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ARTICLE

Impact of multidrug resistance on *Pseudomonas aeruginosa* ventilator-associated pneumonia outcome: predictors of early and crude mortality

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Abstract The prevalence of multidrug-resistant (MDR) *Pseudomonas aeruginosa* has increased over the past decade and a significant rise in these isolates in ventilator-associated pneumonia (VAP) has been observed. However, the impact of MDR on VAP outcome has not been analysed in depth. We investigated the risk factors for early and crude mortality in a retrospective study of microbiologically and clinically documented VAP. Ninety-one VAP episodes in 83 patients were included, 31 caused by susceptible *P. aeruginosa* and 60 by MDR strains, of which 42 (70 %) were extensively drug-resistant (XDR) *P. aeruginosa*. Thirteen episodes concomitantly presented *P. aeruginosa* bacteraemia, in seven of which the origin was the respiratory tract. Whereas susceptible *P. aeruginosa* episodes were more likely than MDR episodes to receive adequate empirical (68 % vs. 30 %; $p<0.001$) and definitive antimicrobial therapy (96 % vs. 50 %; $p<0.001$), susceptible *P. aeruginosa* VAP presented a trend towards early mortality (29 % vs. 15 %; $p=0.06$). A logistic regression model with early mortality as the dependent variable identified multiorgan dysfunction syndrome (MODS) [odds ratio (OR) 10.4; 95 % confidence interval (CI) 1.7–63.5; $p=0.01$] and inadequate antibiotic therapy (OR 4.27; 95 % CI 0.98–18.4; $p=0.052$) as independent risk factors for early mortality. A similar analysis identified MODS (OR 4.31; 95 % CI 1.14–16.2; $p=0.03$) as the only independent predictor of crude mortality. The severity of acute illness clinical presentation was the main predictor of mortality. Despite adequate antibiotic therapy, susceptible *P. aeruginosa* seems to cause major early mortality. Although adequate therapy is essential to treat VAP, the severity of acute illness is a more important factor than drug resistance.

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Introduction

Intubation with mechanical ventilation increases the risk of lower respiratory tract infections, and is associated with crude mortality rates of 30–70 % [1]. *Pseudomonas aeruginosa* is one of the main species implicated in the pathogenesis of ventilator-associated pneumonia (VAP), and the emergence of *P. aeruginosa* strains which exhibit co-resistance to almost all antibiotic classes is growing. The presence of multidrug-resistant (MDR) strains diminishes the treatment options and increases the risk of inadequate empirical therapy.

Guidelines for the management [1] of VAP emphasised the importance of early, adequate, empirical antibiotic therapy based on patient risk factors for infection due to MDR pathogens. Potential disadvantages include excessive use of multiple empirical antibiotic therapy, which may increase antibiotic resistance, toxicity and failure to properly de-escalate when culture data become unavailable.

Multiple antibiotic therapy is commonly administered in cases of suspected or proven *P. aeruginosa* infections, especially hospital-acquired pneumonia (HAP). However, this strategy remains controversial, since the administration of one effective antibiotic therapy achieves similar mortality rates [2, 3]. In fact, it is well known that mortality in these patients is influenced at least as much by their underlying condition as by the organism itself [4, 5]. Several studies have shown an increase in mortality with a delay in adequate antibiotics [6–8], but others have failed to find a

significant difference in mortality when patients received inadequate therapy [9–11]. Furthermore, a recent prospective study [12] suggested that the deleterious effect of the antimicrobial resistance in *P. aeruginosa* may be not as great during the first days of the bacteraemia. It is very important to clarify prognostic factors related to antimicrobial resistance because they may help guide the recommended empirical antibiotic policy in the setting of MDR *P. aeruginosa*. If a delay in adequate antibiotic therapy does not have decisive consequences in most of these patients, then the indiscriminate use of empirical colistin could be avoided, along with the consequent risk of increasing resistance to this drug.

The prevalence of MDR *P. aeruginosa* has increased over the past decade. Nonetheless, and despite a significant rise in these MDR *P. aeruginosa* isolates in VAP infections, few studies of this issue have been published. While the risk factors for MDR organisms [13, 14] or antibiotic treatment of VAP [15] have aroused the interest of clinicians, to our knowledge, few studies have quantified the effect of MDR *P. aeruginosa*, and the possible effect of delaying adequate antimicrobial treatment, on mortality.

A progressive increase in the number of MDR *P. aeruginosa* isolates has been observed in our hospital in an epidemiological setting of a sustained endemic outbreak [16]. We designed a retrospective study among patients with ventilator-associated lower respiratory tract infections, with the main objective of investigating the risk factors for early and crude mortality. We also analysed the impact of multidrug resistance on VAP outcome and compared the epidemiological characteristics of VAP caused by susceptible *P. aeruginosa* and those caused by MDR *P. aeruginosa*.

Materials and methods

Study design

A retrospective study was performed at Hospital de Bellvitge, a tertiary-care university hospital between January 2006 and December 2011. All patients selected met the following criteria: positive results of quantitative culture of specimens from bronchoalveolar lavage (BAL) and microbiologic confirmation of quantitative monomicrobial cultures with a *P. aeruginosa* bacterial count of 1×10^5 colony-forming units (CFU)/mL in BAL fluid specimen [1]. HAP was defined according to the Clinical Pulmonary Infection Score (CPIS) [17] and a score ≥6, indicating the presence of respiratory tract infection, was the condition for inclusion.

The following data were recorded: age and sex; comorbidities (diabetes mellitus, chronic obstructive pulmonary disease, heart failure, chronic renal failure, hepatic dysfunction, haematologic and solid malignancy, neurologic disease and immune deficiency disease) and severity of underlying diseases calculated using the Charlson comorbidity index [18]; the presence of neutropaenia (absolute granulocyte count of <500/ml) and the use of immunosuppressive therapy (chemotherapy, radiotherapy and/or immunosuppressive drugs) during the 30 days prior to VAP presentation; the presence of septic shock, multiorgan dysfunction syndrome (MODS) at VAP presentation [19]; and antimicrobial treatment received. The severity of illness was estimated by the Simplified Acute Physiology Score (SAPS II) at intensive care unit (ICU) admission and at sample collection [20]. The length of hospitalisation prior to the collection of *P. aeruginosa* culture sample and mechanical ventilation at the time of the culture sample were also recorded.

Definitions

HAP is defined as the development of parenchymal lung infection after at least 48 h of hospitalisation. The infection develops after the patient has undergone intubation and received mechanical ventilation for at least 48 h; the condition is termed VAP. Ventilator-associated tracheobronchitis (VAT) is a clinical syndrome similar to VAP, but with no radiographic infiltrate present [21]. VAP and VAT were established according to clinical diagnosis and the collection of a deep respiratory tract sample for culture in order to establish an aetiologic pathogen. The diagnosis of HAP is made in the case of a CPIS≥6 indicating the presence of respiratory tract infection based on criteria of fever, elevated white blood cell count, purulent appearance of respiratory secretions, radiographic findings and growth of pathogens on a lower respiratory tract culture [17]. Bacteraemia of origin other than the respiratory tract was considered when it occurred more than 72 h after VAP diagnosis.

Delay in adequate antimicrobial therapy was defined as the time from VAP until administration of the empirical or definitive adequate therapy. Empirical therapy was considered when an antimicrobial regimen was administered within 24 h of VAP diagnosis and before susceptibility was known; therapy administered after this time was considered to be definitive. Antimicrobial therapy was considered adequate when the *P. aeruginosa* isolate was susceptible to the antimicrobial prescribed. Combination therapy was defined as adequate if the strain was susceptible to both antipseudomonal drugs given simultaneously. Aminoglycoside monotherapy and inhaled colistin alone were considered inadequate treatment for *P. aeruginosa* VAP. In addition, piperacillin–tazobactam treatment was considered inadequate when the strain showed a minimum inhibitory concentration (MIC) in the range 32–64 mg/L in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria [22] and the new breakpoints established by the Clinical and Laboratory Standards Institute (CLSI) [23].

Clinical outcome was classified as follows: (i) clinical cure: resolution of presenting symptoms and signs of infection by the end of antibiotic treatment; (ii) clinical improvement: partial resolution of presenting symptoms and signs of infection; (iii) clinical failure: persistence or worsening of presenting symptoms and signs of infection during the treatment; and (iv) recurrence of infection: occurrence of a new episode of infection at least 72 h after the clinical resolution of a preceding episode.

Microbiological outcome was classified as: (i) eradication: no growth of the pathogen in the final culture of specimens during the entire hospitalisation; (ii) persistence of pathogen: persistent growth of the responsible pathogen regardless of the clinical outcome of the infection; and (ii) recurrence of the pathogen: regrowth of the same pathogen regardless of the clinical outcome of the infection.

Early mortality was defined as death within the 7 days of VAP onset; crude mortality was considered as death during the hospitalisation.

Microbiological data

Microbiological data included all positive *P. aeruginosa* BAL and blood samples. Microbiological data on other organisms causing bloodstream infections at a distal site were also documented. *P. aeruginosa* strains were identified and tested for antimicrobial susceptibility by a MicroScan automated microdilution system using CN1S and CO1S panels (Dade International, West Sacramento, CA, USA). CLSI criteria [23] were used to define susceptibility or resistance to these antimicrobial agents. The antibiotics tested were: piperacillin–tazobactam, ceftazidime, cefepime, aztreonam, imipenem, meropenem, ciprofloxacin, ofloxacin, gentamicin, tobramycin, amikacin, colistin and fosfomycin. Intermediate results were considered to be resistant.

In accordance with recent standard definitions [24], MDR *P. aeruginosa* was defined as a strain non-susceptible to≥1 agent in≥3 antipseudomonal antimicrobial categories. Extensively drug-resistant (XDR) *P. aeruginosa* was defined as non-susceptible to≥1 agent in all but≤2 antipseudomonal antimicrobial categories; thus, an XDR *P. aeruginosa* isolate was also included as MDR *P. aeruginosa*. All other *P. aeruginosa* isolates, including those non-susceptible to≥1 agent in <3 antimicrobial categories, were considered to be non-MDR strains. MDR and XDR *P. aeruginosa* were defined considering the previously indicated agents.

Statistical analysis

Student's *t*-test was used to compare continuous variables. The Chi-square test or Fisher's exact test was used to compare categorical variables. Logistic regression analysis was used to identify the independent risk factors for VAP *P. aeruginosa* outcome. Variables with a $p<0.05$ in the univariate analysis and those found in previous studies were included in the multivariate model. Data were analysed using the statistical software SPSS, version 15.0 (SPSS, Chicago, IL, USA).

Results

Epidemiological and clinical features

We identified 120 episodes of ventilator-associated lower respiratory tract infections for a microbiologically documented *P. aeruginosa* infection during the study period. Of these episodes, 29 were excluded from further analysis because they did not have a clinical lower respiratory tract infection according to the CPIS. Ninety-one episodes in 83 patients with a mean of CPIS of 8.96 (range 6 to 14) were analysed. Six patients experienced a second VAP episode and one a third episode. There were four recurrences of the initial VAP, all caused by XDR *P. aeruginosa* strains; in the remaining four episodes, the initial and subsequent *P. aeruginosa* strains isolated from the respiratory tract from the same patients showed different susceptibility profiles; the intervals between the first and second episodes were 21, 18, 29 and 58 days, respectively. Three patients were classified as VAT; here, we use the terms VAP and ventilator-associated respiratory tract infection interchangeably.

Of the 83 patients, 65 (78 %) were male and the mean age was 69.39±14.15 years. The mean length of ICU admission to VAP was 24.93±22.0 days and the mean time from mechanical ventilation to VAP was 19.06±18.1 days.

Among the 91 VAP episodes, 60 were caused by MDR *P. aeruginosa*, of which 42 (70 %) were XDR strains. Thirteen VAP episodes concomitantly presented *P. aeruginosa* bacteraemia; in seven, the source was the respiratory tract [7] and the remaining six were primary bacteraemias (catheter vascular and unknown origin). Five other bloodstream infections were detected during the VAP clinical evolution: two *Klebsiella pneumoniae* episodes, one *Escherichia coli*, one *Enterococcus faecalis* and one *E. faecium*.

Among the 60 MDR episodes, 11 received intravenous (i.v.) colistin. In all but one, the isolates of MDR *P. aeruginosa* from respiratory specimens were due to XDR strains. Four of the 11 patients survived and in two, the dosage of colistin was adequate; the remaining seven patients died and only two patients received adequate doses of i.v. colistin. None of these deaths occurred within 7 days of VAP onset. In addition, inhaled colistin was administered in 48 (80 %) MDR episodes.

Thirty (50 %) of the MDR *P. aeruginosa* episodes received inadequate definitive therapy, 24 (80 %) of which were caused

by XDR strains. Ten XDR episodes received piperacillin–tazobactam, according to the prior CLSI susceptibility range; nine received antimicrobials (three carbapenems, four anti-pseudomonal cephalosporins, two fluoroquinolones) with intermediate range of activity; and the remaining five episodes received inhaled colistin alone.

The epidemiological and clinical characteristics of the VAP episodes according to the susceptibility of the *P. aeruginosa* strain are shown in Table 1. Among the 91 VAP episodes, the median days to ICU admission from VAP onset was significantly higher in patients with MDR strains, as was the interval of days between the start of mechanical ventilation and VAP diagnosis. Patients in the non-MDR strain VAP group were more likely than those in the MDR group to receive adequate empirical (68 % vs. 30 %; $p<0.001$) and definitive antimicrobial therapy (96 % vs. 50 %; $p<0.001$). We also observed a trend towards early mortality in susceptible *P. aeruginosa* VAP (29 % vs. 15 %; $p=0.06$). The microbiological outcome was better in non-MDR episodes but did not reach statistical significance.

Outcome

Early mortality

Eighteen patients died during the 7 days after VAP onset. The unadjusted analyses for the association of the characteristics with mortality are shown in Table 2. A logistic regression model with early mortality as a dependent variable, adjusted for age, sex, severity of illness, bacteremic VAP, shock, MODS and adequate empirical antibiotic treatment, identified MODS [odds ratio (OR) 10.4; 95 % confidence interval (CI) 1.7–63.5; $p=0.011$] and adequate antibiotic treatment (OR 4.27; 95 % CI 0.98–18.4; $p=0.052$) as independent risk factors for early mortality.

Crude mortality

Forty-seven patients died during hospitalisation [17 (55 %) susceptible group vs. 30 (50 %) MDR group; $p=0.33$] (Table 3). Severity of acute illness and clinical presentation were the variables associated with crude mortality. We also observed a trend towards an association between crude mortality and severity of illness at ICU admission ($p=0.06$). A logistic regression model with crude mortality as the dependent variable, adjusted for age, sex, severity of illness, shock and MODS, identified MODS (OR 4.31; 95 % CI 1.14–16.2; $p=0.03$) as the only independent risk factor for crude mortality. Adjusted analysis with adequate empirical or definitive antimicrobial therapy did not modify the model.

Discussion

Multiple reports over the last decade have alerted on the increase of MDR *P. aeruginosa* strains in hospitals worldwide, mainly in ICUs. In this study, MDR *P. aeruginosa* was frequently identified, with an overall prevalence in respiratory tract infections of 66 %. This high prevalence may be attributed to the epidemiological problem observed in our hospital during the study period [16].

In this series, VAP caused by MDR *P. aeruginosa* had longer duration of mechanical ventilation, longer ICU stay, higher rate of underlying disease and a longer delay in adequate antimicrobial therapy administration, but it was not followed by significant differences in clinical response and crude mortality. In fact, the impact of drug resistance on the outcome of VAP remains controversial; some [6, 25], but not all, studies [26 27] find a relationship between poorer clinical outcome and the presence of resistant organisms.

Conversely, a trend towards early mortality linked to susceptible *P. aeruginosa* respiratory tract infections (29 % vs. 15 %; $p=0.06$) was observed. In fact, empirical antimicrobial therapy and treatment in the first 24 h were seen to be adequate in VAP episodes with early mortality (67 % vs. 36 %), suggesting that patients who have comorbidities and are severely ill at the time of VAP diagnosis are at a high risk of treatment failure, despite receiving adequate antibiotic therapy [28]. A plausible explanation for the association between susceptible strains and worse early mortality is that, hypothetically, they are more virulent than their drug-resistant counterparts [29]. Although we did not observe significant differences in clinical presentation between the two phenotype groups, we cannot rule out the possibility that unmeasured factors predispose to a major deleterious effect in susceptible strains.

The crude mortality rate for HAP may be as high as 70 %, but many of these critically ill patients with HAP die of their underlying disease rather than from pneumonia [4]. In our study, MODS clinical presentation was the only predictor for crude mortality. In fact, previous clinical studies have identified severity of illness at the moment of diagnosis or the development of shock or/and MODS during clinical presentation as key prognostic factors [30, 31]. Thus, our results do not support the idea that VAP caused by MDR *P. aeruginosa* is associated with worse clinical outcome due to inadequate antimicrobial therapy. While these findings challenge those of certain studies [6–8], surprisingly, other reports [9–11] also failed to find any difference in mortality when evaluating this variable in a group of VAP due to *P. aeruginosa* strains susceptible only to colistin.

Regarding definitive treatment, several aspects of our series should be noted. A high number of our patients, indeed, received inadequate definitive treatment, because

Table 1 Baseline characteristics of patients with *Pseudomonas aeruginosa* ventilator-associated pneumonia (VAP)

Characteristic	Non-MDR PA, n=31 (34 %)	MDR-PA, n=60 (66 %)	p-value
Age (mean±SD)	55.84±15.56	62.9±12.3	0.02
Male sex	25 (81)	44 (73)	0.44
ICU admission to VAP (days, median, IQR)	11 (7–22)	26 (13–45)	0.01
MV to VAP (days, median, IQR)	10 (5.–17)	17 (9–43)	0.03
VAP *P. aeruginosa* bacteraemia	2 (6.5)	5 (8)	1.0
Non-VAP *P. aeruginosa* bacteraemia	3 (10)	3 (5.5)	0.41
Other organisms bacteraemia	1 (3)	4 (7)	0.65
Charlson index (median, IQR)	1 (1–4)	2 (1–3.75)	0.07
Underlying condition			
Any	18 (58)	51 (85)	0.004
Solid malignancy	4 (13)	17 (28)	0.12
Haematologic malignancy	2 (6.5)	4 (7)	1.0
Diabetes	4 (13)	20 (33)	0.04
Cardiopathy	6 (19)	14 (23)	0.66
COPD	8 (25)	18 (30)	0.67
Chronic renal failure	2 (6.5)	7 (12)	0.71
Neurologic disease	3 (10)	10 (17)	0.53
Cirrhosis	1 (3)	6 (10)	0.41
Neutropaenia	1 (3)	0	–
Immunosuppressive therapy	4 (13)	25 (42)	0.008
SAPS score on admission (mean±SD)	40.23±13.2	39.05±13.03	0.68
Prior aerosolised colistin	1 (3)	21 (35)	0.001
Prior parenteral colistin	0	3 (5)	–
Clinical presentation			
Shock	17 (55)	29 (48)	0.27
MODS	7 (23)	18 (30)	0.45
SAPS score at diagnosis (mean±SD)	57.19±9.03	53.83±14.1	0.23
Antimicrobial empiric therapy	31 (100)	57 (95)	0.20
Adequate empiric therapy	21 (68)	17 (30)	<0.001
Adequate combined therapy	10 (33)	4 (7)	0.004
Antimicrobial definitive therapy	28 (90)	60 (100)	0.01
Adequate definitive therapy	27 (96)	30 (50)	<0.001
Delay in adequate treatment (mean±SD)	1.28±0.45	1.69±0.46	<0.001
Clinical outcome			
Clinical cure	12 (39)	27 (45)	0.28
Clinical improvement	7 (23)	6 (10)	0.06
Clinical failure	12 (39)	23 (38)	0.48
Recurrence	0	4 (7)	–
Microbiological outcome			
Eradication	9 (38)	11 (23)	0.17
Persistence	14 (58)	36 (75)	0.24
Recurrence	0	1 (2)	–
Outcome			
Early mortality	9 (29)	9 (15)	0.06
Crude mortality	17 (55)	30 (50)	0.33

Adequate empiric and/or definitive treatment excluded 24 episodes that did not receive empiric nor definitive treatment

Microbiological outcome included 23 episodes of non-MDR VAP and 48 episodes of MDR VAP

PA Pseudomonas aeruginosa; *SD* standard deviation; *IQR* interquartile range; *MV* mechanical ventilation; *COPD* chronic obstructive pulmonary disease; *SAPS* Simplified Acute Physiology Score; *MODS* multiorgan dysfunction syndrome

around 50 % of MDR episodes were treated with inhaled colistin and piperacillin–tazobactam, which are currently considered to be inadequate, but were within the susceptible range according to earlier CLSI criteria. Similarly, although

Table 2 Risk factors for early mortality in *P. aeruginosa* VAP: univariate analysis

Characteristic	Survived, *n*=73 (%)	Died, *n*=18 (%)	*p*-value
Age (mean±SD)	60.7±13.3	59.6±16.2	0.77
Male sex	54 (74)	15 (83)	0.54
VAP *P. aeruginosa* bacteraemia	3 (4)	4 (22)	0.026
Non-VAP *P. aeruginosa* bacteraemia	5 (7)	1 (7)	1.0
Other organisms bacteraemia	2 (3)	3 (17)	0.051
MDR *P. aeruginosa*	51 (70)	9 (50)	0.11
Charlson index (mean±SD)	2.2±1.91	2.6±2.27	0.45
Underlying condition	54 (74)	15 (83)	0.40
SAPS score on admission (mean±SD)	37.4±12.1	47.61±13.8	0.003
Clinical presentation			
Shock	30 (41)	16 (89)	<0.001
MODS	12 (16)	13 (72)	<0.001
SAPS score at diagnosis (mean±SD)	52.3±11.8	65.5±.10.3	<0.001
Adequate empiric therapy	26 (36)	12 (67)	0.017
Adequate combined therapy	9 (13)	5 (28)	0.12
Adequate definitive therapy	46 (63)	11 (73)	0.44
Adequate therapy in first 24 h	29 (40)	12 (67)	0.040

the efficacy of colistin has been reported in several series of pneumonia [15], intravenous colistin was administered in only 11 (18 %) VAP episodes. In addition, according to pharmacokinetics/pharmacodynamics studies, the dosage regimens were suboptimal in all but four episodes; moreover, aerosolised colistin was added as adjunctive therapy to other antimicrobials for the treatment of VAP in 80 % of the MDR episodes. The effectiveness of inhaled colistin as monotherapy in 11 of the 21 XDR episodes who survived may be indicative of the clinical benefit of this mode of administration.

Despite the high prevalence of MDR and XDR strains in our hospital, these data merely reflect the fact that colistin was not considered as the first-line therapy, and that a delayed onset of colistin treatment did not entail worse prognosis. These findings could be useful to strengthen the design of empirical antibiotic strategies, reducing colistin consumption and, therefore, reducing the risk of developing resistance. It seems advisable to reserve colistin for use as definitive therapy in critical patients with VAP due to MDR and XDR *P. aeruginosa* isolates.

Table 3 Risk factors for crude mortality in *P. aeruginosa* VAP: univariate analysis

Characteristic	Survived, *n*=44 (%)	Died, *n*=47 (%)	*p*-value
Age (mean±SD)	60.7±13.7	60.36±14.0	0.09
Male sex	30 (68)	39 (83)	0.44
VAP *P. aeruginosa* bacteraemia	2 (4.5)	5 (11)	0.43
Non-VAP *P. aeruginosa* bacteraemia	2 (4.5)	4 (9)	0.67
Other organisms bacteraemia	0	5 (11)	–
MDR *P. aeruginosa*	30 (68)	30 (62.5)	0.66
Charlson index (mean±SD)	2.0±1.89	2.57±2.05	0.16
Underlying condition	31 (70.5)	39 (81)	0.24
SAPS score on admission (mean±SD)	36.82±13.1	41.91±12.60	0.06
Clinical presentation			
Shock	16 (36)	30 (64)	0.009
MODS	5 (11)	20 (43)	0.001
SAPS score at diagnosis (mean±SD)	52.30±12.3	57.49±12.6	0.050
Adequate empiric therapy	18 (41)	20 (43)	0.87
Adequate combined therapy	5 (12)	9 (20)	0.28
Adequate definitive therapy	28 (64)	29 (66)	0.82
Adequate therapy in first 24 h	20 (45.5)	21 (44)	0.86

The present study has the inherent limitations of a retrospective analysis and the sample size is rather small for some comparisons. However, to evaluate the predictors for mortality, we adjusted for confounding variables such as severity of illness at the moment of diagnosis, severity of clinical presentation or the presence of bacteraemia, factors which were associated with fatality in previous studies. SAPS II provides outcome prediction scores that share many variables in their calculation, and the use of this score and the severity of clinical presentation (shock and MODS) in the same model may cause collinearity problems in the interpretation of the results. Due to this potential collinearity problem, and after repeating the analysis with different combinations, only shock and MODS are included in the final analysis. Finally, the inferences that can be made from our data may be limited, since previous data indicate clonal involvement in the XDR phenotype [16]; moreover, a recent study [12] showed that the major XDR clone involved in our hospital was widely disseminated in Spanish hospitals and, likely, other countries. Thus, we believe that these results are applicable to other settings.

In conclusion, this is one of the largest series of monomicrobial *P. aeruginosa* VAP reported to date, with a high prevalence of MDR strains. We found that multidrug resistance does not adversely affect the outcome for patients with VAP. While the adequacy of empirical antimicrobial therapy is, of course, very important in the early outcome of patients with VAP, episodes caused by susceptible *P. aeruginosa* strains seem to have major early mortality, despite more frequently receiving adequate empirical therapy. This information on the implications of resistance for patient outcome suggests that it may be wiser to focus on improving the haemodynamic support sepsis, and may also guide antibiotic policy by allowing a more judicious use of the few antimicrobial options available. Finally, although adequate therapy is essential to treat VAP infection, it seems that the severity of acute illness is more important than resistance.

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Conflict of interest The authors declare that they have no conflict of interest.

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