MAJOR ARTICLE

Pseudomonas aeruginosa Ventilator-Associated Pneumonia: Comparison of Episodes Due to Piperacillin-Resistant versus Piperacillin-Susceptible Organisms

J. L. Trouillet,[1] A. Vuagnat,[1] A. Combes,[1] N. Kassis,[2] J. Chastre,[1] and C. Gibert[1]

[1]Service de Réanimation Médicale and [2]Laboratoire de Bactériologie, Hôpital Bichat Assitance Publique–Hôpitaux de Paris, Paris, France

We sought to determine the epidemiological characteristics of patients in an intensive care unit (ICU) who developed ventilator-associated pneumonia (VAP) caused by piperacillin-resistant *Pseudomonas aeruginosa* (PRPA; $n = 34$) or piperacillin-susceptible *P. aeruginosa* (PSPA; $n = 101$). According to univariate analysis, the factors associated with the development of PRPA VAP were presence of an underlying fatal medical condition, immunocompromised status, longer previous hospital stay, less-severe illness at the time of ICU admission, duration of mechanical ventilation before onset of VAP, number of classes of antibiotic received, and previous exposure to imipenem or fluoroquinolone. Multivariate logistic regression analysis identified the following significant independent factors: presence of an underlying fatal medical condition (odds ratio [OR], 5.6), previous fluoroquinolone use (OR, 4.6), and initial disease severity (OR, 0.8). We concluded that the clinical characteristics of patients who develop PRPA VAP differ from those of patients who develop PSPA VAP. Restricted fluoroquinolone use is the sole independent risk factor for PRPA VAP that is open to medical intervention.

Pseudomonas aeruginosa, one of the main pathogenic agents responsible for nosocomial pneumonia (especially among patients who have undergone intubation and have been hospitalized in intensive care units [ICUs]), ranks second among all pathogens reported to the National Nosocomial Infection Surveillance System or evidenced in the European Prevalence of Infections in Intensive Care Study [1, 2]. Ventilator-associated pneumonia (VAP) caused by this microorganism remains a severe and dreaded complication [3–7]. Compared with community-acquired strains, nosocomially acquired *P. aeruginosa* isolates tend to be more resistant (often, to multiple classes of antibiotics). Thus, infection with multidrug-resistant *P. aeruginosa* has been a growing problem in medical facilities, and the occurrence of infections due to strains that are resistant to almost all commercially available antibacterial drugs has become a not-uncommon event [8].

Although a substantial proportion of cases of nosocomial infection are caused by multidrug-resistant *P. aeruginosa,* there have been few published studies of this topic, with the exception of studies of patients with cystic fibrosis. The few published investigations usually have involved small numbers of patients with mostly extrapulmonary infections, have lacked adequate control subjects, or both [8, 9]. The aim of the present study was to compare the epidemiological character-

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Reprints or correspondence: Dr. Jean-Louis Trouillet, Hôpital Pitie-Salpêtrière, 47-83 Boulevard de l'Hôpital, 75651 Paris Cedex 13, France (jean-louis.trouillet@psl.ap-hop-paris.fr).

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istics, risk factors, and outcomes of patients who received mechanical ventilation (MV) and developed antipseudomonal penicillin–resistant *P. aeruginosa* (PRPA) VAP with those who developed penicillin-susceptible *P. aeruginosa* (PSPA) VAP. Historically, carbenicillin was the first penicillin found to be active against *P. aeruginosa,* but, because piperacillin has become the reference drug, the piperacillin susceptibility of the *P. aeruginosa* strain is used as a marker of multidrug resistance.

PATIENTS, MATERIALS, AND METHODS

Study population. The study was conducted from January 1994 through August 1999 in one ICU in a 1200-bed Parisian university hospital (Hôpital Bichat) that serves as both a referral center and a first-line treatment facility. The only remarkable characteristic of this 17-bed ICU is its recruitment of a large number of patients who experience multiple-organ failure following cardiac surgery (20% of all patients admitted to the ICU).

All hospitalized patients who received mechanical ventilation (MV) for >48 h were eligible for the study, if pneumonia was suggested on the basis of clinical criteria. All the data were prospectively collected and stored in a specially designed database.

It should be noted that, during the study period, no systemic antibiotic regimen was prescribed for nosocomial pneumonia prophylaxis or selective decontamination of the digestive tract. The antimicrobial prescription policy, which was systematically applied by medical staff, was to prescribe the narrowest-spectrum antibiotic as soon as the susceptibility of the causative bacteria became known. For all patients, a heat-moisture exchanger was positioned between the Y-piece and the patient and was changed every 48 h [10]. The oropharyngeal cavity was carefully cleaned with antiseptic solution (hexamedine) 4 times daily. To prevent nosocomial infection, other measures were also applied systematically, including effective surveillance, staff education, identification of high-risk patients, proper isolation techniques, and such practices as handwashing and wearing gloves for each patient contact.

Diagnosis of VAP. "VAP" was defined as any lower respiratory tract infection that developed after a patient received MV for 2 days. The criteria for clinical suspicion of pneumonia were presence of a new or persistent lung opacity on chest radiographs plus 2 of the following findings: presence of either fever (temperature, ⩾38.3°C) or hypothermia (temperature, <36°C), a WBC count of >10,000 cells/mm^3 or <5000 cells/mm^3, and purulent endotracheal aspirate. Every patient suspected of having pneumonia underwent fiberoptic bronchoscopy so that protected specimen brush (PSB) and bronchoalveolar lavage (BAL) fluid samples could be obtained. Specimens were collected and processed according to procedures extensively described elsewhere [11, 12]. Nonbronchoscopic BAL was performed only in rare cases, and its results were taken into account to confirm VAP [13]. Thus, VAP was diagnosed on the basis of microbiological findings from analysis of PSB and BAL samples, according to the following thresholds for significance (i.e., "significant thresholds"): PSB culture yielding $\geqslant 10^3$ cfu/mL, ⩾2% of recovered cells containing intracellular bacteria on direct examination of BAL fluid samples, and/or BAL culture yielding $\geqslant 10^4$ cfu/mL. For nonbronchoscopic BAL, only the last 2 criteria were taken into account. The presence of 2 of the aforementioned criteria was always required for the diagnosis of VAP. VAP was considered to be caused by *P. aeruginosa* when PSB and/or BAL specimens yielded significant concentrations of this pathogen. If microorganisms other than *P. aeruginosa* grew at rates above the significant threshold, or if 2 different strains of *P. aeruginosa* grew to concentrations greater than the significant thresholds, then the episode was categorized as a "polymicrobial VAP episode".

Microbiologic methods. *P. aeruginosa* was identified by standard microbiological methods. Piperacillin susceptibility was determined by the disk-diffusion test. According to the criteria of the Antibiogram Committee of the French Society for Microbiology, the organism was considered "susceptible" when the inhibition diameter was ⩾18 mm, "intermediate" (denoting "intermediately susceptible") when the diameter was 12–17 mm, and "resistant" when the diameter was <12 mm, all for a disk content of 75 μg of antimicrobial agent [14]. Intermediate susceptibility to piperacillin was considered to be resistance, because piperacillin was never prescribed for intermediate strains in such cases. Susceptibilities to ticarcillin, ticarcillin-clavulanic acid, piperacillin-tazobactam, ceftazidime, imipenem, amikacin, or ciprofloxacin were systematically evaluated by use of the disk-diffusion test [14]. For polymicrobial VAP episodes, bacterial identification and susceptibility tests were systematically performed, and their results were taken into account in the choice of antimicrobial therapy.

Risk factors associated with PRPA VAP. Patients with PRPA VAP were compared with patients with PSPA VAP to determine the risk factors for developing PRPA VAP. For the purpose of the study, only the first episode of *P. aeruginosa* VAP was taken into account. If 2 different *P. aeruginosa* strains (1 piperacillin-susceptible strain and 1 piperacillin-resistant strain) were isolated during the same episode, and if they grew to concentrations greater than the previously defined significant thresholds, the episode was classified as having been caused by the piperacillin-resistant strain.

For purposes of comparison, the following information on each patient was collected within the first 24 h after admission to the ICU: age; sex; severity of the underlying medical condition (stratified, according to the criteria of McCabe and Jackson, as "rapidly fatal," "ultimately fatal," or "not fatal" [15]); immunocompromised status (defined according to criteria used in the determination of the Acute Physiology and Chronic Health Evaluation [APACHE] II score [16]). For HIV-positive

Table 1. Epidemiological characteristics at the time of admission to the intensive care unit (ICU) and clinical findings at the time of diagnosis of ventilator-associated pneumonia (VAP) for the 135 patients who developed *Pseudomonas aeruginosa* VAP.

Characteristic or finding	Patients with PRPA VAP (n = 34)	Patients with PSPA VAP (n = 101)	P
At the time of ICU admission			
Age, mean years ± SD	64.6 ± 12.5	65.5 ± 13.4	.67
Male sex	23 (67.6)	65 (64.4)	.83
Underlying medical condition (ultimately or rapidly fatal)	21 (61.8)	40 (39.6)	.03
Chronic obstructive pulmonary disease	5 (14.7)	11 (10.9)	.56
Immunocompromised status	9 (26.5)	7 (6.9)	.004
Direct admission to the ICU	2 (5.9)	14 (13.9)	.36
Duration of hospitalization before ICU admission, mean days ± SD	23.0 ± 16.4	15.9 ± 16.9	.009
APACHE II score, mean ± SD	19.2 ± 6.6	24.2 ± 6.6	.0002
Reason for MV			
Postoperative respiratory failure	26 (76.5)	60 (59.4)	.09
Other	8 (23.5)	41 (40.6)	.09
ARDS at admission	4 (11.7)	27 (26.7)	.09
ODIN score, mean ± SD	2.7 ± 1.1	3.2 ± 1.1	.03
At the time of diagnosis of VAP			
Duration of MV before onset of VAP, mean days ± SD	27.6 ± 21.6	21.5 ± 20.9	.05
Temperature, mean °C ± SD	38.5 ± 0.9	38.4 ± 1.1	.58
WBCs × 10^3/mL, mean no. ± SD	16.8 ± 8.7	16.4 ± 8.4	.82
Pao_2/Fio_2, mean mm Hg ± SD	197.9 ± 69.3	210.9 ± 90.8	.44
Radiological score, mean ± SD	6.8 ± 3.4	6.5 ± 2.7	.61
No. (%) of polymicrobial VAP episodes	8 (23.5)	40 (39.6)	.10
Associated with multidrug-resistant microorganisms[a]	2 (5.9)	14 (13.9)	.35
No (%) associated with bacteremia	3 (8.8)	12 (11.9)	.76
Received previous antibiotic therapy	33 (97.1)	92 (91.1)	.45
No. of antibiotic classes received,[b] mean no. ± SD	2.5 ± 1.1	1.9 ± 1.2	.01

NOTE. Data are no. (%) of patients, unless indicated otherwise. APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; MV, mechanical ventilation; ODIN, organ dysfunction and/or infection; Pao_2/Fio_2, partial pressure of oxygen in the alveoli/fraction of inspiried oxygen; PRPA, piperacillin-resistant *P. aeruginosa;* PSPA, piperacillin-susceptible *P. aeruginosa.*

[a] Methicillin-resistant *Staphylococcus aureus, Acinetobacter baumannii,* and *Stenotrophomonas maltophilia.*

[b] See table 2 for details.

patients, AIDS was defined according to criteria used in the Simplified Acute Physiology Score (SAPS) II [17]. Corticosteroid treatment was considered long term if it was >1 month in duration, and it was considered high-dose treatment if the dosage was 1 bolus of ⩾5 mg/kg given daily. Also collected was information on referral from another hospital or direct admission from our emergency department (i.e., direct ICU admission); prior duration of hospital stay; indications for receiving MV (on the basis of the classification described by Zwillich et al. [18]); presence of pneumonia at admission; presence of chronic obstructive pulmonary disease and acute respiratory distress syndrome [19]; APACHE II score [16]; and organ dysfunction and/or infection (ODIN) score [20].

The parameters recorded at the time of each episode of *P. aeruginosa* VAP were temperature; WBC count; partial pressure of oxygen in the alveoli (Pao_2)/fraction of inspiried oxygen (Fio_2); radiological score (according to the definition of Fagon et al. [21]); associated bacteremia; duration of MV before the diagnosis of VAP (day of the fiberoptic bronchoscopy; recorded as a continuous variable); presence of other causative organisms; and use of any antimicrobial agent for >24 h during the 15 days preceding diagnosis of VAP (day of the fiberoptic bronchoscopy). In addition, we recorded for each patient the use of any of the following 5 antibiotic classes during the 15 days preceding the diagnosis of VAP: imipenem, third-generation cephalosporin, aminoglycoside, fluoroquinolone, and/or other antibiotics (defined by exclusion).

Outcome. A recurrent episode of *P. aeruginosa* VAP was defined by (1) occurrence of an episode at least 72 h after clinical resolution of a prior episode, (2) presence of the criteria for clinical suspicion of pneumonia, as defined in the "Diagnosis of VAP" subsection above, (3) a quantitative bronchoscopic specimen culture that was positive for *P. aeruginosa,* and (4) absence of evidence of a new extrapulmonary source of infection. Finally, the duration of MV, measured from the day of VAP diagnosis, and the mortality rate among patients in the ICU were recorded.

Statistical analyses. Potential risk factors—that is, all the

Table 2. Univariate analysis of the impact of therapy on the piperacillin susceptibility of the causative agent *Pseudomonas aeruginosa,* according to the antibiotic class of antimicrobial therapy prescribed during the 15 days preceding the diagnosis of ventilator-associated pneumonia (the day of fiberoptic bronchoscopy; VAP).

Antibiotic class received	No. (%) of patients with PRPA VAP (n = 34)	No. (%) of patients with PSPA VAP (n = 101)	P
Imipenem	9 (26.5)	12 (11.9)	.04
Third-generation cephalosporin	20 (58.8)	42 (41.6)	.08
Aminoglycoside	15 (44.1)	41 (40.6)	.71
Fluoroquinolone	15 (44.1)	20 (19.8)	.007
Other	26 (76.5)	79 (78.2)	.83

parameters listed above—were subjected to univariate analysis (comparison of means) to identify those that had a significant association with PRPA VAP. Continuous variables were compared using Student's t test; when that was not appropriate, the Mann-Whitney U test was used. The χ^2 test was used for categorical variables; when they were not appropriate, Fisher's exact test was used. Differences between groups were considered to be significant for variables for which $P < .05$.

Only those variables for which $\alpha = 0.05$ were entered into the model of logistic regression analysis to determine independent risk factors for developing PRPA VAP. The discriminating ability of the model was assessed by use of the area under the receiver operating characteristic (ROC) curve. Mortality rates, duration of MV, and susceptibility of strains to other antibiotics, according to piperacillin resistance, were also determined.

RESULTS

For 135 (34.4%) of the 393 consecutive patients who developed ⩾1 episode of VAP, cultures of BAL fluid and/or PSB samples yielded *P. aeruginosa* at concentrations above the significant thresholds. PRPA isolates were recovered from 34 patients (25.2%) and PSPA isolates from 101 patients (74.8%). The epidemiological characteristics of VAP caused by the 2 types of *Pseudomonas* strains are reported in tables 1 and 2.

For 127 patients, diagnosis of *Pseudomonas* VAP was established on the basis of culture results for PSB and BAL samples obtained during fiberoptic bronchoscopy; for the remaining 8 patients, it was established with BAL fluid samples obtained blindly. In 48 episodes (35.6%), ⩾1 other pathogen was isolated at a significant concentration. Details regarding the species of the other pathogens are indicated in table 3. The incidence of polymicrobial VAP episodes was higher in the PSPA group (39.6%) than in the PRPA group (23.5%), but the difference was not statistically significant ($P = .10$).

Distributions of PRPA and PSPA VAP episodes, according to year of diagnosis, are shown in figure 1; no significant trend was observed ($P = .37$). Moreover, throughout the entire study, no period in which there was a peak in the number of *P. aeruginosa* VAP episodes was observed, no epidemic strain was identified, and no temporal-spatial aggregation of cases was found.

Risk Factors for Developing PRPA VAP

Univariate analysis. According to a univariate analysis comparison of means, the factors that were significantly associated with PRPA VAP were the presence of an underlying fatal medical condition ($P = .03$), immunocompromised status ($P = .004$), longer previous stay in the hospital ICU ($P = .009$), lower APACHE II score ($P < .0002$), lower ODIN score at the time of admission to the ICU ($P = .03$), longer duration of MV at the time of VAP diagnosis ($P = .05$), more different classes of antibiotics administered before VAP ($P = .01$), and prior antimicrobial therapy with imipenem ($P = .04$) or a fluoroquinolone ($P = .007$). A third-generation cephalosporin had been prescribed more frequently to the PRPA group, but the difference between groups did not reach statistical significance ($P = .08$).

Multivariate analysis. When all the variables that were significantly different in univariate analysis were subjected to logistic regression multivariate analysis, 3 remained in the final model: presence of an underlying fatal medical condition, prior use of a fluoroquinolone, and APACHE II score (table 4). The odds ratio associated with the APACHE II score is expressed

Table 3. Identification of microorganisms in polymicrobial episodes of ventilator-associated pneumonia, according to piperacillin-resistant *Pseudomonas aeruginosa* (PRPA) or piperacillin-susceptible *P. aeruginosa* (PSPA) group.

Microorganisms identified	No. of microorganisms In PRPA group[a]	No. of microorganisms In PSPA group[b]
MRSA	2	5
MSSA	0	1
Acinetobacter baumannii	0	5
Stenotrophomonas maltophilia	0	4
Streptococcus species	4	15
Enterobacteriaceae	2	11
Miscellaneous[c]	6	5
Piperacillin-susceptible *P. aeruginosa*	6	0
Total[d]	20	46

NOTE. MRSA, methicillin-resistant *Staphylococcus aureus;* MSSA, methicillin-susceptible *S. aureus.*

[a] Eight polymicrobial VAP episodes.
[b] Forty polymicrobial VAP episodes.
[c] *Neisseria* species, *Haemophilus* species, and diphtheroids.
[d] The total values are greater than values listed in footnotes a and b because >1 microorganism was associated with individual episodes.

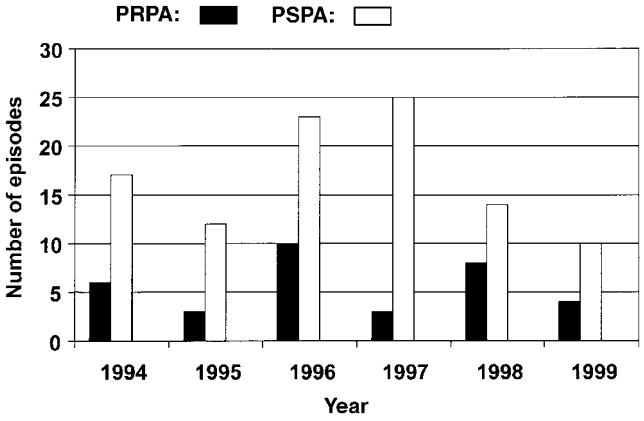

Figure 1. Distribution of episodes of *Pseudomonas aeruginosa* ventilator-associated pneumonia, according to year of diagnosis. Only episodes that occurred during the first 8 months of 1999 were included. PRPA, piperacillin-resistant *P. aeruginosa;* PSPA, piperacillin-susceptible *P. aeruginosa.*

per point accorded and indicates that this parameter is a risk factor when lower values are recorded at admission. The overall discriminating value of this multiple regression model to predict the probability of developing PRPA VAP, as assessed by ROC analysis, was 0.82. Table 5 shows the percentages of PRPA VAP episodes, according to the presence or absence of a fatal underlying disease and previous exposure to a fluoroquinolone.

Outcome

Ten patients (7 in the PSPA group and 3 in the PRPA group) had recurrence of *P. aeruginosa* VAP (i.e., relapse with the previous strain or infection with a new one). The second episode developed at a median of 17.4 days (range, 6–36 days) after the initial episode. For 6 patients, the antibiotic-resistance patterns of strains isolated during this second episode differed from those of strains isolated during the first episode.

The mean duration of MV ($\pm$SD), measured from the day of diagnosis of VAP, was 17.3 $\pm$ 17.4 days for the PRPA group and 21.0 $\pm$ 26.0 days for the PSPA group (P value not significant). A total of 20 patients (58.8%) in the PRPA group died versus 50 patients (49.5%) in the PSPA group (P value not significant).

Susceptibility to Other Antibiotics with Antipseudomonal Activity, According to Piperacillin Resistance

A significant relationship was found between piperacillin resistance and cross-resistance to other antibiotics active against *P. aeruginosa* infections (table 6). When *P. aeruginosa* strains were susceptible to piperacillin, they were <20% resistant to other antibiotics, except for ciprofloxacin. Piperacillin-resistant strains were ⩾50% resistant to each drug tested. Thirteen strains (9.6%) were resistant to piperacillin-tazobactam plus ceftazidime plus imipenem, and 8 strains were resistant to these 3 antibiotics and amikacin. All strains were susceptible to colistin.

The resistance of strains to imipenem, ceftazidime, or ciprofloxacin, according to previous administration of imipenem, a third-generation cephalosporin, or a fluoroquinolone, is reported in table 7. As expected, patients who had received 1 of these 3 antibiotics had a higher probability of becoming infected with a strain resistant to the given antibiotic class. Moreover, VAP episodes due to imipenem-resistant strains were more frequently associated with prior fluoroquinolone administration than were VAP episodes due to imipenem-susceptible strains ($P = .05$).

DISCUSSION

We analyzed 135 consecutive patients who developed an episode of *P. aeruginosa* VAP, using strict criteria to define pneumonia. PRPA VAP episodes (25% of all *P. aeruginosa* VAP episodes) were significantly associated with 9 factors. According to multivariate analysis, a fatal underlying medical condition, prior use of a fluoroquinolone, and APACHE II score remained independently associated with PRPA VAP.

The high percentage of VAP episodes due to *P. aeruginosa* (34.4%) confirms findings reported elsewhere [22]. This high percentage can be explained by the fact that the ICU is an area of endemicity for *P. aeruginosa* colonization [23] and, also, by the characteristics of the studied populations. Most of our patients were transferred from another ICU or ward after a mean hospital stay of >2 weeks. All but 1 episode of *P. aeruginosa* VAP occurred >7 days after initiation of MV, and all were classified as late-onset VAP [7].

We observed a high rate of increased resistance among the *Pseudomonas* strains isolated from the patients with VAP seen at our ICU. This finding has been noted at other European ICUs, as was shown by Hanberger et al. [24] in their study comparing the antibiotic susceptibilities of aerobic gram-negative bacilli in 5 European countries. Except in Sweden, the percentage of *Pseudomonas* strains resistant to piperacillin was >14%, reaching 22% in Portugal and 26% in France [24], which is similar to our findings. The percentage of strains resistant to other antibiotics (e.g., imipenem and ciprofloxacin) was also high (in France, 24% were resistant to imipenem and 35% were resistant to cipro-

Table 4. Multivariate analysis of risk factors for penicillin-resistant *Pseudomonas aeruginosa* ventilator-associated pneumonia.

Risk factor	OR (95% CI)	*P*
Underlying medical condition that is rapidly or ultimately fatal	5.6 (2.0–16.2)	.001
Previous exposure to fluoroquinolone	4.6 (1.7–12.7)	.003
APACHE II score, per point accorded	0.8 (0.7–0.9)	<.001

NOTE. APACHE, acute physiology and chronic health evaluation.

Table 5. Number of episodes of piperacillin-resistant *Pseudomonas aeruginosa* (PRPA) ventilator-associated pneumonia (VAP), according to the presence or absence of a fatal underlying disease and previous exposure to fluoroquinolone.

Risk factor	No. of PRPA VAP episodes/total no. of patients	PRPA VAP episodes, %
No prior exposure to fluoroquinolone		
No fatal underlying medical condition	6/53	11.3
Fatal underlying medical condition	13/47	27.7
Prior exposure to fluoroquinolone		
No fatal underlying medical condition	7/21	33.3
Fatal underlying medical condition	8/14	57.1

floxacin). Similar results have been observed for *Pseudomonas* strains in the United States [1], even if strict comparison of the studies is made difficult because standards provided by the National Center for Clinical Laboratory Standards are defined using a disk content of 100 μg of piperacillin for the same threshold diameter of $\geqslant$18 mm. Moreover, our data confirm that PRPA isolates are more likely to be resistant to other antipseudomonal agents than are PSPA isolates (table 6).

The specific objective of our study was to determine independent risk factors that lead to the emergence of PRPA VAP. The results of our multivariate analysis indicate that exposure to antibiotics appears to be a crucial factor in the emergence of multidrug-resistant bacteria and confirms previously reported data for other resistant pathogens [25, 26]. Finally, the results of the present study highlighted the major role of fluoroquinolones in the emergence of multidrug-resistant *P. aeruginosa* responsible for VAP. These findings are in accordance with the results of Harris et al. [8], who found multidrug and lengthy antipseudomonal antibiotic exposures to be factors that predispose for the development of an infection with multidrug-resistant *P. aeruginosa.* One pertinent finding is that recent exposure to a fluoroquinolone was also found to be an independent risk factor for carriage of and persistent colonization with methicillin-resistant *Staphylococcus aureus* [27–29]. This information could provide an extremely simple way to identify subgroups of patients from whom PRPA are likely to be isolated.

Our multivariate analysis identified 2 other independent risk for PRPA: less-severe disease at the time of admission to the ICU, as assessed by APACHE II score, and presence of an underlying medical condition that is rapidly or ultimately fatal. It is unclear why the presence of more-severe disease at admission to the ICU protects patients from infection with multidrug-resistant *P. aeruginosa* strains. This finding may indicate a subgroup of patients who carry this marker, rather than reflect a direct causal relationship. The major limitations of interpreting the marker accurately are the observational nature of the data and the relatively small number of episodes that may lower the power of this study. The other major predisposing factor associated with PRPA pneumonia was the presence of an underlying medical condition, as assessed by the MacCabe and Jackson score. This factor might reflect a lower degree of immune function that leads to infections caused by less virulent strains, as has been claimed for multidrug-resistant strains of *P. aeruginosa* [4].

Two other factors identified in the case-control study by Arruda et al. [9] were confirmed by our univariate analysis but were eliminated in the multivariate analysis: immunocompromised status and prolonged length of hospital stay before the occurrence of nosocomial infection. In the case-control study, the occurrence of nosocomial infections due to *P. aeruginosa* resistant to all antimicrobials commercially available in Spain was associated with the use of immunosuppressants, neutropenia, or prolonged prior hospitalization. Prolonged length of hospital stay before infection was also reported by Harris et al. [8], but their study did not include any control population. In our study, immunocompromised patients were few in number and low in proportion, precluding a powerful analysis of this point.

Table 6. Percentage of antibiotic-piperacillin cross-resistance among *Pseudomonas aeruginosa* isolates recovered from 135 patients with ventilator-associated pneumonia (VAP).

	Percentage of isolates	
Antibiotic	PRPA (n = 34)	PSPA (n = 101)
Ticarcillin	91.2	16.8
Piperacillin-tazobactam	88.2	0
Ticarcillin–clavulanic acid	94.1	13.9
Ceftazidime	61.8	3
Imipenem	58.8	9.9
Ciprofloxacin	70.6	21.8
Amikacin	50	6.9

NOTE. PRPA, piperacillin-resistant *P. aeruginosa;* PSPA, piperacillin-susceptible *P. aeruginosa.*

Table 7. Resistance of *P. aeruginosa* strains to imipenem, ceftazidime, or ciprofloxacin, according to previous therapy with imipenem, a third-generation cephalosporin, or a fluoroquinolone.

	No. (%) of patients, by previous drug therapy received					
	Imipenem		Third-generation cephalosporin		Fluoroquinolone	
Strain resistance	No (n = 114)	Yes (n = 21)	No (n = 73)	Yes (n = 62)	No (n = 100)	Yes (n = 35)
To imipenem	19 (16.7)	11 (52.4)[a]	12 (16.4)	18 (29.0)	18 (18)	12 (34.3)[d]
To ceftazidime	17 (14.9)	7 (33.3)	6 (8.2)	18 (29.0)[b]	14 (14)	10 (28.6)
To ciprofloxacin	35 (30.7)	11 (52.4)	25 (34.2)	21 (33.9)	26 (26)	20 (57.1)[c]

NOTE. All P values in footnotes are for comparison of the "No" and "Yes" groups.

[a] $P = .0009$.
[b] $P = .003$.
[c] $P = .001$.
[d] $P = .05$.

Finally, inclusion of polymicrobial VAP episodes could introduce another limitation in our result, but the rate of polymicrobial episodes was not statistically different between the 2 groups. Concerning outcome, mortality rates were similar in the monomicrobial and polymicrobial groups (50.6% versus 54.2%, respectively, without trend, as found by Crouch Brewer et al. [5]). In addition, the proportion of associated multidrug-resistant microorganisms, a factor usually associated with a poorer prognosis, was not statistically different between the PRPA and PSPA groups (table 1). In summary, the results of the present study showed that (1) PRPA VAP episodes frequently occurred in this type of ICU population, (2) piperacillin-resistant strains were clearly more resistant to other antipseudomonal drugs than were piperacillin-susceptible strains, and (3) the mortality rate among patients with PRPA VAP was >50%.

Statistical analyses suggested that the clinical characteristics of patients who subsequently develop PRPA VAP differ from those of patients with PSPA VAP episodes. Because previous use of a fluoroquinolone was the only independent factor open to medical intervention that was identified in the present study, these data support the recommendation that in-hospital prescription of broad-spectrum antibiotics, especially fluoroquinolones, should be restricted.

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