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Impact of piperacillin resistance on the outcome of *Pseudomonas* ventilator-associated pneumonia

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Abstract *Background:* The impact of antibiotic resistance on the outcome of infections due to Gram-negative bacilli, especially *Pseudomonas*, remains highly controversial. *Study objective, design, and patients:* We evaluated the impact of piperacillin resistance on the outcomes of *Pseudomonas aeruginosa* ventilator-associated pneumonia (VAP) for patients who had received appropriate empiric antibiotics before enrollment in the PNEUMA trial, a multicenter randomized study comparing 8 vs 15 days of antibiotics. *Results:* Despite similar characteristics at intensive care unit (ICU) admission, patients infected with piperacillin-resistant *Pseudomonas* strains were more acutely ill at VAP onset and had a higher 28-day mortality rate (37 vs 19%; $P = 0.04$) than those with piperacillin-susceptible *Pseudomonas* VAP. Factors associated with 28-day mortality retained by multivariable analysis were: age (OR: 1.07; 95% CI: 1.03–1.12); female gender (OR: 4.00; 95% CI: 1.41–11.11); severe underlying comorbidities (OR: 2.73; 95% CI: 1.02–7.33); and SOFA score (OR: 1.17; 95% CI: 1.03–1.32), but piperacillin resistance did not reach statistical significance (OR: 2.00; 95% CI: 0.72–5.61). The VAP recurrence rates, either superinfection or relapse, and durations of mechanical ventilation and ICU stay did not differ as a function of *Pseudomonas*-resistance status. *Conclusions:* For patients with *Pseudomonas* VAP benefiting from appropriate empiric antibiotics, piperacillin resistance was associated with increased disease severity at VAP onset and higher 28-day crude mortality; however, after controlling for confounders, piperacillin-resistance was no longer significantly associated with 28-day mortality. The VAP recurrence rates and durations of ICU stay and mechanical ventilation did not differ for susceptible and resistant strains.

Keywords Antibiotic-resistant bacteria · Artificial respiration · Outcome assessment · Multivariable models

Introduction

Ventilator-associated pneumonia (VAP) remains one the most serious complications of mechanical ventilation (MV) and the nosocomial infection with the highest associated mortality [1]. *Pseudomonas aeruginosa*, one of the bacteria most frequently responsible for VAP, is also one of the most virulent, associated with the worst morbidity and mortality rates [2, 3]. In addition, antibiotic resistance of this bacterium has markedly increased in recent years, reaching rates > 30% for antipseudomonal third-generation cepholosporins or quinolones [4].

It has been hypothesized that infections caused by this highly antibiotic-resistant pathogen might result in higher mortality, longer durations of hospitalization, and greater costs, compared with infections due to antibiotic-susceptible strains [5, 6]; however, to date, conflicting data from a limited number of studies on the impact of

antibiotic resistance on the outcomes of severe infections due to Gram-negative bacilli, especially *Pseudomonas*, have been reported [5, 7, 8, 9, 10, 11, 12, 13, 14]. Furthermore, inappropriate initial empiric antimicrobial treatment, which was among the strongest independent determinants of in-hospital mortality in two recent studies on *Pseudomonas* bacteremia [10, 12], might represent one of the major confounders in studying the consequences of antibiotic resistance on infection outcomes.

The aim of this study was therefore to evaluate the impact of piperacillin resistance on the outcomes of *Pseudomonas* VAP for patients who had received appropriate empiric antibiotics for VAP before enrollment in the large cohort of the PNEUMA trial [15].

Patients and methods

The PNEUMA trial [15] was a prospective multicenter, randomized, double-blind (until day 8) clinical trial conducted at 51 intensive care units (ICUs) in France, that demonstrated the equivalence of 8 vs 15 days of antibiotics in terms of clinical outcomes for patients with microbiologically proven VAP. Among the 401 patients enrolled in that trial, 115 had *Pseudomonas aeruginosa* VAP.

Data collection

At ICU admission, the following data were recorded for each patient: age; gender; severity of underlying medical condition, according to the criteria of McCabe and Jackson [16]; Simplified Acute Physiology Score (SAPS II) [17]; Sepsis-related Organ Failure Assessment (SOFA) score [18]; Organ Dysfunctions and/or INfection (ODIN) score [19]; and the primary reason for initiating MV.

On the day of bronchoscopy (day 1), we recorded the following: duration of prior MV; SAPS II; ODIN and SOFA scores; temperature; leukocyte count; PaO_2/F_IO_2 ratio; radiological score [20]; blood-culture positivity; and presence of shock or acute respiratory distress syndrome [21]. Only piperacillin susceptibility for *Pseudomonas aeruginosa* was recorded in the PNEUMA database.

Microbiological methods

Pseudomonas aeruginosa was identified by standard microbiological methods. Piperacillin susceptibility was determined using 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 susceptibility") when the diameter was 12–17 mm, and "resistant" when the diameter was < 12 mm, all for a disk content of 75 mg of antimicrobial agent [22]. Intermediate susceptibility to piperacillin was considered to be resistance, because piperacillin was never prescribed for intermediate strains in such cases.

Follow-up

The following data were recorded daily during the 28-day period following the initial bronchoscopy: temperature; leukocyte counts; PaO_2/F_IO_2; presence or absence of purulent tracheal secretions, whether the patient was still mechanically ventilated or not; vital signs, and ODIN score. The SOFA and radiological scores were determined on days 3, 7, 14, 21, and 28. Extreme vigilance for pneumonia recurrence was maintained throughout the study period to detect any possible relapse or new episode of pulmonary infection, and fiberoptic bronchoscopy was performed before the introduction of any new antibiotics as soon as a patient became febrile, had purulent tracheal secretions, and/or a new pulmonary infiltrate developed or an existing infiltrate progressed. Distal pulmonary secretions were also collected bronchoscopically when unexplained hemodynamic instability required higher vasopressor doses ($> 30\%$) or their introduction; in the case of unexplained deterioration of blood gases, with a PaO_2/F_IO_2 decrease of $> 30\%$; or when an intercurrent event imposed an urgent change of antibiotic therapy, regardless of the reason. Any antibiotic use was recorded daily until day 28.

Outcome measures

Death from any cause was recorded until day 60. We recorded the durations of MV and ICU stay after VAP onset. We calculated the number of MV-free days as the number of days during the 28 days after inclusion when the patient was alive and not on MV. Patients were considered to have microbiologically documented recurrent pulmonary infection when at least one bacterial species grew at a significant concentration from samples collected during a second bronchoscopy. Recurrence was considered a relapse if the initial causative bacterial strains (i.e., same genus, species, and serotype when available) grew at a significant concentration from a second distal sample; otherwise, it was considered to be a superinfection.

Statistical analyses

Continuous variables were compared with Student's *t*-test or the Mann–Whitney *U*-test, as appropriate. Categorical variables were compared with chi-square tests. To examine the univariate effects of patients' clinical characteristics

and initial ICU events on the outcome of interest, a logistic regression model was used to test each characteristic. Thereafter, we undertook multiple logistic regressions using backward stepwise variable elimination (with variable exit threshold set at $P > 0.05$). Factors with $P \leq 0.10$ in our univariable analysis were entered into the model and treatment duration was forced into each of the final models as a covariate [23]. All potential explanatory variables included in the multivariable analyses were subjected to a correlation matrix for analysis of colinearity. Variables with association among each other were not included in the multivariable model. Interactions were explored between the substantive variables that remained in the multivariablemodels. Cumulative-event curves were estimated with the Kaplan-Meier method, and the groups compared using the log-rank test. Statistical significance was defined as $p < 0.05$. Analyses were performed using StatView 5.0 (SAS Institute Inc., Cary, N.C.) and SPSS 11.5 (SPSS Inc., Chicago, Ill.) software.

Table 1 Clinical characteristics at ICU admission of patients who developed piperacillin-susceptible or piperacillin-resistant VAP. *ICU* intensive care unit, *SAPS II* Simplified Acute Physiology Score, *SOFA* Sepsis-related Organ Failure Assessment, *ODIN* Organ Dysfunctions and/or INfection, *MV* mechanical ventilation

Characteristic	PSPA ($n = 52$)	PRPA ($n = 63$)	*P*
Age (years, mean ± SD)	63 ± 18	66 ± 13	0.377
Gender (male, *n*)	39 (75)	45 (71)	0.833
Type of admission			
Medical (*n*)	39 (75)	42 (67)	0.622
Elective surgery (*n*)	9 (17)	14 (22)	
Emergency surgery (*n*)	4 (8)	7 (11)	
McCabe and Jackson score ≥2 (*n*)	19 (37)	33 (52)	0.089
SAPS II (mean ± SD)	47 ± 15	46 ± 15	0.746
SOFA score (mean ± SD)	7.1 ± 3.6	7.2 ± 4.6	0.976
ODIN score (mean ± SD)	2.4 ± 1.1	2.3 ± 1.3	0.645
Reasons for MV (*n*)			
Cardiovascular failure	5 (10)	8 (13)	0.394
Acute respiratory failure	27 (52)	28 (44)	
Trauma	4 (8)	1 (2)	
Neurological failure	4 (8)	10 (16)	
Sepsis	7 (13)	7 (11)	
Miscellaneous	5 (10)	9 (14)	

Numbers in parentheses are percentages

Results

Study population

Of the 115 *Pseudomonas aeruginosa* VAP episodes, 63 (55%) were due to piperacillin-resistant (PRPA) and 52 (45%) to piperacillin-susceptible (PSPA) strains, respectively. At ICU admission (Table 1), no statistically significant difference was detected as a function of *Pseudomonas*-resistance status, although PRPA-infected patients tended to have more severe premorbid conditions; however, at VAP onset (Table 2), PRPA patients had significantly higher SAPS II, SOFA, and ODIN scores, and had signs of more severe pulmonary lesions, as indicated by their higher radiological scores. Early onset, polymicrobial VAP rates, and physiological parameters did not differ significantly between the two groups. Finally, the percentages of patients included in the 15-day and 8-day treatment groups were similar.

Antibiotic therapy

Every patient included in the PNEUMA trial received, within the 24 h following bronchoscopy, appropriate antibiotic therapy directed against the microorganism(s) responsible for the pulmonary infection, as determined by their susceptibility patterns. During the first week of treatment, every patient received at least two antibiotics active

Table 2 Clinical characteristics on day 1 (day of bronchoscopy) of patients with piperacillin-susceptible or piperacillin-resistant *Pseudomonas aeruginosa* VAP. *MV* mechanical ventilation, *VAP* ventilator-associated pneumonia, *SAPS II* Simplified Acute Physiology Score, *SOFA* Sepsis-related Organ Failure Assessment, *ODIN* Organ Dysfunctions and/or Infection, *WBC* white blood cells, *MRSA* methicillin-resistant *Staphylococcus aureus*

Characteristic	PSPA ($n = 52$)	PRPA ($n = 63$)	*P*
Days of MV before day 1, median (Q1, Q3)	13 (7, 22)	10 (7, 20)	0.391
Early-onset VAP (MV duration < 6 days; *n*, %)	8 (15)	10 (16)	0.943
SAPS II (mean ± SD, median IQR)	38 ± 7	44 ± 11	0.002
SOFA score (mean ± SD)	5.1 ± 2.0	6.8 ± 4.1	0.014
ODIN score (mean ± SD)	1.4 ± 0.7	2.0 ± 0.9	0.001
Radiologic score (mean ± SD)	5.1 ± 2.5	5.8 ± 2.4	0.129
Temperature (°C, mean ± SD)	38.6 ± 0.9	38.5 ± 1.1	0.531
PaO_2/F_IO_2 (mmHg, mean ± SD)	211 ± 84	257 ± 105	0.825
Leukocytes × 10^3/ml (mean ± SD)	15.0 ± 6.6	17.0 ± 8.0	0.160
Acute respiratory distress syndrome (*n*, %)	9 (17)	17 (27)	0.217
Polymicrobial episode (*n*, %)	18 (35)	25 (40)	0.576
MRSA coinfection (*n*, %)	0	2 (3)	0.191
Shock (*n*, %)	12 (23)	21 (33)	0.222
Positive blood culture (*n*, %)	4 (8)	4 (6)	0.782
15 days of antibiotics (vs 8 days; *n*, %)	28 (54)	33 (52)	0.876

against *Pseudomonas*: 112 received an anti-pseudomonal β-lactam agent in association with an aminoglycoside (94 cases), a fluoroquinolone (49 cases) or colimycin (8 cases), and three received a fluoroquinolone in association with an aminoglycoside and/or colimycin. The β-lactam agent administered to PRPA-infected patients after microbiological culture results was ceftazidime in 28 cases, piperacillin/tazobactam in 18 cases, imipenem in 10 cases, cefipime in 3 cases, and ticarcillin/clavulanate in 2 cases.

Factors associated with death within 28 days of bronchoscopy

By day 28, 10 (19%) PSPA-infected and 23 (37%) PRPA-infected patients had died (OR = 2.42, 95% CI, 1.02–5.70; $P = 0.04$; Table 3). Univariable analysis of factors potentially associated with 28-day mortality identified age, female gender, McCabe and Jackson score, day-1 disease-severity and organ-dysfunction scores, shock on day 1 and piperacillin resistance (Table 4). Independent predictors of 28-day mortality retained by multivariable logistic-regression analysis were: age; female gender; McCabe and Jackson score; and day-1 SOFA score; but not piperacillin resistance (OR = 2.00, 95% CI, 0.72–5.61, $P = 0.19$, when this variable was forced into the final multivariable model).

Other clinical outcomes

As indicated in Table 3, 60-day and in-hospital mortality were significantly higher for PRPA-infected patients. All the other outcomes evaluated—percentages of patients developing VAP recurrence, either relapse or superinfection,

Table 3 Main outcomes and associated factors as a function of piperacillin-susceptible or piperacillin-resistant *Pseudomonas aeruginosa* VAP. *MV* mechanical ventilation, *ICU* intensive care unit

Characteristic	PSPA ($n = 52$)	PRPA ($n = 63$)	P
28-day mortality (n)	10 (19)	23 (37)	0.042
60-day mortality (n)	13 (25)	29 (46)	0.021
In-hospital mortality (n)	14 (27)	30 (48)	0.023
Pulmonary infection recurrence (n)	15 (29)	23 (37)	0.391
Pseudomonas aeruginosa relapse (n)	10 (19)	15 (24)	0.550
Superinfection (n)	7 (14)	11 (18)	0.562
No. of MV-free days, days 1–28 (mean ± SD)	8.7 ± 9.4	5.7 ± 8.9	0.081
MV duration, days 1–28 (mean ± SD)	17.5 ± 9.1	17.8 ± 8.8	0.842
ICU stay after VAP onset (days, mean ± SD)	29.3 ± 17.7	26.4 ± 17.7	0.394
For patients alive on day 28			
No. of MV-free days, days 1–28 (mean ± SD)	10.6 ± 9.5	9.0 ± 9.7	0.454
MV duration, days 1–28 (mean ± SD)	17.5 ± 9.5	19.1 ± 9.7	0.446
ICU stay after VAP onset (days, mean ± SD)	31.8 ± 18.5	32.6 ± 19.1	0.848

Numbers in parentheses are percentages

Table 4 Univariable and multivariable logistic-regression analyses: factors associated with 28-day mortality. *OR* odds ratio, *CI* confidence interval, *MV* mechanical ventilation, *VAP* ventilator-associated pneumonia, *SAPS II* Simplified Acute Physiology Score, *ODIN* Organ Dysfunctions and/or Infection, *SOFA* Sepsis-related Organ Failure Assessment

Factor	Univariable analysis OR (95% CI)	P	Multivariable analysis OR (95% CI)	P
Age	1.07 (1.03–1.12)	< 0.001	1.07 (1.02–1.12)	0.006
Gender (female)	3.45 (1.43–8.33)	0.006	4.00 (1.41–11.11)	0.009
McCabe and Jackson score ≥2	3.47 (1.48–8.13)	0.004	2.73 (1.02–7.33)	0.044
Acute respiratory failure	1.23 (0.55–2.76)	0.622		
MV duration prior to VAP onset	1.00 (0.98–1.03)	0.789		
Day 1 radiological score	1.04 (0.88–1.23)	0.633		
Day 1 SAPS II score	1.06 (1.01–1.10)	0.008		
Day 1 ODIN score	2.00 (1.23–3.26)	0.005		
Day 1 SOFA score	1.14 (1.02–1.27)	0.022	1.17 (1.03–1.32)	0.022
Day 1 temperature	0.69 (0.46–1.03)	0.072		
Day 1 leukocyte count	1.03 (0.98–1.09)	0.263		
Day 1 PaO_2/F_IO_2 ratio	1.00 (0.99–1.01)	0.441		
Shock on day 1	2.40 (1.02–5.69)	0.046		
ARDS on day 1	1.43 (0.56–3.65)	0.449		
Positive blood culture	0.34 (0.04–2.83)	0.315		
Polymicrobial infection	0.65 (0.27–1.53)	0.321		
15 vs 8 days of antibiotics	1.29 (0.57–2.92)	0.541		
Piperacillin resistance	2.42 (1.02–5.70)	0.044	2.00 (0.72–5.61)	0.194 [a]

[a] Piperacillin resistance was forced into the final multivariable model

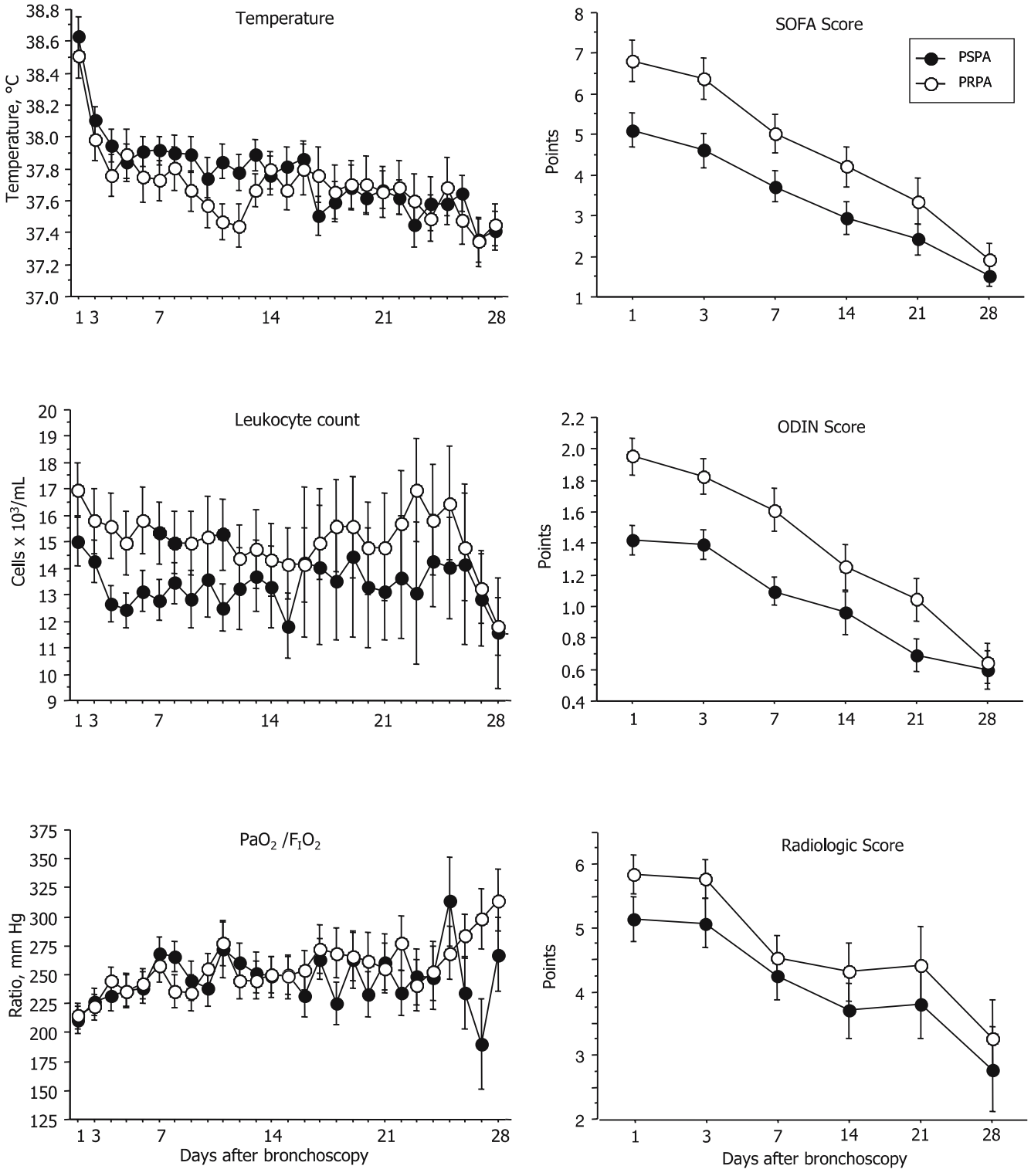

Fig. 1 Physiological and functional score changes from day 1 (day of bronchoscopy) to day 28. *Open circles:* patients with piperacillin-resistant *Pseudomonas aeruginosa* VAP; *closed circles:* patients with piperacillin-susceptible *Pseudomonas aeruginosa* ventilator-associated pneumonia (VAP). *SOFA* Sepsis-related Organ Failure Assessment; *ODIN* Organ Dysfunction and/or INfection

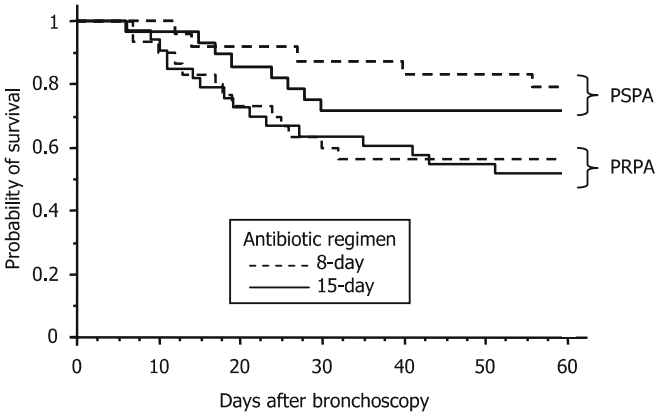

Fig. 2 Kaplan-Meier estimates of the probability of survival as a function of antibiotic regimen: 8 days (*dashed line*) vs 15 days (*solid line*), for patients with piperacillin-resistant or piperacillin-susceptible *Pseudomonas aeruginosa* VAP

or durations of MV, MV-free days, and ICU stay after VAP onset—did not differ significantly between groups.

Figure 1 shows the evolution of physiological and functional scores from day 1 to day 28. Temperature, leukocyte count, PaO_2/F_IO_2, and radiological score did not differ significantly between groups, whereas leukocyte count and radiological score tended to be higher for PRPA VAP. Organ-dysfunction scores were higher for PRPA VAP patients, but improved in parallel with those of PSPA episodes, with the significant differences fading at later time points.

Finally, as shown in Fig. 2, Kaplan-Meier estimates of the cumulative probabilities of survival were not different for the 8-day and 15-day treatment groups, for PSPA- and PRPA-infected patients (log-rank = 0.49 and 0.76, respectively).

Discussion

The aim of this study was to evaluate the impact of piperacillin resistance on the outcome of *Pseudomonas* VAP on a large cohort of patients who had received appropriate empiric antibiotics. Our main findings were that, despite similar characteristics at ICU admission, patients infected with PRPA strains were more acutely ill at VAP onset and their mortality rate was higher. Factors associated with death 28 days after VAP onset retained by multivariable analysis were age, female gender, severity of underlying comorbidities, and SOFA score, but not piperacillin resistance. Rates of VAP recurrence, either superinfection or relapse, and durations of MV and ICU stay were comparable for the two patient groups.

To date, no published study has specifically addressed the impact of antibiotic resistance on the outcomes of Gram-negative bacilli VAP. In a retrospective cohort study evaluating epidemiological characteristics of 34 PRPA and 101 PSPA VAP episodes, our analysis demonstrated that factors associated with PRPA VAP were underlying fatal medical condition, prior fluoroquinolone use, and less severe disease at ICU admission [14]. In that study, we did not find higher recurrence or death rates for PRPA infections, but we did not control for the appropriateness of empiric antibiotics and patients with PRPA VAP had been less severely ill at ICU admission [14].

Other studies comparing outcomes of susceptible and resistant Gram-negative bacilli infections are scarce. In a case-control study on Gram-negative infections, significant predictors of a fatal outcome were age, APACHE II score, and site of infection, but not antibiotic resistance (23.6 vs 29.2%; $P = 0.35$) [13]. Furthermore, analysis of all *Pseudomonas aeruginosa* infections in that population demonstrated no significant difference in mortality between resistant and sensitive strains (18.9 vs 20.0%, $P = 0.85$) [13]. In a study evaluating health and economic outcomes of resistant *Pseudomonas* infections, Carmeli et al. [5] found that only the emergence of these resistant strains during the hospital stay was associated with prolonged length of stay and higher in-hospital mortality, while patients with resistant strains at hospital admission did not have a poorer prognosis. In a more recent study by the same group, patients infected with multiresistant *Pseudomonas* strains had higher mortality rates and longer duration of hospital stays [9], but the control patients in that study did not have *Pseudomonas* infections. Data from the few studies of Gram-negative bacteremia have also provided similar results. In a case-control study on neutropenic cancer patients, Spanik et al. [24] failed to demonstrate that attributable mortality was higher for antibiotic-resistant Gram-negative bacilli. Similarly, in a retrospective study on antibiotic-susceptible and antibiotic-resistant nosocomial Gram-negative bacillus bacteremia, Blot et al. [7] did not find higher mortality for patients infected with resistant strains. In that study, in-hospital mortality was 57% for antibiotic-resistant and 64% for antibiotic-susceptible *Pseudomonas* strains. More recently, analyzing data of 190 episodes of *Pseudomonas* bacteremia, Kang et al. [11] reported that 30-day mortality was comparable for susceptible and resistant strains (34 vs 44%, $P = 0.16$, respectively).

The higher crude mortality frequently reported for infections caused by antibiotic-resistant organisms could reflect characteristics of the bacterium itself (enhanced virulence for resistant strains), host factors (patient characteristics may differ between groups), or to the antimicrobial treatment administered to patients infected with antibiotic-resistant bacteria [6]. Indeed, inappropriate initial empiric antimicrobial treatment was among the independent factors associated with death according to multivariable analyses in two recent studies on *Pseudomonas* bacteremia [10, 12], and this factor might also confound the results of former studies. Pertinently, Kang et al. [10] observed a trend

towards higher mortality rates as the interval before appropriate treatment administration increased; thus, our trial population offered a unique opportunity to adequately control for this major confounding factor when evaluating the attributable mortality of resistant infections.

To date, no data on increased virulence of resistant *Pseudomonas* strains have been published. Virulence factors of this bacterium include: a type-III secretion system that confers the ability to inject toxins into host cells; quorum-sensing systems; a complex regulatory circuit involving cell-to-cell signaling which enables *P. aeruginosa* to regulate genes in a density-dependent manner through the production of autoinducers and secretion of various toxins, such as elastase, leukocidins, exotoxin A, and the diffusible pyocyanin pigment [25]. Additionally, these virulence factors sometimes trigger an exaggerated immune response, which participates in the bacterium-induced injury targeted at the lungs and other organs [25].

Host-related factors that might adversely affect outcome of infections due to resistant bacteria include more comorbidities, longer hospital stays, or patients' immunocompromised status at the time of infection onset [11, 14, 26, 27, 28, 29, 30]. In this study, we found no significant differences between ICU admission characteristics of the patients who would develop *Pseudomonas* VAP, except a non-significant trend towards a higher rate of underlying rapidly or ultimately fatal conditions in the PRPA group; however, the more severely ill status (higher SAPS II, SOFA, and radiological scores) at VAP onset and the higher crude mortality rate of our PRPA group are intriguing. Whether these higher morbidity scores and crude mortality rates for PRPA strains reflect more aggressive bacterial virulence factors, or that these bacterial strains found their niche in more acutely ill patients, remains to be determined.

Apart from ICU or in-hospital mortality, other significant outcomes also need to be assessed when evaluating the impact of antimicrobial resistance. The economic burden of such infections is heavy, due to prolonged hospitalization leading to higher care costs [6, 31]. Carmeli et al. [5] reported that emergence of resistance in *Pseudomonas* strains during the hospital stay was associated with a longer stay and an average increased cost of almost US $12,000. In the present study, we did not observe longer hospital stays or durations of MV, either for the whole cohort or when analyses were restricted to survivors being discharged. Similarly, rates of VAP recurrence, either superinfection or relapse, were comparable for our PRPA- and PSPA-infected patients.

Several limitations of the present study should be acknowledged. Firstly, we did not record *Pseudomonas* susceptibility to other antimicrobial agents, such as quinolones, aminoglycosides, carbapenems or third-generation antipseudomonal cephalosporins. Notably, resistance to at least one of these drugs was observed in 3–22% of PSPA strains in an earlier study [14]. The impact of antibiotic resistance on *Pseudomonas* VAP outcomes might be different for those antibiotics. Indeed, Kang et al. [11] recently observed that bloodstream infections due to imipenem-resistant *Pseudomonas* strains had the highest mortality rate, when compared with bacteremia due to piperacillin-, ceftazidime-, or ciprofloxacin-resistant strains. Secondly, since most patients with early onset VAP, immunocompromised status or a high probability of death (defined as a SAPS II > 65) were excluded from the PNEUMA trial, our conclusions may not be applicable to all patients developing *Pseudomonas* VAP. Thirdly, antibiotic-treatment duration was not the same for every patient (some patients were treated for 8 or 15 days in the PNEUMA trial); however, pertinently, treatment duration was not associated with 28-day mortality for patients with PSPA or PRPA VAP in this study. Finally, we cannot exclude that piperacillin-resistance might have been retained in the multivariable model predicting 28-day mortality if more patients had been included and thus the power of the study had been increased; nonetheless, our study is by far the largest to date to evaluate the impact of piperacillin resistance on *Pseudomonas* VAP.

Conclusion

In conclusion, we observed that for patients with *Pseudomonas* VAP benefiting from appropriate empiric antibiotics, piperacillin-resistance was associated with more severe disease at VAP onset and higher 28-day crude mortality; however, after controlling for confounders, piperacillin resistance was no longer significantly associated with 28-day mortality. The VAP recurrence rates and durations of ICU stay and MV did not differ for susceptible and resistant strains. Whether this more severely ill status at VAP onset is due to bacterium- or host-related factors remains to be determined. Finally, early identification of patients with risk factors favoring antibiotic-resistant infections, such as more severe comorbidities, multiple hospitalizations, or prior antibiotic use and good knowledge of the bacterial ecology of the department in which the bacterium is isolated, are of utmost importance when initiating an empiric antibiotic regimen covering these highly resistant bacterial strains. This empiric antibiotic regimen may be de-escalated when results of microbiological sample cultures become available 48–72 h later.

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