

Risk factors for infection by *Pseudomonas aeruginosa* in patients with ventilator-associated pneumonia

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Abstract. *Objective:* to investigate the epidemiology of infection by *Pseudomonas aeruginosa* in patients with ventilator-associated pneumonia (VAP).

Design: prospective clinical study.

Setting: a medical-surgical ICU in a university hospital.

Patients: we followed-up 568 mechanically ventilated patients and 83 episodes of VAP with etiologic diagnosis in 72 patients were retained for analysis.

Results: *Ps. aeruginosa* was isolated in 22 (26.5%) episodes in 18 patients. Of these episodes 7 were directly responsible for death. Using logistic regression analysis, the risk of VAP due to *Ps. aeruginosa* was increased in patients with chronic obstructive pulmonary disease (relative risk (RR) = 29.9, 95% confidence interval (CI) = 4.86–184.53), a mechanical ventilation period longer than 8 days (RR = 8.1, 95% CI = 1.01–65.40) and prior use of antibiotics (RR = 5.5, 95% CI = 0.88–35.01).

Conclusions: patients with VAP and these factors have a greater risk of infection by *Ps. aeruginosa* and empirical therapy for these episodes should include anti-pseudomonal activity until etiologic diagnosis is established.

Key words: Ventilator-associated pneumonia – Risk factors – *Pseudomonas aeruginosa*

Ventilator-associated pneumonia (VAP) continues to complicate the course of 7–41% of patients receiving mechanical ventilation (MV) and it is associated with a high mortality [1–5]. Etiologically, over 60% of cases of VAP are due to Gram-negative bacilli, and *Pseudomonas aeruginosa* ranks first or second on most lists of causative organisms [1–3].

Ps. aeruginosa frequently causes a necrotic lung lesion associated with unusual debility and a relapsing course [6]. Despite major advances in caring for critically

ill patients and the advent of effective broad-spectrum antibiotics, the morbidity and mortality of nosocomial lung infections caused by *Ps. aeruginosa* remain unacceptably high [1, 6]. Further advances in the prevention and treatment of this infection will depend on a better understanding of the epidemiology and on risk factors for its development.

Multiple regression analysis can be used to identify independent risk factors for infection [7] and this methodology has also been used in previous studies to determine risk factors for nosocomial pneumonia [3, 5, 8, 9]. Colonization of the oropharynx and digestive tract is frequent in intubated patients [10]; the bacteria are then aspirated, overcoming pulmonary defense mechanisms, and patients may develop pneumonia. For reasons not yet completely clear, bacterial adherence determines which micro-organism is most likely to colonize epithelial sites [6, 11]. In addition, host factors such as underlying disease [8, 12], demographics [13], antibiotics [14] or other drugs [15] may be important in selecting flora. Interestingly, the factors specifically influencing the development of infection by *Ps. aeruginosa* in mechanically ventilated patients with nosocomial pneumonia have not been analyzed using a multivariate technique.

We studied prospectively all patients admitted to our ICU who developed VAP from January 1988 to October 1990. This has given us an opportunity to examine the importance of *Ps. aeruginosa* as a cause of VAP and to describe its epidemiologic characteristics. In this paper we specifically seek to identify, using both univariate and multivariate statistical techniques, the risk factors for *Ps. aeruginosa* pneumonia in comparison with other ventilated patients with an established etiologic diagnosis of VAP.

Patients and methods

Population study

Our intensive care unit (ICU) is a 16-bed medical-surgical unit, with an average of 600 admissions per year, in a 1000-bed university hospital that serves both as a referral center and a first-line hospital. It is located

in an urban area with a population of more than 3 million. All patients admitted to our ICU received antacids or/and H₂-blockers, and no selective decontamination regimen was used. A prospective infection control surveillance program has been performed since 1988 and the data have been stored in an on-line computer system. During a period of 34 months, all patients who developed pneumonia in our ICU were initially eligible and evaluated by one of the investigators, as part of a prospective study of VAP.

A diagnosis of pneumonia was considered when new and persistent pulmonary infiltrates not otherwise explained appeared on chest X-rays. Moreover, at least two of the following criteria were also required: (i) fever $\geq 38^\circ\text{C}$; (ii) leukocytosis $\geq 10000\text{ mm}^3$; (iii) purulent respiratory secretions. A pneumonia was considered ventilator-associated when its onset occurred after 48 h of MV and was judged not to have been incubated before starting MV [3]. Fiberoptic bronchoscopic examination using a protected specimen brush was performed on each of these patients within the first 12 h after the development of a new pulmonary infiltrate. The diagnosis of VAP was retained only if the protected specimen brush yielded $\geq 1000\text{ cfu/ml}$ of at least one micro-organism. When *Ps. aeruginosa* was isolated in these samples, a diagnosis of VAP due to *Ps. aeruginosa* was established. Episodes during which etiologic diagnosis was not established were excluded.

To analyse the predisposing factors for developing VAP due to *Ps. aeruginosa*, the following variables were recorded: age, sex, underlying disease, severity, previous lung infection, previous infection, prior trauma or surgery, the presence of COPD, diabetes, dialysis, the leukocyte count, persistence of coma during MV, the duration of MV prior to the development of VAP, prior antibiotic therapy, prior corticosteroid use, prior barbiturate use, prior cytotoxic therapy and antecedent of drug use.

COPD was diagnosed using the standard criteria recommended by the American Thoracic Society [16]. Coma was diagnosed when a score lower than 9 was obtained using the Glasgow Coma Scale [17]. Criteria for neutropenia, diabetes or corticosteroid use have been previously defined [8]. Severity of underlying medical conditions was stratified in five categories according to NNIS ICU severity-of-illness clinical classification codes [18]. Surgery or trauma were considered to be present if they took place within 2 weeks prior to the episode.

Microbiology

Fiberoptic bronchoscopic examination was performed using the telescoping plugged catheter (TPC) technique to obtain uncontaminated lower airway secretions for bacterial cultures [19, 20]. A telescoping canula brush with a distal polyethylene glycol occlusion (Model BWF/10/70/90, Meditech Inc., Watertown, MA) was inserted through the inner suction channel of the bronchoscope (Model BF 10; Olympus Corp. of America, New Hyde Park, NY). This protected brush was advanced to a wedged, peripheral position after dislodging the distal catheter plug to obtain lower airway secretions for microbial cultures. The brush was advanced and aseptically cut into a sterile tube containing 1 ml of sterile saline solution. Specimens were transported to the laboratory immediately after collection. 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 agar plates for aerobic and anaerobic culture; one agar plate with selective buffered charcoal-yeast extract medium for isolation of *Legionella* species was included [21]. Bacterial counts $\geq 1000\text{ cfu/ml}$ were the cut-off point to diagnose pulmonary infections, according to the standards adopted in previous studies [22]. Bacterial identification and susceptibility testing were performed by standard methods [23].

Statistical analysis

Contingency tables were analysed using the two-tailed χ^2 test. The cut-off point for those variables with more than two categories was chosen depending upon the univariate analysis results. Relative risks (RR) and 95% confidence intervals (CI) were calculated using standard methods [24]. A relative risk of *Ps. aeruginosa* infection of 1 was arbitrarily assigned to the lowest risk category for each variable. Multivariate analy-

ses were performed using the enter logistic regression model of the SSPS software package. Two separate analyses were performed either for episodes or for patients. In the patient analysis, the variables were selected at the moment that the first infection by *Ps. aeruginosa* was diagnosed; for patients in the control group, the variables were selected at the moment that the last VAP was diagnosed, taking into account temporal modifications in potential risk factors such as previous infection or mechanical ventilation period.

Results

During the period of study, 568 patients needed MV for a period longer than 48 h; they developed 121 episodes of VAP. This represents an incidence of VAP of 21.3 cases per 100 patients with prolonged MV. There were 38 episodes rejected from the study because the agent responsible could not be identified. We studied a total of 83 episodes of VAP in 72 patients in whom etiologic diagnosis was established using a protected specimen brush and quantitative cultures. Underlying diseases of patients who suffered such episodes are shown in Table 1. The mean \pm SD age of these patients was 52.5 ± 19.3 years; 52 (72.2%) were men and 20 (27.7%) were women. In 36 (43.3%) episodes, they were receiving antibiotics for more than 48 h prior to the development of VAP. No patient had neutropenia.

A total of 22 episodes of VAP occurred in 18 patients due to *Ps. aeruginosa*. Two patients had positive blood cultures. In 5 (22.7%) of these episodes, *Ps. aeruginosa* was accompanied by other micro-organisms (3 *Serratia marcescens*, 1 *Alcaligenes faecalis*, 1 *Enterococcus faecalis*). Of these 18 patients 10 (55.5%) died in the intensive care unit, the infection being active in 7 of them when they died. Characteristics of these 22 episodes of VAP due to *Ps. aeruginosa* are shown in Table 2.

Table 3 shows the clinical and epidemiologic data of the episodes of VAP included in this study. The category with the lowest risk rate was arbitrarily assigned to have a relative risk of infection by *Ps. aeruginosa* of 1. Distribution of etiologies according to previous days on mechanical ventilation is shown in Table 4. From 33 episodes of VAP and less than 9 days of MV, three had infection by *Ps. aeruginosa* and 30 by other etiologies; previous lung disease was present in 3 and 4 of them, respectively. The presence of COPD, previous infection, prior antibi-

Table 1. Main underlying conditions of 72 patients with ventilator-associated pneumonia

Diagnosis	Patients
Multiple trauma	23
Cardiac surgery	14
Community-acquired pneumonia	7
Abdominal surgery	6
Neurosurgery	6
COPD	4
Pancreatitis	3
Diabetes	2
Status epilepticus	2
Tetanus	1
Guillain-Barré syndrome	1
Caustic burns	1
Stroke	1

Table 2. Characteristics of ventilator-associated pneumonia due to *Pseudomonas aeruginosa*

Case	Age	Sex	Diagnosis	Risk factors	Days of ventilation	Outcome	Other microorganisms
1	62	M	COPD	COPD	6	Died	<i>Serratia marcescens</i>
2	72	F	CS	S	22	Cured	<i>Serratia marcescens</i>
3	59	M	COPD	COPD	38	Cured	–
					79	Cured	–
					120	Died	–
4	74	M	COPD	COPD	16	Died	–
5	55	M	Caustic burns	S, HD, G, COPD	10	Died	<i>Alcaligenes faecalis</i>
6	20	M	CET	C, T	5	Cured	–
7	33	F	Intracranial tumor	S, G, C	9	Cured	<i>Serratia marcescens</i>
8	65	M	Multiple trauma	C, T, G, COPD	21	Cured	<i>Enterococcus faecalis</i>
9	56	M	Pancreatitis	S, COPD	32	Died	–
10	76	M	CET	C, T, G, S, Dm, COPD	3	Died	–
11	68	M	Renal failure	HD, C, COPD	10	Cured	–
					35	Died	–
12	77	M	Esophagous neoplasia	S, C, COPD, Q	35	Cured	–
13	46	M	COPD	C, COPD, G	9	Cured	–
					22	Died	–
					20	Cured	–
14	49	F	CS	S	19	Cured	–
15	71	F	CS	C, COPD	34	Cured	–
16	56	F	Diabetes	Dm, C, COPD	11	Died	–
17	65	M	CS	S, HD	16	Died	–
18	72	F	Pancreatitis	S, HD			

M = Male, F = Female; COPD = Chronic obstructive pulmonary disease; CS = Cardiac surgery; CET = Cranioencephalic trauma; S = Surgery; HD = Haemodialysis; G = Corticosteroids; T = Trauma; C = Coma; Dm = Diabetes; Q = Cytotoxic drugs

otic therapy, a MV period longer than 8 days and previous lung infection were associated with a significantly greater risk of developing infection by *Ps. aeruginosa* in the univariate analysis. In contrast, the remaining 12 variables were not significant.

The data were further analysed using an enter logistic regression model. The dependent variable was *Ps. aeruginosa* infection; the independent variables were: trauma antecedent, age, previous antibiotic use, MV period, COPD antecedent, previous lung infection and previous infection. After adjustment for confounding, the presence of COPD (RR = 18.3, 95% CI = 3.76–89.77) and a MV period longer than 8 days (RR = 7.5, 95% CI = 1.1–49.2) were statistically significant. The RR of prior antimicrobial use was 4.8 and although the CI contained the null value, the low limit of CI was near to 1. The complete results for all the variables examined are shown in Table 5. After excluding 11 episodes, this analysis was repeated again for the 72 patients with VAP, and it gave similar results (Table 6).

Discussion

The study reported herein was conducted to determine the most important risk factors associated with the development of VAP due to *Ps. aeruginosa* in a medical-surgical intensive care unit. This organism is of particular interest because of the frequency with which it causes respiratory tract infections and the severity of VAP due to this organism. Our analysis addressed risk factors for *Ps. aeruginosa* versus other types of VAP but not for incident *Ps. aeruginosa* VAP per se. Consequently, common risk factors for both groups cannot be identified in this study.

Nevertheless, our analysis has important implications as regards the selection of the most appropriate antibiotics for empiric treatment of mechanically ventilated patients with pneumonia. Seventeen potential risk factors were recorded and multiple logistic regression analysis was performed to detect the independent risk factors which together best predict this etiology. In Table 5, we analysed episodes of VAP, and several included patients counted twice for analysis, due to the fact that they presented more than one episode of VAP. The introduction of the variable “previous lung infection” partially ruled out a possible bias by including some common variables for patients with multiple episodes. However, since there still remains a possible bias for the analysis, outweighing other factors in patients who were included more than once, it was repeated excluding 11 episodes to include patients only once. Both studies show that the risk factors which independently influenced the development of VAP by *Ps. aeruginosa* were: presence of COPD; a MV period longer than 8 days and prior antimicrobial use. Although the 95% CI for the last variable contained the null value with the sample of population studied, we feel that with the magnitude of its RR and the proximity of the low limit of its 95% CI to 1, it should be considered clinically relevant.

The incidence of *Ps. aeruginosa* in our 83 episodes of VAP was 26.5%. Previous studies in MV patients using similar diagnostic techniques also found a similar percentage [1–3, 25]. Of the 18 patients who developed VAP due to *Ps. aeruginosa*, 10 (55.5%) died in the intensive care unit. Furthermore, this infection was judged to have been directly responsible for lethal outcome in 70% of these patients. These data agree with previous studies [6, 9] reporting a very high morbidity and mortality asso-

Table 3. Risk factors for episodes of infection by *Ps. aeruginosa*: univariate analysis

Variable	Episodes of VAP ^a		VAP due to <i>Ps. aeruginosa</i>		Relative risk	p Value
	(n)	(%)	(n)	(%)		
Age (years)						
≥55	35	(42.1)	6	(17.1)	1	0.056
<55	48	(57.8)	16	(33.3)	2.4	
Sex						
Male	60	(72.2)	16	(26.6)	1	0.84
Female	23	(27.7)	6	(26.1)	1	
Trauma						
Yes	27	(32.5)	4	(14.8)	1	0.09
No	56	(67.4)	18	(32.1)	2.7	
Surgery						
Yes	37	(44.5)	10	(27.0)	1	0.92
No	46	(55.4)	12	(26.1)	1	
Previous antibiotic therapy						
Yes	36	(43.3)	16	(44.4)	5.4	0.001
No	47	(56.6)	6	(12.8)	1	
Corticosteroid use						
Yes	19	(22.8)	6	(31.6)	1.3	0.56
No	64	(77.1)	16	(25.0)	1	
MV duration						
≤8 days	33	(39.7)	3	(9.1)	1	0.003
>8 days	50	(60.2)	19	(38.0)	6.1	
Diabetes						
Yes	9	(10.8)	2	(22.2)	1	0.75
No	74	(89.1)	20	(27.0)	1.2	
Dialysis						
Yes	10	(12.0)	4	(40.0)	2	0.30
No	73	(87.9)	18	(24.7)	1	
Drug addiction						
Yes	1	(1.2)	0	(0)	—	0.39
No	82	(98.7)	22	(26.8)		
Coma						
Yes	32	(38.5)	9	(28.1)	1.1	0.79
No	51	(61.4)	13	(25.5)	1	
Barbiturate use						
Yes	4	(4.8)	0	(0)	—	0.28
No	79	(95.1)	22	(27.8)		
Cytotoxic drugs therapy						
Yes	3	(3.6)	1	(33.3)	1.4	0.60
No	80	(96.3)	21	(26.3)	1	
COPD antecedent						
Yes	24	(28.9)	16	(66.7)	17.6	<0.00001
No	59	(71.0)	6	(10.2)	1	
Severity ^b						
Codes A,B	10	(12.0)	1	(10.0)	1	0.26
Codes C,D,E	73	(87.9)	21	(28.7)	1.1	
Previous lung infection						
Yes	15	(18.1)	8	(53.3)	3.1	0.01
No	68	(81.8)	14	(20.6)	1	
Previous infection						
Yes	29	(34.9)	15	(51.7)	2.9	0.0003
No	54	(65.0)	7	(13.0)	1	

MV = Mechanical ventilation

COPD = Chronic obstructive pulmonary disease

VAP = Ventilator-associated pneumonia

^a Ten patients had multiple episodes and they were included independently^b NNIS ICU severity-of-illness clinical classification

Table 4. Temporal distribution of etiologies

Days of ventilation	Etiologies	
	<i>Pseudomonas aeruginosa</i>	Other
≤ 4	1	11
5 – 8	2	19
9 – 12	5	10
13 – 16	2	7
17 – 20	2	4
21 – 24	3	2
≥ 25	7	8

ciated with nosocomial pneumonia caused by *Ps. aeruginosa*. Fagon et al. [1] previously noted that the mortality specifically attributed to pulmonary infection was significantly higher in patients with VAP caused by *Pseudomonas*, *Acinetobacter*, or *Staphylococcus* species (47%) than in patients with pneumonia caused by other organisms (0%, $p < 0.05$). The prognostic factors of patients who develop VAP caused by *Ps. aeruginosa* using a multivariate statistical approach have not been reported in the literature.

The presence of COPD was the most significant predictor of infection by *Ps. aeruginosa* in our study. Our finding can be explained by the fact that patients with COPD are at greater risk of airway colonization by Gram-negative bacilli [12, 26]. The loss of epithelium integrity and the impairment of mucosal clearance predispose patients with COPD to colonization [27]. Indeed, patients with COPD are at greater risk of developing VAP than patients without this pulmonary disorder [3]. This risk factor was also identified by Celis et al. [9] in

a multivariate analysis of non-MV patients with nosocomial pneumonia, as well as in a previous report studying the incidence and epidemiology of nosocomial pneumonia in a respiratory ICU [25]. Neither demographic characteristics nor any other medical condition of the 72 patients studied showed significant influence on the risk of developing VAP by *Ps. aeruginosa* compared to other etiologies.

Fagon et al. [1] have reported that the incremental risk for developing VAP is over 1% per day of ventilation. Other investigators, using multivariate analysis, have demonstrated that the duration of MV was a risk factor for development of VAP [3]. Van Saene et al. [10] classify VAP into “early” and “late” onset, day four being the cut-off. According to this classification, they found that *Pseudomonadaceae*, *Acinetobacter* species and *Enterobacteriaceae* are the most common isolates in “late” onset pneumonia. Our data agree with these observations. On the other hand, *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Haemophilus influenzae* were the flora responsible for the majority of “early” onset pneumonia, but *Ps. aeruginosa* was only responsible for one of these episodes. Although there are no previous data from multivariate analysis regarding the duration of MV as a risk factor for developing VAP due to *Ps. aeruginosa*, our findings are consistent with these observations.

Some clinicians have not made a sufficient effort to identify the etiology of febrile nosocomial illness, especially in intubated patients, and instead opted for the liberal use of broad-spectrum antimicrobial agents. However, such management is expensive and compromises efforts to document the causative agents of such infections precisely. Moreover, our finding that previous antimicrobial use is associated with a 5-fold increase in the risk for

Table 5. Risk factors for episodes of infection by *Ps. aeruginosa*: multivariate analysis

Variables	Estimated coefficient	Estimated standard error	<i>p</i> -Value	Relative risk	95% Confidence intervals
COPD	2.9106	0.8095	0.0003	18.37	3.76 – 89.77
MV > 8 days	2.0222	0.9568	0.03	7.55	1.16 – 49.28
Previous ATB use	1.5740	0.8310	0.05	4.83	0.95 – 24.60
Previous infection	1.1879	0.8755	0.17	3.28	0.59 – 18.24
Trauma	0.6624	0.9795	0.49	1.94	0.28 – 13.23
Age ≥ 55 years	-0.6624	0.9795	0.92	0.92	0.17 – 4.85
Previous lung infection	-0.4919	1.0482	0.63	0.61	0.08 – 4.77

COPD = Chronic obstructive pulmonary disease; ATB = Antimicrobial; MV = Mechanical ventilation

Table 6. Risk factors for patients with infection by *Ps. aeruginosa*: multivariate analysis

Variables	Estimated coefficient	Estimated standard error	<i>p</i> -Value	Relative risk	95% Confidence intervals
COPD	3.3997	0.9276	0.0002	29.96	4.86 – 184.53
MV > 8 days	2.0939	1.0646	0.04	8.12	1.01 – 65.40
Previous ATB use	1.7129	0.9402	0.06	5.55	0.88 – 35.01
Trauma	0.8935	1.0721	0.40	2.44	0.30 – 19.98
Previous infection	0.7381	0.8352	0.37	2.09	0.41 – 10.75
Age ≥ 55 years	0.2239	0.9481	0.81	1.25	0.20 – 8.02

COPD = Chronic obstructive pulmonary disease; ATB = Antimicrobial; MV = Mechanical ventilation

the development of VAP by *Ps. aeruginosa*, suggests that this strategy may cause unnecessary morbidity and supports a more restrictive antibiotic policy in critically ill patients, with the aim of reducing the risk of this life-threatening infection. Suppression of the normal bacterial flora by antibiotics, with the subsequent emergence of a resistant Gram-negative flora may explain this observation. Fagon et al. [1] have reported that the distribution of infecting organisms responsible for VAP differs in patients who received prior antimicrobial therapy, with a large increase in multiresistant organisms; these authors found that the rate of VAP caused by *Ps. aeruginosa* or *Acinetobacter* spp. was higher in the 31 patients who had received prior antibiotics (65% versus 19%, $p < 0.01$). Further studies are needed to examine the relationship between epidemiologic factors from patients (such as days on MV, level of consciousness or underlying diseases), antimicrobial exposure, protease activity, cell surface fibronectin, the type of colonizing bacteria and the rate of nosocomial pneumonia. Future advances in the understanding of these interactions should provide additional insight into the pathogenesis of VAP and offer new diagnostic and therapeutic approaches.

In summary, our results would be useful to clinicians seeking to identify, among the population with VAP, which patients have a significantly greater risk of *Ps. aeruginosa* infection. Since respiratory tract infections by this organism are associated with a high mortality, empiric treatment of VAP episodes in this population should have a strong anti-pseudomonal activity until culture data are available. According to our findings, this condition is not mandatory in patients without prior lung disease who develop pneumonia during the first week of mechanical ventilation and they can be empirically treated using a regimen without anti-pseudomonal activity. Furthermore, we suggest a restrictive antibiotic policy in mechanical ventilated patients with the purpose of reducing the risk of this life-threatening infection.

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