Epidemiology and Outcomes of Ventilator-Associated Pneumonia in a Large US Database*

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Objectives: **To evaluate risk factors for ventilator-associated pneumonia (VAP), as well as its influence on in-hospital mortality, resource utilization, and hospital charges.**
Design: **Retrospective matched cohort study using data from a large US inpatient database.**
Patients: **Patients admitted to an ICU between January 1998 and June 1999 who received mechanical ventilation for > 24 h.**
Measurements: **Risk factors for VAP were examined using crude and adjusted odds ratios (AORs). Cases of VAP were matched on duration of mechanical ventilation, severity of illness on admission (predicted mortality), type of admission (medical, surgical, trauma), and age with up to three control subjects. Mortality, resource utilization, and billed hospital charges were then compared between cases and control subjects.**
Results: **Of the 9,080 patients meeting study entry criteria, VAP developed in 842 patients (9.3%). The mean interval between intubation, admission to the ICU, hospital admission, and the identification of VAP was 3.3 days, 4.5 days, and 5.4 days, respectively. Identified independent risk factors for the development of VAP were male gender, trauma admission, and intermediate deciles of underlying illness severity (on admission) [AOR, 1.58, 1.75, and 1.47 to 1.70, respectively]. Patients with VAP were matched with 2,243 control subjects without VAP. Hospital mortality did not differ significantly between cases and matched control subjects (30.5% vs 30.4%, $p = 0.713$). Nevertheless, patients with VAP had a significantly longer duration of mechanical ventilation (14.3 ± 15.5 days vs 4.7 ± 7.0 days, $p < 0.001$), ICU stay (11.7 ± 11.0 days vs 5.6 ± 6.1 days, $p < 0.001$), and hospital stay (25.5 ± 22.8 days vs 14.0 ± 14.6 days, $p < 0.001$). Development of VAP was also associated with an increase of > $40,000 in mean hospital charges per patient ($104,983 ± $91,080 vs $63,689 ± $75,030, $p < 0.001$).**
Conclusions: **This retrospective matched cohort study, the largest of its kind, demonstrates that VAP is a common nosocomial infection that is associated with poor clinical and economic outcomes. While strategies to prevent the occurrence of VAP may not reduce mortality, they may yield other important benefits to patients, their families, and hospital systems.** ***(CHEST 2002; 122:2115–2121)***

Key words: critical care; hospital costs; ICU; mechanical ventilation; outcome; ventilator-associated pneumonia

Abbreviations: AOR = adjusted odds ratio; CI = confidence interval; CIC = Cardinal Information Corporation; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; KCF = key clinical finding; VAP = ventilator-associated pneumonia

Ventilator-associated pneumonia (VAP) is reported to be the most common hospital-acquired infection among patients requiring mechanical ventilation.[1,2] Risk factors associated with VAP have been identified using multivariate statistical methods.[3,4] These risk factors appear to predispose patients to either colonization of the aerodigestive tract with pathogenic microorganisms and/or aspiration of

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contaminated secretions.[3–5] Several investigators[6–9] have assessed the impact of VAP on patient out-

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comes, including attributable hospital mortality, demonstrating variable results. Most clinical studies evaluating VAP and its clinical importance have analyzed patients from single centers outside of the United States. Vincent et al[2] assessed the prevalence of nosocomial pneumonia among ICU patients in Europe, and Heyland et al[8] examined the attributable mortality of VAP in Canadian hospitals. The largest US study[1] published to date reported the prevalence of hospital-acquired pneumonia from US ICUs without analysis of risk factors or attributable mortality.

We performed a study involving a large US database with two main goals: to identify risk factors associated with the development of VAP among patients admitted to ICUs, and to assess the influence of VAP on patient outcomes, including attributable hospital mortality, inpatient resource utilization, and medical care costs. These study goals were selected to assist in the future design of interventional studies aimed at the prevention of VAP and to help assess the potential impact of such interventions on patient and economic outcomes.

Materials and Methods

Study Design

A retrospective matched cohort study was undertaken to examine the incidence of VAP, to identify risk factors associated with its development, and to assess the impact of VAP on clinical and economic outcomes. Data were obtained for all patients admitted to an ICU from January 1998 to June 1999 who received mechanical ventilation for > 24 h. Cases of VAP were defined as patients with hospital-acquired pneumonia diagnoses occurring ≥ 24 h following intubation. Control subjects without VAP consisted of all patients in the study cohort who did not meet the definition for cases.

To identify risk factors for VAP, the entire cohort was evaluated in order to identify risk factors that would be applicable to the entire study population. Demographic and clinical characteristics of cases were compared to control subjects, including age, gender, race, severity of illness on admission, use of cardiopulmonary resuscitation, presence of coma or stupor, and the type of hospital admission (*ie*, medical, surgical, trauma). To evaluate outcomes of VAP, cases were matched with up to three control subjects on four variables: duration of mechanical ventilation (control subjects had to be intubated for at least as long as cases prior to the onset of VAP), severity of illness on admission, type of hospital admission (medical, surgical, trauma), and age in 20-year intervals. A matched analysis was selected to evaluate the impact of VAP on clinical outcomes in order to minimize confounding from the matching variables. Outcomes evaluated included hospital mortality, days on mechanical ventilation, days in the ICU, days in the hospital, and total billed inpatient charges.

Data Source

Data for this study were obtained from the MediQual Profile database, which is maintained by the Cardinal Information Corporation (CIC) [MediQual Division; Marlborough, MA]. CIC manufactures and distributes Atlas software to US acute-care hospitals for the collection and analysis of detailed clinical and administrative data. Each participating hospital submits data to CIC for use in proprietary comparative databases (including the MediQual-Profile database), which are employed primarily by the hospitals for risk-adjusted benchmarking and internal outcome studies. The MediQual-Profile database is the largest of these databases, and contains information on approximately 750,000 inpatient admissions annually to > 100 US acute-care hospitals. These hospitals are similar in bed size and geographic region to American Hospital Association member hospitals. Hospitals participating in the MediQual-Profile database must collect data on all patients admitted to their facility, thus minimizing selection or reporting biases. CIC audits these hospitals periodically to ensure compliance with proper data collection.

Data available for each patient admission in the MediQual-Profile database include patient demographics (*eg*, age, gender, race/ethnicity), admission source, type of ICU (*ie*, medical, surgical, trauma, pediatric, neonatal, and other), all documented procedure and diagnosis codes (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]), admission and discharge dates for each stay in the ICU, total length of stay in the hospital, billed total and ancillary hospital charges, and discharge disposition. Detailed information also is included on specific interventions received during the hospital admission (*eg*, mechanical ventilation) as well as unplanned events (*eg*, medication errors, respiratory events [including hospital-acquired pneumonia]). Importantly, all intervention and unplanned event data are dated to allow for their examination on a temporal basis.

In addition to administrative data elements, information also is available on > 400 key clinical findings (KCFs). Trained abstractors at each participating hospital use a standardized glossary to obtain KCFs through chart review from admission through the fifth hospital day. As with the intervention and event data described above, KCFs are dated to allow for time-dependent examination of the clinical course of each hospital admission. KCFs also are used to calculate clinical severity; severity scores are derived based on the probability of in-hospital mortality, which is calculated using disease-specific logistic regression models.[10,11] The predictive capabilities of these models have been shown to be comparable to those of other severity adjustment methodologies (*eg*, APACHE [acute physiology and chronic health evaluation] II, disease staging).[12,13] For this study, all available clinical and financial data were obtained for all patients in the MediQual-Profile database who were hospitalized between January 1, 1998, and June 30, 1999, meeting the sample-selection criteria set forth below.

Study Sample

The study sample was constructed stepwise. First, we identified all patients who were admitted to an ICU and received mechanical ventilation for > 24 h. For patients with multiple ICU admissions, only the first admission was considered for analysis. Second, we excluded all patients admitted to the ICU with a diagnosis of pneumonia on or before the first day of mechanical ventilation, so that the sample would include only patients who had hospital-acquired pneumonia develop while receiving mechanical ventilation. All remaining patients constituted the study cohort, from which cases and control subjects were selected. VAP cases were identified by a secondary diagnosis of bacterial pneumonia (ICD-9-CM codes 481–483) and the presence of either a KCF or an event code indicative of pneumonia, such as an abnormal chest radiographic finding,

documentation of hospital-acquired pneumonia in physician progress notes, and/or positive respiratory culture finding. VAP, as defined by KCFs, was ascertained using data for days 2 through 5 of the hospital admission (the day of admission was not included because KCFs recorded on this date likely represent cases of community-acquired pneumonia). Hospital-acquired pneumonia, as defined by the presence of a coded respiratory event, was ascertained on the basis of information recorded any time during hospital admission documenting the presence of hospital-acquired pneumonia. Control subjects were defined as all patients in the study cohort who did not meet the criteria for the definition of cases, and also did not have secondary diagnoses of viral, fungal, or unspecified pneumonia (ICD-9-CM codes 480, 484–486).

Statistical Analysis

The first part of the analysis examined the entire cohort of patients. Univariate analysis was used to compare variables for the outcome groups of interest, and all tests of significance were two tailed. Continuous variables were compared using Student *t* test for normally distributed variables and Wilcoxon rank-sum test for nonnormally distributed variables. The χ^2 statistic or Fisher exact test were used to compare categorical variables as appropriate. The primary data analysis compared patients with VAP to patients without VAP. We confirmed the results of these tests, while controlling for specific patient characteristics and severity of illness (Table 1), with multiple logistic regression analysis using a commercial statistical package.[14]

Table 1—*Characteristics of Patients With and Without VAP**

Characteristics	Patients With VAP (n = 842)	Patients Without VAP (n = 8,238)	p Value
Age, yr	61.7 ± 19.2	64.6 ± 17.7	< 0.001
Gender			
Male	540 (64.1)	4262 (51.7)	< 0.001
Female	302 (35.9)	3976 (48.3)	
Race			
White	655 (77.8)	6207 (75.3)	0.303
African-American	122 (14.5)	1240 (15.1)	
Asian	3 (0.3)	37 (0.4)	
Other	62 (7.4)	754 (9.2)	
Predicted mortality, %			
0–10	399 (47.4)	4305 (52.2)	0.015
11–20	130 (15.4)	1273 (15.5)	
21–30	76 (9.0)	678 (8.2)	
31–40	62 (7.4)	484 (5.9)	
41–50	45 (5.3)	320 (3.9)	
51–60	35 (4.2)	270 (3.3)	
61–70	26 (3.1)	224 (2.7)	
71–80	33 (3.9)	233 (2.8)	
81–90	21 (2.5)	198 (2.4)	
91–100	15 (1.8)	253 (3.1)	
Presence of coma/stupor	344 (40.9)	2981 (36.2)	0.007
Use of CPR	38 (4.5)	412 (5.0)	0.534
Type of admission			
Medical	320 (38.0)	3497 (42.5)	< 0.001
Surgical	334 (39.7)	3667 (44.5)	
Trauma	188 (22.3)	1074 (13.0)	

*Data are presented as mean ± SD or No. (%). CPR = cardiopulmonary resuscitation.

Multivariate analysis was performed using variables that were prespecified by the members of the VAP Outcomes Scientific Advisory Group. This approach minimized the number of comparisons and avoided data-derived analyses.[15] We examined model overfitting by evaluating the ratio of outcome events to the total number of independent variables in the final model, and we tested for interactions between the individual variables included in our analysis. Results of the logistic regression analyses are reported as adjusted odds ratios (AORs) with their 95% confidence intervals (CIs). All values are expressed as the mean ± SD (continuous variables), or as a percentage of the group they were derived from (categorical variables). All p values ≤ 0.05 were considered to indicate statistical significance.

Cases of VAP were matched on duration of mechanical ventilation, severity of illness on admission (predicted mortality), type of admission (medical, surgical, trauma), and age within 20 years with up to three control subjects. Mortality, resource utilization, and billed hospital charges were then compared between cases and control subjects. The McNemar test for correlated proportions was used to compare mortality, and the Wilcoxon signed-ranks test was used to compare resource utilization (*eg*, days) and hospital charges in the case-control analysis.

Results

Patient Characteristics and Risk Factors for VAP

In the database, 9,080 patients met all study entry criteria. Among these patients, VAP developed in 842 patients (9.3%). The mean interval between intubation, ICU admission, hospital admission, and identification of VAP was 3.3 ± 6.6 days, 4.5 ± 7.5 days, and 5.4 ± 7.7 days, respectively. Patients with VAP were significantly younger, more likely to be male, had intermediate deciles of illness severity, had a greater incidence of coma or stupor, and were more frequently admitted for trauma compared to patients without VAP (Table 1). Multiple logistic regression analysis demonstrated that male gender (AOR, 1.58; 95% CI, 1.36 to 1.83), trauma admission (AOR, 1.75; 95% CI, 1.41 to 2.18), and intermediate deciles of underlying illness severity at the time of hospital admission (31 to 40% [AOR, 1.48; 95% CI, 1.10 to 1.99], 41 to 50% [AOR, 1.61; 95% CI, 1.15 to 2.26], 51 to 60% [AOR, 1.47; 95% CI, 1.01 to 2.14], and 71 to 80% [AOR, 1.70; 95% CI, 1.15 to 2.51]) were independently associated with the development of VAP.

The patients with VAP were stratified according to time of onset of VAP from both hospital admission and the start of mechanical ventilation. Three hundred eighty-one episodes (45.2%) of VAP occurred during the first 2 days of hospitalization, compared to 245 episodes (29.1%) occurring between days 3 to 6, and 216 episodes (25.7%) diagnosed after hospital day 6. Similarly, 532 episodes (63.2%) of VAP developed within 48 h of mechanical ventilation, compared to 135 episodes (16.0%) between 48 h and 96 h of mechanical ventilation, and 175 episodes

(20.8%) after 96 h of mechanical ventilation. Among patients with VAP, 603 patients (71.6%) had a microorganism identified in a respiratory culture. *Pseudomonas aeruginosa* was isolated most frequently in patients with VAP occurring > 4 days after the start of mechanical ventilation (19.7%), while *Staphylococcus aureus* was isolated most frequently in patients whose episode of VAP was diagnosed during the first 4 days of mechanical ventilation (23.7%).

Impact of VAP on Outcomes

Eight hundred sixteen patients (96.9%) with VAP were matched to at least 1 of 2,243 patients without VAP (2.7 control subjects were matched for each case of VAP). Twenty-six cases were excluded from the analysis because no suitable control subjects were identified. Patients with VAP in the case-control population were significantly more likely to be male (Table 2). There was no statistically significant difference in hospital mortality among patients with and without VAP (30.5% vs 30.4%, respectively; p = 0.713). Kaplan-Meier curves demonstrated that patients with and without VAP had similar in-hospital survival, although these curves suggest that the mortality was higher for patients without VAP during the first 30 hospital days (Fig 1). Patients with VAP had a significantly longer duration of mechanical ventilation (14.3 ± 15.5 days vs 4.7 ± 7.0 days, p < 0.001), a greater number of ICU days (11.7 ± 11.0 days vs 5.6 ± 6.1 days, p < 0.001) and a longer hospital length of stay (25.5 ± 22.8 days vs 14.0 ± 14.6 days, p < 0.001) compared to patients without VAP (Fig 2). Similarly, mean billed hospital charges were significantly greater for patients with VAP ($104,983 ± $91,080 vs $63,689 ± $75,030, respectively; p < 0.001) compared to patients without VAP. Outcomes for the 26 patients with VAP who were unmatched were as follows: hospital mortality, 26.9%; duration of mechanical ventilation, 19.8 ± 19.4 days; ICU days, 16.2 ± 19.4 days; hospital days, 35.7 ± 34.9 days; and hospital charges, $183,312 ± $222,176.

Table 2—*Characteristics of Patients With and Without VAP (Matched Sample)

Characteristics	Patients With VAP (n = 816)	Patients Without VAP (n = 2,243)	p Value
Age, yr	62.3 ± 19.1	63.0 ± 17.7	0.389
Gender			
Male	522 (64.0)	1210 (53.9)	< 0.001
Female	294 (36.0)	1033 (46.1)	
Race			
White	639 (78.3)	1687 (75.2)	0.143
African-American	117 (14.3)	332 (14.8)	
Asian	3 (0.4)	14 (0.6)	
Other	57 (7.0)	210 (9.4)	
Predicted mortality, %			
0–10	399 (48.9)	1142 (50.9)	0.928
11–20	130 (15.9)	389 (17.3)	
21–30	75 (9.2)	187 (8.3)	
31–40	56 (6.9)	146 (6.5)	
41–50	39 (4.8)	91 (4.1)	
51–60	32 (3.9)	76 (3.4)	
61–70	21 (2.6)	50 (2.2)	
71–80	32 (3.9)	81 (3.6)	
81–90	18 (2.2)	43 (1.9)	
91–100	14 (1.7)	38 (1.7)	
Presence of coma/stupor	329 (40.3)	824 (36.7)	0.071
Use of CPR	38 (4.7)	119 (5.3)	0.472
Type of admission			
Medical	320 (39.2)	923 (41.2)	0.517
Surgical	312 (38.2)	851 (37.9)	
Trauma	184 (22.5)	469 (20.9)	

*Data are presented as mean ± SD or No. (%). See Table 1 for expansion of abbreviation.

Discussion

This is the largest US study of patients with VAP performed to date. These data suggest that VAP is a common hospital-acquired infection occurring in 9.3% of patients requiring mechanical ventilation for > 24 h. Male gender, trauma admission, and intermediate predicted risks of mortality were identified as independent risk factors associated with VAP. The case-control analysis we performed demonstrated no attributable mortality associated with VAP. However, patients with VAP had other statistically significant outcomes that indicate they fare poorly compared to patients without VAP: on average, 9.6 additional days of mechanical ventilation, 6.1 additional days in the ICU, and 11.5 additional days in the hospital. The inpatient billed charges were also significantly higher among patients with VAP, averaging > $40,000 more compared to patients without VAP.

Previous studies[3–5] have identified male gender, trauma, and severity of illness as risk factors for VAP. Cook and Kollef[3] performed a systematic review of risk factors for VAP using multiple logistic regression analysis. In their analysis, most risk factors associated with VAP appeared to either predispose patients to colonization of the aerodigestive tract with pathogenic bacteria (*eg*, prior use of antibiotics, treatment with histamine type 2 receptor antagonists) or aspiration (*eg*, supine positioning, patient transport out of intensive care). Male gender and trauma may be markers for other risk factors, predisposing patients to either colonization with pathogenic bacteria or aspiration. Similarly, intermediate underlying illness

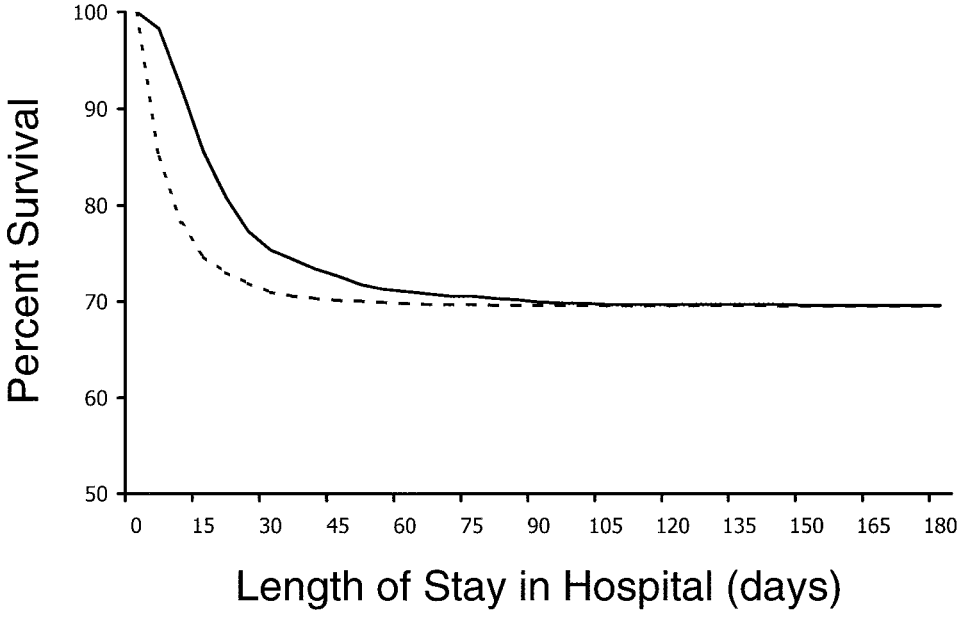

FIGURE 1. In-hospital survival among patients with (solid line) and without (dashed line) VAP from the matched case-control analysis; p = 0.1733 using the log-rank test for analysis of Kaplan-Meier survival curves.

severity suggests that patients with either low or high illness severity are less likely to have VAP develop. Potential explanations for this finding have been reported previously: very low-risk patients may not have sufficient exposure time to mechanical ventilation to acquire VAP, and high-risk patients may receive earlier treatment with antibiotics thus reducing the likelihood of acquiring VAP.[8]

Hospital mortality was not attributable to VAP in our analysis. This finding is consistent with the recent analysis of Bregeon et al,[6] and the results of several interventional studies[6,16–18] examining continuous aspiration of subglottic secretions, selective digestive decontamination, and semirecumbent positioning, which showed reduced rates of VAP but no associated survival advantage. However, other investigators[7,19] found hospital mortality to be increased among patients with VAP, particularly among patients with antibiotic-resistant bacteria infection. Furthermore, mortality associated with VAP may differ by population, with attributable mortality higher for medical patients than for surgical patients.[8] This may explain the greater survival for patients with VAP during the first 30 hospital days, as there were more medical patients and fewer trauma patients in the group without VAP. The treatment of VAP may also be an important determinant of patient outcome. Several studies[8,20–22] have shown that inappropriate initial antibiotic treatment of VAP is associated with excessive hospital mortality.

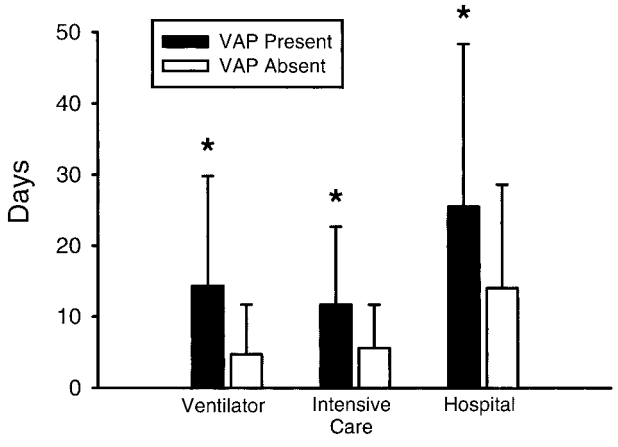

FIGURE 2. Health and economic outcomes associated with VAP. Mean values and SDs are shown; *p < 0.001 for all comparisons.

Our study has several potential implications for design of future interventional trials. In terms of patient eligibility, our findings suggest that trauma patients may be a suitable, discrete population to target. A significant drawback of limiting inclusion criteria to this population, however, is the generalizability of the findings to other at-risk populations. Given the lack of association between VAP and mortality, it is unknown whether interventional studies aimed at preventing or reducing VAP will demonstrate a survival benefit. End points that are potentially more achievable to meet, yet are still clinically and economically important, include days of mechanical ventilation, days in the ICU, hospital

days, and perhaps health-care costs. Although not evaluated in this study, end points that capture use of antibiotics ("antibiotic-free" days) would also be clinically meaningful and important to measure.

Strengths of our study include use of a national multicenter database that contained temporal information to examine clinical and economic variables (*eg*, mechanical ventilation) as both risk factors for, and outcomes of, VAP. Our sample size was larger than those in previous case-control studies examining attributable mortality from VAP, even though we only considered the first ICU admission. This was done to avoid entering repetitive data on the same patients, although it may have resulted in an underestimation of the VAP incidence. We also identified cases of VAP based on diagnoses made at participating institutions reflecting a spectrum of diagnostic approaches used in current US clinical practice. The availability of financial information also allowed us to quantify the extra costs associated with VAP. However, patients with VAP and control subjects were not matched for the same hospital. Therefore, variability in charges among different hospitals could account for some of the cost differences we observed. Finally, microbiology data were available for most patients and appeared consistent with that reported in the literature.[1,23–26]

This analysis has several important limitations. First, the variables entered into the database did not allow us to ascertain the importance of other potential risk factors for VAP (*eg*, supine positioning, chronic lung disease, specific surgical procedures, prior antibiotic use). Second, the time cutoff of 24 h following intubation to define the presence of VAP may have included some patients with community-acquired pneumonia that was not diagnosed earlier. Third, the diagnosis of VAP, and other unplanned events, likely varied among hospitals. Fourth, the identification of VAP cases may have biased the study toward early-onset cases, not allowing the identification of some late-onset cases in the control group. This may also have contributed to our inability to identify a difference in mortality between patients with and without VAP. No information was available on antibiotic utilization; therefore, we could not ascertain the role of antibiotics on outcome. Additionally, we may have underestimated the impact of VAP on resource utilization by excluding the 26 unmatched patients with VAP. Finally, as with most retrospective studies, we cannot exclude the possibility that our findings simply reflect the effects of systematic differences between patients with and without VAP, above and beyond those for which the matched study design controlled.

Despite the above-mentioned limitations, this study provides data highlighting the clinical and economic importance of VAP. It suggests that the occurrence of VAP is an important determinant of excessive hospital length of stay and inpatient medical care costs. Moreover, these data support the need to develop effective strategies for the prevention of VAP and other nosocomial infections.[27] Implementation of such interventions should be cost-effective because they should lower the incidence and lessen the sequelae of VAP.

Appendix

Members of the VAP Outcomes Scientific Advisory Group include Marc Bonten, MD, PhD, University Medical Center, Utrecht, the Netherlands; Jean Carlet, MD (Co-Chair), Hôpital St. Joseph, Paris, France; Deborah Cook, MD, St. Joseph's Hospital, Hamilton, ON, Canada; Jean-Yves Fagon, MD, Hôpital European Georges Pompidou, Paris, France; Mike Niederman, MD, Winthrop University Hospital, Mineola, NY; and Janet Wittes, PhD, Statistics Collaborative, Washington, DC.

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