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ORIGINAL ARTICLE

Infections in intensive care unit adult patients harboring multidrug-resistant *Pseudomonas aeruginosa*: implications for prevention and therapy

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Abstract The purpose of this paper was to report the burden and characteristics of infection by multidrug-resistant *Pseudomonas aeruginosa* (MDR-PA) in clinical samples from intensive care unit (ICU) adults, and to identify predictors. This was a retrospective observational study at four medical-surgical ICUs. The case cohort comprised adults with documented isolation of an MDR-PA strain from a clinical specimen during ICU stay. Multivariate analysis was performed to identify predictors for MDR-PA infection. During the study period, 5667 patients were admitted to the ICU and *P. aeruginosa* was isolated in 504 (8.8%). MDR-PA was identified in 142 clinical samples from 104 patients (20.6%); 62 (43.6%) of these samples appeared to be true infections. One hundred and eighteen (83.1%) isolates were susceptible only to amikacin and colistin, and 13 (9.2%) were susceptible only to colistin. Overall, the MIC_{50} to meropenem was 16 μg/mL and the MIC_{90} was >32 μg/mL, with 60.4% of respiratory samples being MIC >32 μg/mL to meropenem. Independent predictors for MDR-PA infection were fever/hypothermia [odds ratio (OR) 9.09], recent antipseudomonal cephalosporin therapy (OR 6.31), vasopressors at infection onset (OR 4.40), and PIRO (predisposition, infection, response, and organ dysfunction) score >2 (OR 2.06). This study provides novel information that may be of use for the clinical management of patients harboring MDR-PA and for the control of the spread of this organism.

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Background

Multidrug-resistant *Pseudomonas aeruginosa* (MDR-PA) has become a significant problem in the intensive care unit (ICU). A report by the Centers for Disease Control and Prevention (CDC) published in 2013 classified it as a "serious antibiotic resistant threat" [1], estimating that 6700 patients were affected by MDR-PA (resistant >3 antibiotics) in the USA in 2013 and that around 440 had died as a result. *Pseudomonas aeruginosa* possesses an impressive ability to develop antibiotic resistance; it represents a serious challenge in the management of infections in the ICU, especially since MDR-PA pneumonia is associated with higher morbidity than infection by susceptible strains [2]. In the last decade, there has been a rise in MDR-PA strains, especially in the ICU setting [3–5]. ICU patients usually have concomitant problems and elevated inflammatory markers that may be due to either infectious or non-infectious causes. Consequently, differentiating between colonization and infection in clinical samples in this setting can be challenging, and failure to do so effectively may result in unnecessary antibiotic treatment, with the detrimental consequences that this entails. Factors associated with the isolation of MDR-PA have been studied in hospitalized patients,

but the current guidelines are not reliable predictors of infection in the ICU [2, 6, 7].

Thus, the main objective of this study was to identify predictors of MDR-PA infection in ICU patients with positive clinical samples. A secondary objective was to take a snapshot of the characteristics of clinical samples with MDR-PA isolates. Outcome considerations are far from the objectives of this study. Our hypothesis was that risk factors for MDR-PA differ in patients who develop infection and in patients who are only colonized.

Methods

Patients and study design

A retrospective cohort study was carried out at four general ICUs (36 beds) of a major tertiary teaching hospital in Barcelona, Spain (Vall d'Hebron University Hospital). These ICUs were not used as recovery rooms (except for transplant) and burns, cardiac surgery, cardiology, and head trauma patients were admitted to other ICUs. We included all clinical samples in which MDR-PA was isolated for the first time in the ICU between January 2010 and April 2015, taken from all adult patients consecutively admitted to these ICUs with suspected infection (clinical samples) and without previous isolation of MDR-PA during the current admission. Surveillance samples (rectal, skin, and nasopharyngeal swabs) and patients with prior MDR-PA isolation during the current admission were excluded. Given that standard ICU care includes the performance of multiple and simultaneous cultures when infection is suspected, all clinical samples retrieved simultaneously from the same patient were included and recognized as one case. Epidemiological, clinical, and microbiological data were recorded and each case was then classified as either infection or colonization. Patients' records were reviewed up to death or ICU discharge. Further isolations were recorded and included only if they were infections. The study was approved by the local institutional review board, and the need for written consent was waived due to the observational nature of the study.

Variables included were demographic data, comorbidities, and risk factors for MDR-PA isolation (diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease, cystic fibrosis, immunosuppressive state, malignancy, neurological sequel, and pressure ulcers) [5]. Baseline comorbidity was assessed with Charlson's comorbidity score [8]. Severity scores were recorded at admission (APACHE II [9] and SOFA [10]) and at the time of sample collection (SOFA and PIRO). The PIRO (predisposition, infection, response, and organ dysfunction) is a severity score that allows the prediction of the mortality risk in patients with ventilator-associated pneumonia (VAP) [11]. ΔSOFA was defined as SOFA score at culture minus SOFA score at admission, in order to assess the patient's progress at the time of the culture. Clinical, microbiological, and laboratory data related to infection status, severity of illness, and the appropriateness of initial antibiotic therapy were also recorded.

ICU characteristics and infection control

Patients were admitted to four independent units on two different floors. Two beds in five closed rooms were available in each ICU, which each admitted eight patients. Overall, the nurse to patient ratio was 1:2. Infection control measures were standardized, and included the standard precautions applied in all ICU admissions and contact precautions in patients known to be colonized by methicillin-resistant *Staphylococcus aureus* (MRSA) or MDR Gram-negative agents. Surveillance cultures were limited to transfers from other centers, patients colonized in prior admissions, or in the presence of potential outbreaks. Patients with extended-spectrum beta-lactamase or carbapanemase-producing Enterobacteriaceae, MDR-PA, *Acinetobacter baumannii*, resistant *Stenotrophomonas maltophilia*, MRSA, and *Clostridium difficile* were maintained alone in the ICU rooms. Hand washing with 2% chlorhexidine was performed with dispensers at each room gate. Overall compliance with hand washing (assessed by blinded audits) was estimated to be 70.5% over the study period. All patients used disposable bedpans. Selective digestive decontamination (SDD) was performed in all patients with mechanical ventilation (MV) and comprised administration every 6 h of an antibiotic solution containing tobramycin 0.8% and colistin 1% through a nasogastric tube and topical oral paste containing tobramycin 2%, colistin 2%, amphotericin B 2%, and vancomycin 4%.

Microbiology

Pseudomonas aeruginosa was isolated from respiratory samples (sputum, endotracheal aspirate, and bronchoalveolar lavage), blood, urine, cerebrospinal fluid (CSF), peritoneal fluid, catheter tips, surgical wounds, and ear exudate. The microbiology laboratory identified MDR-PA using the VITEK MS automated system (bioMérieux, Marcy l'Etoile, France). Antimicrobial susceptibility of isolates was tested using disk diffusion, and resistant strains were checked using the gradient diffusion method. Minimum inhibitory concentrations (MICs) were classified using the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints [12]. MDR was defined as non-susceptibility to at least one agent in ≥3 antimicrobial categories, and extensive drug resistance (XDR) as non-susceptibility to at least one agent in all but ≤2 antimicrobial categories [13]. Inadequate initial antibiotic treatment was defined as the absence of any antibiotic with in vitro susceptibility administered at the adequate dose [14].

Definitions

- *Previous P. aeruginosa colonization*:

– At least two positive samples for *P. aeruginosa* within the 6 months prior to current admission, OR
– One positive sample for *P. aeruginosa* during current admission (minimum of 14 days earlier).

- *Index isolate*: first isolation of MDR-PA in ICU (either infection or colonization). It could include isolates from more than one sample site taken simultaneously.
- *Infection*: specimens associated with clinical signs of inflammation (fever, alteration in WBC, presence of purulence) and categorized as:

– Respiratory: Ventilator-associated pneumonia (VAP) and hospital-acquired pneumonia (HAP) were diagnosed according to American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) 2005 guidelines [15]. Ventilator-associated tracheobronchitis (VAT) was defined according to Craven et al. [16].
– Non-respiratory: Defined following International Sepsis Forum consensus definitions [17].
– Bloodstream: Blood culture isolates.

- *Superinfections*: MDR-PA positive sample occurring 14 days after a case, in addition to meeting the infection criteria described above.
- *Colonization*: MDR-PA positive specimens that did not fulfil the infection criteria.
- Shock: New presence of sustained hypotension and/or vasopressor initiation (noradrenaline) or increase of ≥20% in less than 24 h.

Statistical analysis

Continuous variables were tested with the Kolmogorov–Smirnov test to assess deviations from normality. Discrete variables were summarized as frequency (%) and continuous variables as mean and standard deviation (SD) or median and interquartile range (IQR). Univariate analysis was performed using Pearson's Chi^2, two-tailed Fisher's exact test, or the Mann–Whitney *U*-test, as appropriate. Multivariate logistic regression analysis was used to determine predictors for MDR-PA infection/colonization, and variables were included if they were statistically significant in the univariate analysis and/or if they were considered clinically relevant according to current knowledge with a $p \leq 0.10$ level of significance. A logistic regression analysis with the stepwise forward method was applied to identify association with infections among the MDR-PA isolates. Odds ratios (ORs) are presented 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

Clinical isolates: incidence and distribution

During the study period, 5667 patients were admitted to the ICU and *P. aeruginosa* was isolated in 504 (8.8%). A total of 142 (21%) MDR-PA clinical samples (from 104 patients) were identified, 20 (14.1%) in blood, 108 (76.1%) respiratory, and 54 (38%) non-respiratory. Bacteremia was secondary to respiratory, urinary, and catheter samples in 9, 4, and 3 isolates, respectively. Distribution between ICUs was balanced (data not shown). MDR-PA was isolated in more than one site (per case) in 32 cases (22.5%). Respiratory MDR-PA were mainly associated with MV [30 VAP: median onset 25.5 days (IQR: 19–32) and 26 VAT: median onset 20.5 days (IQR: 9–31)], 83.9% being associated with tracheotomy. Twenty-nine (43.3%) required vasopressors. Non-respiratory sites were the urinary tract in 34 cases (23.9%), abdomen in 10 (7%), catheter tip in 7 (4.9%), and other in 10 (7%). In 47.7% of these samples, another microorganism was also isolated; 11 (25%) were MDR. Enterobacteriaceae were the most common concomitant microorganisms isolated (38.6%), followed by *Enterococcus* spp. (27.3%), other Gram-positive cocci (18.2%), and yeasts (13.6%). Eleven (7.8%) isolates were MDR, of which seven were isolated from the same MDR-PA sample.

Index isolates appeared to be true infections in 62 samples (43.6%). Twenty-four (23.1%) of these patients developed subsequent infections. Indeed, a total of 100 infections were identified in 72 patients (69.2%). A group flow diagram of patients and cases is shown in Fig. 1.

Demographics

The patient population was predominantly male (72/104, 69.2%), with a median age of 59 years (IQR: 48–69) and low baseline comorbidities (median Charlson's index: 2, IQR: 1–3.5), but high severity at ICU admission (median APACHE II: 22.5, IQR: 17–28). At the time the samples were obtained, the median SOFA score was 6 (IQR: 3–8), similar to the score at admission (median ΔSOFA 0, IQR: −2–2).

The median pre-ICU ward stay was 1 day (IQR: 0–16) and the median ICU stay was 15.5 days (IQR: 3–34) before the index isolate. Of the 104 patients with MDR-PA, 22 were admitted from the emergency department (21%), 19 from

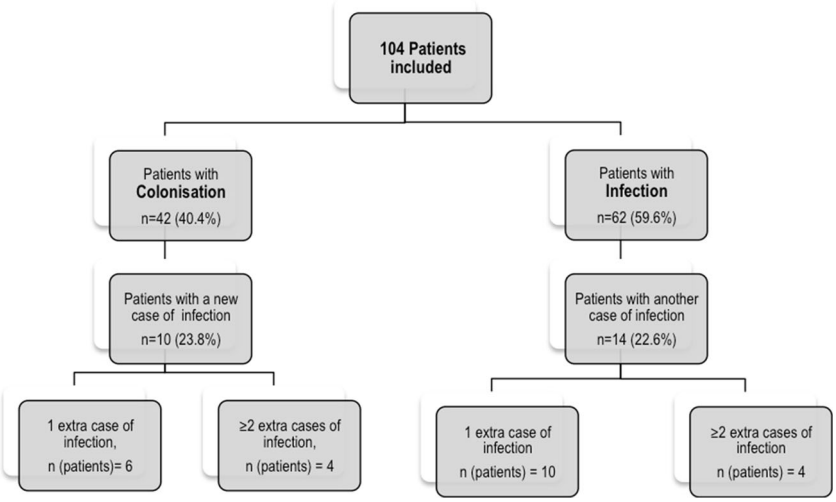

Fig. 1 Group flow diagram of patients and cases of multidrug-resistant *Pseudomonas aeruginosa* (MDR-PA). One hundred and six patients were included: 62 were classified as infected and 44 as colonized. Twenty-five patients had infection after the first isolation: 12 were previously colonized and 13 were previously infected. Patients had more than one infection following the first isolation, resulting in a total of 100 infections in 74 patients

the surgical theater (18.3%), eight from the recovery room (7.7%), and 36 from hospitalization wards (34.6%). Nineteen were referred from another hospital (18.3%). Sixty-seven were medical admissions, 15 had undergone thoracic surgery, three cardiac surgery, 14 abdominal surgery, and two neurosurgery; none had trauma and three were miscellaneous. Regarding comorbidities, immunosuppression was present in almost half of the cohort (51, 49%), of whom 25 had undergone solid organ transplant (17 lung/4 liver/3 kidney/1 hepatorenal) and two bone marrow transplant. Moreover, 32 (30.8%) had chronic lung disease; 22 (21.2%) had either chronic obstructive pulmonary disease (COPD) or cystic fibrosis (CF) and 23 (22.1%) had chronic heart disease. Patients' baseline characteristics and risk factors are detailed in Table 1. When clinical samples were retrieved, 121 patients (85.2%) underwent MV, 102 (71.8%) with a tracheostomy, and 54 (38.3%) with parenteral nutrition.

Prior antibiotic exposure

Most MDR-PA isolates (118, 83.1%) were susceptible only to amikacin and colistin, and 13 (9.2%) were extensively multidrug-resistant (susceptible only to colistin). Overall, the MIC_{50} to meropenem was 16 μg/mL and MIC_{90} was >32 μg/mL, with 60.4% of respiratory samples being MIC >32 μg/mL to meropenem. Figures for prior antibiotic exposure were as follows: 36.5% for carbapenems, 18.3% for quinolones, 58.7% for penicillins, and 38.5% for cephalosporins (cefepime 9.7% and ceftazidime 13.6%). Only 13.5% had prior aminoglycoside exposure. Overall, prior antipseudomonal exposure was 77.9%. Additionally, 80.8% of patients had prior exposure to colistin due to SDD. Previous antibiotic exposure to antipseudomonal cephalosporins was significantly associated with infection [OR 3.88 (95% CI: 1.21–12.49)], which, in turn, was associated with cefepime exposure (10 vs. 0 patients, $p < 0.01$) but not with ceftazidime.

MDR-PA infection

In total, 100 infections were recorded, of which 67 (67%) were respiratory and 33 (33%) were non-respiratory. In the order of frequency, we observed: 30 VAP, 26 VAT, 18 urinary infections, 11 HAP, seven mixed infection (including abdominal), and three catheter infections (see figure in the electronic supplementary material). Initial antibiotic therapy was inadequate in 78 of 100 infections, and was more frequent (80.7% in the first infection vs. 73.7% in secondary infections, $p = 0.4$). The mean time to adequate antibiotic therapy was 1.3 days (±1.7 SD) and was significantly longer in the first infection (1.9 ± 1.9 vs. 0.7 ± 1.3, days ± SD, $p < 0.01$). The majority of demographic data did not differ between the infection and colonization subgroups. Only the Charlson's index was significantly higher in the infection group than in the colonization group among clinical isolates: median 3 (IQR: 1–4) vs. 1 (IQR: 0.3); $p < 0.05$. Variables at the time of sampling that were associated with infection are detailed in Table 2. In the univariate analyses, multiple sites of MDR-PA isolation were also significantly associated with infection (OR 8.57, 95% CI [1.95–37.78], $p < 0.01$).

Respiratory infections had lower rates of associated bloodstream infections than non-respiratory infections (13.4% vs. 33.3%, $p < 0.05$). However, HAP was significantly associated with bloodstream infection: 5 of 11 cases (45.5%) vs. 15 of 89 (16.9%) in the rest of the infections, $p < 0.01$. VAT was not associated with any positive blood cultures ($p < 0.05$). Among non-respiratory infections, the urinary tract was the most common site. Out of the 62 clinical isolates that appeared to be infections, 14 (22.6%) developed at least another infection during the ICU stay. The median time between infections was 23.5 days (IQR: 18–32). The median time between index colonization and subsequent infection was 15.5 days

Table 1 Univariate analysis of demographics and risk factors associated with multidrug-resistant *Pseudomonas aeruginosa* (MDR-PA) infection and colonization

	All, 104	Infection, $n = 62$	Colonization, $n = 42$	Infection OR (95% CI), p
Age, years, median (IQR)	59 (48.5–68)	58.5 (49–66)	59.5 (47–70)	
Sex				
Male	72 (69.2%)	45 (72.6%)	27 (64.3%)	
Female	32 (30.8%)	17 (27.4%)	15 (35.7%)	
Charlson comorbidity index, median (IQR)	2 (1–3.5)	2.5 (1–4)**	2 (1–3)**	
Origin				
Ward	36 (34.6%)	24 (38.7%)	12 (28.6%)	
Emergency room	22 (21.2%)	16 (26.3%)	6 (13.9%)	
Operating theater	19 (18.3%)	11 (17.7%)	8 (19.1%)	
Other center	19 (18.3%)	7 (11.3%)*	12 (28.6%)*	0.32 (0.11–0.89), $p = 0.03$
Recovery room	8 (7.7%)	4 (6.5%)	4 (9.5%)	
Admission diagnosis				
Infectious	33 (31.7%)	20 (32.3%)	13 (30.9%)	
Respiratory	26 (25%)	18 (29%)	8 (19.1%)	
Neurological	16 (15.4%)	8 (12.9%)	8 (19.1%)	
Cardiovascular	11 (10.6%)	5 (8.1%)	6 (14.3%)	
Gastrointestinal	9 (8.7%)	6 (9.7%)	3 (7.1%)	
Oncohematologic	3 (2.9%)	2 (3.2%)	1 (2.4%)	
Other	5 (4.8%)	2 (3.2%)	3 (7.1%)	
Severity at admission				
APACHE II, median (IQR)	22.5 (17–28)	22.5 (17–28)	22.5 (17–29)	
SOFA at admission, median (IQR)	6 (4–8)	6 (4–9)	5.5 (3–7)	
Risk factors for MDR-PA isolation				
Comorbidities				
Diabetes mellitus	27 (25.9%)	16 (25.8%)	11 (26.2%)	
Neurological sequelae	7 (6.7%)	4 (6.5%)	3 (7.1%)	
Skin ulcers (chronic or previous pressure ulcers)	4 (3.8%)	3 (4.8%)	1 (2.4%)	
Chronic lung disease (not COPD/CF)	32 (30.8%)	20 (32.3%)	12 (28.6%)	
COPD or CF	22 (21.2%)	17 (27.4%)	5 (11.9%)	
Chronic renal disease	19 (18.3%)	9 (14.5%)	10 (23.8%)	
Chronic heart disease	23 (22.1%)	15 (24.2%)	8 (19.1%)	
Chronic liver disease	14 (13.5%)	9 (14.5%)	5 (11.9%)	
Immunocompromised	51 (49%)	35 (56.5%)	16 (38.1%)	
Malignancy (active)	19 (18.3%)	14 (22.6%)	5 (11.9%)	
Neutropenia	5 (4.8%)	4 (6.5%)	1 (2.4%)	
HIV/AIDS	5 (4.8%)	5 (8.1%)	0	
Solid organ transplant (previous and current)	25 (24%)	14 (22.6%)	11 (26.2%)	
Pharmacological (non-SOT)	8 (7.7%)	7 (11.3%)	1 (2.4%)	
Admission to hospital in the previous 90 days***	27 (27.6%)	15 (26.3%)	12 (29.3%)	
Admission to ICU facility in the previous 90 days	34 (32.7%)	20 (32.3%)	14 (33.3%)	
ICU admission >5 days	84 (80.8%)	53 (85.5%)	31 (73.8%)	
Pre-culture total LOS, median (IQR)	29.5 (11–45)	23 (11–43)	33 (15–59)	
Hospital LOS pre-ICU, days, median (IQR)	1 (0–16)	2 (0–13)	1 (0–17)	
ICU LOS pre-culture, days, median (IQR)	15.5 (3–34)	14.5 (5–33)	15.5 (1–35)	
Previous MV	77 (74%)	44 (70.9%)	33 (78.6%)	
MV pre-culture, days, median (IQR)	11.5 (0–35)	11 (0–35)	15 (5–38)	
Previous antibiotic (30 days)	101 (97.1%)	60 (98.4%)	41 (95.4%)	
With antipseudomonal activity	81 (77.9%)	47 (77.1%)	34 (79.1%)	
Antipseudomonal cephalosporin	22 (21.2%)	18 (29%)**	4 (9.5%)**	3.88 (1.21–12.49), $p = 0.02$
Previous CRRT	21 (20.2%)	13 (20.9%)	8 (19.1%)	
Previous colonization with *Pseudomonas* (non-MDR)	16 (15.4%)	10 (16.4%)	6 (13.9%)	

CF = cystic fibrosis;' *COPD* = chronic obstructive pulmonary disease; *CRRT* = continuous renal replacement therapy; *LOS* = length of stay; *MV* = mechanical ventilation; *OR* = odds ratio; *SOT* = solid organ transplant

*$p < 0.01$

**$p < 0.05$

(IQR: 10–25.5). Variables associated with developing multiple infections were: transfer from post-surgical reanimation unit (21.3% vs. 2.1%, $p < 0.05$) and Rh-negative type of blood (35.7% vs. 10.4%, $p < 0.05$).

Multivariate analysis

Variables introduced in the logistic regression analysis using the stepwise forward method were: Charlson index,

Table 2 Univariate analysis of clinical findings associated with MDR-PA infection and colonization

	All, 42	Infection, $n = 100$	Colonization, $n = 42$	Infection OR (95% CI)
Severity at the time of culture				
SOFA, median (IQR)	6 (3–8)	6 (3–9)	5 (3–7)	
ΔSOFA, median (IQR)	0 (−2–2)	0 (−2–3)	0 (−2–2)	
PIRO, median (IQR)	1.9 ± 1.4	2.4 ± 1.5*	1.2 ± 1*	
Risk factors at the time of culture				
Previous PA colonization	44 (30.9%)	38 (38%)*	6 (14.3%)*	3.84 (1.48–9.96)**
Proton pump inhibitors	142 (100%)	100 (100%)	42 (100%)	
Selective digestive decontamination	114 (80.3%)	76 (76%)**	38 (90.5%)**	0.32 (0.10–0.98)**
Parenteral nutrition	54 (38.3%)	43 (43%)	11 (26.8%)	
Mechanical ventilation	121 (85.2%)	83 (83%)	39 (90.7%)	
Tracheostomy	102 (71.8%)	73 (73%)	29 (69.1%)	
High-flow nasal cannulae	8 (5.6%)	5 (5.1%)	3 (6.9%)	
Arterial/venous catheter	141 (99.3%)	99 (99%)	42 (100%)	
Nasogastric tube	115 (80.9%)	78 (78%)	37 (88.1%)	
Vesical catheter	140 (98.6%)	98 (98%)	42 (100%)	
Other tube or drain	51 (35.9%)	35 (35%)	16 (38.1%)	
Pressure skin ulcers***	10 (7.3%)	7 (7.1%)	3 (7.7%)	
Clinical findings at the time of culture				
Temperature <36 or ≥38 °C	66 (46.8%)	59 (59%)*	7 (16.7%)*	6.19 (2.60–14.71)*
Leukocyte count <4 or ≥9.9 × 10E9/L	92 (66.7%)	74 (74%)*	18 (42.9%)*	3.52 (1.63–7.59)*
CRP (mg/dL), median (IQR)***	13.45 (6–24.6)	14.7 (6–27.5)	9.2 (4.9–23.7)	
Shock	51 (35.9%)	47 (47%)*	4 (9.5%)*	6.59 (2.39–18.16)*
Other source of SIRS/active infection***	26 (27.4%)	16 (21.9%)**	10 (45.5%)**	0.34 (0.12–0.92)**
Antibiotic susceptibility				
Susceptible to colistin and amikacin	118 (83.1%)	82 (82%)	36 (85.7%)	
Susceptible only to colistin	13 (9.2%)	9 (9%)	4 (9.5%)	
R ≥ 3 antipseudomonal families, other	11 (7.8%)	9 (9%)	2 (4.8%)	

CRP = C-reactive protein; *SIRS* = systemic inflammatory response syndrome

*$p < 0.01$

**$p < 0.05$

*** Missing data >5%

immunosuppression, COPD/CF, previous PA colonization, previous exposure to antipseudomonal cephalosporins, SDD, fever/hypothermia, vasopressors at infection onset, PIRO score >2 when sampling, and isolates from a non-respiratory sample. The model shows an association between MDR-PA infection and PIRO score >2 when sampling (OR 2.06), vasopressors at infection onset (OR 4.40), previous antipseudomonal cephalosporins (OR 6.31), and fever/hypothermia (OR 9.09) (Table 3). A similar model was identified when ICU stay over 2 weeks was entered into the model. Finally, no differences in the predictors between respiratory and non-respiratory episodes were identified.

Discussion

This study provides novel, potentially useful information for the clinical management of patients harboring MDR-PA and

Table 3 Multivariate analysis showing the predictors for MDR-PA infection from clinical samples

Independent variable	*p*-Value	OR (95% CI)	Hosmer and Lemeshow test
PIRO score >2 at sample	<0.05	2.06 (1.18–3.58)	$p = 0.196$
Vasopressors at infection onset	<0.05	4.40 (1.05–18.39)	
Previous antipseudomonal antibiotic	<0.01	6.31 (1.59–25.13)	
Fever/hypothermia	<0.01	9.09 (2.81–34.89)	

for the control of the spread of this organism. Our findings suggest that MDR-PA isolation in critically ill patients is not terminal; indeed, more than 50% of episodes occurred in patients younger than 50 years of age with a predicted survival of at least 10 years. Half of them were immunocompromised patients with multiple organ dysfunction at ICU admission, who presented MDR-PA isolation with a tracheostomy in situ and prolonged ICU stay. *Pseudomonas* clinical samples were obtained in 10% of our ICU patients, with MDR-PA representing 25% of isolates. MDR-PA was identified particularly in clinical samples from blood and the respiratory tract, and was associated with true infection in two-thirds of these isolates. More than 60% of MDR-PA were highly carbapenem-resistant, more than 80% were only susceptible to amikacin and colistin, and an additional 10% were susceptible only to colistin (an agent used in the SDD protocol in this ICU and the only antibiotic to which all of the strains were susceptible). Interestingly, prior exposure to antipseudomonal cephalosporins was associated with a 4-fold increased risk of MDR-PA infection, a finding which stresses the implications of antibiotic stewardship in ICU patients. Our predictive model identified different variables associated with infection or colonization among positive clinical samples. These findings may be of help in improving appropriate empiric antimicrobial prescriptions in the ICU.

A recent report [18] published the global epidemiology of *P. aeruginosa*, but specific studies of patients harboring MDR-PA remain scarce [19, 20] and great uncertainty exists regarding the management implications in specific ICU patients harboring MDR or extensively-resistant strains. Indeed, in our cohort, there were not many differences in the clinical samples harboring MDR-PA with regard to whether patients developed infection or merely remained colonized. Our predictive model identified different risk factors for samples associated with infection versus colonization, but not for colonization per se. The model identified PIRO score >2 at sampling, fever/hypothermia, shock, and previous exposure to antipseudomonal antibiotic as independent predictors of MDR-PA infection. These findings may help to increase the choice of appropriate empiric antibiotic prescription. The PIRO score is a severity assessment score for CAP and VAP, based on the PIRO concept [11, 21]. It is a simple, practical clinical tool for predicting ICU 28-day mortality. It allows an easy risk stratification of patients at different levels of severity with progressive rates of mortality, and it is associated with progressive healthcare resources utilization. The PIRO concept considers the predisposing conditions, the nature and extent of insult, the nature and magnitude of the host response, and the degree of concomitant organ dysfunction. So, taking into account the different features of infection with a pathophysiological focus; it is reasonable to be associated with respiratory as well with non-respiratory infection. Additionally, we found that patients coming from post-surgical recovery or with Rh-negative type of blood were more likely to present multiple infections, as reported elsewhere for other bacterial, viral, and parasitic infections [22–24].

The main limitation of this study is its single-center retrospective design, which means that the data should be treated with caution. Given the inherent limitations of current diagnostic definitions, a misclassification bias is possible (i.e., in the colonization group, there may be undiagnosed infections). However, misclassification is probably minimized, since all cases were assessed by the same investigator (BB) and since cultures were retrieved based on suspected infection and simultaneously from all possible infection sites, a design that reflects the reality of clinical practice and provides results that can be applied to bedside decision-making. In fact, this counts as a strength, since it lowers the probability of false-positive infections. The sample size is relatively small for the multivariate model and some variables, like duration of prior antibiotic exposure, were not recorded. Thus, further studies might identify additional variables. Finally, clonal analysis of MDR-PA was not performed; nevertheless, it is highly likely that these strains belonged to an epidemic high-risk clone (ST175, ST111, and ST235) currently reported in other hospitals in Barcelona [24, 25].

Conclusions

Multidrug-resistant *Pseudomonas aeruginosa* (MDR-PA) infections represented two-thirds of clinical isolates of MDR-PA in the intensive care unit (ICU), with an incidence of 25.0 per 1000 hospitalized adults, in spite of high compliance with hand hygiene and infection control. The typical index case was a non-terminal adult who underwent 2 weeks of ventilation via a tracheostomy. The respiratory tract was the most common clinical site. Restriction of antipseudomonal cephalosporin use might help to reduce its incidence of MDR-PA. High levels of carbapenem resistance are common and worrisome for therapy. Thus, early use of colistin and amikacin in patients at risk might help to reduce delays in providing effective treatment. Further research is warranted to assess the implications of MDR-PA for outcomes and identification of newer antimicrobial agents susceptible to these isolates.

Compliance with ethical standards

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Conflict of interest J.R. is on the speaker's bureau for Cubist, AztraZeneca, 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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