was observed between the three groups for length of mechanical ventilation, length of ICU stay, nonpulmonary nosocomial infections and mortality. **Conclusion:** Once-a-week routine quantitative EA cultures may help to improve the adequacy of empiric antibiotic therapy for VAP.

**Keywords** Endotracheal aspiration · Broncho-alveolar lavage · Ventilator-associated pneumonia · Nosocomial pneumonia · Antibiotic therapy · Mechanical ventilation

### Abbreviations

VAP	Ventilator-associated pneumonia
EA	Endotracheal aspiration
BAL	Broncho-alveolar lavage
ICU	Intensive care unit
SAPS II	Simplified acute physiology score II
SOFA	Sequential organ failure assessment score
CPIS	Clinical pulmonary infectious score
ESBL	Extended-spectrum beta-lactamase
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
MSSA	Methicillin-sensible <i>Staphylococcus aureus</i>
FiO <sub>2</sub>	Fraction of inspired oxygen

## Introduction

Ventilator-associated pneumonia (VAP) is the most frequent nosocomial infection in the intensive care unit (ICU). Although its attributable mortality remains controversial [1–4], VAP is associated with an increased length of ICU stay and duration of mechanical ventilation [3–5]. Approximately 50% of all antibiotics are administered for respiratory tract infections [6], and the additional cost of evaluating and treating a patient with VAP is between 8,000 and 10,000 euros per episode [2, 7]. Delaying adequate treatment is associated with a greater risk of hospital mortality [8–10]. To improve the prognosis of VAP, clinicians should prescribe “early and adequate” antibiotic therapy. However, the systematic prescription of broad-spectrum antibiotics to achieve this goal stimulates the emergence of multidrug-resistant pathogens [11].

Recently, Michel et al. [12] proposed twice-weekly examinations of quantitative cultures of endotracheal aspiration (EA) in all mechanically ventilated patients as a means of assisting the choice of initial antibiotic therapies for VAP. The result of the most recently performed EA was similar to that of broncho-alveolar lavage (BAL) in 83% of assessable cases. This strategy, performed in a medical ICU, allowed an initially adequate treatment in 95% of situations and was superior to therapy derived from use of the ATS guidelines [1]. To our knowledge, no study has evaluated the impact of routine once-weekly EA to guide initial treatment in both medical and surgical patients. We therefore evaluated the impact of routine weekly EA in patients who later had VAP confirmed by a BAL. We then described the outcome of these patients. We tested the hypothesis that therapeutic use of EA results obtained prior to the BAL diagnosis would allow an “early and adequate” treatment in a larger proportion of patients with suspected VAP than that obtained by using current guidelines. This study has been presented in abstract form [13].

## Methods

This study was conducted from January 1997 to December 2004 in a 12-bed medical–surgical ICU at the Montpellier University Hospital. We performed a retrospective analysis of prospectively collected data. In accordance with the French law, informed consent was not mandatory, given that this observational study did not modify current diagnostic or therapeutic strategies.

### Study population

Patients >18 years of age who had received mechanical ventilation for >48 h were prospectively included if VAP

was confirmed by a BAL. Their analysis was performed retrospectively. If VAP was clinically suspected, BAL was performed as described elsewhere [1, 14]. The threshold for diagnosing pneumonia was  $10^4$  or  $10^3$  cfu/ml when an antibiotic therapy was initiated 48 h before BAL [15].

### Endotracheal aspirates

Routine surveillance including microbiological analysis of endotracheal aspirates (EAs) was performed using a validated technique upon the patient’s admission and then every Tuesday [1, 14]. The EA analysis was quantitative. Only EAs above the threshold of  $10^4$  cfu/ml were compared with BAL.

### Our VAP antibiotic policy

Antibiotic therapy, initiated after EA and BAL sampling, was guided by the last available EA specimen culture and then adjusted according to the BAL culture results. For patients with risk factors for multiresistant pathogens [1] and in whom EA has not been performed, the empiric regimen was guided by the ATS guidelines and consisted of a combination of two antipseudomonal antibiotics (noncarbapenem betalactam, fluoroquinolone or aminoglycoside) and a glycopeptide if methicillin-resistant *Staphylococcus aureus* (MRSA) was suspected (previous history of nursing home or hemodialysis or positive cocci on gram staining). If piperacillin or ticarcillin had previously been used, carbapenem was indicated to limit the risk of inadequacy of our initial treatment. We then compared our local antibiotic strategy (guided by the EA) to the antibiotics that would have been prescribed if EA was not available (as recommended by the ATS guidelines).

### Studied parameters

Upon ICU admission, we recorded demographic data and severity scores [16, 17], length of stay in hospital before admission to the ICU, length of mechanical ventilation before VAP and data for antibiotic therapy administered before VAP. On the day of inclusion (day of BAL), we recorded the clinical pulmonary infection score (CPIS) [18], the antibiotic therapy prescribed for the episode of VAP and the results of the last EA performed before the BAL. We assessed the concordance between EA and BAL. Antibiotics prescribed were compared to those that would have been prescribed if the ATS guidelines had been followed.

ATS guidelines stratify patients in two categories: early onset (before day 5 of ventilation) and/or without

risk factors for multiresistant pathogens and late onset (after day 5 of ventilation) and/or risk factors for multi-resistant pathogens. The antibiotic strategy is then divided into broad spectrum or limited spectrum antibiotics.

## Endpoints

The primary endpoint was the concordance of the antibiotic therapy guided by the results of EA with an antibiotic therapy that would have been prescribed if the ATS guidelines had been applied. The antibiotic therapy was judged adequate if all species were sensitive to at least one of the antibiotics prescribed except for *Pseudomonas aeruginosa*, for which a double therapy was required. Positive concordance between EA and BAL was determined if the same species was identified as having exceeded the thresholds for positivity for both specimens and had the same antibiotic susceptibility patterns [12]. Finally, we compared the clinical outcomes between the three groups.

## Statistical analysis

Data are reported using mean values  $\pm$  SD and the number of cases in percentages. Three groups were analyzed. The first group was constituted by concordant EA and BAL. The second group was constituted by discordant EA and BAL and the third group was characterized by the absence of EA before the BAL. We considered only the first episode of VAP for the analysis. Continuous variables were compared using nonparametric tests of Mann–Withney, Kruskal–Wallis and Friedman. The  $\chi^2$  test was used to compare categorical variables. A  $P$  value  $< 0.05$  was considered to be statistically significant. Tests were performed by Statview<sup>®</sup> 5.0 software (SAS Institute, USA).

## Results

### Patient population

During the study period, 2,036 patients were admitted to our ICU. Sixty-two percent of them received mechanical ventilation for at least 48 h. During the study, 295 BAL were performed on 255 patients for VAP suspicion. Of 137 confirmed VAP cases, we included the 113 first episodes of VAP for the study.

The incidence of VAP was 11%. The main characteristics of the patients are reported in Table 1. There were no statistical differences between groups except for the length of ICU stay before VAP onset, which was shorter when EA was not performed than in the EA–BAL

concordant group. Fifty patients developed early-onset pneumonia, whereas 63 patients developed late-onset pneumonia. Fifty-four patients (48%) were already treated by antibiotics upon admission to our ICU (Table 1). The most common pathogen was *P. aeruginosa* (35/113, 31%).

### Concordance between BAL and endotracheal aspirations cultures

Among the 113 VAP episodes, EA was performed for 90 (79%) and not performed for 23. In those 23 cases, patients were not intubated when admitted in ICU. We did not perform a pre-BAL EA, because clinical suspicion of VAP was high and therefore BAL was the first sample performed, or simply because EA was forgotten. Sixty-six of the 90 patients (73%) were already treated by antibiotics when the EA was performed. We only considered EAs obtained within the 7 days preceding the BAL. Six EAs were culture-negative, one below the threshold of  $10^4$ , and 83 were considered positive. Among the 90 EAs performed, 65 (72%) were concordant with the results of the BAL (concordant group). Twenty-five EAs (28%) were not concordant with the BAL and constituted the “discordant” group, described as follows: no growth on EA the day of the BAL in ten cases (i.e., delay between EA and BAL less than 2 days), negative in seven cases and another microorganism than BAL in eight cases. In the 25 discordant cases, the sensibility of EA to diagnose pathogens found by the BAL was 4/13 (31%) and specificity 4/16 (25%). The EA–BAL concordance rate was not effected by the time of onset of VAP [25/34 (74%) and 40/56 (71%) for early and late onset VAP], the existence of previous antibiotic therapy (81 vs. 77% with or without previous treatment) or the delay between EA and BAL ( $2 \pm 2$  days in the concordant group and  $3 \pm 2$  days in the discordant group) (Table 1).

### Adequacy of antibiotic therapy according to the strategy used

Antibiotic choice based on the available results of pre-BAL EA cultures was adequate in 77 of 90 patients (85%). In contrast, if the ATS guidelines had been used, the empiric antibiotic treatment would have been adequate in 64 patients (71%) ( $P = 0.04$ ).

In 13 cases, our strategy allowed an adequate initial treatment, whereas the ATS guidelines did not (Table 2). Although EA and BAL results were discordant in four of those 13 patients (Table 2), the initial antibiotic therapy was adequate, but broad-spectrum antibiotics were not necessary (patients 2, 4 and 6) and treatment was de-escalated just after the BAL result.

**Table 1** Demographic characteristics at ICU admission and at the day of BAL

Characteristics of the 113 patients	All (n = 113)	Group I concordant BAL/EA (n = 65)	Group II nonconcordant BAL/EA (n = 25)	Group III EA not performed (n = 23)
At ICU admission				
Age (years)	61 ± 15	60 ± 15	57 ± 18	64 ± 14
Sex (male/female)	85/28	45/20	20/5	20/3
ICU diagnostic category, n (%)				
Medical	53 (47)	27 (41)	14 (56)	12 (52)
Surgical	60 (53)	38 (59)	11 (44)	11 (48)
Origin, n (%)				
Home	17 (15)	7 (11)	9 (36)	1 (4)
Medical ward	37 (33)	23 (36)	6 (24)	8 (35)
Surgical ward	46 (40)	27 (41)	7 (28)	12 (52)
Other ICU	13 (11)	8 (12)	3 (12)	2 (9)
Underlying disorders for mechanical ventilation, n (%)				
Chronic respiratory disease	16 (14)	8 (12)	3 (12)	5 (22)
Dialysis-dependent end-stage renal disease	2 (2)	2 (3)	0 (0)	0
Cirrhosis	19 (17)	11 (17)	2 (8)	6 (26)
Diabetes mellitus	18 (16)	9 (14)	4 (16)	5 (22)
Cancer	21 (19)	11 (17)	3 (12)	7 (30)
NYHA class IV	5 (4)	1 (2)	2 (8)	2 (9)
Length of hospital stay before ICU admission, days	9 (17)	8 (13)	5 (9)	19 (29)**
Immuno-suppressed patients, n (%)	19 (17)	11 (17)	2 (8)	6 (26)
SAPS II score	48 ± 14	47 ± 14	50 ± 16	49 ± 12
SOFA score	7.3 ± 4.3	7.1 ± 4.4	7.2 ± 4.1	7.8 ± 4.2
At the day of BAL				
CPIS score	6.2 ± 2.1	6.3 ± 2.0	6.1 ± 1.8	6.1 ± 2.2
Early/late VAP, n (%)	50 (44)/63 (56)	23 (36)/42 (65)	11 (44)/14 (56)	16 (69)/7 (31)*
Patients under antibiotics the day of BAL, n (%)	103 (89)	59 (90)	23 (88)	21 (91)
Prior ICU antibiotic therapy, n (%)				
SAPS II score	49 ± 16	48 ± 16	50 ± 15	49 ± 13
SOFA score	7.9 ± 4.7	7.7 ± 5.0	7.2 ± 4.1	8.0 ± 4.9
Length of hospital stay before VAP, days	23 (24)	25 (25)	18 (15)	21 (29)*
Length of ICU stay before VAP, days	13 (15)	17 (17)	12 (12)	5 (5)*
Length of mechanical ventilation before VAP, days	12 (16)	16 (18)	12 (12)	4 (6)*
Interval between EA and BAL, days	3 (2)	3 (2)	3 (2)	NA

\*  $P < 0.01$  between EA not performed group and concordant group; \*\* $P < 0.05$  between EA not performed group and nonconcordant group

In the absence of a pre-BAL EA, initial antibiotic therapies were adequate in only 15/23 cases (65%). The causes of nonadequacy were nonenzymatic beta-lactam *P. aeruginosa* resistance (two cases), although imipenem was ongoing for an abdominal infection; misclassified “early-onset VAP without any risk factors for multiresistant pathogens” because of occurrence before the fifth day of mechanical ventilation but more than 10 days after admission to the ward (three cases); MRSA without anti-gram positive antibiotic (one case); extended-spectrum beta-lactamase (ESBL)-related VAP with ongoing piperacillin-tazobactam (one case) and VAP related to cefepime-resistant *P. aeruginosa*, initially treated with this antibiotic (one case). Double antibiotic therapy was performed as frequently as possible with

either fluoroquinolone or aminoglycoside. When both antibiotics were ineffective and *P. aeruginosa* was the pathogen (one case), aerosolized colimycin was added. Monotherapy on ESBL was prescribed once.

Table 3 reports the clinical outcome of the patients. No significant differences were observed between the groups for length of mechanical ventilation, length of ICU stay, nonpulmonary nosocomial infections and mortality.

## Discussion

The main findings of the study are that (1) the results of the most recent performed EA were concordant with the

**Table 2** Description of the 13 cases of adequate initial EA-guided antibiotic therapy

Case number	ATS category <sup>a</sup>	Concordant or nonconcordant EA/BAL	Direct examination of BAL	Etiology of VAP
1	1	Nonconcordant	Negative	<i>S. maltophilia</i> , MSSA
2	2	Nonconcordant	Negative	<i>A. baumannii</i>
3	2	Concordant	Gram-positive Cocci	MRSA
4	2	Nonconcordant	Negative	ESBL <i>E. coli</i>
5	2	Concordant	Gram-positive Cocci	<i>P. aeruginosa</i> resistant to antipseudomonal penicillin
6	2	Nonconcordant	Gram-negative Bacilli	ESBL <i>E. coli</i>
7	1	Concordant	Not performed	<i>P. aeruginosa</i> ticarcillin-resistant, fluoroquinolones resistant, aminoglycoside intermediate
8	2	Concordant	Gram-negative Bacilli	ESBL <i>E. aerogenes</i>
9	2	Concordant	Gram-negative Bacilli	<i>P. aeruginosa</i> ticarcillin-resistant, fluoroquinolones resistant
10	2	Concordant	Gram-negative Bacilli	<i>P. aeruginosa</i> resistant to antipseudomonal penicillin
11	2	Concordant	Gram-positive Cocci and Gram-negative Bacilli	<i>P. aeruginosa</i> resistant to antipseudomonal penicillin
12	2	Concordant	Gram-negative Bacilli	<i>P. aeruginosa</i> ticarcillin-resistant, fluoroquinolones resistant
13	2	Concordant	Gram-negative Bacilli	<i>S. maltophilia</i>

Patient 1: EA detected *S. maltophilia* although BAL detected *S. maltophilia* and MSSA

Patient 2: EA detected *E. coli*, *Providencia rettgeri* and *A. baumannii* although BAL detected *A. baumannii*

Patients 4 and 6: EA detected *E. coli* and MRSA although BAL detected ESBL *E. coli*

<sup>a</sup> We considered that a patient is included in ATS guidelines category 1 when he did not have any risk factor for multiresistant pathogen and in ATS guidelines category 2 when he had at least one risk factor for multiresistant pathogen

BAL in 65 patients (72% of assessable cases) and discordant in 25 (28%); (2) our antibiotic strategy based on the pre-VAP EA was adequate in 85% of situations, significantly superior to that obtained with the ATS guidelines [1]; (3) when the clinicians did not have a pre-VAP EA to guide their treatment (23 cases, EA nonperformed), only 61% of overall antibiotic strategies were adequate; (4) there were no statistical differences in duration of mechanical ventilation, length of stay in ICU, extrapulmonary infections or mortality between patients whose treatment was based on a pre-BAL EA (concordant and discordant groups; local strategy) and those whose treatment was not EA-based (EA not performed). Few studies have reported the importance of routine colonization surveillance to predict the treatment or even the pathogens implicated in VAP.

Our study is in accordance with a study showing that tracheal colonization was an independent predictive factor of VAP in head trauma patients [19] and with a study showing a 83% concordance between BAL and the results of twice weekly EA [12], but not with those published by Hayon et al., who reported a poor correlation between routine multisite surveillance and pathogens diagnosed by the BAL [20]. More recently, Depuydt et al. [21] showed that thrice weekly EA surveillance allowed 69% of concordance between EA and blood culture in patients presenting bacteriemic nosocomial pneumonia. Our study is the first, to our knowledge, to evaluate the impact of once weekly EA to guide the initial treatment of VAP in 113 medical and surgical patients.

Our strategy allowed us to improve the adequacy of initial treatment compared to the treatment that would have been prescribed if the ATS guidelines had been followed in 13 patients (Table 2). Our results are in accordance with a previous study who reported the superiority of initial treatment guided by twice weekly EA over the ATS guidelines [1].

In our ICU, most patients were already on antibiotics and came from wards where they developed a VAP; they presented a high incidence of risk factors for multiresistant pathogens as defined by the ATS (Table 1). This particularity of some ICUs has been reported elsewhere [5, 22–24], and although it may not be applicable to all ICUs, it brings to light the importance of knowing local ecology of nosocomial infections. Because delays in the administration of adequate therapy have been associated with excess mortality from severe infections in the ICU, the prompt administration of empiric therapy for patients likely to have VAP is essential [25–27]. However, the extensive use of antibiotics, especially broad-spectrum antibiotics, is associated with the emergence of resistant pathogens [23]. In our unit, initial antibiotic therapy is given without delay after the BAL, but is oriented by the results of airway colonization diagnosed by the pre-BAL EA.

Although our strategy based on the colonization was more frequently adequate than the one recommended by the ATS ( $P < 0.05$ ), the ATS-guideline strategy was more often appropriate than that prescribed when no EA was available. Among the 23 cases where the clinicians

**Table 3** Clinical outcome of the patients from the three groups

	All ( <i>n</i> = 113)	Group concordant BAL/EA ( <i>n</i> = 65)	Group discordant BAL/EA ( <i>n</i> = 25)	Group EA not performed ( <i>n</i> = 23)
Post-VAP length of mechanical ventilation (days)	17 ± 18	16 ± 15	12 ± 11	21 ± 20
Total length of mechanical ventilation (days)	26 ± 23	27 ± 24	22 ± 16	25 ± 26
Post-VAP length of ICU stay (days)	23 ± 20	23 ± 17	19 ± 16	23 ± 17
Total ICU length of stay (days)	36 ± 27	39 ± 27	30 ± 19	33 ± 33
Nonpulmonary ICU-acquired infections, <i>n</i> (%)	55 (49)	34 (52)	15 (60)	8 (34)
ICU mortality, <i>n</i> (%)	33 (29)	19 (29)	7 (28)	7 (30)

Values are expressed as mean ± standard deviation or number (%)

There was no significant difference between the three groups for the studied parameters

did not have a pre-BAL EA, the initial antibiotic therapy was not adequate in eight situations. In five of them, the cause of discrepancy was related to the nonadhesion to the international guidelines, a finding well described elsewhere [28].

Length of stay before ICU was longer for the patients of the EA nonperformed group than for those of concordant group (Table 3). Length of ICU stay and length of mechanical ventilation before VAP were shorter for the patients of the EA nonperformed group than for those of the concordant group. This was mainly due to the decision to bypass the EA and to perform a BAL in the first intention.

#### Limitations of the study

Some limitations of the present study must be noted. It is an epidemiological, retrospective analysis of a prospectively acquired database, which reflects the results of a single center.

In our study, we did not consider the impact of routine surveillance of nasal carriage or rectal screening, which could contribute to improve the proportion of initially adequate antibiotic therapy [21], but may result in an increase of broad-spectrum antibiotic use [20]. We did not consider EAs to be positive when below the threshold of  $10^4$  cfu/ml; however, only one EA below this threshold was actually positive, without any consequences on our results.

The overall mortality was nearly 30% and was not different between groups (Table 3). The primary endpoint of this retrospective study was to compare different antibiotic strategies and not to evaluate the mortality; the analysis of this small cohort may explain this absence of difference for this outcome.

#### Conclusion

This study showed that an initial antibiotic treatment for VAP guided by the results of weekly systematic pre-VAP EA allowed an adequate treatment in 85% of patients. Routine surveillance cultures may limit the inadequate prescription of broad spectrum antibiotics and could perhaps help to prescribe a better targeted antibiotic therapy in patients infected with multiresistant pathogens. However, the ATS guidelines [1] remain the gold standard to initiate antibiotic therapy for VAP when the clinicians do not have any data on airway colonization. The impact of this strategy “early and guided by lower respiratory tract colonization” on patient outcomes and resistance rates is still unknown and needs to be determined by a randomized clinical trial.

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