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Is Ventilator-associated Pneumonia an Independent Risk Factor for Death?

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Background: **Ventilator-associated pneumonia (VAP) has been implicitly accused of increasing mortality. However, it is not certain that pneumonia is responsible for death or whether fatal outcome is caused by other risk factors for death that exist before the onset of pneumonia. The aim of this study was to evaluate the attributable mortality caused by VAP by performing a matched-paired, case-control study between patients who died and patients who were discharged from the intensive care unit after more than 48 h of mechanical ventilation.**

Methods: **During the study period, 135 consecutive deaths were included in the case group. Case-control matching criteria were as follows: (1) diagnosis on admission that corresponded to 1 of 11 predefined diagnostic groups; (2) age difference within 10 yr; (3) sex; (4) admission within 1 yr; (5) APACHE II score within 7 points; (6) ventilation of control patients for at least as long as the cases. Precise clinical, radiologic, and microbiologic definitions were used to identify VAP.**

Results: **Analysis was performed on 108 pairs that were matched with 91% of success. There were 39 patients (36.1%) who developed VAP in each group. Multivariate analysis showed that renal failure, bone marrow failure, and treatment with corticosteroids but not VAP were independent risk factors for death. There was no difference observed between cases and controls concerning the clinical and microbiologic diagnostic criteria for pneumonia.**

Conclusion: **Ventilator-associated pneumonia does not appear to be an independent risk factor for death.**

THE mortality rate remains high for intensive care unit (ICU) patients despite dramatic advances in pharmacologic and nonpharmacologic therapeutics that have been used since the 1970s. There is evidence that mechanical ventilation is the principal risk factor for lower respiratory tract infection.[1,2] Indeed, more than 30% of patients develop at least one episode of pneumonia within 3 weeks of mechanical ventilation.[3] The occurrence of pulmonary infection in ventilated patients could affect the prognosis. However, despite recent publications, [4–7] the question of whether ventilator-associated pneumonia (VAP) affects ICU mortality requires more investigation. There is evidence that patients who need more than 48 h of mechanical ventilation represent a selected population with particularly severe associated pathologies leading to a fatality rate of more than 40%.[8–11] Demonstration of causality between death and VAP is a difficult feat epidemiologically. Indeed, in ventilator-assisted patients, it is very difficult to distinguish between the deaths caused by VAP and deaths occurring while VAP was present at the time of death but not directly the cause. Moreover, multiple noninfectious diseases can mimic the clinical presentation of VAP. In a previous report, we failed to demonstrate any excess mortality caused by VAP in a cohort of patients with VAP matched with a cohort of patients without VAP.[5] This result was in opposition with that of another study of the same design.[12] In another study, we showed that mortality rate was not different whatever the microbiologic definition of VAP.[13] After obtaining these results, we thought it would be of interest to assess VAP mortality with a different methodologic approach. To our knowledge, no case-control study using a well-identified terminal event (death–survival) that studies VAP as a potential risk factor for death has been published. Moreover, in our previous published study, only protected specimen brush (PSB) samples were taken into account.[5] The aim of the current work was to determine whether VAP is an independent risk factor for death in patients undergoing mechanical ventilation. We therefore performed a matched-paired, case-control study between patients who died and patients who were discharged after more than 48 h of mechanical ventilation.

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Methods

Patients

This study was conducted in the medico-surgical ICU of Sainte Marguerite University Hospital, which is an 850-bed teaching hospital. Each year, an average of 455 patients are admitted to the ICU. The ICU is divided in 12 separated rooms and 3 isolation rooms. During a 3-yr period (from July 1, 1993, to June 30, 1996), the charts of 1,552 patients admitted to the ICU were re-

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viewed. Patients included in the study were selected from a cohort of 475 patients who were not immunosuppressed and who required mechanical ventilation for more than 48 h. During the study period, 135 consecutive patients who died represented the case group. Control patients were selected among the 340 survivors. Ventilator circuit changes were performed every week for all patients. The patients were all ventilated in a semirecumbent position, and sucralfate was routinely used for stress-ulcer prophylaxis.

Surveillance Program

For all patients, data were prospectively entered into a computer program. Each episode of VAP was identified and recorded prospectively. The prospective surveillance using a nosocomial infection surveillance program is routinely performed in this ward and has previously been described in detail elsewhere.[13] Briefly, for respiratory tract infections, a bacteriologic examination is routinely performed three times a week, even in the absence of suspicion of any infection, using quantitative endotracheal aspirate (EA) analysis. In case of suspicion of VAP, additional examinations are performed using PSB, bronchoalveolar lavage (BAL), mini-BAL, or protected telescoping catheter.

Diagnosis and Treatment of Ventilator-associated Pneumonia

A pulmonary infection was defined as VAP if the onset was recorded after at least 48 h of mechanical ventilation and if the following criteria were present[14]: (1) chest radiograph showing a new and persistent infiltrate consistent with pneumonia; (2) purulent sputum; (3) elevated temperature greater than 38.3°C or leukocyte count more than or equal to 10,000/μl or less than or equal to 1,500/μl; (4) alteration of gas exchange; (5) microorganisms isolated from at least one of the following samples: PSB, BAL, mini-BAL, protected telescoping catheter, and EA. The threshold for considering a sample positive was 10^3 colony-forming units per milliliter (CFU/ml) for PSB and mini-BAL and 10^4 CFU/ml for BAL and EA. Patients were considered as not having VAP when at least one clinical sign of VAP was missing with no positive culture and no curative antibiotic prescribed. When patients presented with a clinical picture of VAP but with microbiologic results under the necessary thresholds, they were not considered as having a VAP. To avoid delaying the treatment of suspected VAP, antibiotics were administered just after completion of sampling procedures according to previous routine EA cultures if positive (directed antibiotherapy). In case of sterile culture of previous systematic EA, empirical treatment was started. After 48 h, antibiotics were adapted to the definite results of the sampling procedures performed on the day of clinical suspicion. If at least one of the five techniques was positive, antibiotics were continued with possible modification according to the antibiogram. If all sampling procedures were negative, antibiotics were stopped.

Matching Procedure

Cases were matched to controls without knowledge of the presence or absence of VAP. The conditions necessary to constitute a matched pair were as follows: (1) same diagnosis on admission; (2) age difference less than or equal to 10 yr; (3) same sex; (4) admission within 1 yr; (5) APACHE II[15] score $\pm$ 7 points; (6) ventilation of control patients for at least as long as the cases. The following system was used to select an adequate control for each case: the whole cohort was stratified according to the date of admission to the ICU and according to the diagnosis on admission. Patients were then stratified by age, using decades, and by gender. Finally, APACHE II score calculated within the first 24-h period in the ICU and duration of respiratory support were examined. When more than one potential control on the list appeared to be well matched with a case patient, the closest date of admission to the case was used to assign the control patient. When the case and the control differed by more than one matching criteria, the control was rejected.

Other Variables Recorded

Concerning VAP, the following variables were noted: date of onset of VAP, temperature, leukocyte count, results of sampling techniques, antibiotic use, and arterial oxygen pressure–inspired oxygen fraction ratio. We also recorded other factors that could have introduced bias into the matching method because they are recognized or are supposed to be risk factors for VAP, *i.e.*, patient preadmission status according to McCabe and Jackson classification,[16] organ-system failures evaluated by the Organ System Failure score calculated during each day during hospitalization in the unit,[17] previous antibiotherapy in the 10 days preceding the pulmonary infection, stress-ulcer prophylaxis, steroid treatment, patient preadmission origin, and type of surgery (scheduled or emergency). Appropriate initial antimicrobial therapy was considered when at least one effective drug was included in the initial antibiotic treatment of VAP. We also recorded the presence or absence of continuous hemofiltration, coinfection with cytomegalovirus, duration of mechanical ventilation, duration of hospitalization in the ICU, and the date of hospital discharge.

Statistical Analysis

Results are expressed as mean $\pm$ SD. Statistical calculations were performed using the Statistical Analysis System software package (SAS version 5, SAS Institute, Cary, NC).[18] The chi-square test was used to compare categoric variables. One-way analysis of variance or Wilcoxon signed-rank test (when analysis of variance could

Table 1. Effectiveness of Matching for the Six Variables Used, Number of Exact Matched Pairs, and Maximum Difference When Mismatched

	Exact Matched Pairs (n/n (%))	Maximum Difference (When Mismatched)
Same sex	103/108 (95)	
Same diagnosis on admission	94/108 (87)	
Same age (±10 yr)	105/108 (97.2)	21 yr
Same APACHE II score (± 7)	92/108 (85)	10
Date of hospital admission within 12 months	100/108 (92.5)	30 months
Duration of mechanical ventilation longer for the control than for the patient	98/108 (90.7)	

APACHE II = Acute Physiology and Chronic Health Evaluation II.

not be applied) was performed to compare demographic characteristics. Continuous variables were compared using the Student *t* test for normally distributed variables and Wilcoxon rank sum test for non-normally distributed variables. Only VAP diagnosed during the same duration of mechanical ventilation as cases were taken into account in paired controls. In other words, if the case was ventilated for 14 days and the matched control for 30 days, only VAP diagnosed during the first 14 days was taken into account for the control patient. The McNemar test with continuity correction was used to compare the incidence rate of VAP between cases and controls.[19] Two multivariate analyses, one using mortality as the outcome and one using the development of VAP, were performed using the logistic regression technique. A stepwise approach was used for entering terms into the model, with 0.10 as the limit for accepting and removing newly entered terms. For all statistical tests used, a P value < 0.05 was considered statistically significant.

Results

Effectiveness of Matching

Among the 135 case patients, 108 were matched with a control, with 27 cases for whom no compatible control was found. These 27 unmatched case patients presented the following characteristics: age 66 ± 16 yr; APACHE II score on admission, 25 ± 9; and length of stay in the ICU, 27 ± 29 days. Details concerning the successful matching are reported in table 1. The overall effectiveness of matching was 91.3% (592 of the 648 matching criteria). Fifty-two patients were matched successfully on all six factors. Ten pairs consisted of control patients who were ventilated during a shorter period (at least 24 h) than cases. Only four of these pairs were discordant for the occurrence of VAP. However, VAP occurred in the case patient in three of these four pairs. The APACHE II score difference was greater than 7 in 9 case patients (difference of 8, n = 7 pairs; difference of 9, n = 2 pairs) and in 7 control patients (difference of 8, n = 6 pairs; difference of 10, n = 1 pair) (table 2). Unmatched characteristics are presented in table 3.

Incidence of Ventilator-associated Pneumonia

There were 39 (36.1%) case patients who developed at least one episode of VAP. The analysis of the controls over a period corresponding to the same duration of mechanical ventilation revealed exactly the same number of patients who developed VAP. Thirteen of the 27 (48%) unmatched case patients presented at least one episode of VAP during their stay in the ICU. The reason for the inability to find a control was the diagnosis in 12 cases, the duration of mechanical ventilation in 8 cases, and the APACHE II score in 7 cases. If 27 controls not developing a VAP during their ICU stay had been found for these 27 unpaired cases, the incidence of VAP would have been 38.5% for the cases and 28.9% for the controls. The difference would not have been statistically significant. If the entire period of mechanical ven-

Table 2. Potential Confounding Factors Used for Matching

	Patients	Controls
Diagnosis at admission		
Respiratory failure after abdominal surgery	26	25
Respiratory failure after thoracic surgery	17	19
Respiratory failure after other surgery	6	5
Total surgical patients	49	49
Multiple trauma with head injury	3	4
Multiple trauma without head injury	3	2
Total multiple trauma patients	6	6
Acute exacerbation of COPD	16	16
Neurologic disease	15	16
ARDS of indirect cause	10	10
Septic shock	9	8
Acute pancreatitis	1	1
Other medical diagnosis	2	2
Total medical patients	53	53
APACHE II score*	20.7 ± 6.2	21.5 ± 6.8
Age (yr)*	63.0 ± 13.5	64.0 ± 14.9
Mean duration of mechanical ventilation*†	17.0 ± 13.8	29.0 ± 20.7
Sex (M/F)	73/27	69/31

* Mean ± SD. † $P < 0.05$.

COPD = chronic obstructive pulmonary disease; ARDS = adult respiratory distress syndrome; APACHE II = Acute Physiology and Chronic Health Evaluation II.

Table 3. Comparison of the Study Cohort Regarding Unmatched Characteristics

	All Patients	All Controls
OSF score (mean ± SD)	1.56 ± 0.7	1.33 ± 0.5*
Previous admission to another ICU (n)	22	30
Previous admission in other wards (n)	80	85
Emergency surgery (n)	24	19
Cancer (n)	29	27
Hemofiltration (n)	15	11
Previous steroids (before admission to the ICU, n)	15	3*
Stress ulcer prophylaxis (n)	106	93
ARDS (n)	40	32

OSF = Organ System Failure; ICU = intensive care unit; ARDS = adult respiratory distress syndrome.

* $P < 0.01$.

tilation of controls was considered, 16 more patients developed VAP. During the study period, 25% of the 340 patients mechanically ventilated more than 48 h and who survived developed at least one episode of VAP.

There were 23 concordant pairs (both case and control agreed concerning the presence or absence of VAP) and 32 discordant pairs. In 16 of these discordant pairs, VAP was diagnosed in the control, and in the 16 other pairs, VAP was diagnosed in the case. Statistical analyses confirmed the absence of difference (odds ratio = 1), *i.e.*, VAP did not appear as a risk factor for death.

Multivariate Analysis

Multivariate analysis took into account all of the variables used for the matching process and some additional variables that could affect outcome such as all organ failures that appeared during ICU stay, the development of VAP, appropriate initial antimicrobial therapy for the treatment of VAP, prior corticosteroid treatment, cancer, immunosuppressive agents, the use of antibiotics for infections other than VAP (before the diagnosis of VAP in patients developing VAP), and the presence of potentially resistant bacteria responsible for VAP. This stepwise logistic regression showed that renal failure, bone marrow failure, and treatment with corticosteroids were independently associated with patient mortality (table 4).

The stepwise logistic regression analyzing risk factors of VAP such as age, sex, duration of mechanical ventilation, diagnosis, APACHE II score, Organ System Failure score, sucralfate, prior corticosteroid treatment, cancer, immunosuppressive agents, and the use of antibiotics for infections other than VAP (before the diagnosis of VAP in patients developing VAP) concluded that only the use of antibiotics was independently associated with the risk of developing a VAP (odds ratio, 2.69; 95% confidence interval, 1.44–5.03; $P = 0.002$).

Table 4. Independent Risk Factors Associated with Mortality

	OR	95% CI	*P*
Renal failure	3.04	1.6–5.6	0.0001
Corticosteroids	6.12	1.7–22.4	0.006
Bone marrow failure	12.06	1.5–98.9	0.02

Renal and bone marrow failures that appeared during intensive care unit stay and as defined by the Organ System Failure score.

OR = odds ratio; CI = confidence interval.

Diagnostic Criteria of Pneumonia

There was no difference between cases and controls concerning the diagnostic criteria for VAP (table 5). Appropriate initial antimicrobial therapy was administered to the patients during the 48-h period after the suspicion of VAP in 79% of the cases and in 82% of the controls. Initial antimicrobial therapy was based on the results of the previously performed routine EA in 28 cases and in 27 controls presenting with VAP. Empirical treatment was therefore prescribed in the remaining 11 cases and 12 controls presenting with VAP. All patients initially received a combination of antibiotics. This antimicrobial therapy was considered inappropriate in 8 of the 39 cases and 7 of the 39 controls presenting with VAP. If only initial antimicrobial therapy based on the results of the previously performed routine EA was considered, antibiotherapy was appropriate in 26 of the 28 cases and 24 of the 27 controls receiving an EA-directed antimicrobial treatment. The duration of antimicrobial therapy was greater than 2 weeks in 35% of the cases and 41% of the controls. EA was performed in all cases and was always associated with at least one of the other sampling techniques. We recorded a positive result for EA in 28 of the 39 incidences of VAP in the case group compared with 29 of the 39 incidences of VAP in the control group. There was also no statistically significant difference between cases and controls concerning the number of positive mini-BAL (14 and 14, respectively), protected telescoping catheter (18 and 16, respectively), PSB (19 and 21, respectively), and BAL (17 and 16, respectively). Details on culture results of the sampling procedures at different thresholds are reported in table 6.

Concerning VAP diagnosed in cases, a total of 56 microorganisms were identified (table 7). The mean delay between the beginning of mechanical ventilation and the onset of infection was 12.5 ± 12.8 days. Forty-one percent were gram-negative bacilli. Potentially resistant bacteria (*Pseudomonas aeruginosa*, *Acinetobacter baumanii,* methicillin-resistant *Staphylococcus aureus*, or *Stenotrophomonas maltophilia*) represented 34% of the bacteria recovered in cases and 26% in controls (nonsignificant). Microorganisms producing extended spectrum β-lactamases were identified in 4 cases and 8 controls.

Discussion

A review of the literature on VAP reveals that only a few investigations focusing on patient prognosis have

Table 5. Characteristics of the Pneumonias in the Two Groups

Parameters	Patients with VAP (n = 39)	Controls with VAP (n = 39)	*P*
Age	64.0 ± 14.3	63.4 ± 12.3	NS
APACHE II	19.3 ± 5.7	19.0 ± 5.8	NS
OSF	1.6 ± 0.5	1.4 ± 0.6	NS
Clinical diagnosis			
Maximum t°	38.4 ± 0.7	38.4 ± 0.8	NS
Minimum t°	37.0 ± 0.8	37.3 ± 0.7	NS
Leukocyte count (G/l)	13.5 ± 0.6	14.2 ± 0.8	NS
Previous antibiotics (within 10 days before VAP)	64%	46%	NS
Bacteremia	13%	10%	NS
Appropriate initial antimicrobial therapy	79%	82%	NS

VAP = ventilator-associated pneumonia; NS = not significant; APACHE II = Acute Physiology and Chronic Health Evaluation II; OSF = Organ System Failure.

sufficiently taken into account the numerous risk factors for death present in this kind of severely ill population. However, only studies that consider such "confounding factors" (*i.e.*, using a matching design or a multivariate analysis) can really make interpretable conclusions on prognosis. To our knowledge, all of the studies using this kind of method and a precise definition of VAP except one group[6,12] found no overmortality attributable to VAP. Numerous studies that were not especially designed to analyze patient outcome reported a higher fatality rate for patients developing VAP. However, these studies did not take into account confounding factors on prognosis and should therefore not be used to argue this point. Among studies using a matching procedure, all case-control studies matched patients with VAP to patients without VAP.[5,12,20,21]

The current case-control study on VAP is the first that matches deceased patients and survivors. The advantage of such a design is that the case refers to a specific outcome that does not suffer from the drawback of a controversial definition such as the definition of VAP. VAP can therefore be described in detail. Thus, if different readers have different definitions of VAP, particularly concerning the positive threshold of microbiologic samples, they can find food for thought in the details of our results (table 6). When a cohort analysis is performed, it is necessary to classify the patients (with VAP, without VAP) using a more or less pertinent diagnostic criteria before the beginning of the matching process. When a case control is designed with the outcome as the criteria differentiating cases from controls, it is possible to analyze the incidence of VAP after the matching process, taking into account more or less pertinent criteria.

This study finally showed the same VAP rate for cases and controls (36.1%). Using a multivariate analysis, Kollef[22] showed from a cohort of 277 patients that mortality was independently associated with the number of organ system dysfunctions, Patient Preadmission Lifestyle score, and head positioning, but not with VAP. Another multivariate analysis has been conducted by Timsit *et al.*[23] in 387 patients. The investigators introduced both clinically suspected VAP and bacteriologically confirmed VAP in a Cox model and failed to demonstrate an overmortality for bacteriologically documented VAP. The case-control analysis conducted by Baker *et al.*[20] matched 29 trauma patients with VAP documented on BAL or PSB with 58 controls without VAP. No mortality was attributable to pneumonia in that work, whereas age and severity of injury were controlled using a matching process. Fagon *et al.*[6,12] reported an increased fatality rate attributable to VAP using two different methodologies: a multivariate analysis and a case-control study. They described VAP documented on PSB at a threshold of 10^3 CFU/ml or BAL at a threshold of 10^4 CFU/ml, which

Table 6. Number of Patients with Bacteria Recovered by the Different Techniques in the Two Groups

Sampling procedure	Threshold (cfu/ml)	Patients (n = 108)	Controls (n = 108)
Endotracheal aspirate	$\leq 10^3$	10	10
	10^4	4	8
	10^5	9	10
	10^6	13	9
	10^7	2	2
Protected telescoping catheter	$\leq 10^2$	3	7
	10^3	10	8
	10^4	5	8
	10^5	1	0
	10^6	2	0
Mini-BAL	$\leq 10^2$	3	2
	10^3	4	5
	10^4	6	6
	10^5	1	2
	10^6	3	1
Protected specimen brush	$\leq 10^2$	3	2
	10^3	17	19
	10^4	1	1
	10^5	1	1
Bronchoalveolar lavage	$\leq 10^2$	7	15
	10^3	8	7
	10^4	5	7
	10^5	2	2
	10^6	2	0

Results are given for different thresholds (colony forming units per milliliter; cfu/ml).

Mini-BAL = mini–bronchoalveolar lavage.

Table 7. Microorganisms Identified in Pneumonia Cases and in Pneumonia Controls

	Cases (n)	Controls (n)
Methicillin-sensitive *Staphyloccus aureus*	9	5
Methicillin-resistant *S. aureus*	7	2
Pseudomonas aeruginosa	9	9
Enterobacter species	7	8
Escherichia coli	6	4
Klebsiella pneumoniae	6	3
Serratia marcescens	1	6
Hemophilus influenzae	3	3
Streptococcus pneumoniae	3	3
Proteus species	1	4
Stenotrophomonas maltophilia	2	2
Morganella morganii	0	2
Acinetobacter baumanii	1	1
Citrobacter freundii	1	1
Total	56	53

were the same criteria used in other studies that found opposite results.[5,20,21,23] Nevertheless, several differences can be found that can explain that this group found an increased mortality attributable to VAP. Their populations appeared to be severely ill according to their APACHE II scores, which were more than 24, compared with other study populations in which this score was approximately 20. They included more postoperative patients than we did and did not exclude immunosuppressed patients. Patients with postoperative complications after cardiac surgery are known to represent a selected population commonly excluded from studies on prognosis[15] and have been shown in a specific study to have an increased mortality rate if nosocomial infection develops.[11] Such patients represented a large part of the studied population (20%) in the reports by Fagon *et al.*[6,12] In addition, it is possible that some differences concerning patient characteristics or therapeutic management not specified in these studies could explain these conflicting results.

In addition to studies especially designed to investigate patient prognosis, numerous other well-conducted reports lead readers to conclude on the absence of increased mortality linked to VAP. For example, several prospective randomized controlled trials evaluating some therapeutic approaches for the prevention of VAP[24–27] or the prevention of stress ulcer in ventilated patients[28] have reported similar outcome for patients with and without VAP.

From the initial cohort of 475 patients who required more than 48 h of mechanical ventilation, our analysis concerned 108 pairs. Concerning risk factors for death, some have been shown in well-designed studies as major elements in ICU patients' prognosis: APACHE II score,[15] duration of mechanical ventilation,[8] age,[10] Organ System Failure score,[17,22] and nonscheduled surgical status. Some factors have been reported to be prognostic factors for patients who developed VAP. They include age,[2] underlying condition,[6] shock, noncardiac surgery, worsening acute respiratory failure,[29] clinical presentation (severe or uncomplicated),[21] and *Pseudomonas* or *Acinetobacter* species.[2,12] Several investigators have suggested that the adequacy of initial antimicrobial therapy is an important factor determining outcome.[30–33] In two of these latter studies,[30,31] fewer than 30% of the patients received appropriate initial antimicrobial therapy. In the current study, 79% of the cases and 82% of the controls presenting VAP received appropriate initial antimicrobial therapy. We found that the adequacy of appropriate initial antimicrobial therapy was not an independent risk factor for death. The wide discrepancy concerning the adequacy of initial antimicrobial therapy observed between these previously published studies and the current work could be explained by the diagnostic strategy. Indeed, the choice of initial antimicrobial therapy is based on routine endotracheal aspirates analysis performed before or during the appearance of clinical signs of pneumonia. Therefore, the initial antimicrobial therapy is not empirical for the great majority of patients.

The diagnostic criteria proposed to define VAP are still a controversial issue. We used all of the commonly accepted blind and directed, invasive and noninvasive, protected and nonprotected techniques. For the definition of a positive culture, we used the thresholds that were validated by experts in reference studies using a histologic gold standard.[34–38]

In conclusion, it seems that there are enough arguments in the literature today to say that VAP does not have an overall effect on patient outcome. This could be a result of the effectiveness of antibiotics, management of mechanical ventilation, or improvement in hemodynamic and other organ-failure supports. Nevertheless, the fact that VAP does not appear as a risk factor for death must be interpreted with caution. Indeed, in some subgroups, such as immunosuppressed patients or patients suffering complication after cardiac surgery, VAP could worsen outcome *per se*.

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