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Clinical outcomes of *Pseudomonas aeruginosa* pneumonia in intensive care unit patients

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Abstract *Purpose:* Our aim was to identify the clinical profile of intensive care unit (ICU) patients with *Pseudomonas aeruginosa* (PA) pneumonia and the impact on ICU mortality and duration of mechanical ventilation (MV) of multidrug resistance (MDR) in the PA isolate and inadequate initial antibiotic therapy (IIAT). *Methods:* We conducted a retrospective analysis of data prospectively collected in the 18-bed general ICU of a major teaching hospital in Rome, Italy. The study cohort consisted of 110 adult patients with culture-confirmed PA pneumonia consecutively diagnosed in 2008–2010. ICU survivor and non-survivor groups were compared to identify factors associated with ICU mortality. *Results:* In 42 (38 %) of the 110 cases of PA pneumonia analyzed, the PA isolate was MDR. Fifty-six (50.9 %) of the patients received IIAT, and 49 (44.5 %) died in ICU. In logistic regression analysis, IIAT, diabetes mellitus, higher Simplified Acute Physiology Score (SAPS) II scores, and older age were independently associated with ICU mortality. Among survivors, those who received IIAT or had MDR PA pneumonia had significantly longer median (interquartile ranges, IQR) periods of post-pneumonia onset MV (16.5 [14.5–20] and 15 [12–18] days, respectively) compared with those whose initial therapy was adequate (8 [6–13] days, $P < 0.001$) and those whose infections were caused by non-MDR PA (10.5 [6.5–13] days, $P = 0.01$). *Conclusions:* Our findings highlight the importance of IIAT as a risk factor for mortality in ICU patients with PA pneumonia. MDR in the PA isolate, like IIAT, can significantly increase the need for MV.

Keywords Pneumonia · Ventilator-associated pneumonia · *P. aeruginosa* · Multidrug resistance

Introduction

Pseudomonas aeruginosa (PA) is one of the Gram-negative pathogens most commonly isolated in patients with health-care-associated pneumonia (HCAP), hospital-acquired pneumonia (HAP) (in intensive care unit [ICU] and non-ICU patients), or ventilator-associated pneumonia (VAP), and its incidence as a nosocomial lung pathogen has doubled over the last three decades [1–4]. PA is intrinsically resistant to several antimicrobial agents, and it can acquire resistance to many others. The frequency of multidrug-resistant (MDR) strains is increasing, especially in nosocomial and ICU-acquired infections [5–7], and these infections can be associated with increases in mortality, morbidity, and hospital costs. Delays in initiating appropriate antibiotic therapy could

obviously increase the rates of treatment failure and attributable mortality [8–10], but even if effective treatment is started promptly, up to 43 % of patients with PA VAP die [11, 12].

The risk factors for PA pneumonia and the major determinants of its outcome in ICU patients have been investigated by various groups [13–21]. However, most have focused mainly on VAP and/or infections acquired in the ICU, and none have explored the impact on outcomes of multidrug-resistance in the PA strain causing the infections. To address these gaps, we analyzed the clinical profile of a cohort of critically ill ICU patients with PA pneumonia. The impact of adequacy of initial antibiotic treatment on mortality and duration of mechanical ventilation were also evaluated.

Methods

Setting and study design

This retrospective cohort study was conducted in the 1500-bed Medical Center of the Catholic University of the Sacred Heart in Rome, Italy; the protocol was approved by the University's Ethics Committee, and informed consent was waived because of the observational retrospective nature of this study. We searched the ICU's clinical and microbiological databases to identify all cases of PA pneumonia diagnosed between January 1, 2008, through December 31st, 2010, that met the following criteria: patient age ≥18 years; pneumonia onset shortly before (≤24 h) or after admission to the medical center's general ICU; diagnoses confirmed by quantitative culture of bronchoalveolar lavage fluid (BAL) showing PA growth of $>10^4$ cfu/ml.

HAP was diagnosed when a new, persistent, progressive radiographic lung infiltrate, that was not evident within the first 48 h following hospital admission, and two or more of the following clinical criteria were met: (1) new onset of purulent bronchial sputum, (2) body temperature >38.8 °C or <35.5 °C, (3) white blood cell count >10,000/mm^3 or <4,000/mm^3. VAP was defined as ICU-acquired pneumonia occurring ≥ 48 h after endotracheal intubation and/or mechanical ventilation. HCAP was defined as pneumonia developed in patients who (1) were hospitalized in an acute care hospital for two or more days within 90 days of the infection; (2) were residents in a nursing home or long-term care facility; (3) had received intravenous antibiotic therapy, chemotherapy, or wound care within the 30 days preceding the index infection; or (4) were in regular hemodialysis treatment.

Cases of VAP were excluded if the patient's retrospectively calculated Clinical Pulmonary Infection Score (CPIS) was <6 [22].

Survivor and nonsurvivor subgroups were compared to identify factors associated with ICU mortality. Patient data (collected from electronic medical records and laboratory databases) included demographic characteristics, medical history, clinical and laboratory findings, the Simplified Acute Physiology Score II (SAPS II) and Sequential Organ Failure Assessment (SOFA) score calculated by ICU physicians at the time of ICU admission and at onset of pneumonia, respectively; treatment; and outcome [23, 24].

Microbiological analyses

BAL specimens were collected blindly with telescopic catheters (Combicath; Plastimed, Saint-Leu-la-Forêt, France) in almost all patients (with the exception of eight patients for whom a bronchoscopic guide was required) and a calibrated loop of aspirate (0.0025 mL) was quantitatively cultured on blood agar, chocolate agar, McConkey agar, and when necessary *Legionella* agar (blood charcoal yeast extractB). Three or more sets of blood cultures had also been collected for each patients in Lytic/10 Anaerobic/F and Plus Aerobic/F bottles and incubated in the automated Bactec 9240 system (all from Becton–Dickinson, Sparks, MD). Bacterial isolates were identified with the VITEK 2 (bioMérieux, Inc., Hazelwood, MO) and/or Phoenix (Becton–Dickinson) systems. All isolates were subjected to E-testing (bioMérieux) and minimum inhibitory concentrations (MICs) were classified according to current (2008) Clinical Laboratory Standards Institute (CLSI) guidelines [25].

Definitions

PA isolates were classified as *MDR* if they displayed in vitro resistance to at least 1 antipseudomonal agent in 3 or more of the following categories: β-lactam/β-lactamase inhibitors (i.e., piperacillin–tazobactam); cephalosporins (i.e., cefepime and ceftazidime); carbapenems (i.e., imipenem and meropenem); quinolones (i.e., ciprofloxacin and levofloxacin); and aminoglycosides (i.e., amikacin and gentamicin) [8]. Colistin-only-susceptible (COS) PA strains were resistant to all commercially available drugs except colistin.

Pneumonia onset coincided with the collection date of the first BAL culture yielding the study isolate (index culture), and *septic shock* was defined as recommended by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee [26]. We recorded the length (days) of the *period at risk for* PA *pneumonia* (i.e., from hospital admission to pneumonia onset); the *total ICU stay* and the *post-pneumonia-onset ICU stay* (both ending at ICU discharge or death, whichever occurred first); and the *duration of mechanical ventilation [MV]* before pneumonia onset

(when applicable) and after pneumonia onset. *Prior antimicrobial therapy* was defined as the use of any antimicrobial for ≥48 h during the 3 months preceding pneumonia onset. The empirical antimicrobial regimen (i.e., that used before in vitro susceptibility data were available for the BAL isolate) was classified as *inadequate* when it did not include any agent displaying in vitro activity against the isolated pathogen.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or medians and interquartile ranges [IQR]. The Student *t* test and Mann–Whitney *U* test were used to assess normally and non-normally distributed continuous variables, respectively. Categorical variables were reported as percentages of the group analyzed and assessed with the χ^2 or two-tailed Fisher exact test. Odds ratios (ORs) and 95 % confidence intervals (CIs) were calculated for all associations.

Logistic regression was used to identify independent predictors of ICU mortality. Variables associated with mortality in the univariate analysis ($P \leq 0.2$) were included at model entry, and a backward stepwise approach was used to identify independent predictors of mortality. Variables with p values ≤0.05 were retained in the final model. The Kaplan–Meier method was used for the survival analysis. Two-tailed tests were used to determine significance; $P < 0.05$ was considered significant. Analyses were performed with the Intercooled Stata program, version 11.

Results

Incidence and population characteristics

Of the 2,136 patients cared for in our ICU during the 3-year study period, 110 had diagnoses of PA pneumonia (overall incidence: 51.5 per 1,000 ICU admissions). In Fig. 1 the flow chart of study inclusion process is reported.

Twenty nine (26.4 %) patients were admitted to the ICU for recent-onset pneumonia acquired elsewhere in the hospital (non-ICU-acquired pneumonia), and all 29 were placed on MV at ICU admission. In the other 81 (73.6 %) cases, pneumonia onset occurred in the ICU. Seventy-one of these patients were already being ventilated at pneumonia onset, and the other 10 were placed on MV at pneumonia onset. The characteristics of these two subgroups are summarized in Table 1.

Resistance profiles of PA isolates

Forty-eight (43.6 %) of the 110 PA isolates displayed in vitro resistance to ceftazidime, 46 (41.8 %) were resistant to cefepime, 47 (42.7 %) to levofloxacin and ciprofloxacin, 47 (42.7 %) to imipenem, 45 (40.9 %) to meropenem, 33 (30 %) to gentamicin, 23 (20.9 %) to piperacillin–tazobactam, 12 (10.9 %) to amikacin, and none were resistant to colistin. Forty-two strains (38 %) were classified as MDR-PA and 9 (8.1 %) as COS-PA.

Treatment

Promptly (i.e., within few hours) after pneumonia onset, all patients were being empirically treated with anti-Gram-negative drugs (alone or with other antibiotics). In particular, the doses used for the most utilized antimicrobials were: piperacillin/tazobactam 18 g q 24 h (continuous infusion) or 4.5 g every 6 h; meropenem 2 g every 8 h (infusion duration at least 3 h); ceftazidime or cefepime 2 g every 8 h; gentamicin 5–7 mg/kg q 24 h, amikacin 15–20 mg q 24 h, ciprofloxacin 400 every 8 h; and colistin 6 000 000–9 000 000 IU/day divided into 2–3 daily doses. All dosages were adjusted for creatinine clearance if necessary.

The antibiotic regimens, empirical or definitive (i.e., post-antibiogram) are shown in Table 3. The overall mean duration of treatment was 12 ± 4 days. For 65 patients (59 %) antibiotic therapy consisted of a single drug and in 45 (40.9 %) of a combination therapy in the empirical phase. The more common second antibiotics used were amikacin (31.1 %), ciprofloxacin (28.9 %), and colistin (24.4 %). The combination therapy was used in 30 % of patients in the definitive phase of treatment. In 11 patients, the definitive drug regimens (based on in vitro susceptibility data) included aerosol therapy with the same drug used intravenously (i.v.) (i.e., colistin or amikacin); 7 of these 11 patients received i.v. monotherapy with colistin because the infection was caused by strains susceptible only to colistin.

The initial antimicrobial regimen was inadequate in 56 (50.9 %) of the 110 cases, and most IIAT regimens (41/56–73.2 %) included only one drug. IIAT was significantly more common among patients with MDR PA pneumonia (66.6 % [28/42] versus 41.2 % [28/68] in the non-MDR subgroup; $P = 0.009$). Antibiograms were reported approximately 62 h (median) after pneumonia onset (IQR 48–76 h), and shortly thereafter 46 of the 56 patients were switched to adequate regimens. The other 10 died before their treatment could be adjusted.

Factors associated with inadequate initial antimicrobial treatment

Fifty-six patients who received IIAT were compared with 54 who received adequate antimicrobial therapy from pneumonia onset in order to identify risk factors for IIAT (Table 2). Patients in IIAT group were more likely to be

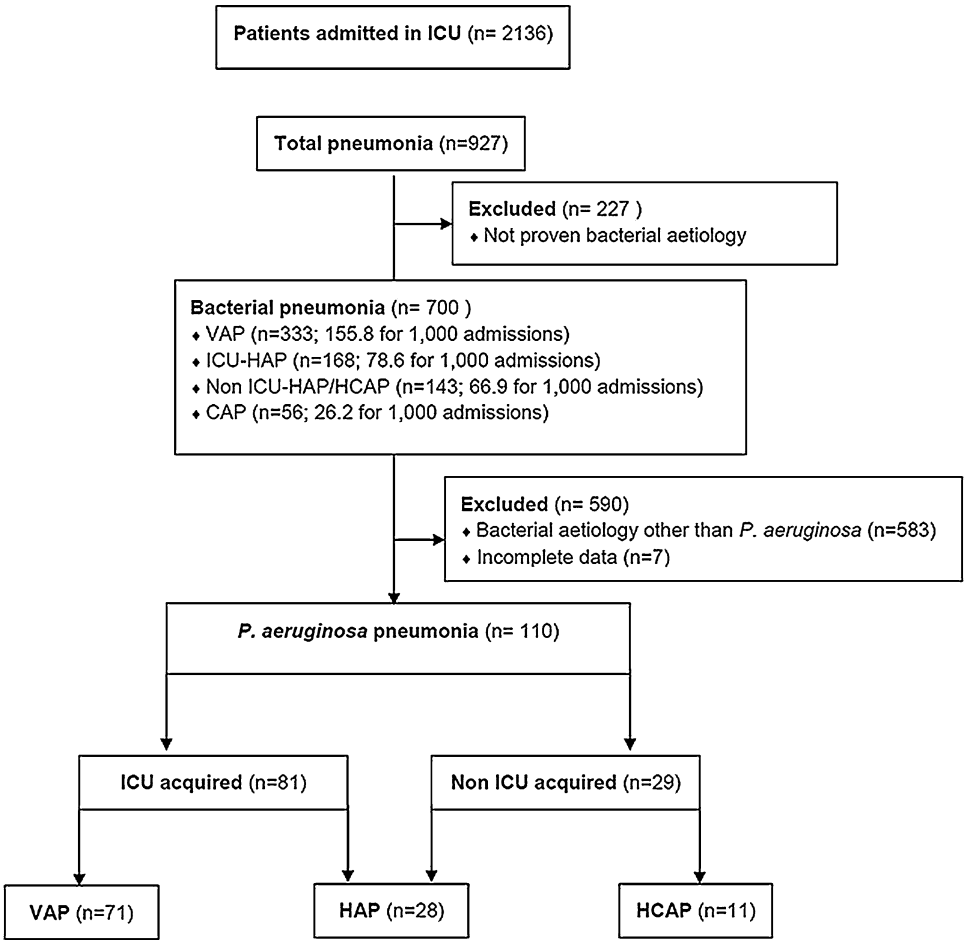

Fig. 1 Flow chart of study inclusion process

admitted in for ICU medical conditions, to have received a carbapenem-based empirical treatment, and to have a MDR PA pneumonia; Conversely, patients adequately treated, more frequently were admitted to the ICU for trauma and received a β-lactam/β-lactamase inhibitors-based regimen and/or a combination therapy in the empirical phase of treatment.

In logistic regression analysis infection caused by MDR PA isolates resulted independently associated with IIAT (OR, 2.67; 95 % CI, 1.16–6.16; $P = 0.02$), whereas the use of combination therapy in the empirical phase was associated with a lower risk of IIAT (OR, 0.31; 95 % CI, 0.14–0.70; $P = 0.005$).

Outcomes

The overall ICU mortality was 44.5 % (49/110) and in-hospital mortality was 47.3 % (52/110). Mortality in the IIAT subgroup was significantly higher than that of the subgroup treated appropriately from the onset: 64.2 % (36/56) versus 24.7 % (13/54) ($P < 0.001$). Survival curve analysis confirmed the increased mortality risk associated with IIAT ($P < 0.001$) (Fig. 2). ICU mortality was also significantly higher in patients with MDR PA infections: 59.5 % (25/42) versus 35.2 % (24/68) in the non-MDR group, ($P = 0.01$), but survival curves in these two subgroups were not significantly different.

We assessed the impact of both these factors on the length of post-pneumonia-onset MV. In the subgroup that survived, significantly longer periods of ventilation were associated with IIAT (16.5 [14.5–20] days versus 8 [6–13] days in those with adequate empirical therapy; $P < 0.001$) and with MDR PA pneumonia (15 [12–18] days versus 10.5 [6.5–13] days in patients with non-MDR isolates; $P = 0.01$) (Fig. 3). Less evident differences were observed when the entire cohort was included in this analysis.

Risk factors for mortality

Univariate analysis revealed significant differences between the survivor and nonsurvivor subgroups (Table 3). In general, nonsurvivors were older with more comorbidities and more severe illness at pneumonia onset. Their pneumonia was also more likely to be caused

Table 1 Characteristics of the 110 ICU patients with *Pseudomonas aeruginosa* pneumonia

Variable	No. (%) of patients		*P* value
	ICU-acquired pneumonia ($n = 81$)	Non-ICU-acquired pneumonia ($n = 29$)	
Demographics and comorbidities			
Male sex—no. (%)	49 (60.5)	23 (79.3)	0.07
Age (years)—median (IQR)	63 (41–76)	74 (65–80)	0.03
Diabetes mellitus	14 (17.3)	3 (10.3)	0.37
Chronic renal failure	8 (9.9)	5 (17.2)	0.29
COPD	7 (8.6)	10 (34.4)	0.001
Liver disease	6 (7.4)	2 (6.9)	0.92
Cancer	8 (9.9)	6 (20.7)	0.13
Immunosuppressive therapy	9 (11.1)	3 (10.3)	0.91
Pre-pneumonia medical history			
Previous hospital admission	25 (30.8)	7 (24.1)	0.49
Previous antibiotic therapy[a]	64 (79.0)	14 (48.2)	0.001
β-Lactam–β-lactamase inhibitors	51 (62.9)	4 (13.8)	<0.001
Glycopeptides	22 (27.1)	2 (6.9)	0.02
Invasive procedures[b]			
Indwelling central venous catheter—no. (%)	76 (93.8)	24 (82.8)	0.07
Indwelling nasogastric tube—no. (%)	81 (100)	26 (89.7)	0.02
Tracheal intubation—no. (%)	42 (51.8)	–	–
Tracheotomy—no. (%)	37 (45.7)	8 (27.6)	0.09
Dialysis—no. (%)	9 (11.1)	1 (3.5)	0.22
Characteristics of pneumonia			
Onset during MV—no. (%)	71 (87.6)[b]	–	–
CPIS—mean ± SD	7.9 ± 1.2		
Causative organisms—no. (%)			
P. aeuruginosa alone	71 (87.6)	27 (93.1)	0.42
P. aeuruginosa associated with:	10 (12.3)	2 (6.9)	0.48
Acinetobacter baumannii	5 (6.2)	2 (6.9)	0.89
Other Gram negative bacteria[c]	5 (6.2)	0	0.17
MDR *P. aeruginosa* isolates	36 (44.4)	6 (20)	0.01
Presenting features			
ARDS	7 (8.6)	3 (10.3)	0.78
Septic shock	33 (40.7)	17 (58.6)	0.09
Concomitant PA bacteremia	20 (24.7)	9 (31.1)	0.51
ICU stay			
Reason for ICU admission—no. (%)			
Medical condition	53 (65.4)	29 (100)	<0.001
Surgical condition	3 (3.7)	0	0.29
Trauma	25 (30.9)	0	<0.001
SAPS II on admission—mean ± SD	40 ± 15	49 ± 16	0.01
SOFA score at pneumonia onset—mean ± SD	6 ± 3	7 ± 3	0.23
Total days in ICU—median (IQR)	25 (18–41)	13 (8–19)	<0.001
Treatment of pneumonia			
Colistin or amikacin aerosol therapy	10 (12.4)	1 (3.5)	0.28
IIAT	42 (51.8)	14 (48.3)	0.74
Outcomes			
Days of MV after pneumonia onset —median, IQR*	11 (7–16)	12 (4–17)	1
Days in ICU after pneumonia onset—median, IQR)	23 (13–34)	21 (10–40)	0.65
Death in ICU—no. (%)	35 (43.2)	14 (48.3)	0.64

IQR interquartile range, *COPD* chronic obstructive pulmonary disease, *CPIS* Clinical Pulmonary Infection Score, *SD* Standard Deviation, *MDR* multi-drug resistant, *ARDS* acute respiratory distress syndrome, *PA Pseudomonas aeruginosa*, *ICU* Intensive Care Unit, *SAPS* Simplified Acute Physiology Score, *SOFA* Sequential Organ Failure Assessment, *IIAT* inadequate initial antimicrobial therapy, *MV* mechanical ventilation

[a] Use of antimicrobials for >48 h during the 3 months preceding pneumonia onset

[b] Any time during the 72 h preceding pneumonia onset

[c] *Klebsiella pneumonia* (3 patients), *Escherichia coli* (1 patient), and *Enterobacter cloacae* (1 patient)

by an MDR PA strain. IIAT and carbapenem-based empirical regimens were observed more frequently in the nonsurvivor group. Survival was associated with admissions for trauma, tracheotomy, and empirical regimens that were based on β-lactams/β-lactamase inhibitors and/or included two or more drugs. In logistic regression

Table 2 Univariate analysis of factors associated with inadequate initial antimicrobial therapy in patients with *Pseudomonas aeruginosa* pneumonia

Variable	No. (%) of patients		*P* value	OR (95 % CI)
	IIAT ($n = 56$)	AIAT ($n = 54$)		
Demographics and comorbidities				
Male sex	38 (67.9)	34 (63.0)	0.59	1.24 (0.53–2.94)
Age (year [median, IQR])	70 (52–79)	64 (40–75)	0.13	–
Diabetes mellitus	12 (21.4)	5 (9.3)	0.08	2.67 (0.79–10.39)
Chronic renal failure	7 (12.5)	6 (11.1)	0.82	1.14 (0.30–4.44)
COPD	11 (19.6)	6 (11.1)	0.21	1.95 (0.59–6.96)
Liver disease	3 (5.3)	5 (9.2)	0.43	0.55 (0.08–3.04)
Cancer	7 (12.5)	6 (11.1)	0.82	1.14 (0.30–4.44)
Immunosuppressive therapy	6 (10.7)	6 (11.1)	0.94	0.96 (0.23–3.86)
Pre-pneumonia medical history				
Previous hospital admission	19 (33.9)	13 (24.1)	0.25	1.62 (0.65–4.09)
Previous antibiotic therapy[a]	41 (73.2)	37 (68.5)	0.58	1.25 (0.51–3.11)
Invasive procedures[b]				
Indwelling central venous catheter—no. (%)	50 (89.2)	50 (92.6)	0.55	0.66 (0.13–3.01)
Indwelling nasogastric tube– no. (%)	55 (98.2)	52 (96.3)	0.54	2.11 (0.11–127.1)
Tracheal intubation—no. (%)	32 (57.1)	31 (57.4)	0.97	0.99 (0.43–2.25)
Tracheotomy—no. (%)	21 (37.5)	24 (44.4)	0.46	0.75 (0.32–1.72)
Dialysis—no. (%)	9 (16.1)	1 (1.8)	0.009	10.15 (1.29–452.96)
Characteristics of pneumonia				
Non-ICU-acquired pneumonia	42 (75.0)	39 (72.2)	0.74	1.15 (0.45–2.95)
ICU-acquired pneumonia	14 (25.0)	15 (27.8)	0.74	0.87 (0.34–2.21)
VAP	37 (66.1)	34 862.9)	0.73	1.15 (0.48.2.69)
HAP	13 (23.2)	15 (27.8)	0.58	0.78 (0.30–2.03)
HCAP	6 (10.7)	5 (9.3)	0.80	1.17 (0.27–5.20)
Presenting features				
ARDS	6 (10.7)	4 (7.4)	0.55	1.50 (0.33–7.65)
Septic shock	22 (39.3)	28 (51.9)	0.19	0.60 (0.26–1.37)
Concomitant PA bacteremia	13 (23.2)	16 (29.6)	0.45	0.72 (0.28–1.83)
MDR *P. aeruginosa* isolates	28 (50.0)	14 (25.9)	0.009	2.86 (1.19–6.94)
ICU stay				
Reason for ICU admission—no. (%)				
Medical condition	45 (80.4)	33 (61.1)	0.03	2.60 (1.02–6.81)
Surgical condition	2 (3.6)	1 (1.9)	0.58	1.96 (0.10–117.95)
Trauma	9 (16.1)	20 (37.0)	0.01	0.33 (0.12–0.87)
SAPS II on admission—mean ± SD	42 ± 16	43 ± 16	0.50	–
SOFA score at pneumonia onset—mean ± SD	6 ± 3	7 ± 3	0.33	–
Days at risk—median (IQR)	13.5 (6.5–25)	12 (6–23)	0.61	–
Days of MV before pneumonia onset—median (IQR)	8.5 (1.5–16)	8 (1–15)	0.63	–
Treatment of pneumonia				
Empirical drug regimens				
Carbapenem-based[b]	31 (55.3)	17 (31.4)	0.01	2.69 (1.15–6.35)
β-lactam-β-lactamase inhibitor-based[c]	18 (32.1)	27 (50.0)	0.05	0.47 (0.20–1.09)
Cephalosporin-based[d]	4 (7.1)	1 (1.9)	0.18	4.08 (0.38–204.4)
Others	3 (5.3)	9 (16.6)	0.06	0.28 (0.04–1.23)
Combination therapy in empirical phase	15 (26.8)	30 (55.6)	0.002	0.29 (0.12–0.70)

IQR interquartile range, *COPD* chronic obstructive pulmonary disease, *ICU* Intensive Care Unit, *VAP* ventilator-associated pneumonia, *HAP* hospital-acquired pneumonia, *HCAP* health-care-associated pneumonia, *SD* standard deviation, *MDR* multi-drug resistant, *ARDS* acute respiratory distress syndrome, *PA Pseudomonas aeruginosa*, *SAPS* Simplified Acute Physiology Score, *SOFA* sequential organ failure assessment, *MV* mechanical ventilation, *IIAT* inadequate initial antimicrobial therapy, *AIAT* adequate initial antimicrobial therapy

[a] Use of antimicrobials for >48 h during the 3 months preceding pneumonia onset

[b] Meropenem or imipenem alone or with aminoglycosides, fluoroquinolones, or colistin

[c] Piperacillin/tazobactam alone or with aminoglycosides, fluoroquinolones, or colistin

[d] Ceftazidime or cefepime alone or with aminoglycosides, fluoroquinolones, or colistin

analysis, only four of these factors were independently associated with ICU mortality: IIAT (OR, 7.89; 95 % CI, 2.61–23.85; $P < 0.001$), diabetes mellitus (OR, 5.46; 95 % CI, 1.05–28.42; $P = 0.04$), higher SAPS II (OR, 1.05; 95 % CI, 1.01-1.09; $P = 0.01$), and older age (OR, 1.05; 95 % CI, 1.01–1.08; $P = 0.01$).

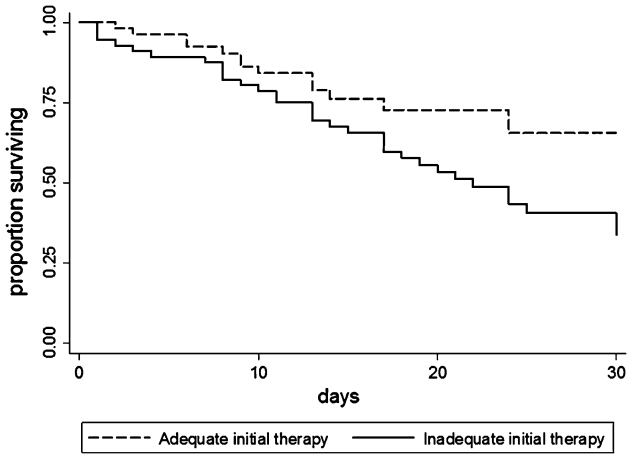

Fig. 2 Kaplan–Meier analysis revealed significantly lower ICU survival rates in patients who received inadequate initial antibiotic therapy ($P = 0.006$)

Discussion

PA pneumonia in an ICU patient is still a life-threatening infection. The ICU mortality rate in our cohort was 44.5 %, which is in line with previous observations [7, 15, 17, 27].

About 80 % of the PA isolates in our study were significantly resistant to one or more of the antimicrobials tested, and 38 % were classified as MDR. In univariate analysis, MDR was strongly correlated with ICU mortality, but this association was not confirmed by multivariate analysis. This finding contrasts with previously reported findings regarding MDR PA BSIs [8, 28, 29], and also with observations on other types of antibiotic-resistant bacteria [30], but the discrepancy might stem from differences in the case mixes (unlike the present study, the ones investigating BSIs also included patients who were not being cared for in the ICU).

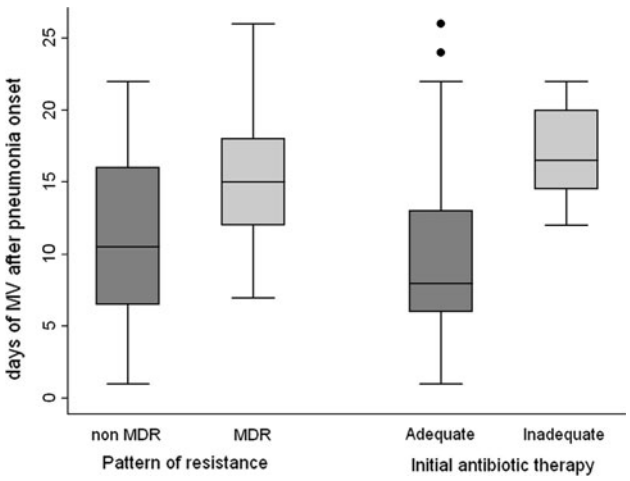

Fig. 3 Days of mechanical ventilation after *P. aeruginosa* pneumonia onset in ICU survivors: significantly longer ventilation periods were associated with inadequate initial antibiotic treatment ($P = <0.001$) and PA isolates with multi-drug resistant (MDR) phenotypes ($P = 0.01$). *Boxes* represent interquartile ranges (*lower border* 25th percentile; *upper border* 75th percentile) and median (50th percentile) (*horizontal line* within the box; *whiskers* indicate minimum and maximum values

IIAT was the most important independent risk factor for mortality and also the only one that is modifiable, and this association was confirmed by survival curve analysis. A recent meta-analysis found that IIAT more than doubles the odds of mortality in patients with VAP [31]. A more recent review examined 14 studies investigating the impact of IIAT in ICU patients with VAP (related to PA in 14.4–100 % of the cases analyzed). IIAT was significantly linked to mortality in only eight of the 14 studies. The authors suggested that the negative findings in the other six might reflect insufficient statistical power or the presence of very severe infections that were fatal despite timely and effective antimicrobial treatment [7].

Not surprisingly, in our study IIAT was independently related to the antimicrobial susceptibility profile of the PA isolate, and MDR PA isolation more than doubled the likelihood of IIAT (OR 2.67). The antimicrobial susceptibility pattern of the infecting organism is obviously not available when empirical therapy is being prescribed. In its stead, however, an epidemiological profile of the ICU itself can do much to improve the choice of an empirical regimen, even if the impact of this information on prescribing practices depends on the way it is used.

The use of antibiotics' combination in the empirical phase of treatment was the only factor significantly associated with a low risk of IIAT, and this is in line with the observation of Garnacho-Montero et al. [10] who found that in patients with PA VAP the odds of IIAT were reduced by use of combined-drug rather than single-drug empirical regimens. In contrast, in this latter study, monotherapy and combined-drug regimens with effective drugs produced similar outcomes during the non-empirical phase, and again this observation is similar to our results.

Given the high mortality rate of PA pneumonia and the shrinking pipeline for new drugs to combat it, recent efforts have been made to make better use of the drugs currently at our disposal. Several groups have highlighted the effects of ureido-/carboxypenicillin (e.g., piperacillin-tazobactam, PTZ) resistance on IIAT rates for PA pneumonia in ICU patients [15–17], but the actual impact of any antipseudomonal agent will obviously depend on local resistance rates. For example, the EPIC I study found that 37 % of the PA isolates recovered in European ICUs were resistant to ureidopenicillins [32], which suggests that PTZ monotherapy is a poor option for empirical treatment of severe infections that may be caused by PA. In our unit, however, while MDR PA is also fairly common, the PTZ resistance rate—about 20 %—is roughly half that observed for the antipseudomonal cephalosporis, carbapenems, and

Table 3 Univariate analysis of factors associated with ICU mortality

Variable	No. (%) of patients		Univariate analysis	
	Died in ICU ($n = 49$)	Discharged from ICU ($n = 61$)	*P* value	OR (95 % CI)
Demographics and comorbidities				
Male sex	30 (61.2)	42 (68.9)	0.40	0.71 (0.30-1.69)
Age (year [median, IQR])	75 (68–81)	52 (32–73)	<0.001	–
Diabetes mellitus	15 (30.6)	2 (3.3)	<0.001	13.01 (2.71–121)
Chronic renal failure	10 (20.4)	3 (4.9)	0.02	4.96 (1.16–29.38)
COPD	9 (18.4)	8 (13.1)	0.50	1.49 (0.46–4.86)
Liver disease	5 (10.2)	3 (4.9 %)	0.29	2.19 (0.39–14.79)
Cancer	10 (20.4)	4 (6.6)	0.03	3.65 (0.96–16.92)
Immunosuppressive therapy	8 (16.3)	4 (6.5)	0.11	2.78 (0.68–13.36)
Pre–pneumonia medical history				
Previous hospital admission	18 (36.7)	14 (22.9)	0.11	1.95 (0.78–4.89)
Previous antibiotic therapy[a]	37 (75.5)	41 (67.2)	0.34	1.5 (0.60–3.86)
Invasive procedures[b]				
Indwelling central venous catheter	43 (87.8)	57 (93.4)	0.33	0.50 (0.09–2.28)
Indwelling nasogastric tube	49 (100)	58 (95.1)	0.25	–
Tracheal intubation	21 (42.9)	21 (34.4)	0.37	1.43 (0.61–3.33)
Tracheotomy	15 (30.6)	30 (49.2)	0.05	0.46 (0.19–1.07)
Dialysis	8 (16.3)	2 (3.3)	0.02	5.75 (1.06–57.79)
Characteristics of pneumonia				
Non-ICU-acquired pneumonia	14 (28.6)	15 (24.6)	0.64	1.22 (0.48–3.13)
ICU-acquired pneumonia	35 (71.4)	46 (75.4)	0.64	1.63 (0.61–4.37)
VAP	30 (61.2)	41 (67.2)	0.51	0.77 (0.32–1.82)
HAP	14 (28.5)	14 (22.9)	0.50	1.17 (0.74–1.83)
HCAP	5 (10.2)	6 (9.8)	0.94	1.02 (0.51–2.02)
CPIS (score [mean ± SD])	8 ± 1	8 ± 1	0.39	–
Causative organisms—no. (%)				
P. aeruginosa alone	42 (85.7)	56 (91.8)	0.30	0.73 (0.43–1.24)
P. aeruginosa associated with *Acinetobacter baumanii*	7 (14.2)	5 (8.2)	0.30	1.86 (0.46–7.96)
	4 (8.1)	3 (4.9)	0.48	1.71 (0.27–12.26)
Other Gram negative bacteria[c]	3 (6.1)	2 (3.3)	0.47	1.92 (0.20–23.78)
MDR *P. aeruginosa* isolates	25 (51)	17 (27.9)	0.01	2.69 (1.14–6.43)
Presenting features				
ARDS	6 (12.2)	4 (6.6)	0.34	1.99 (0.44–10.13)
Septic shock	28 (57.1)	22 (36.1)	0.03	2.36 (1.02–5.49)
Concomitant PA bacteremia	11 (22.4)	18 (29.5)	0.40	0.69 (0.26–1.78)
ICU stay				
Reason for ICU admission—no. (%)				
Medical condition	45 (91.8)	33 (54.1)	<0.001	9.54 (2.88–40.25)
Surgical condition	2 (4.1)	1 (1.6)	0.58	2.55 (0.13–153)
Trauma	2 (4.1)	27 (44.3)	<0.001	0.05 (0–0.24)
SAPS II on admission—mean ± SD	50 ± 18	37 ± 11	<0.001	–
SOFA score at pneumonia onset—mean ± SD	8 ± 3	6 ± 3	0.001	–
Days at risk—median (IQR)	14 (8–29)	11 (3–18)	0.05	
Days of MV before pneumonia onset—median (IQR)	8 (1–16)	8 (2–16)	0.53	–
Treatment of pneumonia				
Empirical drug regimens:				
Carbapenem-based[d]	27 (55.1)	21 (34.4)	0.02	2.33 (1.00–5.44)
β-lactam-β-lactamase inhibitor-based[e]	15 (30.6)	30 (49.1)	0.04	0.45 (0.19–1.07)
Cephalosporin-based[f]	3 (6.1)	2 (3.2)	0.47	1.92 (.20–23.78)
Others	4 (8.1)	8 (13.1)	0.40	058 (0.12–2.38
IIAT	36 (73.5)	20 (32.8)	<0.001	5.68 (2.30–14.24)
Definitive drug regimens (based on in vitro susceptibility data):				
Carbapenem-based[d]	14 (28.5)	22 (36.1)	0.40	0.71 (0.28–1.71)
β-lactam-β-lactamase inhibitor-based[e]	12 (24.4)	20 (32.7)	0.34	0.66 (0.26–1.66)
Cephalosporin-based[f]	7 (14.3)	10 (16.4)	0.76	0.85 (0.25–2.72)
Others	6 (12.2)	9 (14.7)	0.70	0.80 (0.21–2.77)
Combination therapy in empirical phase	14 (28.6)	31 (50.8)	0.02	0.39 (0.16–0.92)
Combination therapy in the definitive phase	12 (24.5)	18 (29.5)	0.55	0.77 (0.29–1.96)
Continuous infusion of piperacillin/tazobactam	5 (10.2)	14 (22.9)	0.08	0.38 (0.09–1.24)

Table 3 continued

Variable	No. (%) of patients		Univariate analysis	
	Died in ICU ($n = 49$)	Discharged from ICU ($n = 61$)	*P* value	OR (95 % CI)
Colistin or amikacin aerosol therapy	3 (6.1)	8 (13.1)	0.34	0.43 (0.07–1.94)

IQR interquartile range, *ICU* Intensive Care Unit, *COPD* chronic obstructive pulmonary disease, *VAP* ventilator-associated pneumonia, *HAP,* hospital-acquired pneumonia, *HCAP* health-care-associated pneumonia, *CPIS* Clinical Pulmonary Infection Score, *SD* standard deviation, *MDR* multi-drug resistant, *ARDS* acute respiratory distress syndrome, *PA Pseudomonas aeruginosa*, *SAPS* Simplified Acute Physiology Score, *SOFA* sequential organ failure Assessment; *MV*, mechanical ventilation; *IIAT* inadequate initial antimicrobial therapy

[a] Use of antimicrobials for >48 h during the 3 months preceding pneumonia onset

[b] Any time during the 72 h preceding pneumonia onset

[c] *Klebsiella pneumonia* (3 patients), *Escherichia coli* (1 patient), and *Enterobacter cloacae* (1 patient)

[d] Meropenem or imipenem alone or with aminoglycosides, fluoroquinolones, or colistin

[e] Piperacillin/tazobactam alone or with aminoglycosides, fluoroquinolones, or colistin

[f] Ceftazidime or cefepime alone or with aminoglycosides, fluoroquinolones, or colistin

fluoroquinolones, so in units like ours, empirical regimens based on antipseudomonal drug combinations that include PTZ should reduce IIAT rates. In addition, in our cohort, antibiogram-driven regimens that were PTZ-based (used in continuous infusion in about one-third of patients) were associated with mortality rates identical to those observed with carbapenem-based therapy (14/36, 38.9 % vs. 12/30, 38.7 %). PTZ might thus be a suitable option for definitive therapy of PA pneumonia in certain ICUs, and this solution could stem the rise in carbapenem consumption, which is particularly worrisome in ICU settings where carbapenemase-producing organisms are becoming more and more common [33]. Definitive PTZ-based therapy is even more likely to be successful in the future since the susceptibility breakpoint for this drug has recently been lowered [34].

In our cohort, patients with MDR PA pneumonia and those who had received IIAT also had significantly prolonged post-infection mechanical ventilation times and consequently, longer post-infection ICU stays, an important determinant of total ICU costs [9]. The impact of antibiotic resistance on the length of hospital stays and costs has been widely demonstrated for severe infections caused by Gram-negative bacteria, including PA [35–37], and for VAP caused by methicillin-resistant *Staphylococcus aureus* (MRSA) [38]. Similarly, IIAT has been linked to longer hospital stays and higher costs in cases of severe sepsis and septic shock related to gram-negative organisms and MRSA sterile-site infections [39, 40]. However, limited data are available on the specific impact of antibiotic resistance or IIAT on ICU stays in patients diagnosed with PA pneumonia. Trouillet et al. found no difference between VAPs caused by piperacillin-resistant and piperacillin-susceptible PA in terms of the post-pneumonia duration of MV [17]. Kollef et al. [9] studied patients with VAP attributed to potentially antibiotic-resistant Gram-negative bacteria and found that post-infection MV and ICU stays were unrelated to the appropriateness of the initial antibiotic regimen. Aside from differences in population characteristics, the discordance between their results and those of our study might be partly related to the fact that we assessed the length of MV and ICU care only in patients who survived (since both of these periods would be shortened rather than lengthened by early death).

Our study has some limitations that have to be acknowledged. Firstly, it was conducted in a single center. Secondly, the retrospective nature of the study could underestimate the role of certain factors. Thirdly, despite the large number of variables included in our analysis, other factors not studied might have influenced the results.

In conclusion, our findings confirm that PA pneumonia is associated with high mortality in ICU patients and highlight the importance of IIAT as a risk factor for this outcome. MDR in the PA isolate is not independently related to ICU mortality in these cases, but, like IIAT, it can significantly increase the length of MV. Our findings also suggest that, depending on local resistance patterns, PTZ-based regimens may be suitable in the empirical and definitive phases of treatment in these cases, an option that could reduce carbapenem consumption in ICU settings.

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