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ORIGINAL ARTICLE

# The clinical significance of pneumonia in patients with respiratory specimens harbouring multidrug-resistant *Pseudomonas aeruginosa*: a 5-year retrospective study following 5667 patients in four general ICUs

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**Abstract** *Pseudomonas aeruginosa* is the leading cause of pneumonia in intensive care units (ICUs), with multidrug-resistant (MDR) strains posing a serious threat. The aim of this study was to assess the clinical relevance of MDR *Pseudomonas* isolates in respiratory clinical specimens. A 5-year retrospective observational study in four medical-surgical ICUs from a referral hospital was carried out. Of 5667 adults admitted to the ICU, 69 had MDR-PA in respiratory samples: 31 were identified as having pneumonia (HAP/VAP): 21 ventilator-associated pneumonia (VAP) and ten hospital-acquired pneumonia (HAP). Twenty-one (67.7%) adults with MDR-PA HAP/VAP died after a median of 4 days (18 of the 21 deaths within 8 days), compared with one (2.6%) without pneumonia at day 8. In a Cox proportional regression model, MDR-PA pneumonia was an independent variable [adjusted hazard ratio (aHR) 5.92] associated with 30-day ICU mortality. Most strains (85.1%) were susceptible to amikacin and colistin. Resistance to beta-lactams (third-generation cephalosporins and piperacillin–tazobactam) ranged from 44.1% to 45.3%. Meropenem showed poor overall activity ($MIC_{[50/90]}$ 16/32 mg/dL), with 47.0% having a minimum inhibitory concentration (MIC) breakpoint >8 mg/L. Twenty-four (77.4%) HAP/VAP episodes received inappropriate empirical therapy. Although empirical combination therapy was associated with less inappropriate therapy than monotherapy (16.7% vs. 88.3%, $p < 0.01$), there was no difference in survival (30% vs. 33.3%, $p = 0.8$). Pneumonia was identified in one-third of adult ICU patients harbouring MDR-PA in respiratory clinical specimens. These patients have a 6-fold risk of (early) death compared to ventilator-associated tracheobronchitis (VAT) and respiratory colonisation. New antibiotics and adjuvant therapies are urgently needed to prevent and treat MDR-PA HAP/VAP.

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## Background

The spread of *Pseudomonas aeruginosa* (PA) multidrug-resistant (MDR) strains over the last decade is a matter of profound concern in the critically ill setting [1, 2] and poses a serious threat. We already know that ventilator-associated pneumonia (VAP) is associated with increased days on mechanical ventilation (MV) [3], and that PA pneumonia is associated with poorer outcomes [4–7]. When compared to susceptible strains, resistant PA infections have increased mortality [8]. Furthermore, it has been shown that MDR-PA isolation and infection in the critically ill is associated with poor prognosis [2, 6, 8], though with conflicting results [9]. Despite extensive

research, the spectrum of outcomes in patients with MDR-PA isolated in different respiratory infections in the intensive care unit (ICU) has not been studied to date. Isolates in respiratory specimens correspond to pneumonia, tracheobronchitis or colonisation, depending on the inflammatory response.

The aim of the study was to assess the clinical relevance of MDR *Pseudomonas* isolates in respiratory specimens. We hypothesised that MDR-PA respiratory infections would be associated with excess morbidity and mortality, and that specific predictors of mortality would emerge for this group of infections in the critically ill. Our research questions were: Is the risk of death due to pneumonia independent of other variables in a cohort of ICU patients harbouring MDR-PA in respiratory specimens? Is combination empirical therapy superior to monotherapy in a cohort of MDR *Pseudomonas* pneumonia? Finally, how should the presence of an MDR-PA clinical isolate in a respiratory specimen influence clinical practice?

## Methods

### Study design

We conducted a retrospective case–control study in four medical-surgical ICUs at Vall d'Hebron University Hospital, a major teaching hospital in Barcelona, Spain. The study population comprised all consecutive adult patients admitted to the ICU between January 2010 and April 2015. Selective digestive decontamination (SDD) with tobramycin and colistin was used in all intubated patients. Patients with MDR-PA isolation previous to ICU admission were excluded. Details of the global epidemiology have been reported elsewhere [10]. For the purposes of these analyses, only respiratory clinical samples harbouring MDR-PA were included. These samples were taken when infection was suspected and were requested by the attending physician. Samples associated with surveillance studies were excluded. In patients with multiple infections, only the last episode was retained. Patients with MDR-PA respiratory samples without evidence of pneumonia and without subsequent MDR-PA infection were included as controls, in accordance with the research questions. All computerised patient records were reviewed up to death or ICU discharge by a consultant intensive care physician (BB). Statistical analysis was performed in the pneumonia and control cohorts. To identify predictors of mortality among ICU adults harbouring MDR-PA in respiratory samples, a univariate analysis of survivors versus non-survivors was performed in patients with pneumonia (hospital-acquired pneumonia, HAP plus ventilator-associated pneumonia, VAP). The local institutional review board approved the study, and the need for written consent was waived due to its observational nature.

Variables included were demographic data, comorbidities and risk factors for MDR-PA isolation [6]. Baseline comorbidity was assessed with the Charlson comorbidity index [11]. Severity scores (APACHE-II [12] and SOFA [13]) were recorded at admission and at the time of sample collection (SOFA and PIRO [14]). Antibiotic exposure in the 30 days prior to culture was recorded. Clinical, microbiological and laboratory data associated with infection state, severity of illness and the appropriateness of initial antibiotic therapy were also collected. Epidemiological, clinical and microbiological data were recorded for each patient. The outcomes analysed were attributable 30-day ICU mortality, excess ICU length of stay (LOS) and excess MV days. Complications included shock, moderate-severe hypoxaemia, acute respiratory distress syndrome (ARDS) and acute kidney injury (AKI), which were recorded if the onset was within a time frame of ±6 days of culture.

### Microbiology

*Pseudomonas aeruginosa* was isolated from respiratory samples (sputum, endotracheal aspirate and bronchoalveolar lavage) and blood. MDR-PA strains were identified in the microbiology laboratory using the VITEK MS automated system (bioMérieux, Marcy l'Etoile, France). The antimicrobial susceptibility of isolates was tested using disk diffusion, and resistant strains were verified using the gradient diffusion method. Minimum inhibitory concentrations (MICs) were classified according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints [15]. Multidrug resistance was defined as non-susceptibility to at least one agent in ≥3 antimicrobial categories, and extensively drug-resistant (XDR) as non-susceptibility to at least one agent in all but ≤2 antimicrobial categories [16]. Adequate initial antibiotic treatment was defined, regardless of lung penetration, as in vitro susceptibility to at least one antibiotic administered at adequate dose [17]. Breakpoints of resistance were >8 mg/L for meropenem, imipenem, ceftazidime and cefepime and >16 mg/L for piperacillin–tazobactam and amikacin.

### Definitions

- *Pneumonia cases*: patients who met VAP or HAP diagnostic criteria according to the 2005 ATS/IDSA guidelines [18].
- *Controls*: patients who met diagnostic criteria for ventilator-associated tracheobronchitis (VAT) and colonisation. VAT was diagnosed according to the definition proposed by Craven and Hjalmarson [19]. Colonisation was diagnosed in positive specimens with MDR-PA that did not meet the criteria for infection.
- *Shock*: new presence of sustained hypotension and/or initiation of vasopressors (noradrenaline) or increase of ≥20% in less than 24 h.

- *Moderate-severe hypoxaemia*: $PaO_2/FiO_2$ or $SpO_2/FiO_2 \leq 200$ only if $FiO_2$ was increased by ≥10% in less than 24 h.
- *ARDS*: according to the Berlin definition [20].
- *AKI*: according to the KDIGO criteria [21].
- *ΔSOFA*: SOFA at culture minus SOFA at admission, in order to assess the patient's evolution from admission to culture.
- *Crude mortality*: all deaths occurring during ICU stay.
- *Attributable 30-day ICU mortality*: the difference between observed 30-day ICU mortalities in the pneumonia and the control groups [22].

### Statistical analysis

Continuous variables were checked with the Kolmogorov–Smirnov test to assess deviations from normality. Discrete variables were summarised as frequency (%) and continuous variables as median and interquartile range (IQR). Univariate analysis was performed using Pearson's Chi-squared test, two-tailed Fisher's exact test or the Mann–Whitney *U*-test, as appropriate. Analysis of variance (ANOVA) and the Kruskal–Wallis test were performed in variables with more than two categories. Kaplan–Meier curves were generated for the survival analysis in the different cohorts. A Cox proportional hazards model using the enter method was applied to analyse predictors of ICU mortality. Variables investigated as predictors of mortality were included if they reached statistical significance in the univariate analysis and if they were considered clinically relevant according to current knowledge with a *p*-value <0.10. Adjusted hazard ratios (aHRs) were expressed with 95% confidence intervals (CIs). Statistical analysis was performed using Stata for Mac version 13 (StataCorp LP, College Station, TX, USA) and SPSS for Mac version 18 (SPSS, Chicago, IL, USA). Statistical significance was set at $p < 0.05$.

## Results

### Patients

During the study period, 5667 patients were admitted to the ICU. Of the 69 adults with MDR-PA isolated in respiratory samples, 31 were identified as having pneumonia (21 VAP) and were compared with the remaining 38 patients (16 of whom had tracheobronchitis), who served as the control group without pneumonia. Bacteraemia was present in only 8 (25.8%) HAP/VAP patients. However, the 30-day mortality rates for HAP, VAP, colonisation and VAT were 90% (9/10), 57.1% (12/21), 22.7% (5/22) and 12.5% (2/16), respectively. Among these HAP/VAP patients, 7 (22.5%) had at least one previous MDR-PA infection and one-third (10, 32.3%) had previous PA colonisation. No differences were observed in the median Charlson scores between the pneumonia and non-pneumonia cohorts: 3 (IQR: 1 to 4) vs. 2 (IQR: 1 to 3), $p = 0.5$.

Patients with MDR-PA HAP/VAP were predominantly male (20; 64.5%), with a median age of 60 years (IQR: 48 to 68), a median APACHE-II at admission of 24 (IQR: 17 to 29) and a median ICU stay of 18 days (IQR: 1 to 41). There was no difference in ΔSOFA between groups: 0 (median, IQR: −1 to 4) in HAP/VAP vs. 0 (median, IQR: −2 to 2) in controls ($p = 0.16$). Twenty-one were immunosuppressed (67.7%), of whom 11 (35.5%) were solid organ transplant patients and 7 (22.6%) had an active malignancy. Table 1 shows the patients' characteristics and compares controls vs. patients with HAP/VAP.

None of the ten HAP patients had 'do not resuscitate' orders. Their primary diagnoses were respiratory failure in six, (respiratory) septic shock in three and urinary sepsis in one. Seven were immunocompromised (three solid organ transplant, two with active malignancy and two neutropaenic). Online Resource 3 compares the causes of immunosuppression between HAP, VAP and controls.

MDR-PA HAP/VAP was significantly associated ($p < 0.05$) with development of organ injury: shock ensued in 20 (64.5%), moderate-severe hypoxaemia also in 20 (64.5%), AKI in 17 (54.8%) and ARDS in 6 (19.4%). HAP was more severe, presenting with as many as 8 patients (80%) presenting at least one organ dysfunction, compared with almost 60% of VAP patients. See Table 2 for a detailed comparison of outcomes and complications between HAP, VAP, VAT and colonisation. The time from culture to organ injury development was very short; injury was usually present at onset and most injuries developed within 48 h (Fig. 1).

### Mortality

In total, 28 out of 69 patients died (40.6%) and the overall 30-day mortality was 37.7% (26/69). HAP/VAP crude and 30-day mortality were the same, rising to 67.7% (21/31). The crude mortality of the control group was 18.4% (7/38) and the 30-day mortality was 13.2% (7/38). The estimated attributable 30-day ICU mortality for HAP/VAP was 54.5% (67.7% vs. 13.2%, $p < 0.01$). The median time to death was significantly shorter in the HAP/VAP group: 4 days [IQR: 3 to 8] vs. 17 days [IQR: 9 to 64] in the controls ($p < 0.01$). Within 8 days of infection, 85.7% (18/21) of deaths in the HAP/VAP group had already ensued and all deaths occurred by day 14. The comparison of time-to-ICU-mortality between HAP/VAP and controls is shown in Fig. 2. Online Resources 1 and 2 show the patients' characteristics and compare them between survivors and non-survivors.

**Table 1** Demographic data and risk factors in patients with multidrug-resistant *Pseudomonas aeruginosa* (MDR-PA) ventilator-associated pneumonia (VAP) and hospital-acquired pneumonia (HAP). Univariate analysis between the pneumonia group (HAP/VAP) and the control group (respiratory colonisation and ventilator-associated tracheobronchitis, VAT)

| Demographics, epidemiological variables and risk factors | All, $n = 69$ | Pneumonia (HAP/VAP), $n = 31$ | Controls, $n = 38$ |
|---|---|---|---|
| Age, years, median [IQR] | 59 [49; 66] | 60 [48; 68] | 57.5 [49; 65] |
| Sex | | | |
| Male | 47 (68.1%) | 20 (64.5%) | 27 (71.1%) |
| Female | 22 (31.9%) | 11 (35.5%) | 11 (28.9%) |
| Charlson comorbidity index, median [IQR] | 2 [1; 3] | 3 [1; 4] | 2 [1; 3] |
| Severity | | | |
| APACHE-II at admission, median [IQR] | 22 [17; 28] | 24 [17; 29] | 22 [17; 27] |
| SOFA at admission, median [IQR] | 5 [3; 8] | 5 [4; 9] | 5 [3; 7] |
| SOFA at culture, median [IQR] | 6 [3; 10] | 8 [5; 12]** | 5 [3; 7]** |
| ΔSOFA, median [IQR] | 0 [−2; 3] | 0 [−1; 4] | 0 [−2; 2] |
| PIRO at culture, median [IQR] | 2 [1; 3] | 3.2 [3; 4.2]* | 1 [0; 2]* |
| Origin | | | |
| Ward | 22 (31.9%) | 12 (38.7%) | 10 (26.3%) |
| Emergency room | 17 (24.6%) | 6 (19.4%) | 11 (28.9%) |
| Operating theatre | 12 (17.4%) | 6 (19.4%) | 6 (15.8%) |
| Recovery room | 7 (10.1%) | 3 (9.7%) | 4 (10.5%) |
| Other centre | 11 (15.9%) | 4 (12.9%) | 7 (18.4%) |
| Surgical patients | 19 (32.2%) | 12 (46.2%) | 7 (18.4%) |
| ICU admission diagnosis | | | |
| Infectious | 20 (28.9%) | 12 (38.7%) | 8 (21.1%) |
| Respiratory | 19 (27.5%) | 11 (35.5%) | 8 (21.1%) |
| Neurological | 10 (14.5%) | 2 (6.5%) | 8 (21.1%) |
| Gastrointestinal | 7 (10.1%) | 4 (12.9%) | 3 (7.9%) |
| Cardiovascular | 6 (8.7%) | 0** | 6 (15.8%)** |
| Other | 4 (5.8%) | 1 (3.2%) | 3 (7.9%) |
| Oncological/haematological | 3 (4.4%) | 1 (3.2%) | 2 (5.3%) |
| Comorbidities | | | |
| Immunocompromised | 35 (50.7%) | 21 (67.7%)* | 14 (36.8%)* |
| Chronic lung disease (not COPD/CF) | 25 (36.2%) | 12 (38.7%) | 13 (34.2%) |
| COPD or CF | 16 (23.2%) | 7 (22.6%) | 9 (23.7%) |
| Diabetes mellitus | 20 (28.9%) | 9 (29%) | 11 (28.9%) |
| Chronic heart disease | 14 (20.3%) | 5 (16.1%) | 9 (23.7%) |
| Chronic renal disease | 13 (18.8%) | 5 (16.1%) | 8 (21.1%) |
| Chronic liver disease | 10 (14.5%) | 4 (12.9%) | 6 (15.8%) |
| Neurological squeal | 5 (7.2%) | 1 (3.3%) | 4 (10.5%) |
| Skin ulcers (chronic or previous pressure ulcers) | 4 (5.8%) | 3 (9.7%) | 1 (2.9%) |
| Current admission | | | |
| Hospital LOS pre-ICU, days, median [IQR] | 1 [0; 12] | 2 [0; 17] | 0.5 [0; 8] |
| ICU LOS pre-culture, days, median [IQR] | 23 [6; 45] | 18 [1; 41] | 25.5 [8; 58] |
| Previous PA colonisation | 18 (26.1%) | 10 (32.3%) | 8 (21.1%) |
| Previous MDR-PA infection | 14 (20.3%) | 7 (22.6%) | 7 (18.4%) |
| Previous mechanical ventilation | 53 (76.8%) | 20 (64.5%)* | 33 (86.8%)* |
| Tracheostomy | 50 (72.5%) | 20 (64.5%) | 30 (78.9%) |
| Previous RRT | 14 (20.3%) | 8 (25.8%) | 6 (15.8%) |
| Parenteral nutrition | 25 (36.2%) | 15 (48.4%) | 10 (26.3%) |

CF = cystic fibrosis, COPD = chronic obstructive pulmonary disease, IQR = interquartile range, LOS = length of stay, RRT = renal replacement therapy

*$p < 0.01$

**$p < 0.05$

## Other outcomes

Only ten patients with HAP/VAP were alive at the time of ICU discharge. Although the difference did not reach statistical significance, HAP/VAP survivors had triple the post-culture duration of mechanical ventilation compared to control survivors, 20.5 days [median, IQR: 5 to 46] vs. 7.5 days [median, IQR: 3 to 22], $p = 0.13$, and double the post-culture ICU stay, 27 days [median, IQR: 13 to 55] vs. 15 days [median, IQR: 10 to 33], $p = 0.31$ (see Table 2 for detailed outcomes in each group).

## Predictors of ICU 30-day mortality

A Cox proportional regression model with the enter method was performed in all patients, using SOFA at culture, immunosuppression, VAT, pneumonia, shock and inadequate initial antibiotic therapy (IIAT) as independent variables. The model identified only MDR-PA pneumonia (HAP + VAP) as independently associated with ICU mortality, with an aHR of death of 5.92 (95% CI 1.19–29.57). See Table 3.

**Table 2** Outcomes in patients with MDR-PA VAP, HAP and VAT compared to controls

| Outcomes | All, *n* = 69 | Respiratory colonisation, *n* = 22 | VAT, *n* = 16 | HAP, *n* = 10 | VAP, *n* = 21 | *p*-Value |
|---|---|---|---|---|---|---|
| Complications | | | | | | |
| Shock | 25 (36.8%) | 4 (18.2%) | 1 (6.67%) | 8 (80.0%) | 12 (57.1%) | <0.01 |
| Moderate-severe hypoxaemia | 27 (39.1%) | 6 (27.3%) | 1 (6.25%) | 8 (80.0%) | 12 (57.1%) | <0.01 |
| ARDS | 6 (8.7%) | 0 | 0 | 2 (20.0%) | 4 (19.0%) | <0.05 |
| AKI | 22 (31.9%) | 5 (22.7%) | 0 | 8 (80.0%) | 9 (42.9%) | <0.01 |
| MV post-culture, days, median [IQR] | 11 [3; 23.5] | 7.5 [4.5; 16.5] | 12 [2; 24] | – | 19 [5; 33] | 0.85 |
| ICU LOS post-culture, days, median [IQR] | 20 [11; 32] | 15 [11; 26] | 17.5 [10; 32] | – | 25 [13; 43] | 0.42 |

ICU length of stay and mechanical ventilation days analysis was performed only in survivors; HAP was not analysed since there was only one survivor

ARDS = acute respiratory distress syndrome, AKI = acute kidney injury, HAP = hospital-acquired pneumonia, LOS = length of stay, MV = mechanical ventilation, VAP = ventilator-associated pneumonia, VAT = ventilator-associated tracheobronchitis

## Antibiotic exposure and susceptibility

Meropenem showed poor overall activity ($MIC_{[50/90]}$ 16/32 mg/L), with 47.0% having an MIC breakpoint >8 mg/L. Only 7 patients (22.6%) with HAP/VAP had prior exposure (during the prior 30 days) to carbapenems. The vast majority of isolates (85.1%) were susceptible only to amikacin and colistin, while 3 (6.4%) were XDR (susceptible only to colistin). Online Resource 4 shows the overall susceptibility of *P. aeruginosa* from ICU respiratory samples. Resistance to beta-lactams (third-generation cephalosporins and piperacillin–tazobactam) ranged from 44.1% to 45.3%. Indeed, differences between meropenem and anti-pseudomonal cephalosporins were lower than 3%. There were no differences in susceptibility between controls and HAP/VAP (see Online Resource 2).

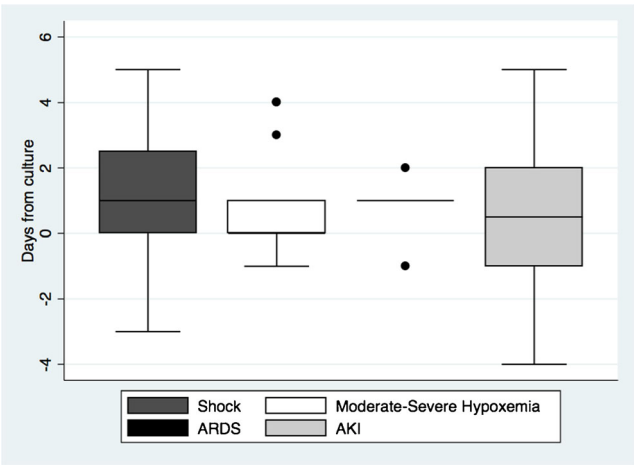


**Fig. 1** Time from culture to organ injury development in patients with multidrug-resistant *Pseudomonas aeruginosa* (MDR-PA) pneumonia (hospital-acquired pneumonia, HAP and ventilator-associated pneumonia, VAP). **a** Shock: 1 day (median, IQR: −1; 2.5); **b** moderate-severe hypoxaemia: 0 days (median, IQR: 0; 1); **c** acute respiratory distress syndrome (ARDS): 1 day (median, IQR: 1; 2); **d** acute kidney injury (AKI): 0.5 days (median, IQR: −1; 2)

Prior systemic exposure to amikacin and colistin was present in 1 (3.2%) and 6 (19.4%) patients, respectively, although all VAP patients had prior exposure to SDD with tobramycin and colistin. In addition, 13 (41.9%) and 5 (16.1%) patients with HAP/VAP had prior exposure to beta-lactams and quinolones, respectively.

As a consequence, 24 (77.4%) HAP/VAP episodes received inappropriate empirical therapy, which was not associated with mortality. The seven subjects who received a susceptible agent were treated with amikacin (five patients) and IV colistin (two patients). Interestingly, these patients with adequate empirical therapy were more ill at the time of culture than those with inappropriate empirical therapy (median SOFA score of 11 [IQR: 8 to 15] vs. 5 [IQR: 3 to 9], $p < 0.05$). Indeed, combination therapy was prescribed in 7/15 patients with SOFA score >8 and in 3/16 patients with SOFA score in the range 0–8. Moreover, no differences in severity scores at ICU admission or in ΔSOFA were seen between the groups.

Thirteen (41.9%) patients received empirical therapy with a beta-lactam, 11 (35.5%) with a carbapenem, 5 (16.1%) with amikacin and 2 (6.5%) with IV colistin. Quinolones were not used. Survival was 1 in 11 patients (9.1%) with carbapenems as empirical therapy and 9 in 20 patients (45%) without carbapenems ($p < 0.05$). Although empirical combination therapy was associated with less IIAT than monotherapy (16.7% vs. 88.3%, $p < 0.01$), there were no differences in survival (30% vs. 33.3%, $p = 0.8$). Details of antibiotic use are summarised in Table 4.

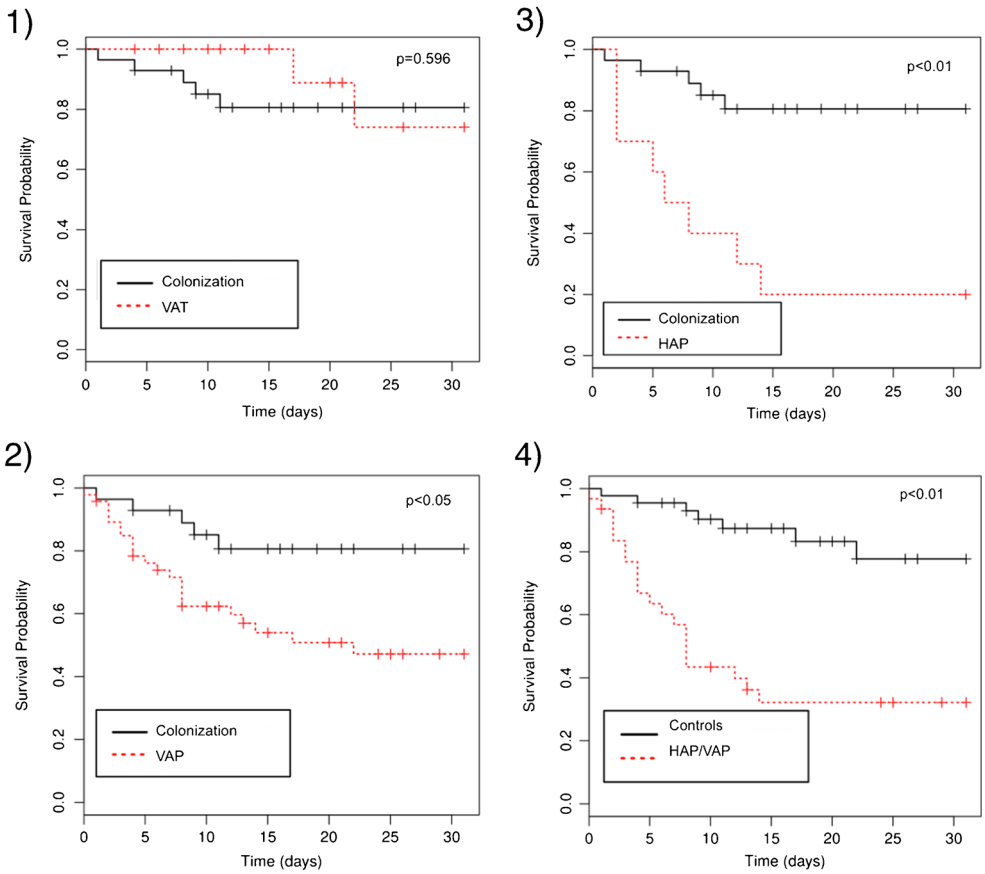


**Fig. 2** Time-to-ICU-mortality compared between patients with MDR-PA respiratory infection or colonisation. Kaplan–Meier curves are shown and groups were compared using the log-rank test; statistical significance is expressed with *p*-values. Data were censored at 30 days after infection onset. (*1*) Time-to-ICU-mortality in patients with MDR-PA ventilator-associated tracheobronchitis (VAT) vs. respiratory colonisation. (*2*) Time-to-ICU-mortality in patients with MDR-PA VAP vs. respiratory colonisation. (*3*) Time-to-ICU-mortality in patients with MDR-PA HAP vs. respiratory colonisation. (*4*) Time-to-ICU-mortality in patients with MDR-PA pneumonia: HAP plus VAP vs. controls

## Conclusions

MDR-PA HAP/VAP is associated with increased mortality. MDR-PA pneumonia was associated with a high percentage of IIAT due to the presence of very high resistance to meropenem. Death ensued within 8 days in at least 3 out of 4 patients. We emphasise that new antibiotics and therapies aimed to reduce infection, as well as adjuvant treatments, are urgently needed to deal with the challenge of MDR-PA HAP/VAP.

**Table 3** Cox proportional hazards model for ICU mortality in patients with MDR-PA pneumonia (HAP + VAP, $n = 31$) and controls (respiratory colonisation + VAT, $n = 38$), sample total $n = 69$

| Risk factors | aHR | 95% CI | *p*-Value |
|---|---|---|---|
| SOFA at culture | 0.96 | 0.81–1.14 | 0.67 |
| Immunosuppression | 1.78 | 0.67–4.74 | 0.25 |
| VAT | 0.79 | 0.11–5.84 | 0.81 |
| Pneumonia (HAP + VAP) | 5.92 | 1.19–29.57 | <0.05 |
| Shock | 2.1 | 0.59–7.54 | 0.26 |
| Inadequate empirical therapy | 1.56 | 0.36–6.79 | 0.55 |

aHR = adjusted hazard ratio

## Discussion

This study is the first comprehensive assessment of the clinical implications of pneumonia in adult ICU patients harbouring MDR-PA in respiratory isolates. Most strains were only susceptible to colistin and amikacin, and the MIC for meropenem is reported. Our results suggest that HAP/VAP is associated with extremely high, rapid mortality and alarming morbidity rates. In contrast, a low and similar 30-day mortality and outcomes was seen in VAT and in respiratory colonisation. After adjusting for known risk factors for increased mortality and comparing with our controls, we identified MDR-PA pneumonia as a predictor of 30-day ICU mortality.

Patients with purulent respiratory secretions can be characterised as being colonised, having tracheobronchitis or having pneumonia, depending on the inflammatory response, biomarkers and alternative collected specimens. The triggers of pneumonia in patients harbouring an organism in the respiratory tract are unknown. We were not surprised to find associations between higher severity, longer MV or more immunosuppression and a higher incidence of pneumonia; this is common in opportunistic organisms like *P. aeruginosa*. Our findings also show that pneumonia was associated with more complications than non-pneumonia. In contrast with what happens with other MDR organisms (e.g. *Acinetobacter*

**Table 4** Details of antibiotic therapy administered in patients with MDR-PA pneumonia (HAP/VAP)

| Antimicrobial agent | HAP, *n* = 10 | | VAP, *n* = 21 | |
|---|---|---|---|---|
| | Empirical | Directed | Empirical | Directed |
| Piperacillin–tazobactam | 3 | 0 | 2 | 0 |
| Cephalosporins* | 0 | 3 | 2 | 3 |
| Carbapenems* | 6 | 4 | 5 | 3 |
| Amikacin | 4 | 4 | 1 | 4 |
| Colistin | 0 | 2 | 2 | 4 |
| Quinolones | 0 | 0 | 0 | 0 |

*Includes only agents with anti-*P. aeruginosa* spectrum. Some patients received multiple antibiotics

*baumannii*) in which death seems to be a terminal event, MDR-PA was associated with a rapid (median 4 days) fatal outcome. In addition, our data showing that VAT is closer to colonisation than VAP represents an addition to the literature.

A novel method [22] was used to estimate attributable mortality, which compares patients with MDR-PA pneumonia and patients with MDR-PA respiratory colonisation or VAT. This approach allows the analysis of patients with MDR-PA pneumonia with a real matched and comparable cohort, and, thus, reduces bias. Indeed, the results of the outcomes (in Table 2) and the Kaplan–Meier analysis in the two groups show that VAT and respiratory colonisation have similar effects on patient mortality and complications, providing support for our methodology. We estimated an attributable mortality for MDR-PA HAP/VAP of 54.5%, whereas the figures for susceptible strains reported in previous studies ranged between 13% and 18% [4–6].

It should be noted that 68% of the pneumonia cohort were immunosuppressed, which may explain the elevated mortality. However, the Cox regression model did not identify immunosuppression as an independent predictor of mortality. Although previous studies have associated MDR-PA pneumonia and VAT with increased LOS [13, 23], we were unable to validate these findings, even though LOS and MV days were both increased. We believe that our results failed to reach statistical significance due to a type II error (i.e. only ten patients with MDR-PA HAP/VAP survived). The severity of the MDR-PA pneumonia was another striking finding: two-thirds of MDR-PA pneumonia patients had at least one organ injury, a proportion that increased to 80% in HAP. Similarly, 20% of both HAP and VAP patients developed ARDS.

Our findings illustrate the complexity of MDR-PA pneumonia, with different implications for outcomes compared with other non-fermentative organisms. Remarkably, a low percentage of meropenem-resistant strains were previously exposed to carbapenems. In contrast, all ventilated patients received SDD with colistin and amikacin, with susceptibility to these agents remaining above 85%. With a difference of resistance lower than 3% with cephalosporins and piperacillin–tazobactam, in an area with low prevalence of *Klebsiella pneumoniae* carbapenemase (KPC) and high prevalence of extended-spectrum beta-lactamase (ESBL), this raises concerns about the appropriateness of de-escalating to beta-lactams as a streamlining strategy. Our findings demonstrate how challenging it is to treat infections caused by MDR organisms and indirectly suggest that infection control should be the cornerstone of prevention.

Interestingly, and contrary to previous evidence [13, 24], we did not find an association between inadequate therapy and increased mortality. Indeed, previous work has shown the most important predictor of mortality in patients with *P. aeruginosa* pneumonia to be illness severity [14], which was included as an adjusting variable to the Cox model. Moreover, we found that the inadequate therapy was due to the presence of high carbapenem resistance in the MDR strains. In contrast with non-MDR *Pseudomonas* pneumonia where initial combination therapy has presented superior survival [25], our cases had high MICs to carbapenems. A recent multicentre study testing ceftolozane/tazobactam as a treatment for carbapenem-resistant *P. aeruginosa* infections supports this [26]. It demonstrated effectiveness in 3 out 4 cases, except when isolates had MICs >8 mg/L, where 100% treatment failure was observed. Similarly, ward patients with positive cultures for meropenem-resistant *P. aeruginosa* had increased mortality, increased ICU admission and increased healthcare costs [27]. This problem is further complicated by the fact that the therapy that is currently considered as 'appropriate', systemic administration of amikacin or colistin as monotherapy, has been proved to be suboptimal in clinical practice due to limited lung penetration.

Our findings also have important practical considerations. In contrast to carbapenem-resistant Enterobacteriaceae or *A. baumannii*, in which carbapenem still plays an important therapeutic role, MDR-PA pneumonia requires a different approach. Finally, our findings in a cohort with extensive carbapenem resistance do not support the recommendation in the 2016 IDSA/ATS guidelines [28] to treat *Pseudomonas* pneumonia with combination therapy. Alternative agents are urgently needed.

The main limitations of the present study are the small sample size and its single-centre retrospective design, which means that the data should be treated with caution because the study is susceptible to an attrition bias. Similarly, given the inherent limitations of the current definitions, a misclassification bias is possible (i.e. there may have been undiagnosed infections in the colonisation group). However, the risk of bias is limitated, since the same investigator assessed all cases and the results are clinically consistent. The decision to consider HAP (*n* = 10) and VAP (*n* = 21) together might also be questioned, even though HAP may be as severe as VAP. Similarly, mixing respiratory specimens associated with

colonisation and VAT is a debatable step. However, the outcomes are consistent, as reported in the Kaplan–Meier survival curves (Fig. 2) and outcomes (Table 2). Regulatory agencies and recent studies [29] on MDR *Pseudomonas* support this classification. Different variables might be identified if other control groups (such as susceptible strains) were used. Our findings concerned the clinical significance of pneumonia in patients with respiratory specimens harbouring MDR-PA. Thus, assessing prognostic factors in a general cohort or when compared with susceptible strains or other organisms would require a different control group.

In summary, it has been demonstrated that MDR-PA HAP/VAP is an extremely severe entity associated with very high mortality and without any modifiable variables that might improve it. This is a matter of particular concern, given that *P. aeruginosa* is one of the main causes of respiratory infections in the ICU setting, the rising resistance rates worldwide and the lack of new antibiotics to effectively control and cure this infection. Efforts should be directed toward finding new effective antibiotics, but also, and probably more importantly, toward developing therapies that reduce the colonisation and infection by MDR-PA and adjuvant treatments that reduce its virulence.

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**Compliance with ethical standards**

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**Conflict of interest** J.R. is on the speaker bureau for Cubist, AstraZeneca, MedImmune, Kenta, Pfizer, Genentech and Paratek. The other authors have no conflicts of interest to report.

**Ethical approval** The study was approved by the local institutional review board, with the identification 'PR_AG_247-2012'.

**Informed consent** Informed consent was waived due to the observational nature of the study.

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