Anesthesiology 2006; 105:709–14

Risk Factors for Ventilator-associated Pneumonia by Pseudomonas aeruginosa *in Presence of Recent Antibiotic Exposure*

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Background: **To facilitate the decision-making process for therapy and prevention of ventilator-associated pneumonia (VAP) in patients undergoing recent antibiotic exposure, this study investigated whether the development of VAP episodes caused by *Pseudomonas aeruginosa* or other pathogens are related to different risk factors, thereby distinguishing two risk population for this serious complication.**

Methods: **A 5-year retrospective case–control observational study was conducted. Cases of VAP caused by *P. aeruginosa* were compared with those caused by other pathogens. Univariate and multivariate analysis was performed using SPSS 11.0 software (SPSS Inc., Chicago, IL).**

Results: **Two groups were identified: *P. aeruginosa* (group P) was isolated in 58 (63.7%) episodes, and 33 episodes served as controls (group C), after a median of 12 days (interquartile range, 4–28 days) and 9 days (interquartile range, 3–12.5 days) of mechanical ventilation, respectively. *P. aeruginosa* was identified in 34.7% of episodes with early-onset pneumonia and in 73.5% with late-onset pneumonia. In a logistic regression analysis, *P. aeruginosa* was independently associated with duration of stay of 5 days or longer (relative risk = 3.59; 95% confidence interval, 1.04–12.35) and absence of coma (relative risk = 8.36; 95% confidence interval, 2.68–26.09). Risk for pathogens different from *P. aeruginosa* (group C) in early-onset pneumonia associated with coma was estimated to be 87.5%.**

Conclusions: **Risk factors in episodes under recent antibiotic treatment caused by *P. aeruginosa* or other microorganism are not the same, a fact that could have implications for preventive and therapeutic approaches for this infection.**

VENTILATOR-ASSOCIATED pneumonia (VAP) is the most common intensive care unit (ICU)–acquired infection. The prevalence of VAP varies, with an incidence ranging from 7% to more than 40%.[1] In intubated patients, rates of pneumonia may be between 6 and 21 times higher than in other patients, and the risk increases between 1% and 3% for each day the patient requires tracheal intubation.[2,3] It is associated with prolonged hospital stays and a high mortality rate.[4–8] Certain pathogens, such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and methicillin-resistant *Staphylococcus aureus*, are particularly lethal.[9,10] Etiologically, more than 60% of cases of VAP are due to gram-negative bacilli, and *P. aeruginosa* ranks first or second on most lists of causative organisms.[11–13] VAP increases hospital costs mainly due to an increase in duration of ICU stay.

Pulmonary infection results if the bacterial inoculum is sufficiently large, if the microorganism is particularly virulent, or if the host defenses breaks down.[11,12,14] When a microorganism has reached the lung, the development of pulmonary infection depends on the interaction between bacterial inoculum size and local pulmonary defenses. It is clear that an effective prophylactic regimen and the right choice of initial therapy could have a significant impact on the survival of mechanically ventilated patients with nosocomial pneumonia.

Multivariate analyses have demonstrated a significant association between previous antibiotic exposure, mechanical ventilation lasting more than 7 days, and *P. aeruginosa* isolates.[15,16] In the past decade, the American Thoracic Society[17] and a further report from France[15] described the distribution of causative organisms for VAP according to easily identifiable risk factors. These studies suggested that classifying patients according to previous duration of mechanical ventilation and previous exposure or no exposure to antibiotics provided a rational basis for anticipating the pathogens. In a recent conference on VAP, Park[18] did a comprehensive review and identified further areas of research.

We performed a study involving a 5-year database with two goals: first, to describe the microorganisms responsible for VAP in the subset with recent (< 2 weeks) antibiotic exposure, and second, to investigate whether VAP episodes caused by *P. aeruginosa* or other pathogens are related to different risk factors. This study's goals were selected to assist in the future design of interventional studies aimed at the prevention of VAP and to help assess a more accurate anticipation of the pathogen for choosing an initial antibiotic in patients developing VAP with recent antibiotic exposure.

Materials and Methods

Study Population

Patients evaluated in this study were medical–surgical ICU patients. All consecutive episodes of VAP identified

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Received from the Critical Care Department, Joan XXIII University Hospital, Tarragona, Spain. Submitted for publication April 10, 2006. Accepted for publication June 22, 2006. Supported in part by CIRIT SGR 2005/920, Comissió Interdepartamental de Recerca I Innovació Tecnológica, Distinciò Recerca Universitaria (to J.R.) (Catalonian Government Grant), and FIS 05/2410, Fondo de Investigación Sanitaria–Instituto de Salud Carlos III, Madrid, España.

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from a prospectively recorded database for nosocomial infections surveillance from January 2000 to January 2005 were identified. Informed consent was waived by the ethics committee (Joan XXIII University Hospital of Tarragona, Spain) because of the observational nature of the study.

All patients had received standard care. This includes oral care with 5% chlorhexidine washing per shift, weaning protocol as daily attempts of discontinuation of mechanical ventilation and a 30-min trial in T-tube, and sedation guided with the Ramsay scale. VAP management is guided by "The Tarragona Strategy."[19,20] Only those episodes with antibiotic exposure other than for surgical prophylaxis within the 2 weeks before pneumonia onset plus a microbiologically confirmed diagnosis of VAP were enrolled. Patients with recent hospitalization, chronic renal failure requiring hemodialysis, or admission from a nursing home were excluded.

To analyze the predisposing factors for development of VAP, the following variables were evaluated: age, sex, underlying disease, Acute Physiology and Chronic Health Evaluation II score, and diagnosis of hospitalization. Thirteen potential risk factors were recorded, and multiple logistic regression analysis was performed to detect the independent risk factors associated with VAP due to *P. aeruginosa*. The variables regarded as possible predisposing factors were chronic structural lung diseases, acute respiratory distress syndrome, steroid use, presence of coma, late-onset VAP ($>$ 4 days), dialysis, immunocompromise, malignancy, tracheotomy, trauma, absence of surgery, absence of heart disease, and cytotoxic drugs. Inclusion criteria were limited to VAP with oral or parenteral antibiotic exposure over the last 2 weeks before pneumonia onset. Patients with absence of antibiotic exposure or unknown pathogen were excluded.

Definitions

Pneumonia was diagnosed when new, persistent pulmonary infiltrates not otherwise explained appeared on chest radiographs. Moreover, at least two of following criteria were also required: (1) fever of 38°C or higher, (2) leukocytosis of 10,000/mm^3 or greater, and (3) purulent respiratory secretions. Pneumonia was considered ventilator associated when its onset occurred after 48 h of mechanical ventilation and was judged not to have been incubated before starting mechanical ventilation.[21] A definition of recurrent pneumonia has been reported elsewhere.[22]

Previous antibiotic therapy was considered when a patient received antimicrobial agents for more than 48 h during the 15 days preceding the episode of VAP.[4] Antibiotics administered for less than 48 h, mainly for perioperative prophylaxis, were not considered, and the corresponding episodes of VAP were classified as exposure free.

Steroid use has been reported elsewhere.[23] Chronic obstructive pulmonary disease was diagnosed using standard criteria recommended by the American Thoracic Society.[24] Coma was diagnosed when a Glasgow Coma Scale score lower than 9 (both in presence and in absence of sedation) was obtained for more than 24 h.[25] Severity of underlying disease conditions was evaluated with Acute Physiologic and Chronic Health Evaluation II score for each patient in the first 24 h after the ICU admission.[26] Pneumonia was defined as late onset if it started more than 4 days after admission, in accordance with the American Thoracic Society guidelines.[27]

Microbiology

Quantitative tracheal aspirates or fiberoptic bronchoscopic examination using a protected specimen brush was performed to obtain uncontaminated lower airway secretions for bacterial cultures. Specimens were transported to the laboratory immediately after collection. For protected specimen brush samples, the vial was then vortexed vigorously for at least 60 s to thoroughly suspend all material from the brush. Two serial 100-fold dilutions were made, and 0.1-ml aliquots of the original suspension and each dilution were inoculated on appropriate plates. Two serial 10-fold dilutions were then done on the recovered quantitative tracheal aspirate fluid, and 0.01-ml aliquots of the original suspension and each dilution were placed onto plates in the same way as for the protected specimen brush sample. In accordance with the standards adopted in previous studies, bacterial counts of at least 1,000 colony-forming units/ml (protected specimen brush) or 100,000 colony-forming units/ml (quantitative tracheal aspirate) were taken as the cutoff points for the pulmonary infection diagnosis.[28] Bacterial identification and susceptibility testing were performed by standard methods.[29] We defined two groups: (1) group P, in which we recorded all episodes of VAP with significant yield of *P. aeruginosa*, alone or identified with other pathogens; and (2) group C (control), in which we recorded all episodes with absence of *P. aeruginosa*.

Statistics

The study sample was constituted by all patients who were admitted to the ICU and received mechanical ventilation for more than 24 h. Contingency tables were analyzed using the two-tailed chi-square test. The primary data analysis compared episodes of VAP by *P. aeruginosa* with episodes without this pathogen. The cutoff point for those variables with more than two categories was chosen depending on the univariate analysis results. Results were reported as odd ratios and 95% confidence intervals, which were calculated using standard methods.[30] A relative risk of *P. aeruginosa* infection of 1 was arbitrarily assigned to the lower risk category for each variable. We confirmed the results of these

Table 1. Epidemiologic Characteristics of 81 Patients with 91 Episodes of VAP

Characteristic	Group P (n = 49)	Group C (n = 32)
Age, mean ± SD, yr	63.0 ± 18.3	53.8 ± 21.5
Male sex, n (%)	35 (71.4)	23 (71.9)
APACHE II score, mean ± SD	19.2 ± 6.2	19.8 ± 8.3
Duration of stay, days	17.6 ± 12.6	18.4 ± 17.5
Outcome, death, n (%)	19 (38.8)	15 (46.9)
Medical, n (%)	46 (93.9)	26 (81.3)
Surgical, n (%)	3 (6.1)	6 (18.7)

APACHE = Acute Physiology and Chronic Health Evaluation; C = control (other than *Pseudomonas*) group; P = *Pseudomonas* group; VAP = ventilator-associated pneumonia.

tests, while controlling for specific patient characteristics and severity of illness, with multiple logistic regression analysis, using the SSPS software package 11.0 (SPSS Inc., Chicago, IL).

Results

In the database, 3,201 patients were ventilated for more than 24 h. During the period of the study, 98 episodes of VAP with recent antibiotic exposure were identified. Seven episodes were excluded because no significant yields of any pathogen were identified in respiratory cultures. Eighty-one patients had a single episode, and the remaining 10 episodes (9 by *P. aeruginosa*) were recurrences.

The characteristics of patients of VAP with recent antibiotic exposure are detailed in table 1. Patients with *P. aeruginosa* were elderly, but the levels of severity of illness and the mortality rate were not significantly different.

Table 2. Isolates in 33 Episodes of VAP in the Control Group*

Isolate	Number of Episodes (n = 40)	Medical (n = 30)	Surgical (n = 10)
Aerobic gram-positive			
MRSA	2	2	—
MSSA	9	9	—
Streptococcus pneumoniae	3	3	—
Other *streptococci*	1	1	—
Aerobic gram-negative			
Acinetobacter baumannii	3	1	2
Klebsiella pneumoniae	3	1	2
Enterobacter aerogenes	3	—	3
Proteus mirabilis	2	1	1
Serratia marcescens	1	1	—
Escherichia coli	3	1	2
Haemophilus influenzae	7	7	—
Citrobacter freundii	1	1	—
Fungi			
Aspergillus fumigatus	2	2	—

* 21% of episodes were polymicrobial (66.6 % of surgical group were polymicrobial).

MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*; VAP = ventilator-associated pneumonia.

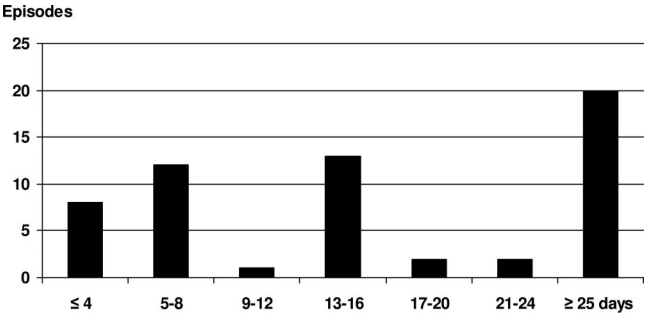

Fig. 1. Temporal distribution of *Pseudomonas aeruginosa* (group P).

Pseudomonas aeruginosa was isolated in 58 (63.7%) of 91 available episodes of VAP with positive quantitative cultures. In 6 of these 58 episodes, *P. aeruginosa* was accompanied by other microorganisms (2 *Escherichia coli*, 1 *Proteus mirabilis*, 1 *Streptococcus pneumoniae*, 1 *Stenotrophomonas maltophilia*, and 1 methicillin-resistant *S. aureus* plus *Morganella morgagnii*). The remaining 52 cases of VAP due to *P. aeruginosa* were monomicrobial. These 58 episodes were compared with the 33 remaining VAP episodes with other microorganisms (table 2).

Distribution of etiologies according to previous days of mechanical ventilation is shown in figures 1 and 2. *P. aeruginosa* developed after a median of 12 days (interquartile range, 4–28 days) of mechanical ventilation, compared with a median of 9 days (interquartile range, 3–12.5 days) for other pathogens. *P. aeruginosa* was identified in 34.7% of episodes with early-onset pneumonia and in 73.5% with late-onset pneumonia. Indeed, presence of *P. aeruginosa* was identified in only one (12.5%) episode of early-onset pneumonia associated with coma (fig. 3). This patient had cardiomyopathy and had received steroid therapy.

Four variables— duration of intubation greater than 4 days, steroid use, presence of acute respiratory distress syndrome, and absence of coma—were significantly associated with *P. aeruginosa* in the univariate analysis. In contrast, the remaining variables analyzed were not sig-

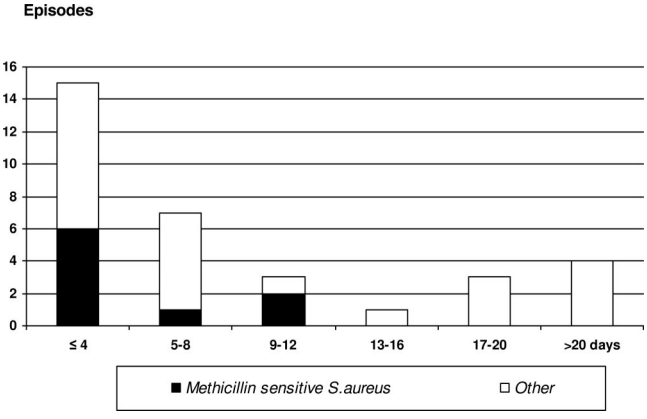

Fig. 2. Temporal distribution of ventilator-associated pneumonia due to other microorganisms (group C).

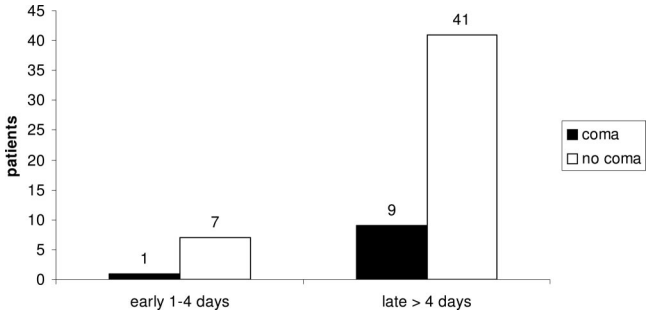

Fig. 3. Distribution of coma in 58 patients with ventilator-associated pneumonia caused by *Pseudomonas aeruginosa*, according to time of pneumonia onset.

nificant (table 3). These data were further analyzed using logistic regression models. After adjustment for confounding factors, VAP caused by *P. aeruginosa* was independently associated with presence of steroid use (odds ratio = 10.5) and acute respiratory distress syndrome (odds ratio = 8.2). On the other hand, duration of stay of 4 days or less (odds ratio = 3.5) and presence of coma (odds ratio = 8.3) were independently associated with different pathogens (group C). Detailed results for all variables analyzed are shown in table 4. The same variables were retained in the model, and duration of stay at pneumonia onset was associated with a relative risk of 1.08 (95% confidence interval, 1.01–1.14) for *P. aeruginosa*, when time from hospital admission was analyzed as a continuous variable. Similarly, the model remained similar when the variable "surgical" patient was entered in the analysis.

Discussion

A unique feature of this study is that it focuses specifically on VAP in previously antibiotic exposed patients. Interestingly, this study suggests that one third of all the antibiotic-treated patients did not have *Pseudomonas*. In addition, in patients under recent antibiotic treatment developing VAP, risk factors for *P. aeruginosa* and other microorganisms are not the same, an observation that could have implications for prevention and therapy.

Clinical evidence suggests that early use of appropriate empirical antibiotic therapy improves patient outcomes and reduces mortality, morbidity, and duration of hospital stay.[31–34] Many studies have reported the association between recent antibiotic exposure and multiresistant pathogens, such as *P. aeruginosa*.[15,16,35,36] *P. aeruginosa* is of particular interest because it is one of the leading pathogens associated with wrong initial antibiotic choices.[37] Our analysis addressed risk factors in patients with previous antibiotic exposure for the development of VAP due to *P. aeruginosa* compared with patients with VAP due to different infectious pathogens. This analysis has important implications for the selection of the most appropriate antibiotics for empirical treatment of mechanically ventilated patients with pneumonia and with previous antibiotic exposure. Our findings show that a duration of intubation of greater than 4 days or corticosteroid use is strongly associated with the development of VAP by *P. aeruginosa*. Although the 95% confidence interval for the variable "corticosteroid use" contained the null value with the sample of population studied, we believe that, given the magnitude of its relative risk and the proximity of the low limit of its 95% confidence interval to 1, the variable should be considered clinically relevant.

In contrast, presence of coma was independently as-

Table 4. Risk Factors for VAP Episodes by *Pseudomonas aeruginosa*: Multivariate Analysis

Variable	Odds Ratio	95% Confidence Interval	*P* Value
Absence of coma	8.3	2.68–26.0	< 0.01
Onset > 4 days	3.5	1.04–12.3	0.04
Corticosteroid use	10.5	0.97–112.8	0.052
ARDS	8.2	0.86–79.4	0.06

ARDS = acute respiratory distress syndrome.

Table 3. Risk Factors for Episodes of Infection by *Pseudomonas aeruginosa*: Univariate Analysis

Variable	Total Episodes of VAP, n (%)	VAP due to *P. aeruginosa*, n (%)*	Odds Ratio	95% Confidence Interval
ARDS	14 (15.3)	14 (100)	10.5	1.31–83.9
Steroid use	14 (15.3)	13 (92.8)	9.24	1.15–74.3
Absence of coma	62 (68.1)	48 (77.4)	8.38	3.0–22.7
Late onset VAP (> 4 days)	68 (74.7)	50 (73.5)	5.21	1.8–14.3
Dialysis	7 (7.6)	7 (100)	4.53	0.5–38.5
Episodes in nonsurgical patients	82 (90.1)	55 (67.0)	4.07	0.9–17.6
COPD	20 (21.9)	16 (80)	2.76	0.8–9.1
Tracheostomy	12 (13.1)	9 (75.0)	1.84	0.4–7.3
Absence of trauma	71 (78.0)	47 (66.1)	1.44	0.5–1.9
Cytotoxic drugs	2 (2.2)	2 (100)	1.18	0.1–13.5
Immunocompromise	3 (3.2)	2 (66.6)	1.14	0.09–13.1
Malignancy	3 (3.2)	2 (66.6)	1.14	0.09–13.1
Absence of heart disease	75 (82.4)	48 (64.0)	1.07	0.3–3.2

* For each variable, percent of ventilator-associated pneumonia (VAP) episodes due to *P. aeruginosa* in all VAP episodes.

ARDS = acute respiratory distress syndrome; COPD = chronic obstructive pulmonary disease.

sociated with other microorganisms, suggesting a different pathogenic mechanism and a different preventive approach. These findings are consistent with a previous report by Antonelli *et al.* [38] The incidence of *P. aeruginosa* in early-onset pneumonia in patients with coma was very low (12.5%). Figure 3 confirms previous observations[39–41] that reported an association between coma and pathogens other than *P. aeruginosa*. Early-onset pulmonary infection is believed to be due mainly to community endogenous pathogens. The most frequent etiologic agents include *S. aureus* and, less frequently, *Streptococcus pneumoniae* and *H. influenzae*.[42,43] Accordingly, it has been argued that tracheobronchial colonization with *S. aureus* and *H. influenzae* may result from direct inoculation during emergency intubation or endotracheal tube manipulation.[23,44,45] However, our current study demonstrates that *P. aeruginosa* was responsible for one third of episodes of early-onset VAP in patients with recent antibiotic exposure.

Patients in coma have an increased risk for early-onset pneumonia and particularly for methicillin-sensitive *S. aureus*.[46–49] It has been reported that these patients have increased levels of fibronectin in respiratory airways. Fibronectin favors binding of *S. aureus* to the respiratory epithelial cells, and it makes the adherence of *P. aeruginosa* difficult.[50,51] The association between *S. aureus* and coma is independent of the cause of coma. In normal hosts, more than 90% of effective clearance of microorganisms from the oropharynx seems to be due to effective salivary flow and swallowing.[52,53] In comatose patients, both the flow and swallowing are frequently abnormal. This reduction in mechanical clearance of potential pulmonary or oropharyngeal pathogens may be the first step in the path that leads sequentially from oropharyngeal colonization to pneumonia.

Finally, the current study has several limitations that should be borne in mind when interpreting the results. First, it is a retrospective observational analysis. Second, the influence of specific previous antibiotic classes administered or whether the antibiotics were started recently was not analyzed because the exact period of exposure and the specific antibiotic class were not recorded. It might be interesting to know which were the antibiotics used in patients who developed *P. aeruginosa* pneumonia and in the control group to try to correlate specific antibiotics with *P. aeruginosa*. Further studies on this issue should identify the specific class of antibiotic exposure. In addition, knowledge of previous antibiotics would be helpful in guiding future empirical therapy.[54] Third, the relatively small sample size may not have sufficient statistical power to identify all potential important risk factors for the development of VAP due to *P. aeruginosa*; similarly, the small sample size precluded the demonstration of a significant effect of certain variables in the multivariate analysis. Additional variables, such as "medical–surgical" condition may become significant in studies with larger study populations. Fourth, interpretation of studies of this kind is complicated by the heterogeneity of the population at risk. Fifth, the findings may be influenced by institution-specific variables: Our study was performed in a single center, raising the possibility of institutional bias either in patient selection or in other institutional practices. Sixth, data are lacking regarding a previous period of hospitalization for patients with *P. aeruginosa* pneumonia because they could be colonized before ICU admission. Our data might be useful as a pilot study to design a large multicenter study to resolve these issues.

In summary, our study offers new insight that should contribute to improve prescription of empirical antibiotics in patients with pneumonia. Risk factors in episodes under recent antibiotic treatment caused by *P. aeruginosa* or other organisms are not the same. Specifically, presence of *P. aeruginosa* was unlikely in early-onset VAP in patients with coma, and this subset of patients can receive narrow antibiotic therapy. On the other hand, our findings confirm that antipseudomonal antibiotics should be prescribed to all those patients with recent antibiotic exposure who develop late-onset VAP.

The authors thank Michael Maudsley, Ph.D. (Professor, Language School of Barcelona University, Spain), and Thiago Lisboa, M.D. (Fellow, Hospital de Clinicas, Universidade Federal Do Rio Grande do Sul, Porto Alegre, Brasil), for editing the final manuscript.

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